Review Article

Cutaneous mucormycosis

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Abstract

Mucormycosis or 'Black fungus' is a fatal, opportunistic, and angioinvasive fungal infection that commonly occurred among the immunocompromised patients. Skin may be affected as primarily or by secondary invasion in disseminated systemic disease. In primary Spores of Mucormycetes can be implanted through trauma, penetrating injury, burn, and agricultural works. A definitive diagnosis needs histopathology, culture, or microscopy of tissue collected by biopsy, smear, or lavage. But these techniques are laborious and unsuccessful in many instances and need the support of new molecular tests. Early diagnosis, managing risk factors, adequate surgical debridement, appropriate systemic antifungal (amphotericin-B, posaconazole, isavuconazoleor fluconazole), and hyperbaric oxygen are the armamentarium against mucormycosis.

Keywords: Cutaneous, Zygomycosis, Mucormycosis, COVID-19, immunocompromised.

Introduction

Mucormycosis, the third common 'rare' invasive fungal infection has been emerged as a disease of concern over the last few decades and especially during the current pandemic of COVID-19.[1-2] German pathologist Paltauf reported a case of systemic fungal infection involving the gastrointestinal tract, paranasal sinuses, and brain in 1885 and he coined it as "Mycosis Mucorina".[3] The class Zygomycetes that cause human invasive opportunistic infection includes two orders of clinically significant filamentous fungi the Mucorales and the Entomophthorales.[4] Among them Mucorales fungi are the culprits for most human zygomycosis and for that reason the terms mucormycosis and zygomycosis are used synonymously (the term phycomycosis is also used).[5] Immunocompromised persons with diabetes and other different conditions are the main unfortunate target of this fatal, invasive, and opportunistic fungal infection.[6] Though a significant number of patients are reported those having no underlying immunodeficiency or risk factor.[6-7] The clinical presentations are determined by the affected sites commonly involved rhinocerebral, pulmonary, cutaneous, gastrointestinal, and central nervous systems though it can involve any organ of the body.[8] Cutaneous form of mucormycosis can affect skin primarily through breached skin barrier or secondarily as dissemination from other severe invasive systemic forms with comparatively unfavorable outcome.[9] This review will discuss different issues of cutaneous mucormycosis.

Incidence and prevalence:

The prevalence of mucormycosis varies according to the population at risk.[10] Globally the burden of diabetes mellitus, malignancy, chemotherapy, solid organ transplantation, use of systemic corticosteroids are increasing.[11-12] The disease frequency and presentation of mucormycosis are

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variable in developed and developing countries. It is rare in western countries whereas the number of mucormycosis is raising in India and other Asian countries.[13-14] In a community-based survey in the USA the incidence of zygomycosis was 1.7 cases per million population per year.[15] In a review of 851 cases of mucormycosis by Jeong et al, 34% were reported from Europe, 31% from Asia, and 28% from North or South America (28%).[16] In Spain the incidence was 0.43 cases per 1,000,000 per year in 2005. In France, the incidence was raised from 0.7 to 1.2 cases per million over ten years, mainly in patients with hematologic malignancies and bone marrow transplantation.[17] There is no available data on the epidemiology of zygomycosis in Bangladesh except few case reports.[18-19] Its incidence is increasing in India. The overall number of cases was raised from 25 per year to 89 per year just over eight years.[20] But recently it has emerged with an unimaginable threat of epidemics of black fungus that is corona virus disease-associated mucormycosis at the time when India facing the second wave of current COVID-19 pandemic.[2]

Age and sex:

Susceptible people of any age can be infected with mucormycosis (from newborn to 87 years) with a mean of 38 years. Males are predominantly affected with a male-female ratio 1.1:1.17,[21-23]

Agents:

Etiological agents of mucormycosis in a different geographical region differ significantly. In European countries Rhizopus spp. (34%) is the most common followed by Mucor spp. (19%) and Lichtheimia spp. (19%).[24] Rhizopus arrhizusis the most common species globally. In India, Rhizopus arrhizus is the commonest followed by Lichtheimia, Cunninghamella, Rhizomucor, and Apophysomyces.[25] Here Apophysomyces variabilis is the second commonly isolated agent that causes cutaneous mucormycosis in the form of necrotizing fasciitis.[25] The genera Apophysomyces and Saksenaea can initiate invasive disease in apparently normal hosts who have sustained penetrating trauma during accidents.[25] mucormycosis fungi have a mostly universal habitat in the environment but they develop in hot, humid weather.[26] These are commonly isolated from mud, dead organic body parts of animals or plants, animal excreta, rotten fruits, and bread.[26]

