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Non-COVID-19 Cutaneous Mucormycosis from a Plastic Surgical Perspective

Vimalendu Brajesh[1] Sneha Sharma[1] Aditya Aggarwal[1] Sukhdeep Singh[1] Sanjay Mahendru[1] Hardeep Singh[1] Ankit Jain[1] Rahul Jain[1] Rakesh Kumar Khazanchi[1]

[1] Department of Plastic, Aesthetic and Reconstructive Surgery, Medanta – The Medicity, Gurugram, Haryana, India

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Address for correspondence Vimalendu Brajesh, MS, MCh, Department of Plastic, Aesthetic and Reconstructive Surgery, Medanta – The Medicity, Gurugram, Haryana 122001, India (e-mail: drvbrajesh@yahoo.co.in).

Abstract

Background Cutaneous mucormycosis is a rare and fulminant infection associated with high mortality. Plastic surgeons come across this infection in the settings of road traffic accidents, surgical site infections, and as a secondary infection with underlying bacterial soft tissue infections. Due to this infection's rarity and aggressive course, it is essential to initiate prompt multidisciplinary management at the first presentation. With this study, we aim to present a protocol for managing the condition.

Methods This is a retrospective observational study of patients with cutaneous mucormycosis managed at a tertiary care hospital from January 1, 2016 to November 30, 2022 excluding patients with mucormycosis who tested positive for coronavirus disease 2019.

Results Of 24 patients, 22 were males, and most were in the age group of 41 to 60 years. Sixteen patients survived and five out of eight deceased had comorbidities, six presented primarily without prior debridement, and six had trunk involvement.

Conclusion A high index of clinical suspicion is necessary for early diagnosis and management of patients with invasive cutaneous mucormycosis. A multidisciplinary approach with appropriate medical and surgical management can improve outcomes in cases that otherwise carry a high mortality rate.

Keywords
- mucormycosis
- fungal infection
- cutaneous mucormycosis
- invasive cutaneous mucormycosis

Introduction

Cutaneous mucormycosis is a rare and fulminant infection associated with high mortality.[1] It is commonly seen in immunocompromised patients.[2,3] Due to the rapidity with which this infection spreads and the associated high mortality, early diagnosis and treatment are imperative for a favorable outcome.[1]

Plastic surgeons come across this infection in the settings of road traffic accidents, surgical site infections, and as a secondary infection with underlying bacterial soft tissue infections.[2] The causative organism for this infection is the ubiquitous fungus of phylum Glomeromycota, subphylum Mucormycotina.[4] Rhizopus arrhizus is the most common agent causing these infections worldwide.[5] These organisms act as opportunistic pathogens capable of proliferating in anaerobic and microaerophilic environments.[6–8] The appearance of the infected wound is characterized by a dry eschar with a surrounding halo of erythema and a central area of white mold-like growth (►**Fig. 1**). The incidence of mucormycosis varies with the region and the disease condition and is difficult to estimate.[5] The estimated global

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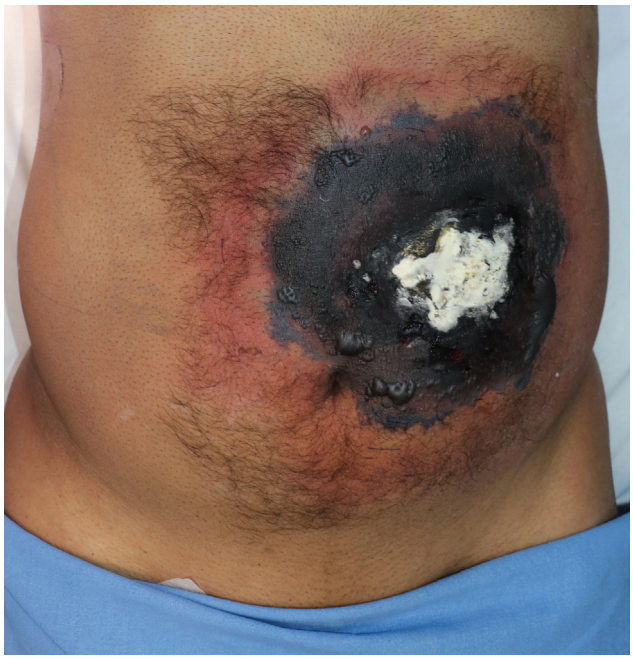

