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Coronavirus Pandemic

Epidemiologic threats and outcome of evolving COVID-19-associated mucormycosis from a referral hospital in Egypt

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Abstract

Introduction: The present study aimed to explore the epidemiologic threats and factors associated with the coronavirus disease 2019 (COVID-19)-associated mucormycosis (CAM) epidemic that emerged in Egypt during the second COVID-19 wave. The study also aimed to explore the diagnostic features and the role of surgical interventions of CAM on the outcome of the disease in a central referral hospital.

Methodology: The study included 64 CAM patients from a referral hospital for CAM and a similar number of matched controls from COVID-19 patients who did not develop CAM.

Results: The most frequent factors among CAM patients were the use of corticosteroids, older age, and diabetes. CAM patients presented with facial pain (98.4%), black coloring on nasal endoscopy examination (87.5%), orbital invasion (70.3%), and loss of vision (68.8%). Despite treatment, CAM led to the death of 30 patients and 34 patients survived until the end of the study. CAM patients with death outcomes had orbital invasion, disturbed consciousness level, referral to intensive care units, and invasive mechanical ventilation. The patients who survived received more surgical interventions than dead patients, including functional endoscopic sinus surgery (FESS) and maxillofacial surgery.

Conclusions: CAM treatment requires complex, time-consuming, and expensive diagnostic approaches. Therefore, preventative measures should focus on early source control, strict glycemic control, and limiting steroids to COVID-19 patients especially older patients (> 40 years). Early antifungal treatment and surgical techniques such as FESS and necrotic tissue debridement were associated with better prognosis, indicating the efficiency of multidisciplinary medical and surgical teams.

Key words: corticosteroids; COVID-19; debridement; diabetes; endoscopic; mucormycosis.

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Introduction

Mucormycosis is a life-threatening disease and its incidence increased significantly among coronavirus disease 2019 (COVID-19) patients [1] during the second and third waves of the COVID-19 pandemic in late 2020 and the first half of 2021 [2]. A resurgence of mucormycosis occurred during the COVID-19 pandemic, either concurrently or after recovery from the viral infection, and led to the creation of a new entity: COVID-19-associated mucormycosis (CAM) [3]. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and may be associated with fungal and bacterial co-infections [4].

Mucormycosis is a rare invasive infection caused by a family of molds known as mucormycetes [5]. It invades the sinus tissues and penetrates the blood

vessels causing vasculitis, thrombosis, and hemorrhage with characteristic neutrophilic infiltrates [6]. Because of the proximity of the paranasal sinuses and the orbit to the brain, a progressive mucormycosis infection can progress to rhino-orbital-cerebral mucormycosis (ROCM) [7].

The precise link between viral and fungal infection is unknown. The most widely accepted theory is that the inadvertent use of immunosuppressive agents, particularly corticosteroids, to treat the viral infection in an already immune-compromised individual, particularly those with poorly controlled diabetes mellitus (DM), is most likely to result in superimposed fungal infection [8]. Another hypothesis is that the combination of biochemical alterations caused by the viral infection, including raised ferritin levels, acidosis, and acute cortisol stress response with elevated serum glucose levels, creates an ideal environment for the growth and propagation of various fungal species [9].

Mucormycosis has a major impact on patients' quality of life; thus, a high clinical suspicion, pre-diagnosis, and prompt treatment are crucial in relieving patients' suffering and ensuring a quick recovery [10]. The CAM disease was first detected in Egypt in May 2021 after the third COVID-19 pandemic. The severe and adverse outcomes, including deaths of early cases of CAM, led to strict measures by health authorities including the General Organization for Teaching Hospitals and Institutes (GOTHI), Egypt, to face this emerging problem. GOTHI assigned a central referral hospital for CAM in Cairo (AL-Gomhorya Teaching Hospital). Therefore, the present study included data from a larger number of CAM patients from the referral hospital than in other studies [11,12]. The present study aimed to explore the epidemiologic threats and factors of the CAM epidemic that emerged in Egypt during the second COVID-19 pandemic wave. The study also aimed to recognize the diagnostic features and the role of surgical interventions of CAM on the outcome of the disease in a central referral hospital.

Methodology

Study design

The present study was a multi-center retrospective study of CAM patients. The study was conducted over four months from May 27, 2021, to September 27, 2021. The study also included a case-control design to compare risk factors and characteristics between CAM patients and their matched controls. The Ethical Committee of the General Organization of Teaching Hospitals and Institutes (GOTHI; HAM 00165) approved the study.

