

COVID-19 Associated Mucormycosis in Head and Neck Region: Our Experiences at a Tertiary Care Teaching Hospital of Eastern India

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ABSTRACT

Objective: To study the COVID-19 associated mucormycosis in the head and neck region of the patients along with patient details, clinical manifestations and management.

Materials and Methods: This is a descriptive and retrospective study of COVID-19 associated mucormycosis (CAM) carried out at a postgraduate teaching hospital. This study was conducted between March 2020 to April 2021. A patient profile such as age, sex, comorbidities, clinical presentations, diagnosis and treatment of the CAM were analyzed.

Results: There were 11 patients of CAM were enrolled in this study. There were eight male and three female patients, aged from 3 years to 72 years. Out of the 11 patients, 8 were diabetic (72.72%). Three patients (27.27%) were taking prolonged systemic steroids with a long hospital ICU stay. One child (9.09%) was under chemotherapy for acute leukemia. The common clinical symptoms were facial swelling, facial pain, nasal block and nasal discharge. The diagnosis was confirmed by histological examination and fungal culture with Sabouraud dextrose agar (SDA) showing *Rhizopus oryzae*. All were treated with endoscopic surgical debridement and amphotericin B. One case died because of cerebral involvement.

Conclusion: Early diagnosis and prompt treatment for CAM are required. Aggressive endoscopic surgical debridement for local control and appropriate systemic antifungal treatment will help to improve the prognosis and survival of the patients.

Keywords: COVID-19; SARS CoV-2; COVID-19 associated mucormycosis; head and neck region; amphotericin B (Siriraj Med J 2021; 73: 423-428)

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by acute respiratory syndrome coronavirus 2 (SARS CoV-2), which has been considered a global public health emergency.¹ COVID-19 has rapidly spread to 212 countries and made approximately five million

laboratory confirmed cases and more than 310,000 deaths worldwide by May 18th 2020.² The first case of SARS-CoV-2 infection was detected in Wuhan, China.³ As this virus is a novel virus, data in relation to clinical manifestations of this COVID-19 disease are insufficient.^{4,5} Mucormycosis is an invasive fungal infection caused by

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an opportunistic and ubiquitous fungus that belongs to the class Phygomycetes, subclass Zygomycetes, order mucorales, family mucroraceae.⁶ Histopathological study, direct, microscopy and culture from the clinical samples are the important diagnostic modalities for mucormycosis.⁷ Early diagnosis and treatment with endoscopic surgical debridement are key for preventing this fatal clinical entity. COVID-19 associated mucormycosis (CAM) is less frequently documented in the literature. The aim of this study is to analyze the detail of patient profile and management of the CAM.

MATERIALS AND METHODS

This descriptive retrospective study was conducted at the otorhinolaryngology postgraduate department of a teaching hospital. This study was conducted between March 2020 to April 2021. Our Institutional Ethics Committee (IEC) accepted this study with the reference number IEC/IMS/SOA/12/08.03.2020. COVID-19 patients infected with mucormycosis during the treatment period at COVID hospital or after discharge from the COVID hospital were included in this study. All of the reverse transcription polymerase (RT-PCR) positive for viral RNA and diagnosed COVID-19 at the time of hospitalization. For RT-PCR testing, the nasopharyngeal swab was used and the sample was taken from nasopharyngeal secretions with wearing personal protective equipment. The COVID-19 patients without mucormycosis or Non-COVID-19 patients with mucormycosis were excluded from this study. All the patients underwent diagnostic nasal endoscopy for assessing the bilateral nasal cavity and nasopharynx. Computed tomography (CT) scan of the nose and paranasal sinus and magnetic resonance imaging (MRI) done to find out the extent of the diseases into orbit and brain. During nasal endoscopy, the tissue from the nasal cavity sent for microscopy, culture and histopathological examination showing broad non-septate hyphae with 900 branchings (Fig 1). Ophthalmological and neurological consultations were done in all cases to find the loss of vision or not and neurological involvement. There were 11 COVID-19 patients with mucormycosis enrolled in this study. Out of 11 patients, 7 was already discharged from COVID hospital attached to our Medical college and the rest 4 were diagnosed during the treatment at COVID hospital. Biopsy was taken from all the cases, which showed the picture of mucormycosis with some foci of non-septate fungal hyphae with right-angled hyphae branches. The diagnosis was based on histopathological examination and fungal culture. The fungal culture was done with SDA showing mycelia growth, features of *Rhizopus oryzae*. All patients underwent endoscopic debridement of the

