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Original article

COVID-19 associated mucormycosis and diabetes mellitus: An exploratory study

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ABSTRACT

Background: Mucormycosis has abruptly increased in Egypt during the third wave of COVID-19 especially in patients with diabetes mellitus (DM). The aim of this study was to investigate the risk factors, clinical presentation and outcome of mucormycosis in COVID-19 patients with diabetes. **Methods:** Prospective cohort study was conducted on 72 COVID-19 patients with DM presented with mucormycosis at intensive care units and Ear, Nose, and Throat Department of Zagazig University Hospitals over a period of three months from May 2021 to August 2021. All participants were submitted to history taking, examination, laboratory investigation, radiological and histopathology and culture testing. **Results:** Post COVID-19 new-onset diabetes mellitus (NOD) was detected in 40% of studied patients. 72.2% of patients had poorly controlled diabetes. Majority of studied patients presented by rhino-orbital mucormycosis (90.3%) and about 86% of them were operated. Hundred percent of patients gave history of antibiotic use and also nearly 99.0% of them received corticosteroids, while only 1.4% of them received tocilizumab. There was statistically significant association between operated patients, hemoglobin (HB) level, lymphocyte count, neutrophil-lymphocyte ratio (NLR), and CRP level with disease prognosis. **Conclusions:** Poorly controlled DM and steroid use are the most important risk for post COVID-19 mucormycosis. Early surgical intervention carried better disease outcome.

Introduction

The pandemic of COVID-19 has affected about 210 million confirmed cases on the day of this report and more than 4 million deaths have been reported to World Health Organization (WHO). Several cases of opportunistic fungal infections have been reported in COVID-19 patients. Mucormycosis case load has been increased recently associated with COVID-19 [1].

Mucormycosis is an angioinvasive fungus that is usually present in the environment and grows on wet surfaces, decaying vegetation and in the soil. Mucormycosis is caused by Mucor Rhizopus, Rhizomucor and Lichtheimia (formerly Absidia) [2]. The most common type is *Rhizopus Oryzae* and

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causing approximately 60% of mucormycosis cases in humans; it is responsible for 90% of the rhino-orbital-cerebral form [3].

Risk factors for mucormycosis in COVID-19 patients may include poorly controlled diabetes mellitus (DM), immunocompromised patients, glucocorticoids therapy, misuse of broad-spectrum antibiotics, long use of multivitamins, and zinc [4]. The use of high flow oxygen and aggressive use of steam inhalation, low-quality oxygen piping system and ordinary tap water in ventilators are also being listed as risk factors [4]. COVID-19 is known also to cause hyperglycemia in some patients, which could increase the risk for developing fungal infection [5].

The most common presentation of mucormycosis is rhino-orbital-cerebral mucormycosis. Gastrointestinal, pulmonary and cutaneous presentations are also recognized.

Mucormycosis has the worst outcome among other invasive fungal infections caused by aspergillosis and candidiasis. The higher degree of difficulty to cure this infection is related to great difficulty in early diagnosis when the 'window' of successful treatment is higher, differences in host–fungus interactions, and pathogenetic mechanisms [6].

The aim of this study is to investigate the risk factors, clinical presentation (the site of affection) and outcome of mucormycosis in diabetic patients with history of COVID-19.

Materials and Methods

Study type and setting

Prospective cohort study was conducted at intensive care units (ICUs) and Ear, Nose, and Throat (ENT) Department of Zagazig University Hospitals over a period of three months from May 2021 to August 2021.

Study sample

The study was conducted on 72 diabetic patients with history of COVID-19 and were diagnosed as mucormycosis.

Sample selection

All patients fulfilled inclusion criteria during the period of study were included in the study (comprehensive sample).

Inclusion criteria

Diabetic patients with history of COVID-19 (all cases were diagnosed by PCR) and were diagnosed with mucormycosis as were defined by the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC MSG) criteria [7].

Study tools

All participants were submitted to the following:

1- History taking (onset of COVID-19 infection, onset of mucormycosis infection, DM (preexisting or postcovid DM) , other comorbidities, immunosuppressive drugs and duration of hospital stay).

2- Full physical examination.

3- Investigations , including:

A- Laboratory: CBC including HB (gm/dl), white blood cells, neutrophils, lymphocytes (per mm^3), glycated haemoglobin (HbA1c) (%), serum creatinine (mg/dl), CRP (mg/l), serum ferritin (ng/mL), serum interleukin-6 (pg/ml).