Fig. 1 Characteristic appearance of a wound infected with *Mucor*.

prevalence is 0.02 to 9.5 cases per 100,000 persons; in India, the prevalence is estimated to be 70 times higher than the global values.[5] The mortality rate ranges between 40 and 80%, depending upon the site of infection and associated comorbidities.[1] Due to this infection's rarity and aggressive course, it is important to initiate prompt and aggressive multidisciplinary management at the first presentation. In this study, we present our experience in managing this condition and aim to provide a protocol for its management.

Materials and Methods

This is a retrospective observational study of patients with cutaneous mucormycosis managed in the Department of Plastic Surgery at a tertiary care hospital between January 1, 2016 to November 30, 2022. This series does not include patients with mucormycosis who tested positive for coronavirus disease 2019 (COVID-19). Given the retrospective nature of the study, the requirement for consent was waived off by the institutional review board. The data was extracted from the departmental registry for the said duration. The departmental registry is maintained digitally and includes all the patients' demographics, blood investigations, notes, and photographs.

All the patients who presented with a wound appearance suggestive of mucormycosis (characterized by a dry eschar with a surrounding halo of erythema and a central area of white mold-like growth) were evaluated by sending a potassium hydroxide (KOH) mount for preliminary diagnosis, magnetic resonance imaging (with contrast whenever possible), and routine blood investigations. The patients were then empirically started on liposomal amphotericin B (L-AmB) in consultation with the internal medicine/infectious diseases team. After clinical stabilization (within 72 hours), the patients underwent surgical debridement, similar to wide local excision of a malignant lesion. A margin of 2 cm of normal tissue surrounding the lesion was excised, and the depth of excision was up to a plane below the plane of involvement whenever feasible (►**Fig. 2**). Many patients needed further sittings of debridement. Once the wound was clean clinically and the KOH mount from the wound bed and margins was negative (clinical and microbiological clearance), a definite wound cover in the form of a skin graft (►**Fig. 3**) or a flap (►**Fig. 4**) was provided. In the meantime, the wounds were dressed using gauze soaked in a solution of topical 250 mg AmB in 250 mL of normal saline.[9] Parenteral antifungal therapy (L-AmB; dosage 5–10 mg/kg/day) was continued till all the surgical processes were complete. Antifungal therapy with an oral antifungal drug (Posaconazole; dosage 300 mg twice daily on day 1, followed by 300 mg once daily) was then continued for 2 weeks or more following wound closure, based on the microbiological and clinical response.

