

Emergence of Mucormycosis during COVID-19 Pandemic and Dermatological Manifestations

Mucormycosis is a ubiquitously present angioinvasive fungi in the environment.^[1] Though uncommon in immunocompetent patients, the extended survival of critically ill and immunocompromised patients, uncontrolled diabetes mellitus, persons living with HIV, and indiscriminate use of systemic antimicrobials has led to an upsurge of systemic mucormycosis in recent years.^[2] Mucormycosis is known since 1885 when it was first described by Paltauf. Later in 1943 Gregory *et al.* reported the first case of rhino-orbital-cerebral mucormycosis. The term “mucormycosis” was coined by an American pathologist R. D. Baker.^[3] The term “Black fungus” is a misnomer and should not be used to describe mucormycosis by scientific community as “black fungus” or “dematiaceous fungi” is used for fungi causing phaeohyphomycosis.

Cutaneous involvement is the third most common manifestation of systemic mucormycosis.^[4] However, unlike systemic mucormycosis, primary cutaneous mucormycosis is not uncommon in immunocompetent individuals, who account for 40%–50% of such cases.^[5] There has been a renewed interest in mucormycosis recently, due to its association with COVID-19 infection.

COVID-19 and Mucormycosis

During the pandemic of COVID-19, an unprecedented increase in the incidence of mucormycosis has been noted in India. COVID-19-associated mucormycosis (CAM) is now recognized as an epidemic in itself and is declared as a notifiable disease. Already >30,000 cases of CAM have been notified in India.^[6] A large multicentric study performed during the first wave of COVID-19 (March 2020-March 2021) from India has revealed a 2.1 time increase of mucormycosis compared to same period before COVID-19 (non CAM cases).^[7]

Uncontrolled diabetes mellitus is the most common cause reported in all the studies,^[1,4,8] followed by history of prolonged use of corticosteroids. In 1/3rd of the patients with CAM, COVID-19 was the only underlying disease, of them majority (78%) received corticosteroids during the management of COVID-19.^[7] It is interesting to note that in 20% of CAM cases, diabetes mellitus was detected for the first time during the COVID-19 disease suggesting the role of SARS-COV2 in causing diabetes mellitus.^[7] Other risk factors such as malignancies or organ transplantation were negligible. Rhino-orbital mucormycosis is the commonest presentation followed by rhino cerebral and pulmonary mucormycosis.^[7] *Rhizopus arrhizus* is the commonest species isolated from CAM cases followed by *Rhizomucor*

pusillus, *Apophysomyces variabilis*, and *Lichtheimia corymbifera*.^[7] The mortality rate (at 6 weeks) in the CAM (38%) is lesser than the non-CAM cases (45%).^[7]

Dermatological Manifestations of COVID-19

The ongoing COVID-19 pandemic has drawn the attention of dermatologists towards a broad spectrum of cutaneous manifestations of SARS-COV2 infection classified into five major clinical patterns: pseudo-chillblain like eruption, vesicular eruption, urticarial eruption, maculopapular eruption including pityriasis rosea like, perifollicular eruption, erythema multiforme like, pseudovesicular or resembling erythema elevatum diutinum, purpuric eruptions, morbilliform eruptions and livedoid/necrotic lesions.^[9] In addition, a plethora of cutaneous reactions including local injection site reactions, urticarial eruptions, morbilliform eruptions, erythromelalgia, delayed inflammatory reaction to hyaluronic acid fillers, chilblains, zoster, herpes simplex flares and pityriasis rosea like reaction have been documented after administration of COVID-19 vaccines.^[10-12]

Dermatological Manifestations of Mucormycosis

Cutaneous involvement in mucormycosis occurs either due to direct inoculation of the fungus by penetrating trauma (primary mucormycosis), dissemination from blood-borne infection (secondary mucormycosis), or through the contiguous spread.^[13] Broadly, primary cutaneous mucormycosis have two distinct presentations; a rapidly progressive angioinvasive necrotising type and the lesser-known gradually progressive chronic granulomatous type. The classification of cutaneous mucormycosis is depicted in Table 1 and the difference between acute necrotising mucormycosis and chronic granulomatous mucormycosis is depicted in Table 2.^[13]

Primary Mucormycosis

Acute necrotising type

This type of primary cutaneous mucormycosis is commonly seen in immunosuppressed individuals and begin at the site of trauma, most common being road traffic accidents, farm accidents, nosocomial use of adhesives, and sites of venepuncture.^[14] Morphologically, it presents variably as erythematous macules, pustules, infiltrative plaques, and retiform lesions. These lesions then rapidly progress to cutaneous ulcers and necrotic eschar with a jagged margin. If left untreated, dissemination of the fungus by angioinvasion and death is likely. Other morphological variants include ecthyma gangrenosum like lesions,

cellulitic plaques, bull’s-eye infarcts and targetoid plaques, and pyoderma gangrenosum like lesions.^[2] Dermatological patients with ulcers and raw skin can acquire mucormycosis directly from the environment and a high index of suspicion is generally required when encountered with non-healing skin ulcers.^[15]

Chronic granulomatous type

This uncommon variant is less well documented in the literature. The epidemiological data show that this presentation is most commonly reported from Asia, with majority of the cases documented from China and India.^[13,16] Unlike acute necrotising type, most of the patients of chronic granulomatous mucormycosis are immunocompetent and trauma is an important risk factor for its occurrence. The common morphological presentation is gradually progressive cutaneous plaques with variable amount of ulceration and scarring.^[13,17] The disease course can run into years, with a risk of dissemination of the fungi to vital organs.