B- Radiological: Non-contrast computed tomography scans of the paranasal sinuses, gadolinium-enhanced magnetic resonance imaging (MRI) scans of brain, paranasal sinuses and orbits.

C- Histopathology and fungal and bacterial culture of excisional nasal tissue.

Follow up of patients regarding medical and surgical management was done and recorded.

Patients were classified regarding the outcome of disease into (patients with poor prognosis (didn't respond to treatment or died) and patients with good prognosis(responded to treatment and discharged).

Ethical consideration

The study was approved by university hospital institutional ethical committee (#698/2-3-2021)*;* written consent form was signed by the patient or his relative to participate in this study.

Data management

The SPSS program (Statistical Package for Social Science) version 15.0 was used to analyze the data where, qualitative data were represented as frequencies and percentages and quantitative data were represented as mean and standard deviation. Chi-square test and fisher exact test were used for comparing descriptive data and independent t test and Mann-Whitney test were used to compare

quantitative data. *p*-value ≤ 0.05 was considered statistically significant.

Results

Table 1 shows that mean age of studied patients was 58.8±9.6 years, about 60% of them were female and 40% of them developed Post COVID-19 new-onset diabetes (NOD). The mean HbA1c was 9.5 (±2.2) on admission. Poorly controlled diabetes was detected in (72.2%) of patients (HbA1c ≥ 8%). Thirty sex percent of patients suffered from other comorbidities. Majority of studied patients were presented by rhino-orbital mucormycosis (90.3%). Hundred percent of patients gave history of antibiotic use and also nearly 99.0% of them received corticosteroids, while only 1.4% of them received tocilizumab. The most common detected organism was Mucor . The mean time interval between onset of COVID-19 and developing mucormycosis was 34.0±28.2 days.

Table 1 also shows the mean values of some laboratory chemical tests of studied patients including HB (10.7±2.2gm/dl), white blood cells(12.3±4.3×10^9/L), neutrophils(9086.1±4307.7 per mm^3) , lymphocytes (1700.7±985.1 per mm^3), HbA1c (9.5±2.2%), serum creatinine (1.7±1.2 mg/dl), CRP (155.4±188.8 mg/l), serum ferritin (619.0±823.0 ng/mL), serum interleukin-6 (44.3±65.3 pg/ml).

Table 2 shows that there was statistically significant association between operated patients , disease outcome , HB level, lymphocyte count, NLR and CRP level and disease prognosis **.**On the other hand, there was no significant association between different comorbidities, the control of diabetes (good or poor) and disease prognosis.

Patients with suspected mucormycosis were initially treated by Amphotericin B/liposomal amphotericin B with tight blood glucose control, then surgical debridement and orbital exenteration and continued on specific antifungal (amphotericin B, posaconazole, itraconazole or voriconazole) depending on the culture results. About 86% (62/72) of patients were operated. Regarding outcome of cases, 10 patients died before surgery and 70.8% of them were discharged.

Table 1. Frequency distribution of patients and disease characteristics.

Patient and disease characteristics		Frequency (%) (N=72)
Age	(X±SD)	58.8±9.6
Sex	-Female	43(59.7)
	-Male	29(40.3)
Diabetes onset:		
-Preexisting		43(59.7)
-Post COVID-19 (NOD)		29(40.3)
Poorly controlled diabetes		52(72.2)
Other comorbidities*		26(36.1)
Clinical presentation of mucormycosis		
Rhino-orbital		65(90.3)
Rhino-orbital –cerebral		7(9.7)
Operated cases		62(86.1)
History of corticosteroids use		71(98.6)
History of antibiotic administration		72(100.0)
History of tocilizumab administration		1(1.4)
Prognosis		
Good		48(66.7)
Outcome		
-Discharge		51(70.8)
-Death		21(29.2)
Interval between (X±SD)		34.03±28.2
Duration of hospital stay (X±SD)		13.7±7.1

Laboratory Findings (X±SD)	Reference values	
HBA1C	9.5±2.2	(4-5.6%)
Lymphocyte count	1700.7±985.1	(1000-4000 per mm^3)
WBC count	12.3±4.3	(4.5 to 11.0 × 10^9/L)
Neutrophil count	9086.1±4307.7	(2500-8000 per mm^3
HB level	10.7±2.2	(12-17 gm/dl)
Creatinine level	1.7±1.2	(0.7-1.3 mg/dL)
CRP level	155.4±188.8	(8-10 mg/L)
Ferritin level	619.0±823.0	(20-250 ng/mL)
IL6	44.3±65.3	(0 - 43.5 pg/ml)
NLR	7.3±6.1	(1-3)

*Hepatitis C, hypertension, cardiac diseases, pancytopenia, CKD, stroke, hyperthyroidism, pancytopenia, scleroderma, Bronchial asthma.

