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Original Article

Management outcomes of mucormycosis in COVID-19 patients: A preliminary report from a tertiary care hospital

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) continues to be a significant health problem worldwide. The unprecedented surge of mucormycosis in patients with COVID-19 is a new emerging challenge. Although a few studies documenting high incidence of mucormycosis in COVID -19 patients have recently emerged in literature, data pertaining to treatment outcomes in such cohorts is lacking. Here, we report our experience in management of mucormycosis in COVID-19 patients at our tertiary care centre.

Method: The clinical, imaging, histopathological and treatment data of 20 patients with mucormycosis (in setting of COVID-19) was analysed.

Results: 35% and 65 % of cases developed mucormycosis in setting of active and recovered COVID-19 infections respectively. Diabetes mellitus was documented in 80% cases, with 55% demonstrating HbA1c >10%. Steroid was administered in 80% during COVID-19 illness. Imaging demonstrated paranasal sinus (PNS), orbital and intracranial extension in 100%, 55% and 20% patients respectively. All received amphotericin and underwent endoscopic debridement, 20% underwent orbital decompression and 5% maxillectomy with orbital exenteration. 6/20(30%) patients died (4 with rhino-orbito-cerebral disease, 1 with extensive orbito-maxillary involvement and 1 sino-nasal disease). All 6 patients received steroids and documented poor glycaemic control.

Conclusion: The strong association of hyperglycemia and steroid intake with mucormycosis in COVID-19 cases warrants judicious use of corticosteroids and optimal glycaemic control.

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Our study highlights that good clinical outcome can be achieved in invasive mucormycosis provided prompt treatment is instituted with aggressive surgical debridement and antifungal medication.

Introduction

The pandemic coronavirus disease 2019 (COVID-19) caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) continues to be a significant health problem worldwide. The role of systemic glucocorticoids in improving survival in moderate to severe COVID-19 infection is globally accepted. However, its widespread use pose a serious risk of secondary bacterial or fungal infections.[1,2] Although the risk of fungal infection with candida, aspergillus and pneumocystitis jiroveci in setting of COVID-19 is well recognized,[2–5] the unprecedented surge in reporting of infection with Mucor in these subset of cases is a new emerging challenge. The rapidity of dissemination and high fatality rate that characterize mucormycosis has further aggravated the immense challenge faced globally by the COVID-19 pandemic.[6] This uncommon but fatal fungal infection initially involves nasal cavity and paranasal sinuses (presenting with features similar to acute sinusitis) but has tendency for rapid spread to orbital and intracranial sites in an immunocompromised host[7–9] with consequent progressively worsening clinical outcome. So, a high index of clinical suspicion with aim of early diagnosis and aggressive management is of paramount importance in these patients for a successful outcome. A few reports documenting mucormycosis affecting COVID-19 patients in varied forms have recently emerged in medical literature.[6,10–13] Herein, we report our experience in management of mucormycosis in COVID-19 patients at our tertiary care centre during a period of four months (Feb 2021 to May 2021).

Materials and methods

Patient selection and characteristics

Institutional Ethics Committee (IEC) approval was obtained for this retrospective study. A total of twenty two cases of mucormycosis (HPE proven) with COVID-19 (nasopharyngeal swab, RT-PCR confirmed) who underwent management at our tertiary care centre between Mar 2021 to May 2021 were initially included in the study. However, two patients denied consent for this study and were subsequently excluded. Finally, 20 patients were included in the study and their demographic, clinical, imaging, histopathological and treatment data was retrieved and analysed. 13 of these 20 patients developed features of mucormycosis atleast 15 days after discharge from hospital, following treatment for COVID-19. The rest of patients developed features of mucormycosis during the course of treatment for COVID-19.