Host defense against Zygomycetes and pathogenesis of zygomycosis:

Breaking of the host's innate immunity is crucial in the pathogenesis of Mucormycosis. The prime defense against filamentous fungi is the innate host immunity comprising of polymorphonuclear neutrophils (PMNs), mononuclear cells (MNCs), and macrophages, especially pulmonary alveolar macrophages and intact skin and mucosal barrier. In an immunocompetent person, phagocytes can kill Mucorales by oxygen-dependent and oxygen-independent mechanisms.[27] Patients with neutropenia or dysfunction of phagocytes are at higher risk of developing zygomycosis. Hyperglycemia, ketoacidosis, and the use of corticosteroids may impair the capacity of phagocytosis.[9] T lymphocytes are not significant for inhibiting fungal proliferation.[28] Higher levels of serum iron ions (Fe2+) increases the susceptibility to develop mucormycosis. The iron-chelating agent deferoxamine is utilized by Rhizopus spp. to supply previously unavailable iron to the fungus. Also in diabetic ketoacidosis or metabolic acidosis, iron ions stay in dissociated form and stimulate the development of mucorales.[26]

Primary cutaneous mucormycosis can be caused by direct inoculation of spores deep to the skin where the normal skin barrier is compromised by trauma, burn, other infections, and maceration for persistent moisture. It can be very aggressive and spread locally deep to subcutaneous tissue, fascia, muscle even to bones.[29] In immune-compromised person infection may be disseminated to internal organs through blood lead to life-threatening situation.[29]

Risk factors:

Mucormycosis classically occurs in patients with uncontrolled diabetes mellitus and has also been reported in patients with hepatic or renal failure, chronic infections (ie, HIV, tuberculosis), vascular access catheters, extensive burns, trauma, iron overload, prolonged prophylactic use of voriconazole, hematologic malignancies, and solid organ transplantation.[9,16-17,26]

Rout of entry:

The infection can be acquired through inhalation, ingestion, implantation, or direct inoculation into the skin. In cutaneous zygomycosis, fungi get entry through damaged skin caused by trauma, burn, infection, or maceration of the skin. Primary cutaneous mucormycosis can also be acquired by an

insect bite, stings, or pecking by birds.[9] Trauma is the commonest type due to day-to-day minor injury, road traffic accident, crush injury, injury from agricultural works where mud is implanted into the skin and deeper and cause zygomycosis. It can also be acquired from insulin injection of diabetic patients, catheter insertion, surgical dressing, and even from contaminated dressing tap.[9,26]

Clinical manifestation:

The clinical hallmark of mucormycosis is vascular invasion and dissection of muscular tunica media of vessels resulting in thrombosis and tissue infarction/necrosis.[9] Its manifestation of mucormycosis depends according to the route of entry of spores and site of involvement.[8] It can be presented in two ways: i. Superficial and Visceral and ii. Localized and Disseminated.[9] Though it can involve any organ of the body it presents as following forms: i. rhino-orbital-cerebral (ROCM), ii. pulmonary, iii. gastrointestinal, iv. cutaneous, v. renal, and vi. disseminated mucormycosis.[8] The most frequent form of zygomycosis is rhinocerebral (34%–49%), followed by cutaneous (10%–22%), pulmonary (10%–20%), disseminated (6%–13%), and gastrointestinal (2%–11%) disease.[30]

Cutaneous mucormycosis:

Cutaneous infection is the second or third most commonly occurring type of mucormycosis.**17,30** Invasive cutaneous and soft tissue mucormycosis occur in case of broken skin barriers due to either traumatic implantation of soil, maceration of the skin by a moist surface, or direct access through intravenous catheters or subcutaneous injections.[9] Cutaneous mucormycosis can be subcategorized into three groups. i. Localized disease: Cases having infection confined to the cutaneous or subcutaneous tissue, ii. Deep extension: Cases having invasion into muscle, tendon, or bone, iii. Disseminated infection: Cases involving another non-contiguous site.[17]