mucormycosis along with exenteration of the orbit in two cases, followed by parenteral infusion amphotericin B (1-1.5 mg/kg/day) and a total dose of 2.5-3 gm. Patient follow-up was done after 6 months' interval after surgery. SPSS Statistics for Windows, version 20, was used for all statistical analyses (IBM-SPSS Inc., Chicago, IL, USA).

RESULTS

Out of 11 patients with mucormycosis, there were 8 male (72.72%) and 3 female (27.27%) patients with a male to female ratio of 2.6:1. The age range of the patients was from 3 year to 72 years. Out of the 11 patients, 8 (72.72%) were diabetic. All 8 diabetic mellitus patients were under treatment with oral hypoglycemic agents/insulins regularly, but their blood sugar was poorly controlled. One child (9.09%) was diagnosed with acute leukemia and three patients (27.27%) were taking a high dose of steroids during the treatment of the COVID-19 infection. Out of the 11 patients, 6 (54.54%) were diagnosed with sinonasal mucormycosis, 2 (18.18%) had rhino-orbital mucormycosis, 1 (9.09 %) had sinonasal and palatal involvement of the mucormycosis and one had rhino-orbital-cerebral mucormycosis. All the patients presented with foul-smelling nasal discharge and nasal block. Out of the 11 patients, 9 (81.81%) of them were presenting with facial pain, but 6 (54.54%) were presented with orbital and facial swelling (Fig 2A&B). Three (27.27%) patients were presenting with headache, one (9.09%) had proptosis, one had nasal septal perforation and one had altered sensorium. (TABLE 1)

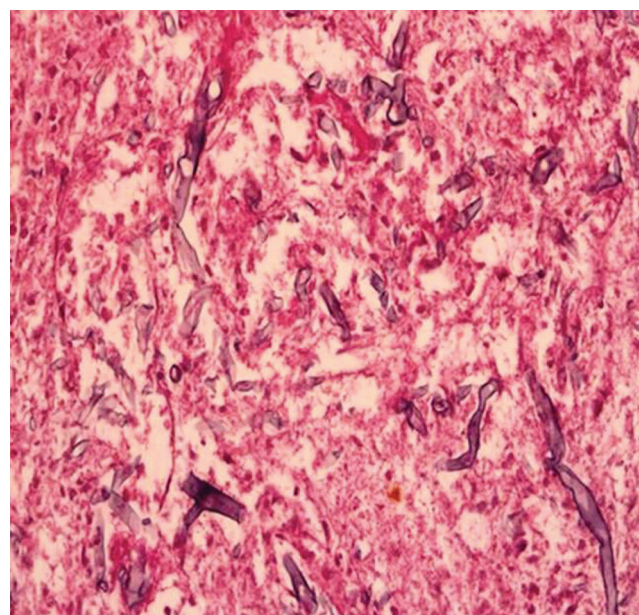


Fig 1. Histopathology microphotograph showing broad non-septate hyphae with 900 branching (Eosin stain and 400 X magnification).



Fig 2. A 14-year-old girl of CAM presenting swelling at the right side orbit (Fig. 2A) and face (Fig. 2B).