Table 2. Relation between patients and disease characteristics and prognosis of disease.

Patient and disease characteristics	**Good (N=48)**	**Poor (N=24)**	**Chi-square test**	***p* value**
Sex				
Female (N=43)	27(56.3%)	16(66.7%)	0.7	0.4
Male (N=29)	21(43.7%0	8(33.7%)		
Diabetes onset:				
-Preexisting(N=43)	28 (58.3%)	15(62.5%)	0.11	0.7
-Post COVID-19 NOD (N=29)	20(41.7%)	9(37.5%)		
Poorly controlled diabetes (N=52)	35 (72.9%)	17 (70.8%)	0.03	0.8
Other comorbidities				
Yes (N=26)	14 (29.2%)	12 (50.0%)	3.01	0.08
Clinical presentation of mucormychosis				
Rhino-orbital (N=65)	45 (93.8%)	20 (83.3%)	1.98	0.16
Rhino-orbital –cerebral(N=7)	3 (6.2%)	4 (16.7%)		
Operated cases(N=62)	47 (97.9%)	15 (62.5%)	Fisher Exact	**0.000***
History of corticosteroid use	48 (100.0)	23 (95.8%)	Fisher exact	0.33
Outcome				**0.000***
-Discharge	48(100.0%)	3(12.5%)	59.3	
-Death	0(0.0%)	21(87.5%)		
Labaratory findings	(X±SD)	(X±SD)	t test	
HBA1C	9.4±2.2	9.8±2.3	.66	.5
Lymphocyte	1911.4±1086.3	1279.2±553.2	2.7	**0.009***
WBC	11.9±4.04	12.9±4.8	.838	.4
Neutophils	8447.9±4030.9	10362.5±4639.9	1.806	0.07
HB level	11.3±2.0	9.4±2.04	3.8	**0.000***
Creatinine	1.5±1.1	2.0±1.4	1.64	0.1
CRP	104.6±99.1	257.1±271.8	3.5	**0.001***
Ferritin	541.2±865.6	773.3±725.1	1.3	.26
IL6	29.7±24.2	79.3±115.2	1.5	.16
NLR	6.1±6.2	9.7±5.3	Mann-whitney 312.5	**0.002***

*Significant

Figure 1. T1 coronal MRI showing hypointensity in the left maxillary, ethmoidal and frontal sinuses with breakdown of the left lamina papyracea.