Primary cutaneous mucormycosis:

In 7-15% of mucormycosis skin and subcutaneous tissue are primarily infected.[17] Individuals having high-risk factors of developing cutaneous mucormycosis are those with disruption of the normal protective cutaneous barrier. The causative organism of mucormycosis is typically incapable of penetrating intact skin. Primary cutaneous mucormycosis is frequently precipitated by skin trauma, usually leading to a necrotic eschar with surrounding erythema and induration.[26]

Secondary cutaneous mucormycosis:

The skin is a less common site of secondary involvement in rhinocerebral and disseminated mucormycosis.[17] The lung is the most common organ associated with dissemination.[5] In disseminated disease a secondary involvement of skin is followed by a rapid and short course (2 to 15 days) with higher mortality (up to 90%).[9,26] Disseminated spores invade nasal and paranasal sinuses and involve carotid, ophthalmic, palatine, or sphenopalatine arteries leading to thrombosis and infarction.[26] It can be presented with features of sinusitis, fever, unilateral periorbital pain, headache, edema, erythema, or congested nasal mucosa. Later area of focal necrosis and bleeding is observed.[26] Oral cavity can also be involved with necrotic, black, or white ulcers.[22] Later it may also progress to ophthalmoplegia, proptosis, loss of vision, and neurological features.[22] Further infarction produces large ulcer, fistula and osteolytic action of fungus cause destruction facial bony structure.[9]

Secondary zygomycosis follows three clinical stages:

stage I. features restricted to the sino-nasal area; stage II. Features of a sino-orbital infection; and stage III. Intracranial extension.[31]

Site of skin involvement:

Cutaneous mucormycosis can be involved at any site of the body but limbs are the common site. Other sites are the head and neck area, chest, breast, back, abdomen, buttock, and perianal region.[23] Physical characteristics of the skin lesions of mucormycosis are variable. Lesions may start slowly and progress or may start dramatically, involve subcutaneous tissue, become gangrenous, and rapidly disseminate through blood.[22] It can be started as an erythematous or purplish-red indurated tender plaque which can later become necrotic with an erythematous halo followed by Escher formation.[22,26] The fungus invades cutaneous vasculature cause infarction causing brownish or blackish skin lesions tending to ulcerate with blackish malodorous discharge.[32] If the disease continues the progression to a deeper structure it will involve fasciae, muscle, tendons, and bones. This deeper extension may cause necrotizing fasciitis, discharging sinuses, or osteomylitis.[33]

Subcutaneous mucormycosis is caused by accidental inoculation of fungal spores deep into the skin or

subcutis from minor trauma, insect bite, intravenous catheter, or even intramuscular injection. It starts as a hard nodule and progresses to form hard, painless swelling. Sometimes become ulcerated and the finger can be easily inserted below the indurated edge but dissemination is rare. Sometimes it develops with a subacute evolution of 5- 25 days.[34] Mucormycosis may start even as blisters or pustules.[22]

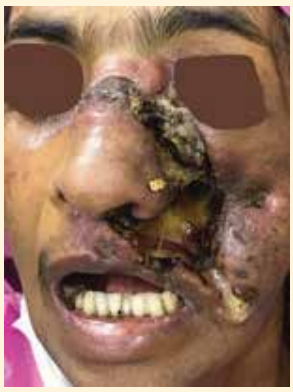

Figure I: Mucormycosis **Figure II: Mucormycosis**

Differential diagnosis:

In primary mucormycosis following differential diagnoses should be considered: cutaneous aspergillosis, synergistic gangrene caused by bacterial infections, multiple autoimmune diseases, drug reactions, infiltrative diseases, tinea corporis, pyoderma gangrenosum, and Sweet syndrome.[9,26,32] Centrofacial lymphomas (N/K T cell lymphoma), rhinoscleromas, sinusitis, anaerobic infection, and aspergillosis are the differentials for secondary mucormycosis.[22,26]

Diagnosis:

Most of the presenting features of mucormycosis are non-specific but their diagnostic value raises when they are correlated with patient's comorbidities. An immune-compromised patient of cancer, diabetes mellitus, having a history of solid organ transplantation, hepatic or renal failure, extensive burn or trauma, or persistent maceration of skin may give some clue for the diagnosis.