Secondary Cutaneous Mucormycosis

Secondary cutaneous mucormycosis is the most common type of cutaneous mucormycosis usually seen in hospital and emergency settings and affects terminally ill and severely immunocompromised patients.^[14] The cutaneous

involvement in this instance is secondary to dissemination from an internal source. The prevalence of secondary cutaneous mucormycosis is increasing due to prolonged hospital stays, indiscriminate use of antimicrobials, use of chemotherapy and cytotoxic agents and uncontrolled diabetes mellitus. The cutaneous morphology is similar to acute necrotising mucormycosis and can present as erythematous to livid plaques, pustules, retiform lesions, and progressive ulcers.

Contiguous Mucormycosis

The cutaneous involvement in this type of mucormycosis is due to contiguous spread from the underlying structures. The well-known form of contiguous mucormycosis is rhino-cerebral mucormycosis. This variant can present with oral ulcers, mucosal eschars, periorbital edema, periorbital cellulitis, ophthalmoplegia, loss of vision, and neurological deficits.^[18]

The majority of cases of CAM reported have been of rhino-orbito-cerebral mucormycosis in which nose/sinus involvement occurs relatively early in the course of infection whereas eye and intracranial infection occur in the advanced disease. Cutaneous involvement subsequent to sinus/nose involvement can occur in the form of pain/loss of sensation on the face, localized facial puffiness, or necrosis of the skin over the cheek, eye or lateral nasal wall area.^[17]

Diagnosis and Treatment of Mucormycosis

Mucormycosis can be easily diagnosed based on clinical and radiological signs along with microbiological or histopathological evidence of aseptate hyphae in the tissues.^[19] Unlike diagnosis of COVID-19, molecular diagnosis is not generally recommended as its sensitivity and specificity are lower than the direct microscopy, culture, and histopathology. For cutaneous and subcutaneous mucormycosis, direct microscopic examination using

Table 1: Classification of cutaneous mucormycosis (adopted from Vinay *et al.*^[13])

Primary cutaneous mucormycosis: Caused by inoculation of causative organism into the damaged skin
Acute necrotising mucormycosis
Chronic granulomatous mucormycosis
Secondary cutaneous mucormycosis: Secondary involvement of the skin due to haematogenous dissemination from another organ system
Contiguity mucormycosis: Involvement of the skin due to contiguous spread, mainly from rhinocerebral mucormycosis.

Table 2: Clinical and histopathological differences between acute necrotising mucormycosis and chronic granulomatous mucormycosis (adopted from Vinay *et al.*^[13])

	Acute necrotising mucormycosis	Chronic granulomatous mucormycosis
Onset	Acute	Chronic
Progression	Rapid	Slow
Cellular immunity	Usually impaired	Usually intact
Causative organism	Rhizopus, Mucor	Rhizomucor
Mode of involvement	Traumatic inoculation, Haematogenous dissemination, Contiguous spread	Traumatic inoculation
Clinical features	Reddish purple indurated plaques progressing to necrosis and eschar formation	Erythematous plaque with a progressive margin and areas of healing and scar formation
Angioinvasion	Present	Absent
Histopathology	Necrotising inflammation	Granulomatous inflammation
Treatment	Control of predisposing condition, surgical debridement and liposomal amphotericin B	Liposomal amphotericin B
Prognosis and mortality	Poor can lead to mortality	Good, no mortality but causes significant morbidity

potassium hydroxide mount with or without calcofluor stain or histopathological examination is preferred. Molecular diagnosis such as polymerase chain reaction (PCR) using Mucorales specific primers are generally recommended for the pulmonary mucormycosis for identification of etiological agent from formalin-fixed paraffin-embedded tissue.^[19-21]

Surgical removal of all infected tissue is essential for the successful management of mucormycosis. For the medical management of any form of the infection, liposomal amphotericin is the recommended first line of therapy.^[19] Posaconazole and isavuconazole may be used as an alternative when liposomal amphotericin B is not available or as a salvage therapy when the patient is intolerant or not responding to amphotericin B.^[19] In resource-poor settings, amphotericin B deoxycholate can also be used as first-line therapy.^[4] Though the *in vitro* activity of itraconazole is comparable to other azoles, no trial has been done to evaluate its efficacy in mucormycosis.^[6,22]

The current COVID-19 pandemic and the concurrent surge of mucormycosis have given us a glimpse of the larger scenario we may face in the later part of the century. Increasingly older population, extended survival of immunocompromised hosts, and indiscriminate use of antimicrobials has led to an upsurge of systemic fungal infections. The medical community including dermatologists should be well aware of clinical presentations and be prepared to tackle increasing number of common and uncommon fungal infections.

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