Case Series

Mucormycosis in COVID-19 patients: The patient profile, contributing factors and postoperative outcome – A case series of 14 patients

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ABSTRACT

Co-infection of coronavirus disease 2019 (COVID-19) patients with life-threatening mucormycosis was seen as a major health crisis during the recent surge of coronavirus disease cases. We have taken 14 affected patients who were operated on at our centre and noted associated risk factors, intraoperative courses and surgical outcome in immediate peri-operative course. Out of 14 patients, 8 were people with diabetes while 2 were freshly detected/had corticosteroid-induced hyperglycaemia. Although our sample size is small, it is evident that patients who had diabetes, who were treated with steroids and who received supplemental oxygen support are more prone to contract mucormycosis infection. Also, patients who have the more severe form of COVID-19 pneumonia and those who need to be operated on early (within 20 days of COVID-19 infection) are likely to have turbulent intraoperative and postoperative courses. Therefore, optimization before surgery is of paramount importance.

KEY WORDS: Corticosteroids, COVID-19, diabetes mellitus, mucormycosis

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INTRODUCTION

Besides the immediate mortality and acute respiratory phase, coronavirus disease 2019 (COVID-19) has been associated with a variety of debilitating multiorgan complications.[1] In the setting of COVID-19 expression, there has been a manifold increase in the incidence of invasive mycoses of the maxillofacial region such as mucormycosis and aspergillosis.[2-4]

Worldwide prevalence of mucormycosis ranges from low to very low (US, UK, Japan and Brazil have 3, 0.9, 2, 2 per million, respectively) whereas India's burden of disease has been alarming (140 cases per million) even in the pre-COVID-19 era.[5] In up to 60% of cases, this infection is caused by fungi belonging to the genus *Rhizopus*, followed by mucor, Rhizomucor and six other genera (and 27 species) of order Mucorales, class zygomycetes.[5] Humans acquire the infection predominantly by inhalation of sporangiospores. Diabetes mellitus (DM) remains the leading risk factor worldwide besides haematological malignancy, solid organ transplants and corticosteroid therapy.[6] The past decade has witnessed an increasing number of cases following rising trauma casualties in

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healthy individuals and healthcare-related mucormycosis as well.[5,7]

Long-standing hypoxia, hyperglycaemia, acidic body medium, impaired leukocyte phagocytic activity and high iron levels, decreased immune function caused by the use of corticosteroids, microangiopathy of diabetes and possible peripheral microthrombi facilitate the growth of Mucorales in COVID-19-affected patients.[8]

Multiple publications have appeared recently to outline the epidemiology and pathophysiology of this disease.[2,6,8,9] At the peak of the second wave, our centre also received a flurry of mucormycosis cases, at times in critically ill patients. Surgical debridement at the appropriate time is required as a treatment modality to contain the spread of disease and for biopsy of tissue as well. Whether general anaesthesia required for functional endoscopic sinus surgery (FESS) and debridement would put the patient at more risk with the ongoing COVID-19 infection than conservative management remained a constant dilemma to us. This prompted us to conduct this study.

The study aims to delineate risk factors in COVID-19 patients with mucormycosis and look at the difference in peri-operative course with active COVID-19 infection versus post-COVID status.

METHODS

This is a single-centre, prospective case study conducted in COVID-19-affected (RT-PCR positive) patients who underwent surgery for mucormycosis (FESS/debridement of sinuses) at our hospital from 30 April 2021 to 26 May 2021 (14 patients). COVID-19-positive/recovered patients who had clinical features suggestive of invasive fungal mucormycosis (ptosis/headache/retro-orbital pain/facial swelling) were tested for the disease by performing KOH stain of the nasal crusts and taken up for surgery. Computed tomography (CT) scan could not be done in all patients, as some were on non-invasive ventilation (NIV), oxygen and for logistic reasons. All patients were treated with amphotericin B pre-operatively as per the institutional protocol for optimization; no adverse events or problems due to anaesthesia were observed, and no blood transfusion was required intraoperatively. Details were recorded in Microsoft Excel and analysed using frequencies and percentages. Blood loss was estimated by visual inspection of the drain and gauze pieces. Patients were observed till postoperative day (POD) 10 for early post-operative/COVID-19-related complications, at least. Some patients had long hospitalization courses and some required repeat admissions.