Before the surgical debridement, the nasal swab sent for KOH mount where all patients showed aseptate hyphae. Culture of the nasal discharge showed *Rhizopus oryzae* in nine patients and the rest showed no growth. All cases underwent endoscopic surgical debridement under general anesthesia. All the patients were also administered an intravenous infusion of amphotericin B. One case (9.09%) was fatal due to cerebral involvement who died during the treatment period.

DISCUSSION

The ongoing COVID-19 pandemic started in Wuhan, China, in December 2019 and became a global pandemic because of its rapid spread.⁸ The spectrum of clinical presentations of symptomatic COVID-19 patient ranges from mild to critical.⁹ COVID-19 patients usually show higher levels of inflammatory cytokines (interleukin (IL)-2R, IL-6, IL-10 and tumor necrosis factor- α), impaired cell-mediated immune response, affect both CD4+ T and CD8+ T cells.¹⁰ So, COVID-19 patients have susceptibility towards fungal co-infections such as mucormycosis is found.¹¹

Mucormycosis is an uncommon opportunistic fungal infection characterized by infarction and necrosis of the host tissue by the invasion of the blood vessels by hyphae.¹² In the head and neck region of the body, the common clinical manifestations of the mucormycosis are due to rhino-orbital-cerebral infection, which secondary to inhalation of the spores into the nose and sinuses.¹³ In this study, out of the 11 patients, 6 (54.54%) were diagnosed with sinonasal mucormycosis, 2 (18.18%) had rhino-orbital mucormycosis, 1 (9.09%) had sinonasal and palatal involvement of the mucormycosis and one had

rhino-orbital-cerebral mucormycosis. The predisposing factors for mucormycosis are diabetes mellitus, systemic corticosteroid use, hematological malignancies, neutropenia, stem cell transplant and immunocompromised persons.¹⁴ The critical ill COVID-19 patients admitted to the intensive care unit (ICU) and required mechanical ventilation or had prolonged duration hospital stays, even as long as 50 days, are likely to get co-fungal infections.¹⁵ In this study, the most comorbidity associated with COVID-19 patient was diabetes mellitus (72.72%). Rest three patients (27.27%) were taking a high dose of systemic steroids for reducing COVID-19 infections and one patient (9.09%) was a known case of acute myeloblastic leukemia.

Mucormycosis is a rapidly progressive fungal infection and often ended in a fatal outcome. Clinical presentations of mucormycosis depend on the site of the disease. The initial clinical symptoms of the CAM are nasal block or congestion, nasal discharge. The color of the nasal discharge appears as bloody or brown or black and facial pain. The patient may present with numbness over paranasal sinuses. Headache and orbital pain are also important features of the CAM. Many patients of CAM may present with fever, toothache, loosening of the maxillary teeth, blurring of vision or double vision. In this study, all the patients were presenting with foul-smelling nasal discharge and nasal block. Out of the 11 patients of this study, 9 (81.81%) of them were presenting with facial pain and 6 (54.54%) were presenting with facial swelling. Three (27.27%) patients were presenting with headache, one (9.09%) had proptosis, one had nasal septal perforation and one had altered sensorium in our study. Diagnostic nasal endoscopy shows black and necrotic tissue (eschar) inside the nasal cavity.

TABLE 1. Clinical profile of the COVID-19 associated mucormycosis patients.