CAM patients (n = 64) inclusion criteria

CAM patients from teaching hospitals in different regions (governorates) in Egypt who were referred to the GOTHI-assigned referral hospital for CAM illness (AL-Gomhorya Teaching Hospital in Cairo) during the period between the second and third COVID-19 pandemic waves were included. These patients met the diagnostic criteria for mucormycosis using the global guideline for the diagnosis and management of mucormycosis published by the European Confederation of Medical Mycology in collaboration with the Mycoses Study Group Education and Research Consortium [13]. These patients also had concurrent or prior COVID-19 infection, confirmed with positive real-time fluorescence reverse transcription-polymerase chain reaction (RT-PCR) and COVID-19 reporting and data system (CORADS) 4/5 in high-resolution computed tomography (HRCT) of the chest (within the last three months). The criteria also included CAM patients who received amphotericin as an antifungal treatment. The endpoint of CAM patients was either death or survival. The patients who had full clinical remission or improvement during or after the research period were assigned a survival outcome.

Matched controls

The study included a similar number of matched controls (n = 64). Controls were matched for age and gender as with each CAM patient. The matched controls were taken from data of 617 COVID-19 patients treated at AL-Gomhorya Teaching Hospital from October 2020 to May 2021. The controls were COVID-19 patients who did not develop mucormycosis after discharge from the hospital. The authors continued to follow up on the discharged patients via telephone calls for three months after the onset of COVID-19 infection to ensure the absence of clinical features suggestive of CAM.

Methods

The authors reviewed hospital records of CAM patients and controls during the COVID-19 epidemic in Egypt to collect data (place, time, and patient data). The data included the place of residence (governorate), time data (dates of COVID-19 infection, CAM patient admission, and the end of the study period), and patient data in the period before mucormycosis surge including age, gender, smoking, obesity (body mass index, BMI) > 30 kg/m^2) [14], DM, hypertension, ischemic heart, pulmonary, hepatic, renal, and malignancy diseases. Data on COVID-19 infection in the pre-CAM stage included place of management of COVID-19 (hospital

or home), chest HRCT findings, medications and corticosteroids administered duration, and route of administration of corticosteroids. The chest HRCT severity score was calculated for each of the five lobes of both lungs to represent the extent of pathologic involvement. The CO-RADS category was rated from 1 to 5, as follows: 0: no involvement (normal); 1: < 5%, mild involvement; 2: 5–25%, mild-to-moderate involvement; 3: 26–50%: moderate involvement; 4: 51-75%, moderate-to-severe involvement; and 5: >75%, severe involvement [15].

Clinical, radiological, and laboratory data included comprehensive clinical evaluation of symptoms, signs, and complications. All CAM patients underwent ear, nose, and throat (ENT) examination, nasal endoscopy (NE), and ophthalmological and neurological examination. Computerized tomography (CT) included paranasal sinuses (CT-PNS) and HRCT of the brain. Magnetic resonance imaging (MRI) or magnetic resonance venography (MRV) was also performed, whenever necessary.

Qualified ENT doctors collected respiratory samples (nasal/oro-pharyngeal swab) under perfect aseptic conditions for SARS-CoV-2 RT-PCR.

Mucormycetes fungus and histo-pathological examination

Specimens obtained from the nasal cavity or paranasal sinuses were prepared with 20% potassium hydroxide (KOH) and then cultured on Sabouraud's dextrose agar, where the mucormycetes fungus appeared as broad aseptate hyphae with right-angled branching, with aggregates of inflammatory cells, vascular invasion, and tissue damage.

Ophthalmologists and the ENT surgery team performed surgical removal and debridement of necrotic lesions and destroyed tissues formed due to mucormycosis according to the site and extension of lesions. The CAM lesions affected mostly eyes, orbits and periorbital tissues, nose, paranasal sinuses, maxillofacial region, and brain.

Statistical analysis

Data entry, mapping, and charting were done through Microsoft Excel spreadsheets. Data and time graphs were analyzed through IBM SPSS Statistics 23 (IBM Corp, Armonk, New York, USA). Student's t-test and paired t-test for normally distributed data and Mann–Whitney test for skewed data were performed. Chi square (χ^2), McNemar tests, and odds ratio (± 95% confidence interval) were calculated. The p value was set at < 0.05.