RESULTS

Among 14 patients included in our study, males and females constituted 7 each [Table 1]. Age ranged from 37 to 67 years, with a mean age of 51.14 years. Eight (57%) were previously known diabetics, while two (14%) were detected to have deranged blood sugar levels for the first time during treatment, owing to prior undetected DM or corticosteroid therapy. Four did not have any hyperglycaemia. Hypertension was the second commonest co-morbidity. Eight (57%) were treated with corticosteroids. Two had received NIV, while nine patients received supplemental oxygen through a face mask (FM)/non-rebreathing mask (non-rebreathing mask (NRBM)/nasal prongs). Adding all these three subsets, a total of 11 (78%) patients received oxygen therapy in some

Table 1: Patient demographics and determinants

Sex	Age (years)	Hyperglycaemia (pre-existing DM/fresh onset)	Comorbidities	Treatment history of COVID	
				Steroid administration	Oxygen therapy
M	47	Pre-existing DM Poor control	Hypertension	Nil	Yes (high flows with NRBM)
M	37	Fresh onset Poor control	Nil	Yes	Yes (with FM)
F	52	-	Nil	Nil	Yes (minimal with nasal prongs)
F	42	-	Nil	Nil	Nil
F	52	Fresh onset	Nil	Nil	Nil
F	50	Fresh onset DM	Hypertension, bronchial asthma, right heart failure	Yes	Yes (with FM)
F	50	Fresh onset DM Poor control	Nil	Yes	Yes (NIV)
M	67	Fresh onset DM	Hypertension, CAD	Nil	Yes (high flows with NRBM)
M	62	-	Nil	Yes	Yes (with FM)
M	58	Fresh onset DM Poor control	Nil	Yes	Yes (with FM)
F	46	-	Hypertension	Yes	Yes (high flows with NRBM)
M	48	Fresh onset DM	Hypertension	No	Nil
F	57	Fresh onset DM Poor control	Hypertension	Yes	Yes (NIV)
M	48	Fresh onset DM Poor control	Nil	Yes	Yes (high flows with NRBM)

DM: Diabetes mellitus, CAD: coronary artery disease, NRBM: non-rebreathing bag mask, NIV: non-invasive ventilation, FM: face mask, POD: postoperative day

form. All these patients received oxygen in one or more combined forms for more than 7 days. One patient did not have any of these risk factors.

Data in Table 2 reveal that eight (57%) patients were taken up for the surgery while they were still COVID-19 positive. From the time of positive (Reverse transcription–Polymerase chain reaction) RT-PCR test, six (43%) patients underwent surgery within 20 days. Considering the time of surgery as the time of onset of mucormycosis symptoms (as all the patients were operated on within 1–2 days of symptom onset), the mean time of onset of symptoms from positive COVID-19 testing was 19.71 days.

Among the two patients on NIV taken up for surgery, one died on POD 6; the other could be extubated on POD 3 and recovered with vision loss. Of the remaining nine on oxygen, one died on POD 2, two were discharged on oxygen and three developed unfavourable sequelae (one developed vision loss, and two had persistent disease). In patients who were not on any supplemental oxygen, two were extubated on the table and discharged in stable condition (although one had residual disease), one was extubated and developed vision loss, and discharged with oxygen.

Table 3 compares the mean duration of surgery and blood loss concerning patients who were on oxygen and those who were not on oxygen requirement pre-operatively (mean duration: 176 min vs. 156 min; mean blood loss: 240 vs. 160 min). Table 4 compares the mean duration of surgery and mean blood loss amongst patients who were operated on earlier and more than 20 days from the date of RT-PCR positivity (mean duration: 174 min vs. 169 min; mean blood loss: 280 vs. 213 ml).

Five who were COVID-19 negative pre-operatively were extubated on table and had satisfactory peri-operative outcome; one patient could be extubated on POD 2 and had extended hospital stay.

DISCUSSION

The association of mucormycosis with COVID-19 disease is well established.[4,10] The incidence of this infection is not related to age and gender. Chanda reported that 66.8% of the Indian population affected with COVID-19 disease until May 2020 was male, and the most vulnerable age group was 20–59 years, with decreasing incidence in each decade of increasing age (24.9%, 21.1%, 16.2%, 11.1%).[11] The data of the second wave were also similar, although this is yet to be published. The mean age of patients in this study was 51.14 years, which reflects the fact that although the incidence of the disease is more in the younger population, it is more severe in older people and that is why a higher incidence of mucormycosis.