| Patient's serial | Age (years) | Sex | Affected part | Clinical presentations | Co-morbid diseases | Treatment | Outcome |
|------------------|-------------|-----|-----------------------|---|---|---|------------------------------------|
| 1 | 3 | M | sinonasal | Facial swelling, facial pain, nasal discharge | Acute lymphoblastic leukemia | Endoscopic surgical debridement plus amphotericin B | Cured |
| 2 | 14 | F | Naso-orbital | Facial pain, nasal block, nasal discharge, facial swelling, nasal septal perforation | Prolonged use of steroids | Endoscopic surgical debridement plus amphotericin B | Cured |
| 3 | 37 | M | Sinonasal | Facial pain, nasal block, nasal discharge | Uncontrolled Diabetes | Endoscopic surgical debridement plus amphotericin B | Cured |
| 4 | 38 | M | Oronasal | Facial pain, palatal black eschar, nasal discharge, nasal block | Uncontrolled diabetes | Endoscopic surgical debridement plus amphotericin B | Cured |
| 5 | 41 | F | Sinonasal | Facial pain, nasal discharge, nasal block | Uncontrolled diabetes | Endoscopic surgical debridement plus amphotericin B | Cured |
| 6 | 53 | F | Naso-orbital-cerebral | Facial swelling, headache, altered sensorium, proptosis, nasal discharge, nasal block | Prolonged use of steroids | Endoscopic surgical debridement plus amphotericin B | Death due to rapid spread to brain |
| 7 | 62 | M | Naso-orbital | Headache, orbital pain, nasal discharge, nasal block | Uncontrolled diabetes | Endoscopic surgical debridement plus amphotericin B | Cured |
| 8 | 63 | M | Sinonasal | Facial swelling, facial pain, nasal discharge, nasal block | Uncontrolled diabetes | Endoscopic surgical debridement plus amphotericin B | Cured |
| 9 | 65 | M | Naso-orbital | Facial swelling, facial pain, proptosis, nasal discharge, nasal block | Uncontrolled diabetes | Endoscopic surgical debridement plus amphotericin B | Cured |
| 10 | 68 | M | Sinonasal | Facial swelling, numbness over face, nasal discharge | Uncontrolled diabetes mellitus | Endoscopic surgical debridement plus amphotericin B | Cured |
| 11 | 72 | M | Sinonasal | Headache, Numbness over face, nasal discharge | Uncontrolled diabetes mellitus and taken steroids | Endoscopic surgical debridement plus amphotericin B | Cured |

Rhino-orbital-cerebral infection is a typical presentation of mucormycosis where fungi invade the paranasal sinuses to orbit and brain.¹⁶ This clinical situation can result in orbital apex syndrome such as complete ophthalmoplegia with rapid loss of vision, involves cranial nerves such as II, III, IV, V and VI, which need urgent treatment with surgical intervention, antifungal drugs and control of risk factors for preventing such morbidity and fatal outcome.^{17,18} Clinical suspicion and early diagnosis and prompt treatment are key steps for preventing the morbidity of the fatal condition like rhino-orbital-cerebral mucormycosis.¹⁹ Proper history taking, physical examination and imaging are important components for the diagnosis of the suspected mucormycosis. In CAM, computed tomography (CT) scan will often show bone destruction. Brain magnetic resonance imaging (MRI) is helpful to rule out any involvement of the brain, sinuses and orbit.²⁰ An MRI of the brain may show multiple areas of infarction and ischemia, indicating invasive fungal disease. In case of unstable hemodynamic and poor respiratory status with the inability to keep the patient in a supine position without oxygen, desaturation made it unfeasible for performing MRI. Bedside diagnostic nasal endoscopy can be done in a timely manner and histopathological processing in case of active COVID-19 infection is useful for starting the treatment for rhino-orbital mucormycosis. Mucor is usually demonstrated via a nasal biopsy and subsequent culture. Tissue is sent for histopathological examination and KOH mount, which confirm the mucormycosis.²¹ Direct microscopy, histopathology and culture from the clinical samples are important diagnostic modalities for mucormycosis.²²

To avoid morbidity in this lethal clinical entity, clinical suspicion and early therapy, as well as endoscopic surgical debridement, is essential. The treatment of the CAM requires a team approach which includes otorhinolaryngologists, neurologist, ophthalmologist, dentist, microbiologist and infection disease specialist. The patient needs control of diabetes and diabetic ketoacidosis. The immunomodulating drugs, if they continue, should be stopped. Endoscopic surgical debridement should be done immediately after confirmation of the CAM. Then amphotericin should be started without delay. Liposomal amphotericin B (L-Amb) is a preferred medical treatment. The dose of the L-Amb is 5 mg/kg/day, diluted in 200 ml 5% dextrose over 2 to 3 hours infusion (avoid slow escalation; higher dose 10 mg/kg/day may be given in cerebral mucormycosis).²³ Amphotericin B deoxycholate (D-Amb) can be given if the cost and availability of L-Amb is an issue. D-Amb is given as 1 mg/kg/day in 5% dextrose, slow infusion for 6 to