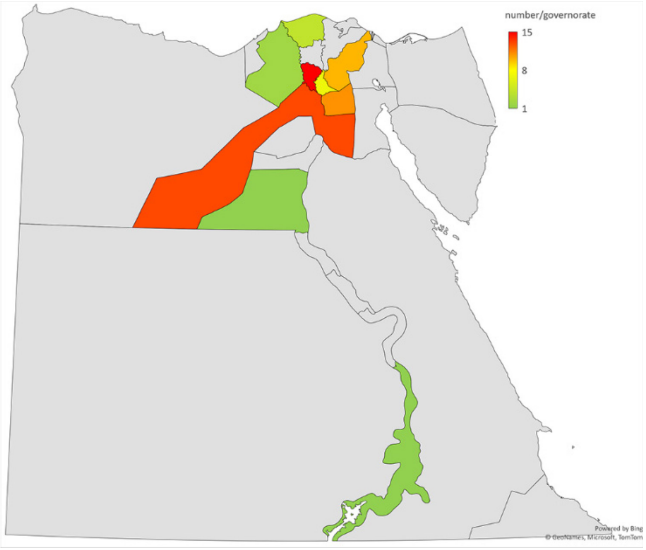
Results

CAM patients (n = 64) came from nine governorates including Monofiya, Giza, Cairo, Sharqiya, Qalioubiya, and Kafr ElSheikh (23.4%, 20.3%, 17.2%, 15.6%, 10.9%, and 6.3%, respectively) and others (Figure 1).

All cases reported COVID-19 onset before or upon admission as CAM patients in the early months of 2021. The outcome (survival, discharge, or death) was studied from 27 May 2021 to 20 September 2021. On 27 May 2021, the first CAM cases (index cases) were admitted to the hospital with a clinical picture of mucormycosis. Three patients – two men (60 and 49 years old) and one woman (65 years old) – were diabetics and died after one, 10, and 26 days, respectively (Figure 2).

CAM patients (n = 64) and matched controls from COVID-19 patients who did not develop mucormycosis included 35 males and 29 females in both groups. Their ages varied from 34 to 84 years, with a mean age of 56.4 ± 10.9 years and a median/interquartile range (IQR) of 58.0/16.0 years. Most patients (89.1%) were over the age of 40, with the highest percentages (34.4%) between 60–69 years old. Obesity and smoking were found in 50.0% and 17.2% of CAM patients, respectively. The most common factors of CAM (vs non-CAM if their data are not missing) were receiving corticosteroid drugs (pre-CAM) (98.4% vs. 37.5%, p = 0.000), followed by antibiotics (pre-CAM) (96.9%), age ≥ 40 years (89.1%), DM (87.5% vs. 46.9%, p = 0.000), anti-coagulants (81.3%), and obesity (50.0%). The CAM patients and the matched controls had hypertension and kidney disease (45.3% vs. 50.0%

Figure 1. Number of coronavirus disease 2019 (COVID-19) associated mucormycosis (CAM) cases referred from 9 governorates in Egypt to a referral hospital for CAM.



respectively and 14.1 vs. 10.9%, respectively), with no significant difference ($p > 0.05$) between the groups. Patients with concomitant ischemic heart disease were less common among CAM patients than in their matched controls (7.8% vs. 17.2%).

Forty-eight CAM patients (75.0%) received management at home during the preceding COVID-19 period. Only 16 CAM patients (25%) received treatment for COVID-19 in the hospital. CT chest findings showed that CO-RADS category 5 was the prevailing radiological category in 54 CAM patients (84.4%), including 32 confirmed COVID-19 (positive RT-PCR) and 22 patients with remarkably elevated levels of suspicion for pulmonary involvement (Table 1).

Most CAM patients received corticosteroids for periods between 3 and 60 days to manage their COVID-19 disease, before developing mucormycosis. CAM patients received corticosteroids through the intravenous parenteral route, oral intake, and parenteral followed by oral routes (16, 7, and 3 patients respectively) (Figure 3).

The most frequent findings were facial pain (98.4%), black discoloration on nasal endoscopy (NE) examination (87.5%), orbital swelling (75.0%), orbital invasion (70.3%), loss of vision (68.8%), sinusitis (radiological, 67.2%), difficulty swallowing (54.7%), and palatal invasion (50.0%). Other findings were less frequent including fever (45.3%), invasion of the surrounding structures (CT-PNS; 40.6%), crustation in NE (7.8%), and mild ischemic changes in NE (4.7%). Computerized tomography, magnetic resonance imaging, and magnetic resonance venography (CT/MRI/MRV) of the brain revealed affection of paranasal sinuses (n = 12), infarctions (n = 12), ischemic changes and invasions (n = 7), and orbital invasion (n = 4) (Table 2).

Despite medical and surgical therapy, CAM resulted in mortality in 30 patients (46.9%) and survival of 34 patients (53.1%). The occurrence of DM did not differ between CAM patients who survived and those

Table 1. Characteristics, COVID-19 status, and treatment (before developing mucormycosis) of COVID-19-associated mucormycosis (CAM) patients and matched controls.