DM and mucormycosis are well correlated.[12] Diabetics who have contracted COVID-19 infection remain prone to moderate-to-severe form of this disease, and also to adverse outcomes and co-infections. Diabetes is worsened by COVID-19 infection and treatment with steroids. Long-term steroid treatment also has been documented to be associated with opportunistic fungal infections. Lionakis *et al*.[13] have linked even a short course of corticosteroid therapy with mucormycosis, especially in patients with diabetes. They found out that a cumulative prednisone dose of greater than 600 mg or a total methylprednisolone dose of 2–7 g may cause mucormycosis in susceptible patients within a month. Mucormycosis has been reported after even a short

Table 2: Peri-operative course

COVID status prior to surgery	Date of first positive RT-PCR	Date of surgery	Oxygen therapy pre-operatively	Duration of surgery (min)	Approx. blood loss	Postoperative course
Negative	10/3/21	30/4/21	NRBM @12 lpm	180	150	Extubated on table. Satisfactory recovery, discharged on POD 10
Positive	29/4/21	11/5/21	FM @4 lpm	180	280	Extubated on table. Loss of vision by POD 10, discharged in stable condition
Negative	23/4/21	13/5/21	NP @2 lpm	180	150	Extubated on table. Satisfactory recovery, discharged on POD 10 with Oxygen with nasal prongs @2 lpm
Negative	25/4/21	12/5/21	Nil	138	250	Extubated on table. Persistent disease on POD 10, discharged in stable condition
Negative	23/4/21	15/5/21	Nil	128	150	Extubated on table. Satisfactory recovery and discharged on POD 5
Positive	8/5/21	16/5/21	FM @4 lpm	180	230	Not extubated, septic shock, death on POD 2
Positive	30/4/21	19/5/21	NIV	150	350	Extubated on POD 3. Discharged with vision loss
Negative	24/4/21	18/5/21	NRBM @12 lpm	180	200	Extubated on POD 2. Persisting disease, not discharged till POD 10
Positive	24/4/21	17/5/21	FM @4 lpm	168	200	Extubated on table. Satisfactory recovery, discharged on POD 8
Positive	29/4/21	20/5/21	FM @4 lpm	180	220	Extubated on POD 2, Recovery with vision loss. Discharged on nasal prongs @3 lpm
Positive	11/5/21	22/5/21	NRBM @12l pm	174	250	Extubated on table. Satisfactory recovery, discharged on POD 8
Negative	14/5/21	23/5/21	Nil	192	240	Recovery with vision loss, discharged on POD 10
Positive	04/5/21	25/5/21	NIV	192	320	Death on POD 6
Positive	08/5/21	26/5/21	NRBM @12 lpm	180	280	Persistent disease, not discharged on POD 10

NRBM: Non-rebreathing bag mask, NIV: non-invasive ventilation, FM: face mask, POD: postoperative day

Table 3: Comparison of patients on NIV, facemask and nasal prongs with no oxygen therapy

	NIV, NRBM, facemask and nasal prongs (*n*=11)	No oxygen (*n*=3)
Mean duration of surgery (min)	176.72	156
Mean blood loss (ml)	240.90	160

NIV: Non-invasive ventilation, NRBM: non-rebreathing bag mask

Table 4: Comparison of patients with more or less than 20 days from being COVID 19 positive to surgery

Parameters	Less than 20 days (*n*=6)	More than 20 days (*n*=8)
Mean duration of surgery (min)	174	169.75
Mean blood loss (ml)	280	213

COVID 19: Corona virus disease

course (5–14 days) of steroid therapy especially in people with DM.[14] John *et al*.[15] have reported 41 confirmed mucormycosis cases in patients with COVID-19, out of whom 93% had DM and 88% were receiving corticosteroids in their systematic review conducted until April 9, 2021. This is consistent with our results. The mean time of COVID-19 infection onset and mucormycosis onset is 19.71 days.

The role of oxygen administration in the spread of mucormycosis infection in these patients needs to be assessed. Theoretically, high flow oxygen administration in COVID-19 patients (who are tachypneic, immunocompromised and with poor glycaemic control) for days may cause infection in sinuses due to contamination of gas supply line, dryness of nasal mucosa and with use of industrial oxygen at some centres in this pandemic situation. However, since these were also the patients who were more ill, better-scrutinized data through large clinical trials are required to derive such a conclusion. Published data in this regard is lacking.

Patients with a more severe form of the disease had a poor outcome, and their surgery was also more difficult (longer duration, more blood loss). Similarly, the time of surgery from the onset of COVID-19 infection had a bearing on surgery duration, blood loss and postoperative outcome, with poor results in patients who were operated on early. There is a need to maximally optimize a COVID-19 patient before taking him up for a mucormycosis debridement surgery, and the best standard of care has to be offered to him to obtain a favourable outcome.

CONCLUSION

Since many patients of mucormycosis with COVID-19 infection already face impending respiratory failure, the decision of debridement surgery for mucormycosis under general anaesthesia is vital. Patients who have poorly controlled blood sugar levels and received steroids and oxygen for treatment of COVID 19 infection are at risk of developing this disease. Those with the severe form of the disease and recent onset have turbulent intraoperative course and the worse outcome too.

Therefore, a very cautious and tailor-made decision should be made to administer steroids (and oxygen too) in the COVID-19 treatment. Maximum possible optimization should be attempted before undertaking the patient for surgery to anticipate a better outcome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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