8 hours. Premedication may be needed to avoid infusion reaction. Renal function and potassium levels should be monitored while treating amphotericin B. Patients who are intolerant to amphotericin B, alternative antifungals such as posaconazole or isavuconazole (injection/tablets) can be started. The dose of posaconazole is Tab. Posaconazole 300 mg twice daily a day on the first day followed by 300 mg once a day. The dose of the isavuconazole is 200 mg three times a day for two days, followed by 200 mg once a day.²⁴ The patients should be monitored clinically and radiologically for the response of the treatment or disease progression. After 3 to 6 weeks of amphotericin B therapy, consolidation therapy (posaconazole/isavuconazole) for 3 to 6 weeks. In this study, all had undergone radical debridement of the mucormycosis along with orbital exenteration in two cases, followed by parenteral infusion of amphotericin B (1-1.5 mg/kg/day) and a total dose of 2.5-3 gm.

Poorly controlled diabetes mellitus is a major issue while managing the CAM, so good glycemic control should be done during the management of COVID-19 patients. Systemic corticosteroids should be used only in case of hypoxemia.²⁴ Oral steroids should be avoided in patients with normal oxygen saturation on room air. If systemic corticosteroid is used, blood glucose should be monitored. The dose and duration of the corticosteroid treatment should be limited to dexamethasone (0.1 mg/kg/day) for 5 to 10 days. Patients should be advised to use a face mask for reducing the Mucorales. During discharge of the COVID-19 patients, the patient should be advised about the early symptoms or signs of mucormycosis such as facial swelling, facial pain, nasal blockage and excessive discharge, loosening of tooth, chest pain and respiratory insufficiency. The worldwide case fatality rate of mucormycosis is approximately 46%.²⁵ The diagnosis of mucormycosis is often difficult. However, the early diagnosis and prompt treatment are always important and late or even six days is associated with doubling of mortality rate from 35% to 66%.²⁵ A high suspicion of mucormycosis is considered in immunocompromised patients. In the case of a high-risk person, the diagnosis of mucormycosis can be anticipated if there is associated with one side facial swelling, pain over the face, orbital swelling or proptosis. The late sign is tissue necrosis which acts as a hallmark for mucormycosis, which occur due to vascular invasion and thrombosis.²⁶ If the diagnosis is confirmed, prompt surgical opinion is required, followed by antifungal agents. Early diagnosis and prompt treatment are necessary for the improvement of the outcome of mucormycosis in COVID-19 patients.

CONCLUSION

Mucormycosis is a dreaded fungal disease resulting in angio-invasion by the hyphae leading to thrombosis and necrosis of the host tissue. Patients with diabetes mellitus or taking systemic steroids or under any immunosuppressive medication with COVID-19 are at greater susceptibility for mucormycosis. In a COVID-19 patient, the severity of the mucormycosis is due to its rapid progression and angio-invasive nature. The clinician should act promptly to identify the mucormycosis, particularly in immunocompromised patients or poorly controlled diabetes mellitus. The widely accepted treatment for mucormycosis is amphotericin B, along with surgical debridement. The rising of mucormycosis or black fungus in COVID-19 patients can be managed effectively if identified early with adequate treatment with amphotericin B, surgical debridement and controlling of the associated risk factors.

Study limitation

This study has a rather small sample size and may restrict the outcome of the aforementioned interpretation. However, the conclusion of this study will undoubtedly inspire the future research effort in this catastrophic clinical entity called COVID-19 associated mucormycosis.

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