Characteristics	CAM patients N=64	Matched controls N=64	*p* value	OR [95% CI]
Demographic factors				
Males	35 (54.7)	35 (54.7)		
Female	29 (45.3)	29 (45.3)		
Age (years)				
Mean ± SD	56.4 ± 10.9	56.4 ± 10.9		
Median /IQR/ min-max	58.0/16/34–84	58.0/16/34–84		
Underlying factors				
Corticosteroid exposure	63 (98.4)	24 (37.5)	0.000**	105.0 [13.7–806.0]
Antibiotic (pre-CAM)	62 (96.9)			
Older age (≥ 40 years)	57 (89.1)	57 (89.1), matched		
DM	56 (87.5)	34 (53.1)	0.000**	6.2 [2.5–15.0]
Anticoagulant (pre-CAM)	52 (81.3)	–		
Treatment at home	48 (75.0)	–		
Obesity (BMI ≥ 30 kg/m^2)	32 (50.0)	–		
Oxygen therapy (pre-CAM)	31 (48.4)	–		
Hypertension	29 (45.3)	32 (50.0)	0.701	
Lactoferrin (pre-CAM)	24 (37.5)	–		
Ever-smokers	11 (17.2)	–		
Renal disease/regular dialysis	9 (14.1)	7 (10.9)	0.774	
Ischemic heart disease	5 (7.8)	11 (17.2)	0.181	
Pulmonary disease	4 (6.3)	0 (0.0)	–	
Chronic liver disease	3 (4.7)	0 (0.0)	–	
Malignancy	3 (4.7)	0 (0.0)	–	
Tocilizumab with corticosteroids (pre-CAM)	1 (1.6)	–		
COVID-19 disease (positive RT-PCR) status				
On admission	34 (53.1)			
Preadmission (Negative on admission)	30 (46.9)			
CO-RADS category and PCR (+/-)				
CO-RADS category 5 (32/22)	54 (84.4)			
CO-RADS category 1 (1/4)	5 (7.8)			
CO-RADS category 3 (2/1)	3 (4.7)			
CO-RADS category 2 (1/1)	2 (3.1)			

BMI: body mass index; CI: confidence interval; CO-RADS: COVID-19 reporting and data system; DM: diabetes mellitus; IQR: interquartile range; OR: odds ratio; RT-PCR: real-time polymerase chain reaction; SD: standard deviation; –: non-available data; **: highly significant (*p* value < 0.01).

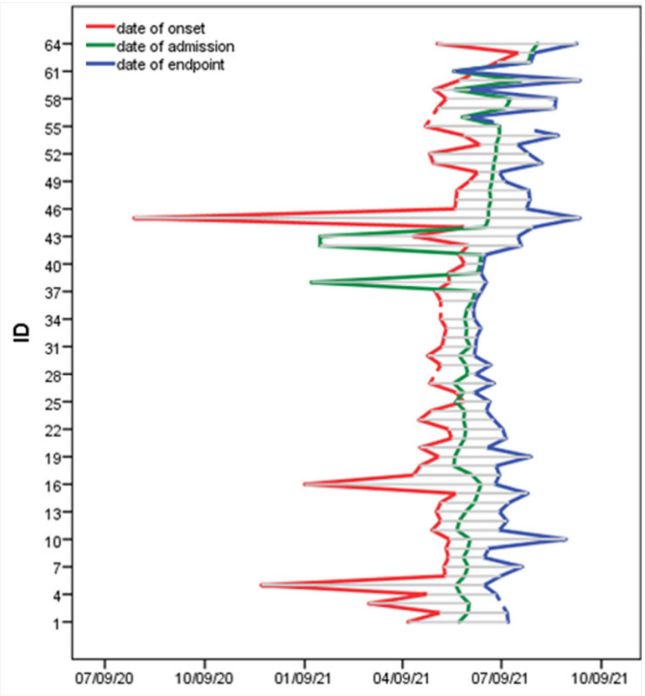
Table 2. Diagnosis of COVID-19-associated mucormycosis (CAM) including clinical manifestations, radiology, and endoscopy.

Clinical manifestations	n	%	Radiological findings	n	%
Facial pain	63	98.4	**1. CT-PNS**		
Orbital swelling	48	75.0	Sinusitis	38	59.4
Black discoloration	46	71.9	Invasion of surrounding structures	26	40.6
Orbital invasion	45	70.3	**2. CT/MRI/MRV brain**		
Loss of vision	44	68.8	Infarctions	12	18.8
Difficult swallowing	36	56.3	Frontal brain abscess/mass	2	3.2
Palatal invasion	32	50.0	Right temporal lobe extension	1	1.6
Fever	26	40.6	**3. CT Orbit**		
DCL	24	37.5	Left orbital abscess	1	1.6
Evidence of brain invasion[a]	16	25.0	CT orbit cellulitis	2	3.1
Black discharge	14	21.9	Proptosis and eye infiltration	1	1.6
Nasal endoscopy					
Black discoloration	56	87.5			
Crustation	5	7.8			
Mild ischemic findings	3	4.7			

