86866_Auto_Edited.docx

WORD COUNT 3692
TIME SUBMITTED 30-AUG-2023 07:30PM
PAPER ID 102370379

9
Name of Journal: *World Journal of Critical Care Medicine*

Manuscript NO: 86866

Manuscript Type: CASE REPORT

Angioinvasive Mucormycosis in Burn ICU : Case Analysis and Literature Review

Angioinvasive Mucormycosis in Burn ICU

Atul Parashar, Chandra Singh

Abstract

BACKGROUND

Mucormycosis is a rare, rapidly progressive and often fatal fungal infection. The rarity of the condition lends itself to unfamiliarity, delayed treatment, and poor outcomes. Diagnosis of fungal infections early enough to enable appropriate treatment occurs in less than half of affected patients

CASE SUMMARY

An 11 year old female child with a history of 15% Total Body Surface Area (TBSA) scald burns involving both the lower limbs progressed to develop angioinvasive mucormycosis. This further led to a thrombosis of the right external iliac artery and vein and rapidly progressive necrosis of surrounding soft tissues. She also had dextrocardia and patent foramen ovale. A right hip disarticulation and serial aggressive debridements were performed but she went on to develop systemic sepsis with multisystem involvement and succumbed to the infection. Pathology revealed Mucor species with extensive vascular invasion

CONCLUSION

This case highlights the importance of maintaining vigilance for mycotic infections and acting appropriately when there are concerning signs and symptoms of serious wound complications. Progressive necrosis outside the confines of the original burn wound should raise concern for fulminant infection which can be further compromised by invasive fungal growth, especially in the setting of co-existent systemic infection or an immunocompromised state.

Key Words: angioinvasive; mucormycosis; burn sepsis; femoral artery thrombosis

Parashar A, Singh C. Angioinvasive Mucormycosis in Burn ICU : Case Analysis and Literature Review. *World J Crit Care Med* 2023; In press

Core Tip: Mucor species are known to cause necrosis of adjacent soft tissues, spread rapidly across fascial tissue planes, cause vascular invasion and hematogenous dissemination, leading to mortality rates as high as 100% once disseminated infection has set in. Aggressive surgical debridement is advocated but even with that, survival may not be ensured in most of the victims. Considering there are only rare reports of mucormycosis in burn wounds , most treating surgeons are not well-versed with its early features. This leads to delay in diagnosis and institution of appropriate medical and surgical care. We came across one such case at our center recently, which prompted us to conduct a review of available literature on incidence of mucormycosis in burn wounds, its pathophysiology, and available guidelines for management. We hereby analyse our case and review relevant literature to raise awareness about this potentially fatal complication.

INTRODUCTION

Historically, mycotic infections in burn patients have been rare events. Burn wounds developing fungal infection should alarm the treating physician because of their association with high mortality rates, disabling amputations and prolonged hospital stay. [1] Because of the rarity of the condition, only 15-40% patients have been shown to be diagnosed early enough to ensure early appropriate treatment. And even in them, outcomes are poor and mortality remains high. Breach in the continuity of skin by trauma or burn injury may lead to colonization of the wound with fungi from surrounding environment, contaminated dressings *etc.* and this has been postulated to be the most common mechanism for cutaneous mucormycosis. Fungal infections, when occuring in burn wounds, tend to present in the second week or later following burn injury. The classic presentation is black deposits over the burn raw area appearing spontaneously in previously healing wounds.[2] Patients with larger surface area burns are at higher risk for acquiring such infections.[3]

Mucor species are known to cause necrosis of adjacent soft tissues, spread rapidly across fascial tissue planes, cause vascular invasion and hematogenous dissemination, leading to mortality rates as high as 100% once disseminated infection has set in. Aggressive surgical debridement is advocated but even with that, survival may not be ensured in most of the victims. Considering there are only rare reports of mucormycosis in burn wounds[4-6] , most treating surgeons are not well-versed with its early features. This leads to delay in diagnosis and institution of appropriate medical and surgical care. We came across one such case at our center recently, which prompted us to conduct a review of available literature on incidence of mucormycosis in burn wounds, its pathophysiology, and available guidelines for management. We hereby report our case and review relevant literature to raise awareness about this potentially fatal complication.