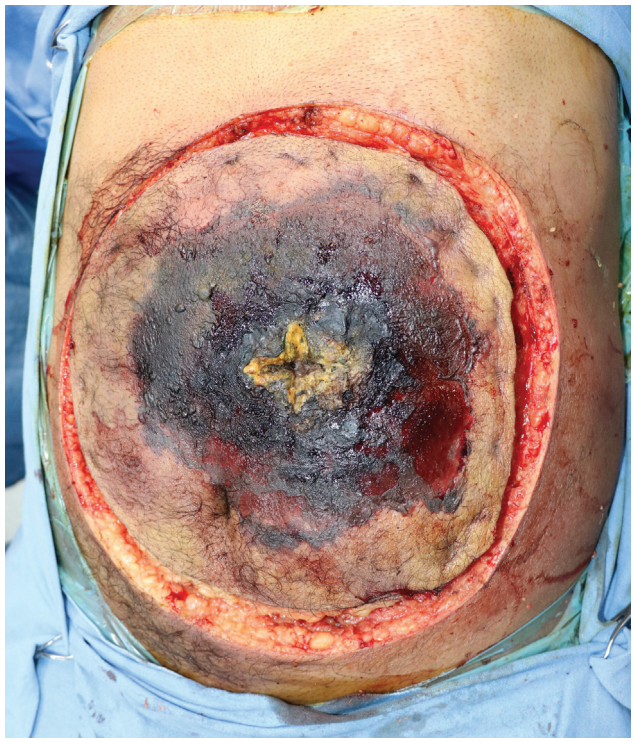

Fig. 2 Aggressive surgical debridement with adequate margins.

Based on the medical records, the patients were assessed based on age, comorbidity, etiology, hospital stay, number of debridements needed, surgery done, and the outcome.

Results

During the period of the study, a total of 24 patients with cutaneous mucormycosis were managed in our department. Of these 24 patients, 22 were males, and 2 were females. Most of the patients were in the age group of 41 to 60 years ($n = 10$). Eight patients had known comorbidities. Fourteen patients developed mucormycosis after primary bacterial infection, for example, in a wound resulting post-abscess or complicating a surgical site infection; nine patients developed the infection after trauma, and one developed the infection after sustaining burns.