Diagnosis of specimens histopathological and cytopathological study of biopsy material and culture for fungus.[8] An early diagnosis is the cornerstone for a successful treatment outcome. Prompt diagnosis is possible by direct KOH microscopic examination identifying non-septated, hyphae with irregular branching at right angles, especially at the periphery of the lesion. Impression smears from the wound margin can also be helpful.[26]

Sample:

A sufficient sample of skin scrapings or biopsy from skin lesions, nasal discharges, scrapings, and aspirates from sinuses in patients with rhinocerebral lesions, bronchoalveolar lavages, and needle biopsies from pulmonary lesions, and biopsy tissue from patients with gastrointestinal and/or disseminated disease should be collected.[8,35]

Microscopic examination and culture:

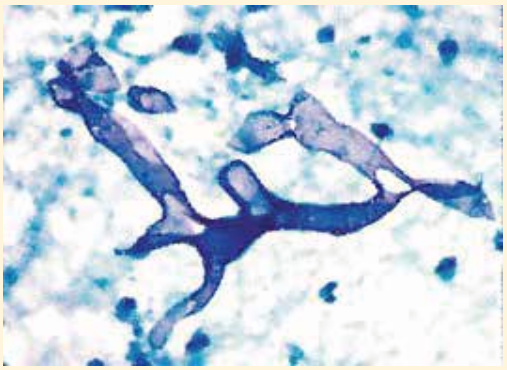

Figure III: Broad non-septate hyphae with right angled branching in mucormycosis

Histopathological study of biopsy specimen and identification fungus in culture growth is the standard means of diagnosis. But culture growth is positive in only 15–25% of cases and fungus can be confirmed by the presence of broad, non-septate hyphae in biopsy samples taken from the necrotic area.[8-9,35] Combining microscopy and culture increase the diagnostic yield by 15–20%.[8]

The biopsy material should be collected from the center of the skin lesion, including subcutaneous tissue. On tissue section features of edema, thrombosis, infarctions, necrosis, acute suppurative inflammation, and focal areas of granulomatous inflammation are found with infiltration of polymorphonuclear cells, plasma cells, and eosinophil.[35]

Fixed tissues are stained with hematoxylin and eosin (H&E) or Grocott methenamine-silver (GMS) or periodic acid-Schiff (PAS)stains. Non-septated. Hyaline, broad-based, ribbon-like hyphae with a variable diameter (6-30 µm) with wide-angle branching (approximately 90) are visible. Sometimes the hyphae show a crinkled or gnarled appearance on the tissue section which has been described as 'crinkled cellophane'. Hyphae are found to invade

the blood vessels at the level of the walls (veins and arteries), due to their angiotrophic properties, which justifies their tendency of dissemination.[8]

Culture:

Sabouraud and potato dextrose agar media are used as culture media and antibiotics should be avoided as they inhibit fungal growth.[26] After an incubation period of 3 to 5 days at a temperature of 25° to 28°C villous, whitish to grayish cotton-like colonies will grow that fill the Petri dishes. According to the experience of Bonafiz et al., cultures are positive in approximately 90% of cases.[8,26] The classical way of isolating Mucormycetes is phenotypic identification based on observing the morphology of fungus, but identification by morphology is laborious and often demands the support of a reference laboratory.

Molecular assays:

Diagnosis of mucormycosis and identification of Mucormycetes is laborious. New molecular tools are available for the identification of mucormycosis in culture and tissues. These techniques including real-time PCR are more rapid and more reliable than standard mycological identification. These tests target the 18S ribosomal DNA and are highly specific with no cross-reactivity with other fil¬amentous fungi.[35-36]

Table I Comparison of primary and secondary cutaneous mucormycosis.[8,26,29]