2

After Aspergillus, Mucorales fungi are the next common pathogens in patients with haematological malignancy, haematopoietic stem cell transplantation and solid organ transplantation.[7,8] Additionally, Mucorales infections are increasingly recognized in individuals with diabetes mellitus [9], after trauma or iatrogenic injury [10,11] and have been associated with outbreaks following natural disasters [12]. A review of the epidemiology, diagnosis, treatment and outcomes of mucormycosis (then 'zygomycosis') by Roden *et al*[10] has provided valuable insights into this important invasive fungal disease.

CASE PRESENTATION

Chief complaints

An 11 year old female child presented to our centre with 51 day old post burn raw areas over bilateral lower limbs.

History of present illness

The patient had 15% Total Body Surface Area (TBSA) burns to begin with. She had sustained the scald burn injuries by spillage of hot milk and was initially treated at several local hospitals where she received supportive care, intravenous antibiotics and

the raw areas were managed with dressings. Since she had deep dermal wounds, there was no epithelization and she continued with local dressings at various peripheral medical centers. During the 50 days she was managed at three separate local hospitals and as the general condition continued to deteriorate, she was finally referred to our centre on Post Burn Day 51.

History of past illness

, she had dextrocardia with small patent foramen ovale . She also had a past history of Left common femoral Vein thrombosis in her neonatal period which was successfully treated but the underlying etiology was not determined.

Personal and family history

Nothing Significant

Physical examination

On presentation, she had systemic systemic signs of inflammation, high fever, tachycardia and hypotension. Her general condition was poor with post burn raw areas over right thigh, groin and left thigh and leg. There right thigh had full thickness involvement over the anteromedial aspect with exposed thigh muscles There was slough & necrosis of surrounding soft tissues. (Figure 1). Left thigh & leg had partially healing raw areas with pale granulation tissue over anteromedial thigh, extending on to the left leg. (Figure 2).

Laboratory examinations

Blood investigations were suggestive of anemia (Hemoglobin - 8.1 gm%), leucocytosis (TLC – 73,700) with shift to the left (91% neutrophils), thrombocytopenia (platelets – 7.14 x 10^5), hypoproteinemia (3.3 g/dL) and hypoalbuminemia (1.3 g/dL). Liver and Kidney function tests were within normal limits. Wound swab on presentation revealed of gram negative coccobacilli.

Imaging examinations

At presentation, Chest X Ray was suggestive of pleural effusion and USG Abdomen, mild hepatomegaly.

Postoperatively, a CT Angiography was performed for bilateral lower limb vessels which revealed acute thrombosis of the right external iliac artery and non-opacification of right lower limb major vessels.

FINAL DIAGNOSIS

Angioinvasive Mucormycosis

TREATMENT

The patient was admitted in burn care unit and intravenous fluid resuscitation, titrated to adequate urine output and central venous pressure, was administered. Empiric antibiotic therapy based on Burn Unit protocol at our center was started. Blood transfusions were given to improve the hemoglobin. The wound surface slough was excised under intravenous sedation. The patient however continued to have regular fevers and hemodynamic instability. On day 3 of admission, the patient's right lower limb turned pale with absent pinprick. She was taken up in operating room for debridement. Thorough debridement of necrotic muscles and soft tissue was performed and the tissue was sent for bacterial and fungal culture sensitivity. Intra-operatively thrombosed right femoral artery and veins were noted. However, the deeper layer of muscles was viable with adequate bleeding. Intravenous Heparin 10 u/kg/hr infusion was started with aPTT monitoring

OUTCOME AND FOLLOW-UP

Intraoperative tissue biopsy showed growth of aseptate hyphae suggestive of Mucor species. The patient was started on intravenous liposomal Amphoterecin B (5 mg/kg).