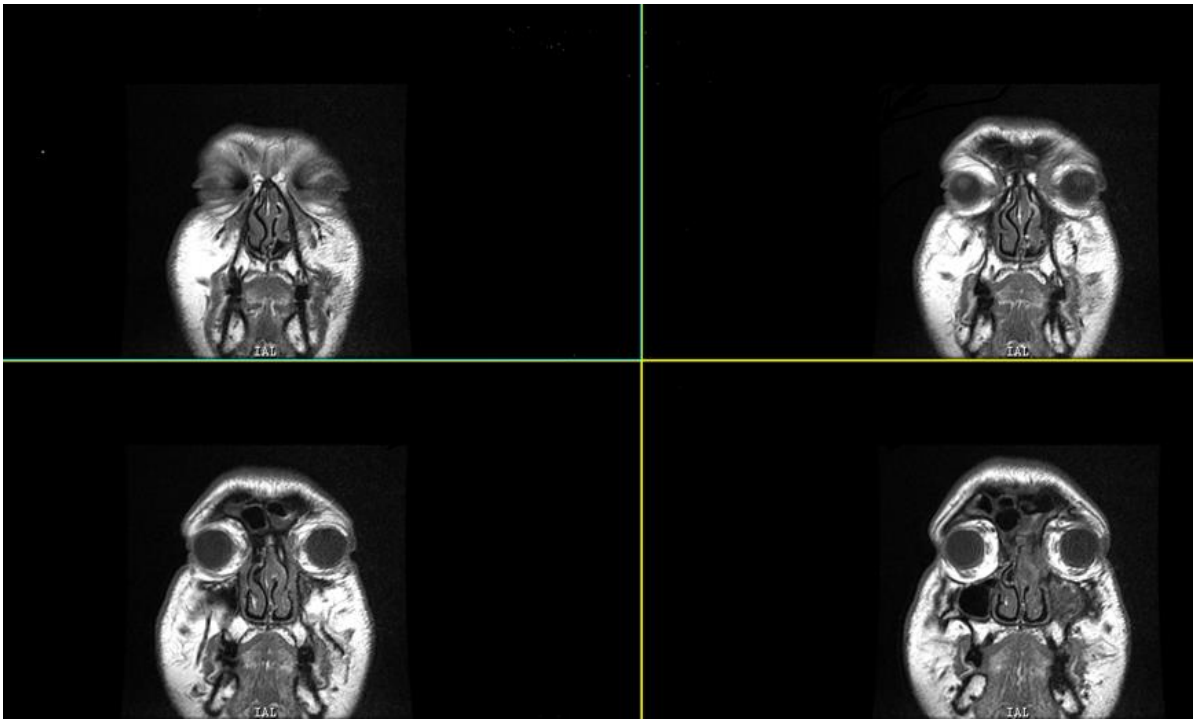

Figure 2. T1 axial imaging with Post gadolinium enhancement showing necrotic devitalized left inferior turbinate (hypointense black turbinate sign) with necrosed upper alveolar margin with mucosal thickening of the left maxillary sinus.

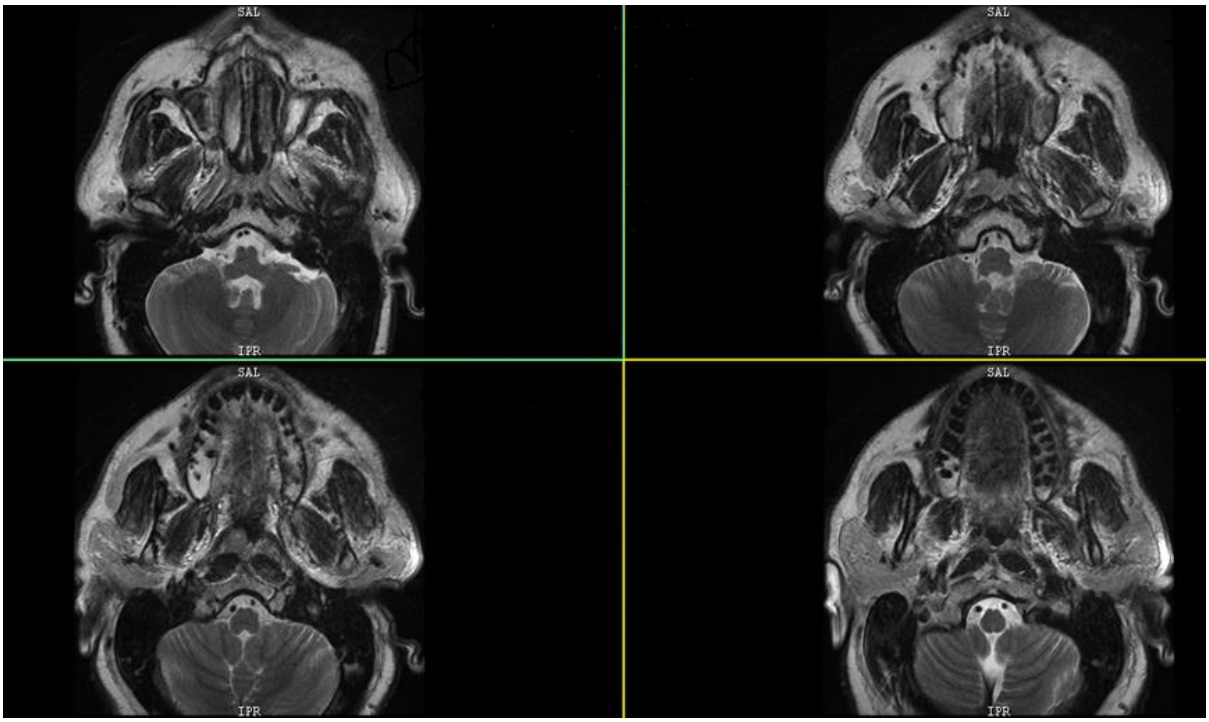

Figure 3. T2 coronal images showing left sided hyperintensity in frontal and maxillary sinuses denoting inflammatory reaction & iso to hypointensity in ethmoid and nasal turbinates in the same side denoting focus of necrotic tissue and fungal element.