Features	Primary cutaneous mucormycosis	Secondary cutaneous mucormycosis
Mode of cutaneous infection	Direct inoculation through burns, traumatized or persistent macerated skin, injection, surgical tap, or catheter.	Dissemination from other locations, more commonly from a rhinocerebral infection.
Onset	Gradual in onset or fulminant	Acute onset
Risk factors	Leukemia and other blood cancer, solid organ transplantation, uncontrolled diabetes mellitus	Leukemia and other blood cancer, solid organ transplantation, uncontrolled diabetes mellitus, and ketoacidosis, deferoxamine (iron binder) therapy.
Major organism	*Rhizopus oryzae* *Apophysomyces elegans* *Lichtheimia corymbifera* *Saksenaea vasiform*	*R oryzae* *Mucor circinelloides* *Mucor spp* *L corymbifera*
Site	Any site of the body but limbs are the common sites. Other sites are the head and neck area, chest, breast, back, abdomen, buttock, and perianal region.	Face, eyelid, palate.
Presenting features	Starts as an erythematous or purplish-red indurated tender plaque, necrotic with an erythematous halo, escher, ulcer, and even necrotizing fasciitis.	Fever, sinusitis, periorbital edema, erythema, ophthalmoplegia, headache. Oral necrotic black Escher, ulcer, palatal ulcer and fistula. Eyelid fistula Loss of facial bone. Loss of vision, loss of wakefulness, seizure.
Treatment	Surgical debridement + amphotericin B and/or posaconazole	Amphotericin B (+ posaconazole); surgical debridement of necrotic tissue.

Management:

Early and accurate diagnosis and prompt treatment is the key point for the survival of mucormycosis. Without treatment, the mortality rate of zygomycosis approaches 100%.[17] Two cornerstones in the management of mucormycosis are surgical debridement and antifungal therapy. Surgical debridement is useful to reduce the fungal load. Along with these addressing underlying immune status, diabetes, and metabolic conditions, malignancy and comorbid infections are crucial. For primary cutaneous mucormycosis, surgical debridement of the wound with complete resection of dead and infected tissue leaving a cuff of apparently living fresh tissue is necessary. Post-operative close monitoring of the wound is important to detect the early feature of disease progression and repeat surgery should be done in such cases.[29] Frozen sections can be useful for demarcation of affected and normal tissues and to determine the surgical margins during surgical debridement.[37]

Sometimes completion of an extensive surgical debridement is challenging in disseminated or secondary cutaneous mucormycosis where necrotic tissues are adjacent to vital structures particularly in sinonasal, rhino-orbital, and, especially cerebral involvement.The use of hyperbaric oxygen has been recommended as adjunctive therapy with antifungals in such cases.[38]

The effective antifungal therapies against Mucormycetes include a different form of amphotericin B (AmB) and posaconazole. Monotherapy with amphotericin is the first-line treatment. Liposomal AmB and other lipid preparations in recommended doses (5–7 mg/kg) are most effective and less nephrotoxic.[9] To increase the survival rate, treatment must be started in the first 5 days after clinical diagnosis and the duration of the treatment is variable from 6 weeks to clinical or radiological resolution.[22,39] Different azole antifungal drugs have shown variable responses against zygomycosis in in-Vitro studies. Posaconazole is the most active followed by isavuconazole and itraconazole. Voriconazole is inactive against mucorales.[22,39-40] Posaconazole is effective at 800 mg per day twice a day. Overall long-term safety posaconazole is established and considered as second-line therapy in mucormycosis.[26,41] Isavuconazole is a new azole recently approved for the treatment of invasive mucormycosis in the United States.[40]

Prognosis:

The prognosis in cutaneous mucormycosis is better than that in the other clinical forms of the disease. Prognosis is favorable if dissemination does not occur, but mortality remains at 31%.[17]

Conclusion:

mucormycosis is a rare but emerging life-threatening invasive opportunistic fungal infection that has reappeared in some countries as a challenge during the current pandemic of COVID-19. Clinical and laboratory features of zygomycosis are mostly nonspecific. A high level of suspicion and molecular tools can help for correct diagnosis. Mucormycosis also has a high mortality rate. Early diagnosis and prompt aggressive treatment are mandatory to save a life. Managing underlying predisposing factors, surgical debridement, treatment with amphotericin-B or azole antifungals (posaconazole, isavuconazole, or fluconazole) is the line of treatment.

Conflict of interest:

No conflict of interest.

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