Despite all these measures, soft tissue necrosis rapidly progressed to involve anterior abdominal wall and perineum over the next 8 h (Figure 4). The patient continued to have high fever and systemic sepsis. Consent for amputation was taken and Right hip disarticulation with external Iliac ligation and aggressive debridement of anterior abdominal wall and perineum were performed. (Figure 5)

Postoperatively, in view of severe acidosis the patient was kept on mechanical ventilation and also required inotropic support. Haemoglobin further fell to 6.8 gm% and multiple transfusions given. The wound condition continued to deteriorate rapidly and the patient was managed with bedside debridement under sedation because her general condition was considered unfit for anaesthesia. The blood oxygenation failed to improve and metabolic acidosis persisted despite mechanical ventilation. Chest X ray revealed bilateral lung infiltrates. She arrested on Day 7 of admission at our centre and could not be revived. The cause of death was deemed to be Angioinvasive cutaneous mucormycosis infection of the burn wound with hematogenous dissemination and secondary pulmonary invasion leading to systemic sepsis and respiratory failure.

DISCUSSION

Zygomycetes were first reported as a cause of human disease in 1885 by Paultauf[13] but it remained a rare diagnosis with fatal consequences for a large part of history. The last decade though, has seen its emergence as an increasingly important pathogen. This with rise in incidence of infection is seen in specific population groups, such as solid organ transplant recipients, diabetics, patients on deferoxamine therapy *etc.*[14] Though still encountered less frequently than other fungal infections like Candidiasis or Aspergillosis, these organisms are special among other fungi because of their disproportionately high propensity to cause life-threatening infections even in patients with no underlying immunodeficiencies or immunosuppressive therapy. Roden *et al*[10] conducted a large scale review all cases of zygomycosis reported in English literature since 1885 and thereby studied a total of 929 cases in their report. They reported an increasing trend in the incidence of these infections and found that 19% cases had no

underlying predisposing condition. Only 1.2% of the cases were reported to be associated with burn injuries. The mortality rate was 64% in this subgroup. Among the others, 44 patients (25%) had associated penetrating trauma and 32 (18%) had undergone some surgery. Mortality was relatively lower in these groups at 23% and 38% respectively. In contrast, the larger majority of patients (81%, *n* = 753) had associated underlying conditions like Diabetes mellitus (36%), Malignancy (17%) Solid organ or bone marrow transplantation (12%) Desferoxamine therapy (6%) Injection drug use (5%) Renal failure (4%) HIV infection (2%).

The term mucormycosis has been interchangeably used with the term zygomycosis. It used to describe infections caused by fungi belonging to Zygomycota, a former phylum which has now become obsolete after revision of nomenclature of the kingdom Fungi.[15,16] Now, mucormycosis is used for infections caused by fungi belonging to the order Mucorales, which include species belonging to the following genera, Rhizopus, Mucor, Rhizomucor, Lichtheimia, Saksenaea, Cunninghamella, and Apophysomyces. Among these, various reviews have reported Rhizopus to be the most common causative pathogen (47%) followed by Mucor spp (14-18%).[17]Causative pathogens also vary by geographical region. Lichthemia infections are largely reported in Europe (23% *vs* 7%) whereas Saksenaea spp has been reported in isolates from North and South America, India and Australia.[17]

These infections occur in patients with disrupted cutaneous barriers, as a result of either traumatic implantation of soil as in road side accidents, burn injuries, contaminated dressings maceration of skin by a moist surface[18 - 21], or even *via* direct access through intravenous catheters or subcutaneous injections (eg. Insulin injections in diabetics) [22-24]. In addition, it has been shown that Rhizopus spp utilize deferoxamine as a siderophore leading to increased pathogenesis in patients on deferoxamine therapy.[25,26]

Based on sites of involvement, mucormycosis may be grossly divided into six clinical categories namely Rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and miscellaneous. Of these, Rhino-orbital-cerebral mucormycosis