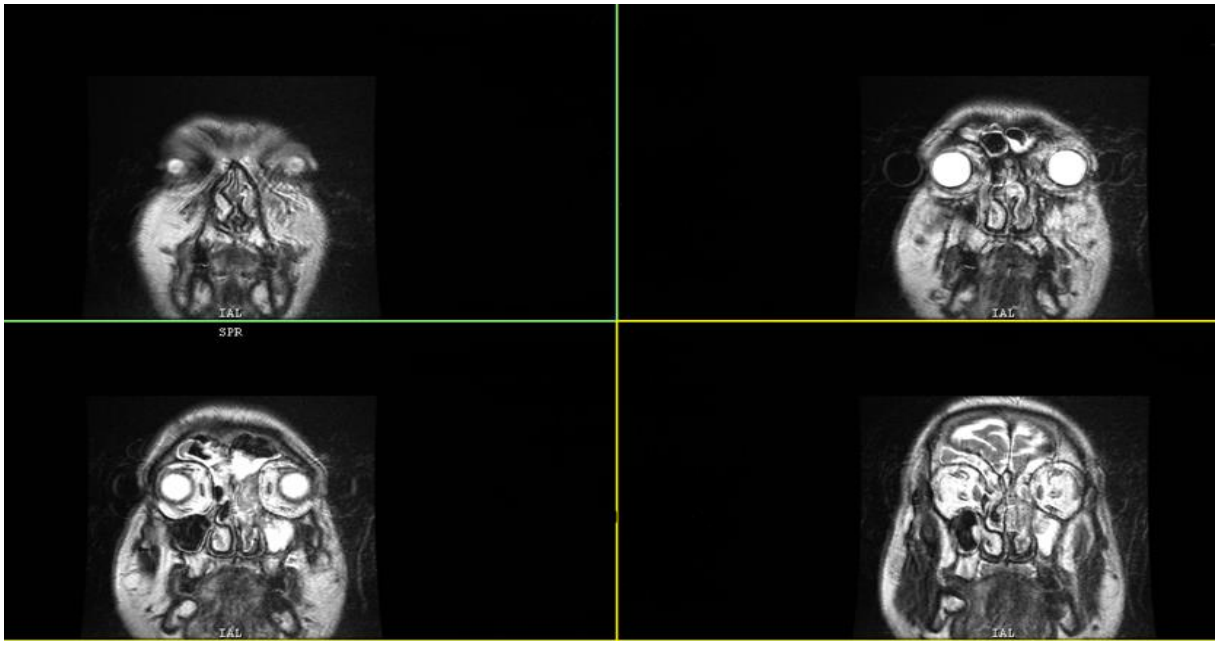

Figure 4. Cutaneous Mucormycosis involving the face in the form of necrotic black eschar and left eye proptosis.

Discussion

Mucormycosis is a serious, may be fatal fungal infection, peaked in COVID-19 pandemic [8]. The relationship between these two infections is unclear but this may be due to corticosteroids over use and/ or uncontrolled DM. Some case reports of post COVID-19 mucormycosis were diagnosed several days after being admitted for COVID-19, while other case reports describe patients who were diagnosed with rhinocerebral mucormycosis and COVID-19 simultaneously [9,10].

Since the beginning of COVID-19 pandemic to august 2021, Zagazig university Hospitals (as tertiary center) admitted about 1589 cases beside 5276 patients were diagnosed and advised for home isolation and treatment.

This study was conducted at zagazig University hospitals on the months of May, June and July during the third wave of COVID-19 in Egypt. During this period about 800 COVID-19 patient was admitted to our hospital, of them 72 patients complicated by mucormycosis with mean age 58.8±9.6 years,43 female(60 %) and 29 male (40 %). All of them had DM (43 patient with preexisting DM and 29 patients with post COVID19 new onset DM (NOD). Diabetes is known to be the most frequent risk factor for mucormycosis. In a study conducted by Mishra et al [8] in India 2021, diabetes was associated with (87.5%) cases of COVID-19 Associated Mucormycosis (CAM), with poor glycemic control (mean HbA1c = 9.06 ±2.19) at time of admission, which was nearly the same in this study.

