A Case Series of Mucocutaneous Mucormycosis and its Risk Factors among SARS-CoV-2 Patients

Abstract
Mucormycosis is a rare, aggressive angioinvasive deep fungal infection caused by mucorales. The epidemiology of mucormycosis has changed in recent times with the increase in incidence, identification of new causative agents, and predisposing factors. The clinical spectrum of mucormycosis includes rhinocerebral, sinopulmonary, cutaneous, and disseminated forms. Cutaneous mucormycosis is an emerging infectious disease especially in post COVID-19 era. Cutaneous mucormycosis can be of two varieties: primary cutaneous and secondary cutaneous. Primary cutaneous mucormycosis is caused by direct inoculation of spores at the site of local trauma resulting in necrotic ulcers, especially, in immunosuppressed patient. Secondary cutaneous mucormycosis results from either dissemination or local invasion to the skin from a rhinocerebral form. The existing data on mucocutaneous mucormycosis is sparse especially in India. Herein, we present a case series describing the demographic factors, predisposing factors, clinical presentation, management of unique cases of mucocutaneous mucormycosis and its association with COVID-19 infection.

Keywords: COVID-19, mucocutaneous mucormycosis, mucormycosis, SARS-CoV-2

Introduction
Mucocutaneous mucormycosis is a rare but fatal deep fungal infection caused by Mucorales (Zygomycetes) with only a handful of cases reported in literature, especially India.[1] Of late, its cases have increased in leaps and bound owing to the recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic making it an intriguing entity to be researched. Here, we present a series of eight cases of proven mucormycosis in SARS CoV-2 positive patients each with unique mucocutaneous manifestations encountered by us during the peak of the second wave of pandemic in India from our COVID-19 dedicated tertiary health care system.

Case Descriptions
Eight cases presented to us with COVID-19 infection, who developed mucocutaneous manifestation of mucormycosis during the course of their illness [Table 1]. Among the 8 cases, 6 were male (75%), while the remaining 2 were females. Most (n = 7; 87.5%) of the patients had one or more underlying risk factors. The most common risk factor among these patients was diabetes mellitus, both type 1 and 2 (4/8, 50%). All the cases were of COVID-19 infection with a positive RT-PCR report.

In case 1, violaceous necrotic plaque with ulceration and eschar [Figure 1] had developed involving the left lower quadrant of abdomen evolving over scalded skin from an accidental burn over 10 days. The diagnosis was confirmed by KOH mount [Figure 2a] and fungal

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culture [Figure 2b] followed by lactophenol cotton blue mount [Figure 2c].

In case 2, a small itchy erythematous papule evolved into an ulcer showing 3 concentric zones, namely an outermost zone of intense erythema, a middle zone of vesiculo-pustular area with a central zone of eschar (typical bull’s eye infarct) with preceding history of insect bite at the site 20 days back.

In case 3, an indurated red plaque developed into an ulcer with eschar [Figure 3a] and diagnosis was confirmed on histopathology [Figure 3b]. Interestingly, this patient also had a history of local trauma prior to the onset of lesions.

![Image](image.png)

**Figure 2:** (a) KOH mount showing broad aseptate ribbon like hyphae with right angle branching (x400), (b) Sabouraud Dextrose agar culture showing cottony fluffy, yellow to dark-grey colonies, (c) Lactophenol blue mount showing rhizopus mucor (x400)

| Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 |
|--------|--------|--------|--------|--------|--------|--------|--------|
| Age (in years) | 75 | 38 | 68 | 42 | 48 | 24 | 62 | 56 |
| Sex | Male | Male | Male | Female | Male | Female | Male | Male |
| Co-morbidities/ risk factors | Chronic obstructive pulmonary disease | Diffuse large B cell lymphoma (on cyclophosphamide, doxorubicin, prednisolone and rituximab) | Diabetes mellitus type 2 | Diabetes mellitus type 2 (diagnosed first time during the evaluation of mucormycosis) | None | Male | Diabetic ketoacidosis, Pulmonary tuberculosis (on antitubercular therapy) | Male |
| History of systemic steroid use | Yes | Yes | Yes | Yes | No | No | Yes | Yes |
| Site and type of lesion | Abdominal wall; violaceous necrotic plaque | Left shoulder; typical bull’s eye infarct | Dorsum of right foot; ulcer with eschar | Lower lip; necrotic ulcer | Oral mucosa; Erythematous indurated plaque with exudation | Hard palate; Erythema and necrosis with impending ulcerations | Left nasolabial fold; Ulcer with black eschar | Hard palate; palatal perforation |
| Diagnostic tests | Impression smear for KOH examination which showed broad aseptate ribbon-like hyphae, confirmed by tissue biopsy/culture in each case. | | | Non-contrast computerized tomography (NCCT) paranasal sinus and orbit in suspected cases of rhino-orbital mucormycosis, confirmed by locally debrided tissue examination and culture in each case. | | | | |
| Treatment | Local debridement, liposomal amphotericin B | | | FESS (Functional Endoscopic Sinus Surgery) and local debridement, liposomal amphotericin B | | | | |
| Outcome | Deceased | Fully recovered | Fully recovered | Fully recovered | Fully recovered | Fully recovered | Lost to follow up | Lost to follow up |

**Table 1:** Demography, risk Factors and the clinical details of the patients with mucocutaneous mucormycosis associated with COVID-19 Infection
Case 4 was a patient with severe pneumonitis being stabilized on a ventilator. There was history of local trauma attributed to multiple attempts of endotracheal tube insertion. 10 days later, patient developed a necrotic ulcer with eschar on lower lip with intense erythema of surrounding labial mucosa [Figure 4].