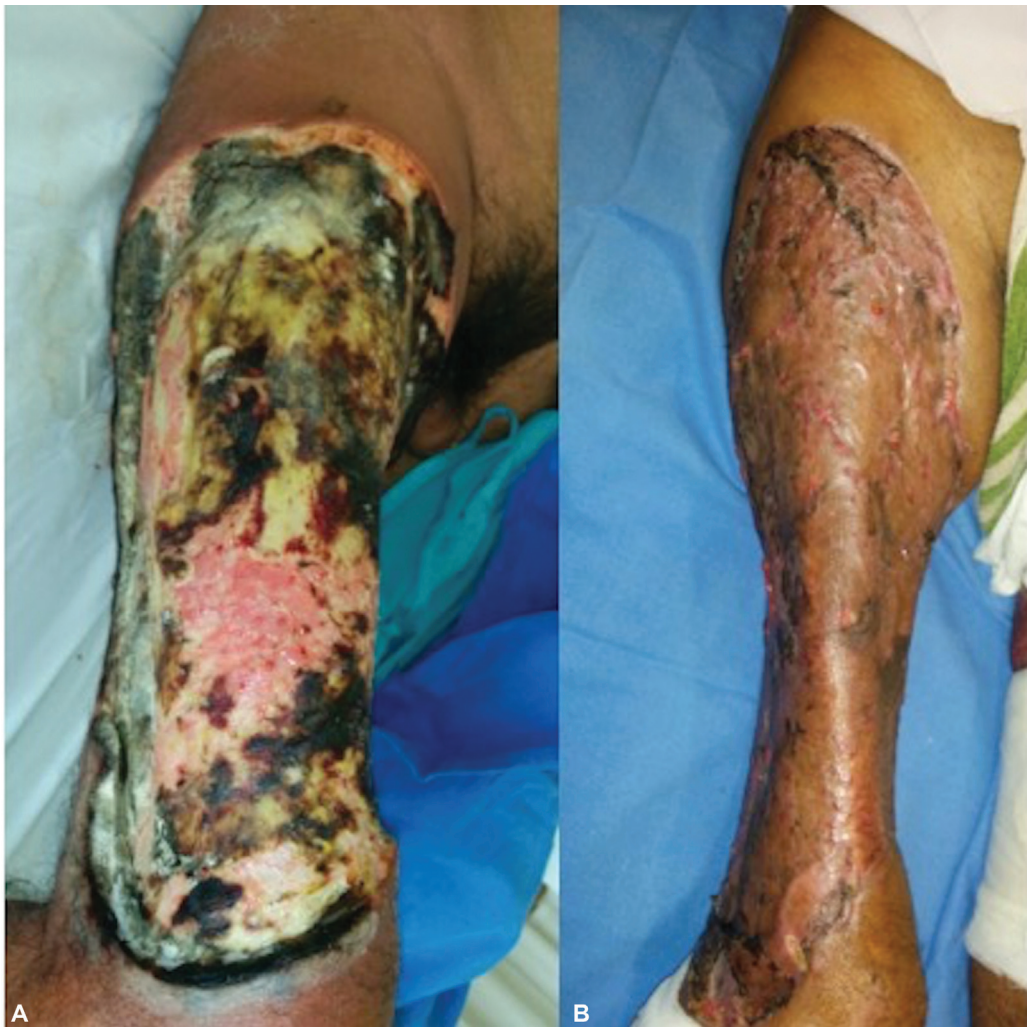

Fig. 3 (**A**) Wound infected with *Mucor* before debridement. (**B**) Wound after successful treatment with debridement and subsequent skin grafting.

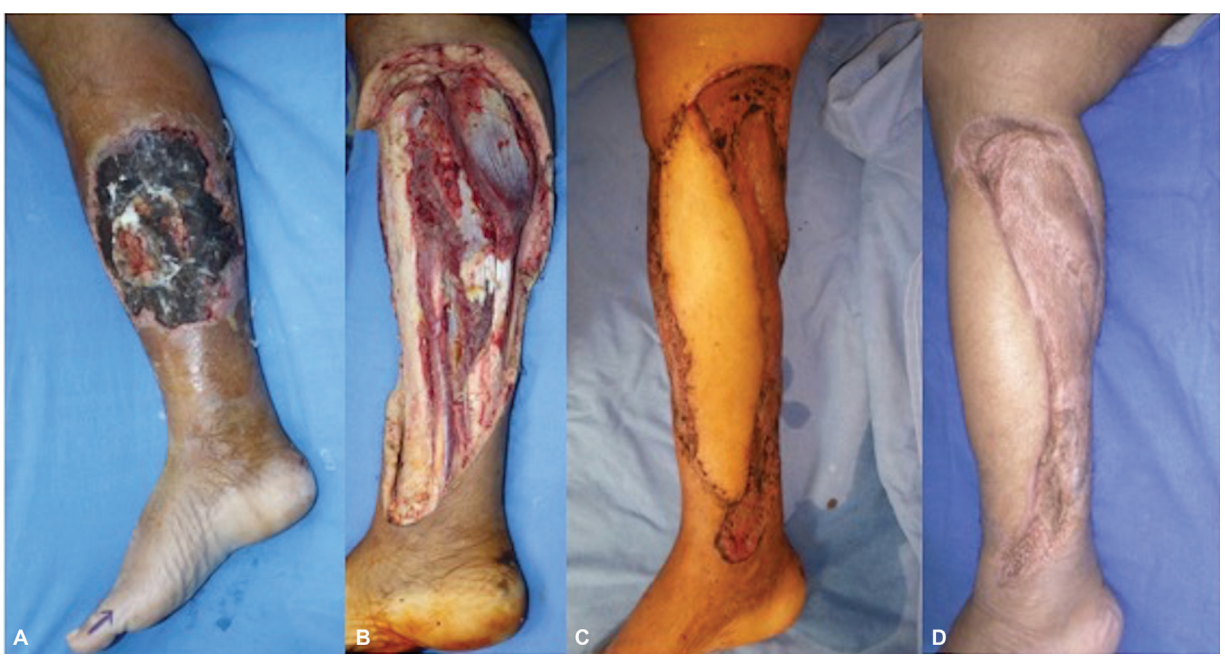

Fig. 4 (**A**). Wound infected with *Mucor* before debridement. (**B**) Wound after debridement. (**C**) Three weeks post-flap cover. (**D**) Six months follow-up post-flap cover.

Five patients had involvement of the face; two patients had involvement of the upper limb; seven patients had involvement of the trunk; seven patients had involvement of only the lower limbs; and three patients had involvement of multiple areas. Six out of the 24 patients presented to us primarily, and the remaining 18 presented secondarily after some intervention had already been done elsewhere. Detailed demographic characteristics of the patients have been presented in ►**Table 1**.