There is a bidirectional relationship between DM and COVID-19 [11]. Diabetes mellitus is associated with a significantly increased risk of severe Covid-19. On the other hand, NOD and exacerbation of preexisting DM have been observed among COVID-19 patients. SARS-COV-2 binds to Angiotensin converting enzyme-2 (ACE-2) receptors in the pancreatic beta cells inducing down-regulation of ACE-2 expression, causing damage of islet-cells resulting in worsening of preexisting diabetes or emergence of NOD [12]. New-onset diabetes mellitus in hospitalized COVID-19 patients could reflect previously undiagnosed diabetes that was discovered incidentally as a result of the increased testing [13]. Acute infection can lead to stress hyperglycemia, which may be transient and resolve once the infection and the associated inflammatory response are resolved [14]. Furthermore, corticosteroids, which are known to cause hyperglycemia, are increasingly being used to treat COVID-19 patients [15].

Thirsty six percent (36%) of our patients had other comorbidities e.g Hepatitis C, hypertension, cardiac diseases, pancytopenia, CKD, stroke, hyperthyroidism, pancytopenia, scleroderma, or bronchial asthma.

The mean interval between COVID-19 and developing mucormycosis in this study was 34.03±28.2 days compared to 17.28 (±11.36) in **Mishra et al.** [8]. There was no significant association between the interval and prognosis of disease.

Most of our patients (90%) presented by rhino-orbital mucormycosis which was similar to WHO report regarding pattern of involvement of mucormycosis in patients with diabetes [16].

Hundred percent of patient gave history of antibiotic use and also nearly 99.0% of them received corticosteroids. Corticosteroids became a corner stone in treatment of COVID19 especially severe cases; unfortunately it is one of most prevalent risk factors for mucormycosis especially with prolonged use or sometimes misuse in COVID-19 patients. Corticosteroids were serving mucormycosis with both immunosuppression and hyperglycemia [17,18].

Regarding disease outcome 48 patients (67%) had good prognosis while 24 patients (33 %) had bad prognosis including 21 patients (about 30%) died. Outcome wasn't related to patient sex, diabetes onset, clinical type of mucormychosis nor history of corticosteroid or antibiotic use. It was noticed that elderly had poor prognosis (mean age 61.9 years) while in patients with good prognosis mean age was 57.2 years despite being statistically not significant (p.value ≥ 0.05).

Outcome was strongly improved in operated patients than non-operated. This is in concordance with a previous retrospective study conducted by **Nithyanandam et al.** [19] in which patients with early surgical treatment had good prognosis and mortality was less than 10%.

Also higher lymphocytic count and hemoglobin level was associated with better prognosis as lymphopenia is prevalent in COVID-19 patients and its degree correlates with disease severity [20]. On the other hand, patients with higher NLR had poor prognosis. NLR has prognostic value in COVID-19 patients as shown in **Yang et al.** [21] study on Chinese patients and concluded that high NLR (>3.3) is independently associated with more severe COVID-19. Furthermore, high NLR (>3.3) was with low patient survival [21]. Another study by **Xia et al.** [22] found high NLR >4.7 is an independent risk factor for severe COVID-19.

Conclusion

Physicians should have a high index of suspicion for mucormycosis particularly within the first month after the COVID-19 diagnosis in individuals with diabetes and immunocompromised individuals.

Timely repeated surgical debridement is important in improvement of patient outcome.

Public health officials should promote the judicious use of steroids, other immunomodulators

and broad-spectrum antibiotics, to avoid flare-up of the fungal infection, also advice to follow COVID-19 guidelines and resist non-evidence-based therapies.

Limitations of study

It is a single-center study with a small number of patients, so it may not precisely reflect the current status of the world. The incidence of mucormycosis in COVID-19 cases could not be calculated due to the absence of a denominator. Limited sample size also prevents subgrouping, lack of a control group (COVID-19 without mucormycosis) to compare the clinical and biochemical parameters as well as treatment between both groups.

Declaration of competing interest: None.

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