Total N = 64 CAM patients; [a]: sudden numbness: confusion: trouble seeing: trouble walking: or severe headache. CT: computerized tomography; DCL: disturbed consciousness level; MRI: magnetic resonance imaging; MRV: magnetic resonance venography; PNS: paranasal sinuses.

who did not. Most CAM patients with death outcomes had orbit invasion more frequently than CAM patients who survived (90.0% vs. 52.9%, respectively) and disturbed consciousness level (DCL) (70.0% vs. 5.9%, respectively). Referral to the intensive care unit (ICU) (96.7% vs. 38.2%) and invasive mechanical ventilation (IMV) (76.7% vs. 5.9%) were similarly more prevalent in dead patients. All CAM patients received amphotericin. The patients who survived had more surgical interventions than those who died (79.4 vs. 26.7%), functional endoscopic sinus surgery (FESS) (67.6% vs. 23.3%), and maxillofacial surgery (52.9% vs. 23.3%; Table 3).

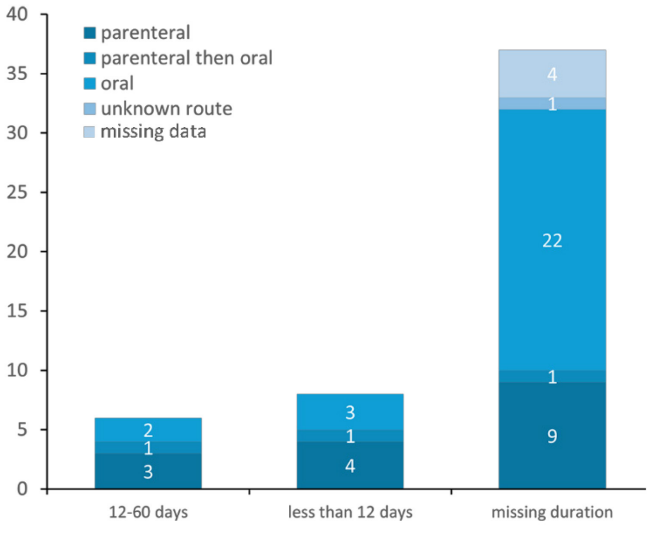
Figure 2. Time distribution of dates of onset of coronavirus disease 2019 (COVID-19) in 64 COVID-19-associated mucormycosis (CAM) patients (in red/left line), dates of admission due to mucormycosis (in green/middle line), and endpoint (discharge or death) of CAM patients (in blue/right line). The horizontal lines (gray) indicate the duration of disease in each subject. (Figure created using SPSS).



Discussion

There is a lack of evidence on the prevalence of mucormycosis in Egypt, which may be higher than the global average due to the health system's debility and the high burden of DM and other immune-compromised illnesses, resembling the situation in India [16]. During recurring COVID-19 waves in India, the prevalence rate of mucormycosis infection has been

Figure 3. Duration and routes of administration of corticosteroids for coronavirus disease 2019 (COVID-19)-associated mucormycosis (CAM) patients during preceding COVID-19 disease (before developing mucormycosis).



reported to have increased by around 2.1 times the rate during the first wave [17]. Globally, invasive CAM is more prevalent in India (55.5%), Egypt (17.8%), Iran (9. 9%), and Türkiye (6.3%); where the high prevalence of CAM is associated with predisposing diseases, like uncontrolled DM; and tropical and subtropical climate zones, particularly during the autumn season [18]. CAM cases have also been reported from other countries like Honduras and Peru [19,20].

COVID-19 itself and the use of immunosuppressive drugs and oxygen therapy are paving the way for opportunistic infections and co-infections with fungi [21]. It has been reported that COVID-19 patients with acute respiratory distress syndrome (ARDS) who needed mechanical ventilation and were treated with

Table 3. Outcome of COVID-19-associated mucormycosis (CAM) in relation to history, clinical findings, investigations, complications, and management.