Most (18/24) patients needed multiple sittings of debridement (average being 2.58) after optimization and starting antifungal treatment. Seven patients could not undergo definitive surgery for wound coverage. Two patients required an above-knee amputation; one required a skin graft to cover the amputation stump. One patient required both below-knee amputation and skin grafting for the coverage of the raw area, a pedicled anterolateral thigh flap (ALT flap) along with skin grafting was needed for one patient, four patients needed a free ALT flap for coverage of exposed vital structures (bone, vessels) and a free ALT with skin grafts was required to cover the defect in one patient. Six patients could be managed with skin grafting alone. The total mortality was 8 out of the 24 patients; of the deceased patients, only one had undergone definitive surgery (above-knee amputation with primary closure of the stump).

The mean age for the survivor group was 40.25 years, with the youngest survivor being 12 years of age and the oldest survivor being 74 years of age. The average hospital stay for

Table 1 Demographic characteristics of mucormycosis cases managed in the department from January 1, 2016 to November 30, 2022

Case	Age	Sex	Etiology	Region	Comorbidity	Sessions of debridement	Hospital stay (days)	Definitive surgery	Final outcome
1	72	M	PI	Face	Nil	2	20	SG+ FF	Discharge
2	74	M	PT	Thigh	Deranged LFT	1	18	SG	Discharge
3	39	M	PT	Leg	Nil	2	30	SG + FF	Discharge
4	72	M	PI	Foot	DM	2	24	FF	Discharge
5	60	M	PI	Abdominal wall	DM	3	11	Nil	Death
6	85	M	PI	Gluteal	Nil	3	3	Nil	Death
7	33	F	PI	Gluteal	HIV, Hypothyroidism	1	2	Nil	Death
8	23	M	PI	Thigh	Nil	3	17	SG	Discharge
9	32	F	PI	Abd wall	Nil	2	42	SG + LF	Discharge
10	35	M	PT	UL + chest wall	Nil	3	35	SG	Discharge
11	18	M	PI	Gluteal	Nil	4	7	LF	Discharge
12	44	M	PI	Face	Nil	3	17	FF	Discharge
13	52	M	PI	Face	Nil	3	10	FF	Discharge
14	41	M	PI	Upper limb	Nil	4	20	SG	Discharge
15	55	M	PT	Leg	Nil	4	18	AKA	Death
16	56	M	PI	Leg	CAD, DM, HTN	4	14	BKA + SG	Discharge
17	42	M	PI	Flank	Steroid abuse	1	9	NIL	Death
18	60	M	PB	LL + abdominal wall + left below elbow amputation stump	DM, CVA, HTN	1	5	NIL	Death
19	43	M	PT	Axilla	Nil	1	4	NIL	Death
20	42	M	PI	Face	Acute on chronic liver failure, ALD, HTN	1	56	NIL	Death
21	12	M	PT	UL	Nil	4	17	SG	Discharge
22	24	M	PT	UL + LL	Nil	4	26	AKA + SG	Discharge
23	26	M	PT	LL	Nil	3	11	SG	Discharge
24	24	M	PT	Face	Nil	3	10	FF	Discharge

Abbreviations: AKA, above knee amputation; ALD, alcoholic liver disease; BKA, below knee amputation; CAD, coronary artery disease; CVA, cerebrovascular accident; DM, diabetes mellitus; FF, free flap; HTN, hypertension; LF, local flap; LL, lower limb; PB, post-burn; PI, post-infective; PT, post-traumatic; SG, skin graft; UL, upper limb.