Workflow at our tertiary care hospital

We followed our institutional protocol with a step by step approach, aiming towards an early and aggressive management of the condition (Fig. 1). An otolaryngologist performed a detailed initial assessment adhering to all COVID-19 precautionary guidelines (including wearing full protective gears). With recent literature documenting increasing cases of mucormycosis amid in COVID -19 patients, the possibility of the former was always borne in mind and patients were accordingly investigated. An aseptically collected medial meatal nasal swab or representative tissue were sent for KOH (potassium hydroxide) staining, microscopy using fluorescent brightener, special stains (Periodic acid–Schiff and Grocott-Gomori methenamine silver), fungal culture, gram stain and bacteriological culture. Also, samples for relevant hematological and biochemical investigations including glycosylated hemoglobin (HbA1c) and RT- PCR for COVID-19 were obtained on admission. Imaging (CT or MRI) to confirm or negate the diagnosis and assess the disease extent (nasal cavity, paranasal sinuses, orbit and intracranial structures) was performed. The contrast enhanced CT was employed as the initial imaging modality with evaluation by MRI limited to those with equivocal CT imaging findings, clinico-radiological mismatch and high index of suspicion for intracranial extension.

Treatment

The patients were managed by multidisciplinary team with an aim of urgent management of invasive mucormycosis and the comorbid condition. Intravenous liposomal Amphotericin was initiated after confirmation of mucormycosis. All patients with limited sinonasal mucormycosis were administered Liposomal Amphotericin at 3–5 mg/kg/day (over a period of 3–4 weeks) for a targeted cumulative dose of 4–5 g, based on clinical findings and investigations (endoscopy, microbiology, histopathology and imaging). For Rhino-Orbital and Rhino – Orbito – Cerebral mucormycosis (ROCM), 5–7 mg/kg Liposomal amphotericin B was administered for targeted cumulative dose of 5–7 g. Daily serum electrolytes and renal function test were monitored for these patients, and dose was titrated accordingly. Patients underwent emergency endoscopic debridement, orbital decompression, orbital exenteration and maxillectomy, based on the extent of disease. Postoperative specimen was sent for fungal culture, sensitivity and

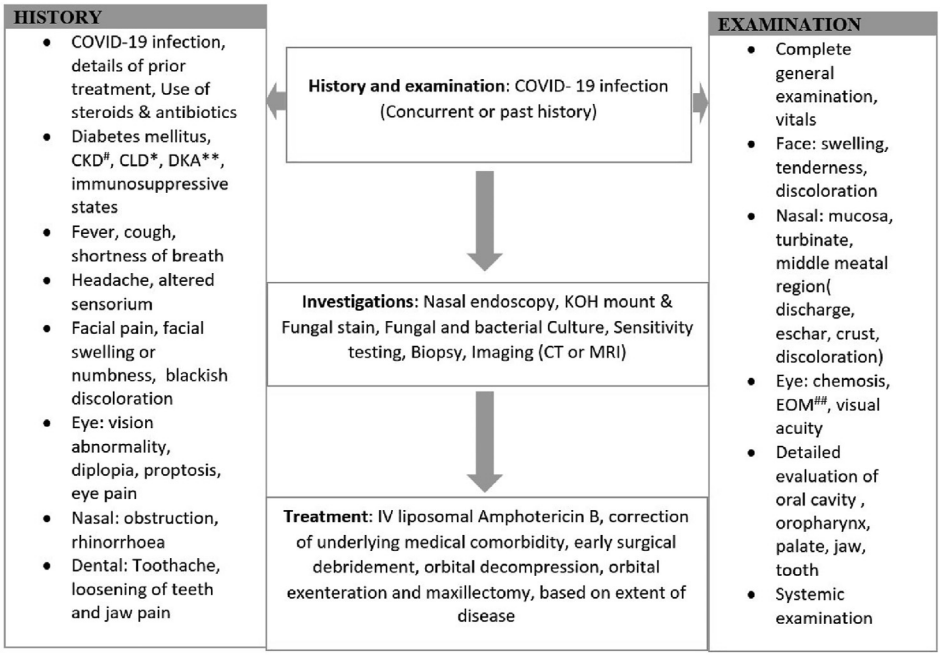

Fig. 1 – Workflow at our tertiary care centre. CKD#: Chronic Kidney Disease, CLD*: Chronic Liver disease, DKA: Diabetic ketoacidosis, EOM ##: Extraocular movements.**

histopathology. Patients were discharged on oral posaconazole daily (400 mg in two-divided doses) with intent of continuing the same till stable disease was reached, evident by two negative microbiological and histopathological samples. Follow up schedule planned was patients will be reassessed with check endoscopy fortnightly for one month, later once a month for 3 months followed by 3 monthly review for 1 year.