Total No. of patients (N = 64)	Survived N = 34		Patients with death outcome N = 30		*p* value	OR	95% confidence interval	
							Upper	Lower
Demographics and history								
Males	19	63.3	16	47.1	0.292			
Females	11	36.7	18	52.9				
Age (years)	54.5	± 10.6	58.6	± 11.0	0.133			
BMI (kg/m^2)	32.2	± 5.6	30.4	± 4.2	0.219			
Smoking	4	11.8	7	23.3	0.372			
Hypertension	14	41.2	15	50.0	0.648			
DM	30	88.2	26	86.7	1.0			
Steroid data								
pre-CAM steroid intake	33	97.1	30	100.0	1.0			
No. of days of steroid intake	14.3	± 12.0	7.5	± 3.0	0.129			
No of cases treated for 3-12 days	9	26.5	8	26.7	0.023*			
No of cases treated for 14-60 days	9	26.5	0	0.0				
Missing duration	16	47.0	22	73.3				
Route of administration								
Parenteral route	9	26.5	7	23.3				
Oral route	5	14.7	2	6.7				
Parenteral then oral route	3	8.8	0	0.0				
Unknown route	17	50.0	21	70.0				
Clinical								
DCL	1	2.9	23	76.7	0.000**	108.4	12.5	942.0
Fever	4	11.8	22	73.3	0.000**	20.6	5.5	77.2
Temperature (°C)	37.26	±.4	38.3	±.9	0.000**			
Orbital swelling	19	55.9	29	96.7	0.001**	22.9	2.8	188.0
Loss of vision	16	47.1	28	93.3	0.000**	15.8	3.2	76.8
Facial pain	33	97.1	30	100.0	1.000			
Black discoloration	24	70.6	24	80.0	0.386			
Difficult swallowing	15	44.1	21	70.0	0.067			
Black discharge	5	14.7	9	30.0	0.240			
Sinusitis	34	100.0	29	96.7	0.469			
Radiology								
CT brain invasion	4	11.8	8	26.7	0.229			
Nasal endoscopy								
Orbit invasion	18	52.9	27	90.0	0.003**	8.0	2.0	31.5
Sinuses invasion	33	97.1	28	96.6	1.0			
Palate invasion	18	52.9	14	46.6	0.802			
ICU admission								
Referral to ICU	13	38.2	29	96.7	0.000**	46.8	5.7	386.4
DCL	2	5.9	21	70.0	0.000**	37.3	7.3	190.2
Sepsis /septic shock	1	2.9	6	20.0	0.075			
Invasive mechanical ventilation	2	5.9	23	76.7	0.000**	52.6	10.0	276.6
Surgical interventions								
FESS	23	67.6	7	23.3	0.001**	0.1	0.0	0.4
Maxillofacial surgery	18	52.9	7	23.3	0.030*	0.3	0.1	0.8
Eye exenteration	13	38.2	9	30.0	0.668			
ENT surgery	4	11.8	4	13.3	0.572			

All cases (n = 64) received amphotericin during the study period. *, significant (p value < 0.05); **, highly significant (p value < 0.05). BMI: body mass index; CI: confidence interval; CT: computerized tomography; DCL: Disturbed consciousness level; DM: diabetes mellitus; ENT: ear: nose: and throat; FESS: functional endoscopic sinus surgery; ICU: intensive care unit; OR: odds ratio.

high doses of corticosteroids, immune-modulators, and interleukin antagonists, were at a higher risk of developing CAM [22]. Older males, smokers, diabetics, hypertensive, and cardiac patients have a higher risk of infection with mucormycosis, as revealed by a study of CAM patients in Assiut University hospitals, in Egypt. This elevated risk can be related to a shift in their innate immunity and contracting a more severe and chronic COVID-19 infection [11].

Debilitating and chronic diseases are common risk factors among CAM patients, as seen in the present study. Shabana *et al.* in their study of 30 CAM patients in a tertiary eye care center in Egypt, revealed that 90% of patients had DM as the common co-morbidity, 63.3% had uncontrolled DM, 66.6% received systemic steroid therapy, and 20% received steroids for more than 10 days [12]. A European study reported DM in 32.5% and immuno-compromised condition in 40% of CAM patients [23]. A Pakistani study reported DM in 70% and receiving corticosteroids in 80% of the patients [24]; and a Chilean study reported 25% of the patients with DM and 93.8% receiving corticosteroids. The patients in neither of these studies were immuno-compromised, implying different predisposing factors in different settings [25] and distinct levels of available healthcare and notification systems. The largest Indian nationwide CAM survey assessed the data of 2,826 patients, 78% of whom had DM and 87% had received corticosteroids for COVID-19, implying that both characteristics are major predisposing factors for CAM [26].

Asdaq *et al.* discovered that blood glucose levels in COVID-19 patients rise rapidly as the coronavirus damages pancreatic beta cells [27]. Hyperglycemia and acidosis impede phagocyte activity, which is the principal host defense mechanism against fungal infections such as mucormycosis; thus, uncontrolled DM is a distinct risk factor for ROCM [28]. Uncontrolled hyperglycemia caused by diabetic ketoacidosis (DKA) can alter this immune response, resulting in a decrease in granulocyte phagocytosis and a change in polymorphonuclear leukocyte response. Furthermore, Mucorales have a ketone reductase enzyme that thrives in high glucose circumstances and DKA, leading to a dismal prognosis [29].

A higher prevalence of CAM was associated with uncontrolled DM and non-compliance with precautionary measures in an Indian study, and the authors referred to the possibility of a referral bias for a difficult-to-treat disease [30]. In the present study, referral of CAM patients to a central referral hospital provided better opportunities for these patients to control their chronic illness, especially DM.