Table 2 Characteristics of the survivor and nonsurvivor groups

Characteristic		Survivors ($n = 16$)	Nonsurvivors ($n = 8$)	Total ($n = 24$)
Mean age (years)		40.25	52.5	44.33
Sex	Male	15	7	22
	Female	1	1	2
Etiology	Post-infective	9	5	14
	Post-traumatic	7	2	9
	Post-burn	0	1	1
Comorbidity	Present	3	5	8
	Absent	13	3	16
Wound status	Previously unexplored	0	6	6
	Previously debrided	16	2	18
Trunk involved		3	6	9
Site of involvement	Single	14	7	21
	Multiple	2	1	3

patients who survived was 19.06 days. Three survivors had comorbidities; one patient had deranged liver function tests (LFTs), one had diabetes mellitus, and one had multiple comorbidities (diabetes mellitus, coronary artery disease, and hypertension).

The average age for the nonsurvivor group was 52.5 years, with the youngest deceased being 33 and the oldest 85. Three of the deceased had no known comorbidities. The characteristics of the survivor and the nonsurvivor group have been presented in ►**Table 2**.

Discussion

As plastic surgeons, we mainly deal with cutaneous mucormycosis, which accounts for 10 to 19% of the total cases of mucormycosis.[10] Invasive cutaneous infections are uncommon; this is also borne out in our series, where we had only 24 cases in the last 6 years. There was a rise in cases of mucormycosis during the pandemic, and to remove the confounding effect, we have excluded all the patients with mucormycosis who tested positive for COVID-19.

Our patients were taken up for surgical treatment under cover of systemic antifungals (L-AmB), followed by oral antifungals (Posaconazole) as per the advice of the infectious disease team. Chamilos et al,[11] in their study, showed that the patients who had an early initiation of antifungal therapy (within 5 days of diagnosis) had a better survival rate than a delayed start of treatment (83 vs. 49% survival). Wound discharge and wound swab culture are positive in only 30% of the cases; therefore, a tissue sample should be sent for culture. However, it cannot be relied upon solely for diagnosis or starting of antifungal treatment. In this series, tissue culture was positive for fungal growth in all the cases.

The decision of starting antifungal therapy with L-AmB was taken based on clinical suspicion after sending samples for KOH mount and tissue culture. The appearance of ribbon like aseptate or pauci-septate hyphae with an irregular branching pattern is diagnostic.[10] The results of the KOH mount are available within 24 hours. Fungal cultures, though the gold standard for diagnosis, take at least a week to be reported. Waiting for such a long time before starting the antifungals does not provide any survival benefit.[11] In case, the KOH mount came to be negative, L-AmB was stopped.

After initiating the antifungal therapy, our patients were given time to stabilize and were taken for debridement within 72 hours after the initiation of antifungal treatment. This protocol is followed in our department as we have observed that in case of concurrent initiation of antifungal therapy, any debridement leads to reinfection of the freshly debrided margins and requires revision of the debridement margins leading to more extensive defects. On the other hand, sequential initiation of antifungal therapy followed by debridement within 72 hours leads to less extensive defects leading to less complex reconstruction. Aggressive debridement is as essential as antifungal therapy. Roden et al[3] reported a survival of 70% in patients who received a combination of antifungal treatment and surgical debridement. Some studies have reported survival rates of up to 80% with this combination. Without any treatment, invasive fungal infection can have a mortality rate of 97%.[10] Medical treatment only increases the survival rate by up to 61%, and surgery alone increases the survival rate by up to 58%.[10]

Our policy is to go ahead with an aggressive clearance of a 2 cm margin from the clinically involved tissue in the first sitting to minimize the requirement of further debridement. This 2 cm margin is taken beyond the clinically indurated area, as the subcutaneous extent of the infection is more than what is apparent on the surface, necessitating a wider margin of excision. Successive sittings of debridement are less extensive, removing only the clinically involved tissue. A consensus

regarding the appropriate surgical margins has not yet been reached.[12]

Eighteen of our patients required multiple debridements despite excision of a 2 cm margin of the surrounding tissue along with the involved region. This might be explained on the basis of microscopic invasion of the fungus into the surrounding tissue and also fresh contamination of the margins during surgery, which cannot be predicted or prevented.