(ROCM) is the most commonly noted site of involvement (34%), followed by cutaneous (22%), pulmonary (20%) and disseminated (13%) involvement.[27] Interestingly, different underlying conditions predispose to specific sites of involvement, For eg. ROCM is significantly more common in patients with diabetes mellitus (51% *vs* 23%). While, cutaneous mucormycosis is more commonly observed in immunocompetent patients with a history of trauma (69% *vs* 11%), and pulmonary mucormycosis is more prevalent in patients with a history of solid organ transplantation and those with neutropenia. Disseminated infection is more frequently seen in patients with underlying haematological malignancy.[27]

Cutaneous infection is reported to be the primary site of involvement in 14-22% cases of mucormycosis overall[10] and in 27% of cases among children.[28,29] Majority of these patients don't have associated neutropenia or underlying predisposing conditions. Instead disruption of the normal protective cutaneous barrier is present in virtually all cases, followed by contamination with fungal spores. It is found to be associated with major penetrating trauma in 34% cases, post-surgical in 33%, post burn raw areas in 11% cases and minor trauma such as cuts, grazes (during gardening *etc.*) in 4% cases. [30,31] In another review by Jeong *et al* eight cases of the total 851 studied, were attributed to the use of contaminated dressings, intravenous access sites or needles.[17] Additionally, Roden *et al* observed female sex and HIV infection to be independent risk factors for cutaneous involvement.[10] In diabetics , cutaneous lesions may arise at subcutaneous insulin injection or catheter insertion sites.[32,33] In cutaneous involvement, the infection may remain limited to the skin or involve the underlying deeper structures, muscles, fascia and even bone. This may lead to necrotizing fasciitis, which has a mortality approaching 80%.[34-36] In 20% cases it may undergo hematogenous dissemination from the skin to other non-contiguous organs.

Extensive angioinvasion leading to vascular thrombosis and tissue necrosis is virtually a hallmark of mucormycosis on histopathology.[27] The pathogen achieves this by invading and damaging the endothelial cells lining blood vessels, thereby achieving the ability of hematogenous dissemination from the primary site of infection to other target

organs (CNS, lungs *etc.*). Incidence of dissemination is noted to be the highest in neutropenic patients with pulmonary mucormycosis. Burn patients are particularly prone to cutaneous disease. Further, once disseminated mucormycosis sets in, it is known to have a very high mortality rate approaching 94%- 100%.[37] Diagnosing disseminated disease is often difficult because patients are usually already severely ill with multisystem involvement and blood cultures turn out to be negative for growth. This diagnosis must be considered if there is evidence of infarction in multiple organs.[27]

Reported independent risk predictors for development of invasive, disseminated zygomycosis are: burns, premature neonate, deferoxamine use, diabetes and HIV infection.[10] Nevertheless, isolated cutaneous mucormycosis (without dissemination) has a favorable prognosis and a low mortality if aggressive surgical debridement is done promptly.[27]

Suspected mucormycosis is an emergency and requires rapid action. In cutaneous involvement, tissue samples must be sent for analysis as follows[38]:

Direct microscopy with fluorescence(calcofluor white) and histopathology with special stains (like HE, PAS or GMS) : To confirm the diagnosis, aseptate/pauci-septate, non-pigmented hyphae that are 6-16 µm wide, ribbon like with irregular branching pattern must be demonstrated. In addition, surrounding tissues show evidence of angioinvasion, vessel occlusion, perineural invasion, coagulative necrosis, and polymorphonuclear infiltration

Culture : performed on routine media at 30°C and 37°C : cottony white or greyish black colony

Molecular identification and Immunohistochemical staining with specific primary reagents