CAM has been reported in cases where there was immunological dysfunction, secondary to the extensive use of broad-spectrum antibiotics, monoclonal antibodies, and steroids, as part of the COVID-19 treatment protocol [27,31–33], consistent with the present study. In addition to the notable rise in blood ferritin levels during COVID-19 infection, it supplies an enriched medium for the growth of this fungus [34].

The mean age of CAM patients in the present study was 56.4 years, with is similar to other studies [12,35] and slightly higher than the systematic review of patients' characteristics utilizing 77 studies by Ghasemi *et al.* where the patients' mean age was 48 years (± 14.3) [10]. Two studies presented a male predominance of CAM [11,36], with evidence of the protective role of estrogen in developing paracoccidioidomycosis which might be responsible for male susceptibility to mucormycosis [37]. On the contrary, in the present study, gender did not seem to play a role in the occurrence of CAM, nor its prognosis.

Obese people are at a higher risk of worsening bacterial, viral, and fungal respiratory infections. Kumar *et al*. found that 49% of mucormycosis patients were obese [38], similar to our findings. Obesity is a low-grade inflammatory condition that is associated with decreased immune function and lung ability. Obesity is also a significant risk factor for other co-morbidities associated with COVID-19 severity, such as DM, hypertension, and cardiovascular disease [39]. Hypertension was the second most common underlying condition among CAM patients, after DM, in other studies [11,36].

A recent review of 8,727 CAM patients from different studies in India, Egypt, and Europe, showed that it mostly affected the head and neck area. ROCM was the most prevalent type that occurred in 98.3% of CAM patients, followed by 1.2% of patients whose pulmonary regions were affected. In Europe, 75% of patients are presented with pulmonary CAM [23]. Mucormycosis manifestations depend on two main factors: the portal of entry of fungal spores into the body via inhalation, ingestion, or direct skin inoculation; and the predisposing factors of the infected patients [40]. Therefore, ocular, nasal, paranasal, and pulmonary mucosa might be susceptible to fungal infection in COVID-19 patients.

In the present study, eye symptoms were the most predominant manifestations of CAM. Fouad *et al.* observed that the initial presenting signs in 12 CAM patients in a tertiary care center in Egypt were lid edema

(50%), conjunctival ecchymosis (50%), diminution of vision (41.7%), proptosis (33.3%), facial edema (25%), nasal crusts (25%), total ophthalmoplegia (16.7%), and paralytic esotropia (8.3%). All patients developed orbital infiltration with cavernous sinus infiltration in 33.3%, bilateral eye involvement in 16.7%, internal carotid artery infiltration in 16.7%, and cerebral abscess in 16.7% [35]. The orbital extension might destroy the ophthalmic artery and optic nerves resulting in eyelid ptosis, proptosis, vision disturbances, and blindness [26]. The findings of an Assiut University hospital study reported that 78.8% of CAM patients had peri-orbital edema and proptosis, which consecutively ended with diminution and loss of vision in 75.8% [11]. In an Indian study, CAM patients reported black discoloration, black spots in front of the eye, and visual distortion [27].

CAM patients also reported headache and nerve palsy in 81.8%, hemiparesis in 9.1% [24], delirium, and memory loss [27]. Other clinical symptoms of head and neck mucormycosis included black necrotic turbinate, facial pain, facial palsy, peri-orbital edema, and blackish-stained skin [41]. Cerebral involvement may manifest as cavernous sinus thrombosis, fungal abscess, meningitis, and cerebrovascular disease [42]. In a multicentric Indian study of 49 patients with cerebrovascular involvement, Kulkarni *et al.* noticed that 91.8% of patients had an ischemic stroke with major artery infracts, followed by intracranial hemorrhage in 6.1%, and sub-arachnoid hemorrhage in 2.0% [43].

Shabana *et al*. reported that half of the orbital CAM patients had both pan-sinusitis and maxillary bone necrosis in CT/MRI and 20% had only maxillary bone necrosis [12]. Hoque *et al*. noticed blackish crusts in the nasal cavity, nasopharynx, nasal septum, and soft palate [21]. Nasal endoscopy could detect early indications such as purplish or blackish spots on the nasal mucosa, as well as late signs such as gangrene [43].