Importance of debridement is also highlighted in this series, as patients with previously unexplored lesions had a poorer prognosis than those with previously debrided wounds. Patients were either referred by the primary institutions due to inability to handle such extensive infections or were brought here after discharge on patient request. But we had no way of knowing objectively what was the reason for referral in most of the cases and therefore, that data has not been included in the study.

The patients who succumbed had extensive involvement, in some cases reaching up to some vital organs or the peritoneal cavity and hence not amenable to complete surgical debridement. All eight patients who succumbed to the infection had a multiorgan failure and developed deranged renal function tests (RFT) and LFTs with a worsening condition. Out of the eight deceased patients only three had multiple organ dysfunction at the time of presentation (cases 5, 7, and 17; refer to ►**Table 1**).

Among the patients who survived, the LFT and RFT remained stable throughout treatment except for one patient with associated comorbidity (diabetes). However, the patient was managed medically and subsequently recovered uneventfully.

Decision for definitive surgery was taken based on the appearance of the wound and a negative KOH mount. Definitive surgery, in the form of a flap cover or skin grafting, was done for 15 patients. We did not find increased graft or flap loss rates in these patients. This might result from adequate debridement and management of underlying infection before going for wound coverage.

Age, previously unexplored wounds, associated comorbidity, and trunk involvement come out as four factors that may have a possible detrimental effect on the patient's outcome.