Case 5 complained of fever and nasal discharge for 15 days with erythematous indurated plaque over gingival and palatal mucosa and small ulcer with yellowish exudates.

Case 6 presented with headache, unilateral facial swelling, and nasal discharge since 8 days. On examination, there was eschar formation around nasal vestibule [Figure 5a] and intense erythema and brownish black discoloration with few discrete foci of necrosis on hard palate [Figure 5b].

Case 7 had initially presented to us with fever, pain, and periorbital swelling since 10 days. Cutaneous examination showed a 2×2 cm ulcer on erythematous base near left nasolabial fold with overlying black eschar [Figure 6].

Case 8 presented with facial swelling, pain and eye discharge for 7 days. Oral examination showed an ulcer with necrotic tissue along its margins draining blood tinged pus like discharge suggestive of palatal perforation.

All of the above-mentioned cases were clinically diagnosed as mucocutaneous mucormycosis, with further lab confirmation initially by impression smear for KOH examination which showed broad aseptate ribbon-like hyphae followed by tissue biopsy and/or fungal culture.

Interestingly, one of our case was newly diagnosed as type 2 diabetes mellitus during the course of evaluation of mucormycosis. Other risk factors included chronic renal insufficiency, hematological malignancies, use of immunosuppressants, metabolic acidosis, etc. Out of 8 cases, 6 patients had a history of steroid intake either as a part of COVID-19 treatment or for chronic immunosuppression and chemotherapy. All the 8 patients were COVID-19 positive and had mild to moderate disease with CT severity index on HRCT chest ranging from 8 to 15, except case no. 8 who had a score of 20. Case 1, 4, and 3 were already positive for COVID-19 on RT-PCR and the lesions evolved over the course of treatment for pneumonitis during the hospital stay. Whereas cases 2, 5, 6, 7, and 8 were diagnosed COVID-19 positive during the course of evaluation of mucormycosis.

**Discussion**

Mucocutaneous mucormycosis is of two types: primary and secondary. The former is caused by direct inoculation of spores at the site of trauma while the latter results from either dissemination or local invasion to the skin from a rhinocerebral form and pulmonary forms.\[2\]
A rapid increase in the incidence of mucormycosis during the COVID-19 pandemic poses a question on its relation with SARS-CoV-2 infection.[3,4] This case series highlights the association between mucormycosis and COVID-19 infection and also delineates the probable causes behind this association.

SARS-CoV2 virus stimulates the release of GRP78 from the endoplasmic reticulum in response to stress. GRP78 binds to the fungal ligand CotH3, thus facilitating the fungal endocytosis. Besides this, raised IL-6 levels, macrophage activation and hepcidin mimetic action of SARS-CoV2 virus results in hyperferritinemia and generation of reactive oxygen species, ultimately causing endotheliitis. Damaged endothelium acts as a fertile soil for fungal angioinvasion.[5-8]

Figure 5: (a) Case 6 with nasal mucosal ulceration and eschar formation around the nasal vestibule, (b) brownish black discoloration of hard palate mucosa with few discrete foci of necrosis

Virus-mediated pancreatic damage and corticosteroid use result in hyperglycemia which increases the risk of mucormycosis by hampering the chemotaxis and phagocytosis by neutrophils, inhibiting iron sequestering proteins, upregulating GRP78 levels and increasing oxidative damage.[5,8,9]

Figure 6: Case 7 with an ulcer near left nasolabial fold with overlying black eschar and blood tinged discharge with periorbital swelling and eye discharge

SARS-CoV2 induced hypoxia results in acidic pH, which impairs the sequestration of iron by ferritin, thus increasing the risk of infection.[5,10] Virus-induced primary innate immune dysfunction like impaired mucociliary clearance results in higher chances of contracting the infection. Any breach in the continuity of nasal or sinus mucosa allows the fungus to adhere to the basal cell layer of the epithelium.[5]

Owing to the severity of COVID-19 induced pneumonitis, many patients require mechanical ventilation, long-term antibiotics and steroids predisposing them to nosocomial infections including mucormycosis.[3]

Conclusion

Our case series exemplifies the importance of identifying various mucocutaneous manifestations of mucormycosis in the COVID-19 era. A dermatologist must always be on the look out to differentiate these clinical features from other similar looking diseases to come to a rapid clinical diagnosis. Early diagnosis and prompt intervention is necessary to limit the mortality rate of cutaneous mucormycosis.

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.
Arora, et al.: Mucocutaneous mucormycosis

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