Two cross-sectional studies from 12 CAM cases were reported from Iran. In these studies, 87.3% had DM, with a mortality rate of 66.6% [44]. Early detection of CAM allows for prompt treatment, which reduces mortality and morbidity. Imaging is critical for evaluating the degree of severity of the disease as well as planning surgical debridement. Non-enhancement of nasal turbinate in patients with acute invasive fungal rhinosinusitis (e.g. mucormycosis) denotes the black turbinate sign. It involves nasal mucosa and causes infarction of the surrounding tissue. The infarcted tissue is non-enhancing on contrast-enhanced MRI. This sign is important for the early detection of invasive fungal rhinosinusitis [45]. The intracranial spread can be direct from the nasal cavities to the frontal lobes or the cavernous sinus via the cribriform plate or the ophthalmic arteries. Filling defects within the cavernous sinus appreciated as non-enhancing areas on CT or MRI is a sign of cavernous sinus invasion [46].

A multidisciplinary approach for diagnosis and prompt treatment with antifungals is essential, as the timing of mucormycosis management is crucial. Surgical interventions support the control of the spread of infection to adjacent structures [47]. Shabana *et al.* utilized a regimen of systemic anti-fungal therapy and FESS with substantial necrotic tissue debridement to control ROCM. A total of 20% CAM patients had orbital exenteration and 80% of the patients lived with clinical, but no visual, improvement [12].

Most patients in the study by Mitra *et al.* underwent FESS with sinus debridement with or without orbital clearance. The fungal infection and necrosis spread to the soft tissues of the cheeks and eyelids, which required debridement with 25% of their patients requiring orbital exenteration [48]. Murthy *et al.* proposed medial orbital wall decompression as a method of lowering intra-orbital pressure in patients of ROCM. They assessed it on 36 patients and found that none of them needed exenteration [49].

In agreement with our study, Elkholy *et al*. and Hussain *et al.* used both antifungal therapy and surgical intervention according to each condition based on the extent of infection. They performed endoscopic or open surgical procedures to improve the clinical outcome. Although this could reduce overall mortality, it was time and money-consuming [50,51].

Despite early detection, along with surgical and medicinal treatment, the prognosis for recovery from mucormycosis was noticeably poor in our study with the death of 46.9% of the CAM patients. These findings agreed with Werthman-Ehrenreich's findings that, even with adequate medical treatment, a rhino-orbital infection caused by the Mucorales fungus had a dreadful prognosis, with a mortality rate of up to 50% [52]. All CAM patients, in the study of Assiut University hospitals, deteriorated and died except for three patients who were still alive due to residual infection. One patient was completely cured after antifungal and surgical debridement; the second and third were cured with by ptosis and ophthalmoplegia treatment and had vision loss [11].

Finally, the most pressing question stays unanswered. Why has the CAM pandemic evolved during this COVID-19 wave in Egypt? Theories have been based on earlier mucormycosis outbreaks and case

reports, highlighting environmental and iatrogenic factors as the source of Mucormycetes, such as contaminated medications, wooden tongue depressors, and linen [53]. Steroid injections were the most used medicines among our patients during the COVID-19 wave; however, we were unable to obtain any of the pharmaceutical batches used before patients' admission for further investigation.

Conclusions

Improved understanding of co-infections in COVID-19 is of critical importance for effective patient management and control of SARS-CoV-2. The alarmingly high incidence of invasive mucormycosis in COVID-19 patients, particularly those in rural locations and with pre-existing risk factors, mandates early diagnosis of the infection, to reduce mortality and morbidity rates. The abuse of steroids, antibiotics, and anticoagulants in the treatment of COVID-19 cases; and uncontrolled DM, obesity, and hypertension; were associated with developing CAM. Research of other causes including obscure sources of fungal contamination will help control the disease. Early antifungal treatment, as well as surgical procedures such as FESS, maxillectomy debridement of necrotic tissue, and eye exenteration, were associated with a favorable prognosis, showing the effectiveness of a multidisciplinary medical team in dealing with the disease.

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Authors' contributions

All authors whose names appear on the submission have made substantial contributions to the conception, design of the work; data acquisition and analysis, interpretation of data; manuscript draft, and critical revision of manuscript for important intellectual content. All authors approved of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy of the integrity of any part of the work are appropriately investigated and resolved.

Conceptual design: SE, MAG, AH; ethical approval: MSM; medical diagnosis: MAG, OA; medical management: MAG, EM, AH, HM, SAH, MSM, SA, EES, FIFI; otorhinolaryngology management: AMM, AEB; oral and maxillofacial surgery management: AMS; ophthalmology management: HME, AAE, AAEF; neurosurgery management: TAG; drug management: SMS; data management: SE, EM, SAH, EES, AEB, AAE; statistical analysis: SE; figures and tables: SE; manuscript – writing: SE, AH, WS, EM, AAEF, MSE; manuscript – review: SE, AH, WS, MSE.

Disclosures

We declare that this manuscript is original; is not published, in press, or submitted elsewhere in English or any other language; and is not currently being considered for publication elsewhere.

We declare that all authors have reviewed and approved the manuscript. They all have contributed significantly to the work.

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