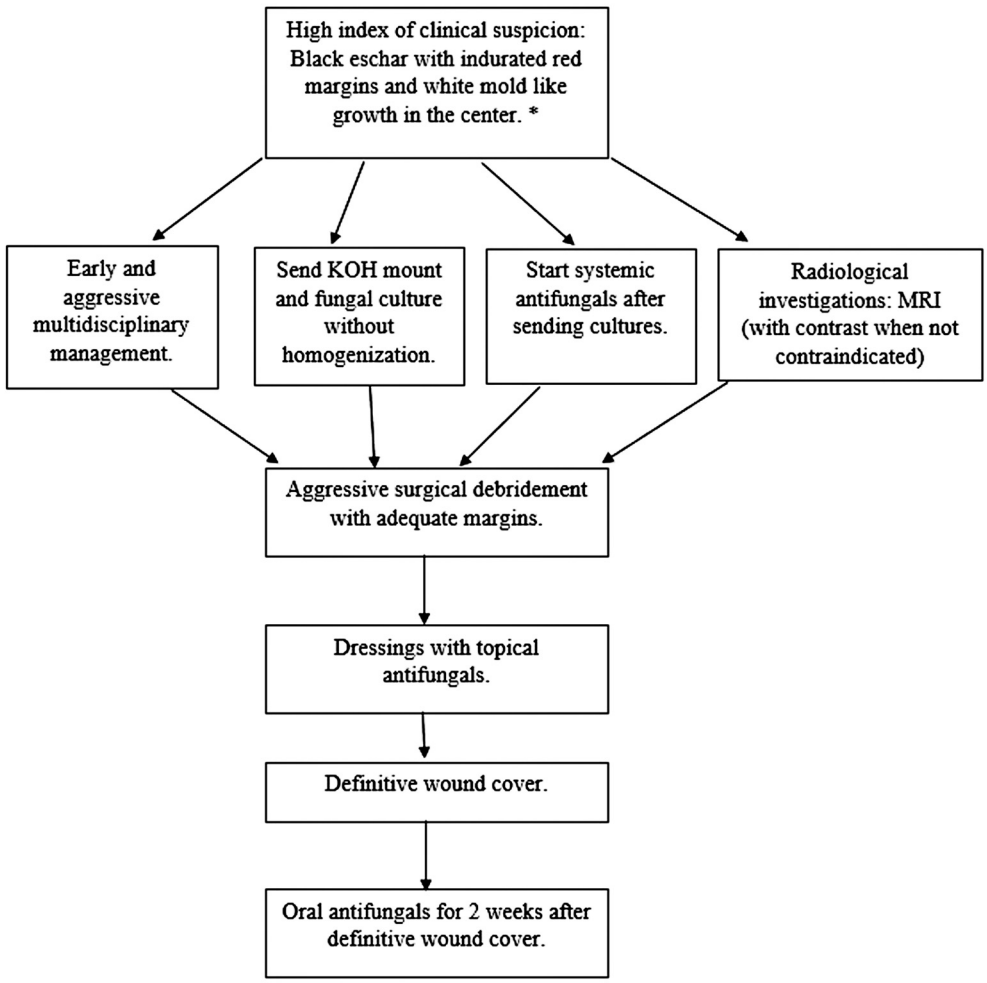

Fig. 5 Recommendations. KOH, potassium hydroxide; MRI, magnetic resonance imaging.

Our study is limited by the small number of patients that presented to us. Therefore, we could not carry out advanced statistical analysis; hence, no relationship between the various risk factors, interventions, and outcomes can be drawn. Further, more extensive studies are required to study such relationships. We would, therefore, like to present some recommendations based on our experience and sensitize fellow plastic surgeons to the problem at hand.

Based on our study's findings and literature review, we would like to propose recommendations for managing patients with cutaneous mucormycosis, as shown in ►**Fig. 5**.

Conclusion

A high index of clinical suspicion is necessary to diagnose and manage patients with cutaneous mucormycosis early. A multidisciplinary approach with appropriate medical and surgical management can give better outcomes in such cases, which otherwise carry a high mortality rate.

Ethical Approval

Ethics committee approval obtained from the institutional ethics committee.

Authors' Contributions

All the authors were involved in the conception of the work, data collection, analysis, and interpretation and throughout the process of the drafting and revision of the manuscript.

Conflict of Interest

None declared.

References

1 Losee JE, Selber J, Vega S, Hall C, Scott G, Serletti JM. Primary cutaneous mucormycosis: guide to surgical management. Ann Plast Surg 2002;49(04):385–390
2 Castrejón-Pérez AD, Welsh EC, Miranda I, Ocampo-Candiani J, Welsh O. Cutaneous mucormycosis. An Bras Dermatol 2017;92 (03):304–311
3 Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 2005;41(05):634–653
4 Kwon-Chung KJ. Taxonomy of fungi causing mucormycosis and entomophthoramycosis (zygomycosis) and nomenclature of the disease: molecular mycologic perspectives. Clin Infect Dis 2012; 54(Suppl 1, Suppl 1):S8–S15
5 Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. J Fungi (Basel) 2019;5(01):26
6 Wirth F, Perry R, Eskenazi A, Schwalbe R, Kao G. Cutaneous mucormycosis with subsequent visceral dissemination in a child with neutropenia: a case report and review of the pediatric literature. J Am Acad Dermatol 1997;36(2 Pt 2):336–341
7 Cocanour CS, Miller-Crotchett P, Reed RL II, Johnson PC, Fischer RP. Mucormycosis in trauma patients. J Trauma 1992;32(01):12–15
8 Lehrer RI, Howard DH, Sypherd PS, et al. Mucormycosis. Ann Intern Med 1980;93(01):93–108
9 Wang K, Jacinto J, Davis A, Hetman A, Kumar A. A case report: utilization of topical amphotericin in postoperative mucormycosis. HCA Healthcare Journal of Medicine 2021;2(03):5
10 Cornely OA, Alastruey-Izquierdo A, Arenz D, et al; Mucormycosis ECMM MSG Global Guideline Writing Group. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis 2019;19(12):e405–e421
11 Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. Clin Infect Dis 2008;47(04):503–509
12 Spellberg B, Walsh TJ, Kontoyiannis DP, Edwards J Jr, Ibrahim AS. Recent advances in the management of mucormycosis: from bench to bedside. Clin Infect Dis 2009;48(12):1743–1751