CT Scans of the chest, sinuses, cranium, abdomen or other parts, as involved must be performed. Halo and Reverse Halo signs and pleural effusion are noted in the chest CT in cases of pulmonary involvement. On CT angiography, vascular occlusion sign defined as interrupted vessel at the border of a focal lesion may be seen. Given the

limitations of imaging studies, diagnosing mucormycosis almost always requires histopathologic evidence of fungal invasion of the tissues In addition, serology for Galactomannan, 1,3-β-D-glucan may be performed.[38] Identification to the genus and species level is strongly recommended for improved epidemiological understanding of mucormycosis and antifungal susceptibility testing.[39,40] Species identification requires use of molecular techniques for DNA detection, which may also yield faster results as compared to culturing the organism. However, their clinical utility is currently limited by lack of technique standardization and clinical validation. [41] Large-scale clinical studies are needed to evaluate the role of molecular approaches as the primary diagnostic modality of mucormycosis.[42]

Before the introduction of amphotericin-B in the 1960s, reported overall mortality from the infection was as high as 85%. The introduction of Amphotericin-B administered systemically is the first line of treatment for the infection and has led to reduction of mortality to 40-60 %. In combination with aggressive surgical therapy, this is seen to decrease to 30%. Overall, four factors are deemed critical for achieving cure in mucormycosis (27) namely early diagnosis, treating the underlying predisposing factors, antifungal therapy, and aggressive surgical debridement . The significance of delay in diagnosis in mucormycosis may be underscored by the fact that several autopsy series have reported that up 50% cases of mucormycosis are diagnosed postmortem.[43-45] Small, localized lesions, diagnosed early can often be surgically excised before they spread to cause extensive disease or disseminate;[46] while delayed diagnosis has been shown to result in dramatically worse outcomes (83% *vs* 43% survival)[47]. Unfortunately, so far there are no serum or molecular tests to allow rapid diagnosis of the entity. Thus, the treating physician must maintain a high index of clinical suspicion and aggressively pursue diagnostic biopsy in suspected cases for improved outcomes.

Mucoraceous fungi are resistant to most antifungals and Amphotericin B is the most active drug, against most isolates. Amphotericin B may be administered as Amphotericin B deoxycholate, Liposomal amphotericin B or Amphoterecin B lipid complex. Other investigational/adjunctive therapies with variable efficacy include

triazoles like, itraconazole, ketoconazole, posaconazole, isavuconazole, caspofungin, hyperbaric oxygen, iron chelation, cytokine therapy such as IFN-λ, granulocyte colony-stimulating factor which may enhance phagocytic activity against the pathogen.[27] A major obstacle for clinicians to choose among the current available antifungal agents in treating mucormycosis is the lack of available randomized clinical trials. The 2016 recommendations from the European Conference on Infections in Leukemia (ECIL-6), as well as the ESCMID/ECMM guidelines, advocate the use of a lipid formulation of amphotericin B as first-line therapy for mucormycosis.[48,49] The currently suggested dose for liposomal amphotericin B is 5 mg/kg/day and as high as 10 mg/kg/day for infection of the central nervous system. But the optimal doses for antifungal agents are still an issue of controversy. In case of renal failure, dose of amphotericin B may be reduced or alternate antifungals such as posaconazole and isavuconazole may be used. Also, in cases of severe disease, rapid progression, or poor general condition, they may be given in addition to amphotericin B.[50] Hyperbaric oxygen may have a role as an adjunct to standard therapy because higher oxygen pressure improves the ability of neutrophils to kill the organism[51] and has been shown to inhibit the germination of fungal spores in vitro[52] , though there is lack of prospective clinical trials to definitely establish its role in the treatment of mucormycosis.