Results

Of the 20 patients analysed, 11 and 9 were male and female respectively with mean age being 53.9 years (Range 35–67 years). 7 (35%) patients were admitted to our hospital with severe COVID 19 infection and developed features of mucormycosis during the course of treatment. 3 of these 7 patients developed clinical features suggestive of mucormycosis between 7 and 10 days since admission, whereas the rest (4/7) presented with features between 11 and 15 days. 13 (65%) were admitted at our institute with clinical suspicion of mucormycosis, history of prior in-hospital COVID treatment and interval of atleast 15 days between the two admissions. Of these 13 cases, 4 underwent prior in-hospital COVID treatment at our institute and the rest were managed for COVID at other hospitals. Diabetes mellitus was documented in 16 (80%) patients with 11 (55%) demonstrating HbA1c level more than 10%, consistent with poor glycaemic control. 3 (15%) cases had other comorbid conditions like chronic kidney and liver disease. Steroid was administered in 16 (80%) cases during course of their severe COVID -19 illness.

Nasal obstruction 15 (75%), eye swelling 8 (40%), facial pain or swelling 7 (35%) and headache 7 (35%) were the common presentation with other symptoms in decreasing frequency being reduced or no vision and toothache. Examination demonstrated, proptosis in 10 (50%), ptosis in 2 (10%), vision loss in 1 (5%), complete opthalmoplegia in 1 (5%) and palate discolouration with loosening of tooth in 1 (5%) patient. Figs. 2 and 3 demonstrates varied clinical examination findings of mucormycosis in COVID-19 patients in our study.

Cross sectional Imaging (CT and/or MRI) demonstrated paranasal sinus, orbital and intracranial extension in 20(100%), 11 (55%) and 4 (20%) patients respectively. Localised collections showing peripheral rim enhancement (consistent with abscess) were demonstrated in buccal space and orbit in 2 (10%) and 1 (5%) cases respectively. Ethmoid and maxillary sinuses were involved in 90% and 80% cases respectively, whereas sphenoid and frontal sinus involvement was less common (40% and 35% respectively). Fig. 4 shows varied imaging findings of mucormycosis in COVID-19 patients in our study.

20 (100%) patients underwent endoscopic debridement, 4 (20%) orbital decompression and 1 (5%) maxillectomy with orbital exenteration. Fig. 5 demonstrates varied nasal and sinus endoscopy findings of mucormycosis in COVID-19 patients in our study. The necrotic and debrided surgical specimen sent for histopathology, fungal stains and culture demonstrated broad based irregular aseptate fungal hyphae with right angled branching resembling mucormycosis. Intravenous liposomal Amphotericin- B was administered (3–5 mg/kg) in consultation with infectious disease specialist to all patients. Of the 6 (30%) patients who succumbed to illness (despite urgent and aggressive management), 4 had rhino-orbito-cerebral involvement, 1 demonstrated extensive maxillary and orbital involvement (underwent orbital exenteration with maxillectomy) and 1 with disease limited to paranasal sinuses. The latter patient underwent endoscopic debridement and died on postoperative day 5 due to severe COVID pneumonia. All these six patients who succumbed to

Fig. 2 – Varied clinical examination findings of Mucormycosis in COVID-19 patients. (A) Bilateral proptosis (left > Right) with prominent chemosis and left sided facial swelling. (B) & (C) shows Right periorbital and facial swelling. (D) Complete ptosis right eye.

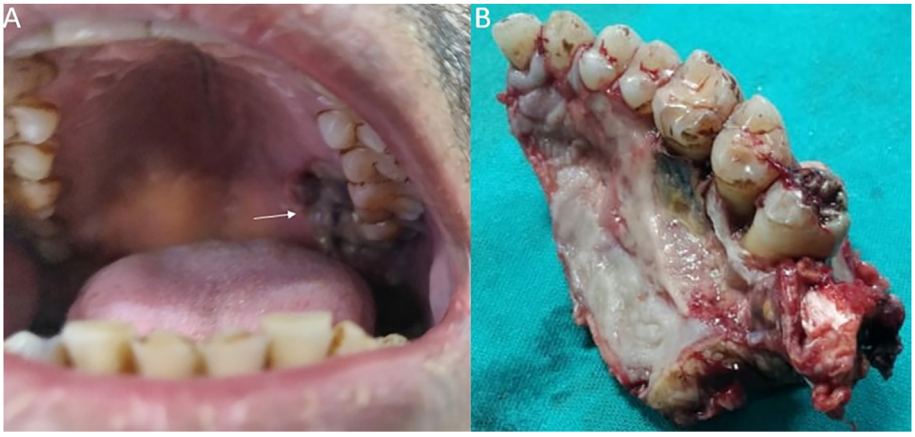

Fig. 3 – (A) Shows Eschar in posterolateral part of left side of the hard palate (arrow). (B) Post Maxillectomy Specimen of the shows gangrenous and devitalised tissue.

disease, documented severe COVID 19 pneumonia, poor glycaemic control and steroids administration.

Overall, of the 20 cases, 14 (70%) patients survived this dreaded disease, with 8 already discharged to home and the rest presently clinically stable, undergoing supportive treatment. Patients at discharge have been instructed to regularly monitor blood sugar level, continue the optimised diabetic medication and oral posaconazole with an advice for follow-up. Table 1 summarises our study data pertaining to Clinical, Imaging and Therapeutic parameters.

Discussion

Mucormycosis, a highly aggressive and relentlessly progressive invasive infection, is caused by a relatively avirulent fungus (normally present as a commensal in nasal mucosa) which usually manifests itself in setting of an underlying immunocompromised state.[14] The presence of diabetes mellitus, diabetic ketoacidosis (DKA), haematological or solid organ malignancies, neutropenia, high dose corticosteroids and post organ transplantation status are among the common predisposing factors for mucormycosis.[15] The presence of hyperglycaemia, acidosis, increased ketones and free iron coupled with decreased phagocytic activity is central to pathogenesis of mucormycosis. The weakened immune system in COVID-19 infection is attributed to the decreased CD4+ and CD8+ lymphocytes, elevated inflammatory cytokines and high incidence of steroids administration.[2,16–18]

Following access to nasal or oral cavity in such subset of patients, these fungal spores can easily gain access to the paranasal sinuses and adjacent structures (orbit and intracranial) due to close vicinity and separation of these structures by a thin bone (cribriform plate and lateral lamella).[19,20]

Based on anatomical site involved, mucormycosis can be classified into ROCM, pulmonary, cutaneous, gastrointestinal and disseminated types. The ROCM and pulmonary types accounts for most of the cases, with the former comprising spectrum of limited sino-nasal disease, limited rhino-orbital disease and rhino-orbital-cerebral disease (ROCD).[17–21] In our study, Imaging with CECT demonstrated presence of sino-nasal disease in 100%, rhino-orbital disease in 55% and ROCD in 20% patients (Fig. 4). Our findings are similar to Study by Gupta et al who documented ROCD in 27% of patients.[22]

The presence of hyperdense foci within sinuses on CT (Fig. 4), hypointensity on T2WI and black turbinate sign are important imaging indicators to the fungal aetiology.[23] MRI in comparison to CT provides better evaluation of intracranial

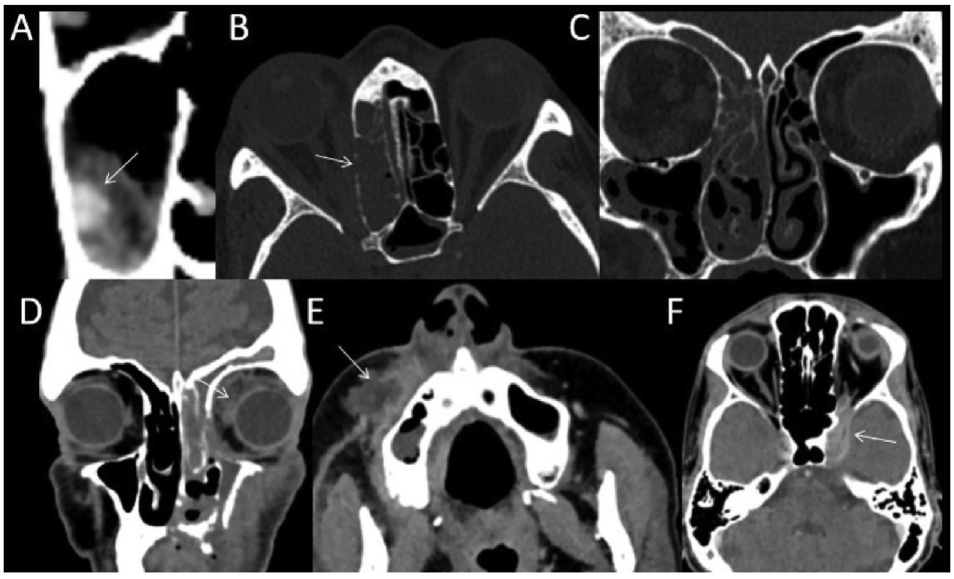

Fig. 4 – Varied findings of Mucormycosis on computed tomography in COVID-19 patients. (A) Coronal CT image shows hyperdense areas (arrow) within the right maxillary sinus contents, finding strongly suggestive of fungal aetiology. (B) Axial CT image shows break in the lamina papyracea (arrow). (C) Coronal CT image shows involvement of right maxillary, bilateral ethmoid sinuses and the right orbit with break in the lateral lamella (right) (D) Coronal CECT image shows involvement of left maxillary and ethmoid sinuses with a collection in the left orbit. (E) Axial CECT image shows extension of infection to involve right buccal space with resultant abscess. (F) Axial CECT image shows involvement of left cavernous sinus.

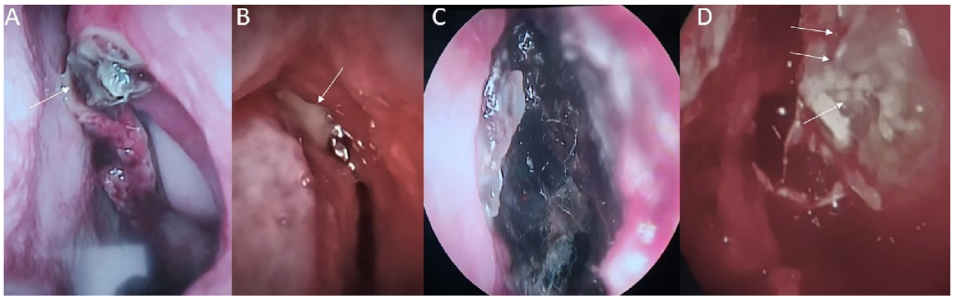

Fig. 5 – Varied findings of Mucormycosis on Nasal and Sinus endoscopy in COVID-19 patients (A) Eschar (arrow) in left middle turbinate. (B) Purulent discharge (arrow) in right middle meatus with edematous middle turbinate. (C) Prominent eschar in left nasal cavity (D) Orbital fat prolapse into nasal cavity (arrow) (arrow) following Orbital decompression surgery.

and soft tissue involvement, skull base invasion, perineural spread and vascular obstruction.[24]

The criteria for clinical diagnosis of mucormycosis published in 1950 by Smith et al.[25] is still considered the gold standard and comprises of characteristics features as black, necrotic turbinates, same sided blood-tinged nasal discharge and facial pain, peri-orbital or peri-nasal swelling with discoloration and induration, ptosis with proptosis of the eyeball and complete ophthalmoplegia and multiple cranial nerve palsies unrelated to documented lesions.

The studies documenting high incidence of mucormycosis in patients with uncontrolled DM prior to COVID-19 pandemic are available in literature.[21,26,27] Studies documenting surge of mucormycosis in clinical setting of COVID-19 are emerging in literature, but are at the best sparse presently. Mehta et al reported a case of rhinoorbital mucormycosis in a 60 year-old -male with COVID 19 disease.[10] Song et al, Sen et al and Sharma et al documented increased risk of developing mucormycosis in patients affected by COVID-19.[2,11,13]

In our study, 80% of patients had diabetes mellitus with 55% of all cases demonstrating HbA1c level more than 10%, consistent with poor glycaemic control. Also, 80% of patients in our study had received steroids for COVID-19 infection. Hyperglycaemia along with high dose steroid intake in setting of weakened immune system (as in COVID-19 infection) is the plausible explanation for high incidence of association of these factors in our study comprising 20 patients with mucormycosis. Our findings are consistent with a recent

Table 1 – Clinical, imaging and therapeutic data from patients with mucormycosis (n = 20).

Variable	Patients (n, %)
Age (years)	
Mean	53.9
Range	35–67
Co-morbidities	
Diabetes mellitus	16 (80)
HbA1c between 7 and 10%	5 (25)
HbA1c > 10%	11 (55)
Chronic kidney disease	1 (5)
Chronic liver disease	1 (5)
Coronavirus association	20 (100)
Concurrent[a]	7 (55)
Post COVID 19[b]	13 (45)
Clinical presentation	
Symptoms	
Nasal obstruction	15 (75)
Facial pain and swelling	13 (65)
Eye swelling	8 (40)
Headache	7 (35)
Complete vision loss	1 (5)
Toothache	1 (5)
Signs	
Proptosis	10 (50)
Reduced visual acuity	5 (25)
Ptosis	2 (10)
Complete opthalmoplegia	1 (5)
Facial palsy	1 (5)
Spread of disease (on imaging)	Rhino
PNS involvement	20 (100)
Ethmoid	18 (90)
Maxillary	16 (80)
Sphenoid	8 (40)
Frontal	7 (35)
Orbital spread	11 (55)
Intracranial Extension	4 (20)
Steroids administered during COVID 19 disease	16 (80)
Treatment	
Intravenous Liposomal Amphotericin- B	20 (100)
Oral Posoconazole (on discharge)[c]	8 (100)[c]
Endoscopic debridement	20 (100)
Orbital decompression	4 (20)
Maxillectomy and orbital exenteration	1 (5)
Treatment Outcome	
Successful	14 (70)
Discharge from hospital	8 (40)
Stable, but not yet discharged	6 (30)
Death	6 (30)

[a] Developed features of mucormycosis during the course of treatment for COVID-19.
[b] Developed features of mucormycosis atleast 15 days after discharge from hospital following treatment for COVID-19.
[c] Patients at discharge have been instructed to continue oral posoconazole (400 mg twice daily) with an advice for follow-up.

systematic review comprising 41 cases of mucormycosis with COVID-19[28] that documented association with corticosteroids administration and DM in 88% and 93% cases respectively.

The literature documenting treatment outcomes in cases of mucormycosis with COVID-19 is at the best sparse. All our 20 patients underwent endoscopic debridement, 4 (20%) orbital decompression and 1 (5%) maxillectomy with orbital exenteration. The orbital decompression procedure was undertaken in view of proptosis, decreased extraocular movements and reduction in visual acuity. Maxillectomy with orbital exenteration was done for one patient with extensive maxillary and orbital involvement with complete vision loss. Overall, of the 20 cases, 14 (70%) patients survived this dreaded disease, with 8 already discharged to home and the rest presently clinically stable, undergoing supportive treatment.

The strengths of our study include relatively large sample size for this rare but devastating disease, adherence to institutional protocol, histopathological confirmation in all cases and one of the first studies documenting treatment outcome in patients with mucormycosis in setting of COVID-19 infection.

Conclusion

The unprecedented surge of mucormycosis in patients with COVID-19 infection is a new emerging challenge. The strong association of hyperglycaemia and steroid intake with development of mucormycosis in both active and recovered COVID-19 cases warrants judicious use of corticosteroids and strict glycaemic control. Considering the good clinical outcome achieved in our study with prompt and aggressive management, the significance of high degree of clinical suspicion, earliest recognition and treatment of mucormycosis with aggressive surgical debridement in combination with antifungal medication cannot be overstated.

Disclosure of competing interest

The authors have none to declare.

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