Mucormycosis is usually rapidly progressive, and antifungal therapy alone is often inadequate to control the infection. Surgical debridement has an important role because, various species of mucor may or may not be susceptible to available antifungal agents and some species may even be resistant to amphotericin B. Moreover, the hallmark angioinvasion, thrombosis, and tissue necrosis in mucormycosis result in poor penetration these agents. Thus, even *in vitro* susceptibility of the pathogen is not a guarantee of its *in vivo* efficacy. The killing the pathogen is not sufficient and Urgent surgical debridement is thereby necessary to remove the infected and necrotic tissue and optimize cure rates.[53]

Currently, mortality rates for mucormycosis vary from 40% to 80% based primarily on predisposing factors and site of involvement. This can rise to 96% for those with

disseminated disease.[10,54] Much of the variability in outcome is due to the various forms of the disease. With respect to site of involvement, mortality is shown to be highest among patients with disseminated disease (68%) and lowest in those with cutaneous disease (31%).[17,55]

Independent risk factors associated with significantly increased mortality include disseminated disease, extensive burns, hematological malignancies, associated renal failure, delayed initiation of therapy and neonatal age group.[10, 17, 38] Conversely, lower mortality are seen patients with immunocompetent status, those without comorbidities, with localised infection of the sinuses or skin and soft tissues, where early tissue-based diagnosis may be obtained and in cure may be possible with early complete surgical debridement.[38]

The case reported by us had delay in referral and administration of proper wound care. There could also be contamination of dressings during two-month long period before reporting to the burn center. Though rapid diagnosis and surgical debridement was done when patient finally reported to our center , the infection was already in invasive stage. This further lead to hematogenous dissemination with major vessel thrombosis, and pulmonary involvement.

CONCLUSION

Incidence of mucormycosis complicating burn wounds ranges from 0.1 – 0.6 % , which may rise to 10-15% during localized outbreaks in treating units. Most common clinical form of mucormycosis in burn patients is cutaneous with higher propensity for dissemination than cutaneous involvement from other causes. Arterial invasion invariably occurs with embolization, thrombosis & infarction. Vascular invasion by the hyphae leads to progressive tissue necrosis. Despite improved understanding of the disease and the availability of more therapeutic options, survival rates in mucormycosis remain poor.[10, 17, 27]

Maximising survival rates requires rapid diagnostic and therapeutic intervention.[38] Patients with suspected mucormycosis should be referred immediately to a facility with

the highest care level. The capability of diagnosing mucormycosis depends on the availability of mycological and histological investigation facilities and trained personnel. When diagnosed, early localized cutaneous mucormycosis treated with aggressive surgical debridement and adjunctive antifungal therapy.[3] Care providers should be especially vigilant for wound infections in patients who demonstrate progressive necrosis outside of the area of initial burn wound. To summarize wound surveillance seems to be the gold standard to avoid the devastating outcome of this rare, life-threatening infection. Treating surgeons must keep a high index of suspicion and send multiple wound biopsies when faced with a non healing burn raw area especially in cases presenting late or with pre-existing immunocompromised state

86866_Auto_Edited.docx

ORIGINALITY REPORT

14%
SIMILARITY INDEX

PRIMARY SOURCES

1	drrajivdesaimd.com Internet	140 words — 4%
2	W. Jeong, C. Keighley, R. Wolfe, W.L. Lee, M.A. Slavin, D.C.M. Kong, S.C.-A. Chen. "The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports", Clinical Microbiology and Infection, 2018 Crossref	122 words — 3%
3	academic.oup.com Internet	85 words — 2%
4	demo.elsevierreprint.com Internet	46 words — 1%
5	www.ncbi.nlm.nih.gov Internet	46 words — 1%
6	medcraveonline.com Internet	18 words — < 1%
7	mafiadoc.com Internet	17 words — < 1%
8	www.ecmm.info Internet	16 words — < 1%

9	f6publishing.blob.core.windows.net Internet	14 words — < 1%
10	"Essentials of Clinical Mycology", Springer Science and Business Media LLC, 2011 Crossref	12 words — < 1%
11	David A. Enoch, Huina Yang, Sani H. Aliyu, Christianne Micallef. "Chapter 2 The Changing Epidemiology of Invasive Fungal Infections", Springer Science and Business Media LLC, 2017 Crossref	12 words — < 1%
12	www.opastonline.com Internet	12 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS