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Case Report

Use of topical amphotericin in a case of refractory sino-orbital angioinvasive mucormycosis

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ABSTRACT

The standard of care for treatment of sino-orbital mucormycosis involves aggressive surgical debridement and liposomal amphotericin, and the roles of adjunctive and topical therapies are less clear. Here we describe a case of severe refractory sino-orbital mucormycosis in an immunocompetent patient who responded to combination therapy with liposomal amphotericin, isavuconazole, micafungin, and topical amphotericin deoxycholate after failing to achieve negative surgical margins.

1. Introduction

Mucorales molds are common environmental saprotrophic fungi that can present as a necrotic, rapidly progressive, and often fatal disease. It is classically diagnosed among the severely immunocompromised (such as bone marrow transplant recipients), patients with uncontrolled diabetes, and occasionally in trauma patients from cutaneous inoculation [1]. The most common presentation, sino-orbital (SO), can lead to significant disfigurement. Those who can be managed endoscopically have both a favorable morbidity and mortality compared to open debridement and exenteration [2].

The standard of care requires aggressive surgical debridement and intravenous liposomal amphotericin (L-AMB) with the ideal goal of achieving negative surgical margins [3]. Isavuconazole and posaconazole are reserved for step-down and salvage therapies, and little else remains for acceptable alternatives. Combination therapy with L-AMB plus posaconazole or isavuconazole may be considered for use in cases of extensive disease, rapid progression, or poor response to initial therapy. However, enhanced toxicity and lack of evidence limits this strategy as a marginal recommendation in current guidelines [3].

There is currently no recommendation for the role of topical amphotericin in modern medical guidelines, and it is rarely discussed as adjuvant medical therapy in the clinical setting. To our knowledge, this is the first reported case of refractory SO mucormycosis (confirmed with persistently positive surgical margins) despite orbital exenteration that responded to combination therapy with liposomal amphotericin, isavuconazole, micafungin, and topical amphotericin deoxycholate. We aim to highlight the role of these particular adjuvant therapies given high mortality of this scenario.

2. Case presentation

A traumatic motorcycle accident launched a 47-year-old immunocompetent, non-diabetic, helmet-wearing male into a muddy ditch, resulting in a 3 cm linear right infraorbital laceration without evidence of facial fracture on computerized tomography (CT). The laceration was irrigated and repaired without complication on admission (hospital day 1 (HD1)). On HD7, he developed rapid and significant right-sided periorbital edema concerning for orbital compartmental syndrome requiring emergent lateral canthotomy. Repeat CT showed no evidence of facial fracture, abscess, or orbital cellulitis. One week later he was taken to the OR for extensive debridement, including total right orbital exenteration, for suspected necrotizing fasciitis. Post-op contrast-enhanced Magnetic Resonance Imaging (MRI) was negative for intracranial extension, and rigid endoscopy revealed normal pink nasal mucosa.

Two days later (HD19), intraoperative cultures grew a *Rhizomucor* species, and histopathology confirmed angioinvasive mucormycosis involving the soft tissue, skeletal muscle, and optic nerve (Fig. 1). He was emergently started on L-AMB and isavuconazole during repeat

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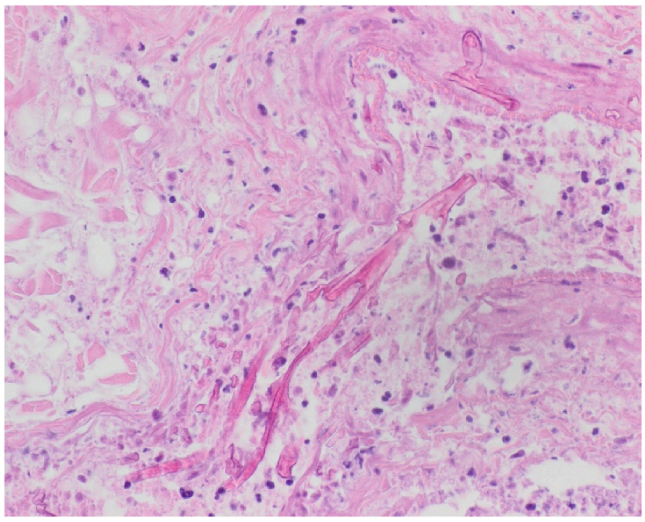

Fig. 1. Hematoxylin and eosin stain revealing intravascular invasion at 400× magnification.

debridement that same day. L-AMB was dosed at 5 mg/kg/day for the first two days, then was increased to 10 mg/kg/day after debridement failed to obtain negative surgical margins. Isavuconazole was dosed as 372 mg IV/PO q8h x 3 doses followed by 372 mg daily without therapeutic drug monitoring. He suffered ongoing clinical deterioration and advancing tissue necrosis despite five consecutive debridements over a ten-day span (see Fig. 2).

The fifth and final debridement was electively stopped prior to entering the central nervous system (CNS) barrier. Angioinvasive mucormycosis was still present at the margins of all intra-op tissue and bone specimens. At this point we focused on optimizing any remaining medical options and continued L-AMB and isavuconazole. After literature review, a salvage attempt was made on HD27 by adding topical amphotericin-B deoxycholate (dAMB) directly onto the exposed post-op tissues as well as starting intravenous micafungin 100 mg daily for theoretical polyene synergy. We soaked his facial gauze dressings in a 0.05 mg/mL solution of dAMB in sterile water, then applied directly to the skin and changed twice daily. The following day, serum creatinine doubled (from 1.47 mg/dL to 2.87 mg/dL), so L-AMB was decreased to 7.5 mg/kg/day. Necrosis abated, and debrided tissues began to successfully granulate. His mentation steadily improved to the point that he was answering questions appropriately and independently. Twenty-three days after initiating salvage therapy, he successfully underwent free flap facial reconstruction. Micafungin had been stopped 8 days prior to flap surgery, and topical dAMB was continued until post-op day 2.

In total, he received 48 days of combination anti-fungal therapy, consisting of 25 days of dual therapy (L-AMB, isavuconazole), 15 days of quadruple therapy (L-AMB, topical dAMB, isavuconazole, micafungin) and 8 days of triple therapy (L-AMB, topical dAMB, isavuconazole). At the time of hospital discharge on HD66 he was transitioned to isavuconazole monotherapy. Renal function recovered to pre-hospital baseline status by post-discharge week 6, and he returned to full-time work by post-discharge week 18. He remained on isavuconazole without graft failure or infectious complication for over one year. He successfully underwent orbital prothesis placement at post-discharge month 14. He was switched to posaconazole DR tab 300 mg daily at month 16 due to insurance complications with isavuconazole. Tentatively, his therapy will be stopped at month 24.

3. Discussion

Here we describe a successful case of severe refractory SO angioinvasive mucormycosis and the use of experimental adjunct therapies. Whether by coincidence or a true causal relationship, our patient's improvement occurred distinctly after adjunctive therapy with topical dAmB was added. We believe its role deserves further discussion given the significant inflection point in his clinical course and a dearth of literature on this aspect of a highly fatal condition.

The true benefit of topical dAmB application is not well-conferred in the literature as it is not considered to be standard of care for mucormycosis, even at the salvage level [3]. Of the few case reports that exist, most are aimed at localized treatment (such as nasal rinses or retrobulbar injections) for prevention of more radical surgery such as exenteration, and are not included here [4]. Other studies are limited to endoscopic or outpatient management and exclude severe cases involving the orbit [2]. However, very few cases cite topical use after radical surgery, and none have reported surgical margins to corroborate the role of salvage medical therapies. Those cases using some form of topical amphotericin following radical surgery are listed below in Table 1.

Most cases of SO mucormycosis center around whether or not to exenterate the orbit given the reciprocation between the morbidity of a disabling surgery and mortality risk without it. Exenteration itself is a significantly negative prognostic factor [2,5]. Given that Mucorales cause angioinvasive tissue necrosis and thrombosis, surgical debridement remains the cornerstone of treatment [3]. Without it, concomitant intravenous antifungal therapy may not achieve adequate tissue concentrations at the site of infection [6,7]. Specifically, liposomal amphotericin 5 mg/kg may not reach the site of infection in concentrations that exceed the minimum inhibitory concentration for Mucorales [8]. This is compounded by the ability of Mucorales to limit the host inflammatory immune response, suppress phagocytic response, and generally evade host defenses [9].

Intuitively, topically applied amphotericin would have minimal systemic toxicity and maximal tissue concentration, particularly since application to debrided tissue bypasses the need for absorption across the *stratum corneum* [10]. Historically, topical amphotericin deoxycholate has been used for dermatologic infections, gastrointestinal decontamination, and bladder irrigations for resistant Candida infections and is considered relatively safe, although questionably effective [11]. The majority of evidence for topical polyene therapy has primarily focused on dAmB, and is therefore the formulation we used in our case. From a safety standpoint, we chose a 0.05 mg/mL solution based on clinical experience in use for bladder irrigation [11]. Additionally, higher concentrations have been applied directly to brain tissue without apparent toxicity [12].

The effects of amphotericin on host immunomodulation are varied, complex, and may be formulation specific. In vitro human and mouse models have demonstrated the ability of dAmB to stimulate angiogenesis and nitric oxide release, which, when applied topically, could promote wound healing and counteract the virulence mechanisms of mucormycoses [13]. dAmB may also upregulate the transcription and production of cytokines, chemokines, and prostaglandins via the toll-like receptor pathway, stimulating a protective host immune response [14]. On the other hand, the pro-inflammatory effects of dAmB may lead to local tissue toxicity similar to the commonly experienced adverse reactions of intravenous administration. In high concentrations such as those used in topical formulations, dAmB is associated with higher rates of apoptosis of host cells and higher induction of free-radical oxygen species which could impede tissue healing and macrophage function [15]. In effect, dAMB applied topically may cause a chemical debridement beyond what is performed in the operating suite. In addition to potential host tissue destruction, amphotericin at a concentration of 50 mcg/mL would exceed the suggested epidemiological cutoff values (minimum inhibitory concentrations) for the majority of Mucorales species (1–2 mcg/mL) [16].

L-AMB may also provide benefit when administered topically, but its effects on immunomodulation differ from dAmb. L-AMB exerts an anti-inflammatory effect on tissues via its action on the toll-like receptor 4 in

polymorphonuclear leukocytes (PMNs) [17]. Since it is surrounded by a liposomal layer, L-AMB requires either engulfment by tissue macrophages or fusion with the fungal cell wall to exert its antifungal effect [18]. In an environment ravaged by tissue necrosis, recruitment of host defenses including macrophages may be reduced, leading to a reduced ability to activate L-AMB's antifungal response. Given the potential anti-inflammatory effects of L-AMB, further study of topical L-AMB versus dAMB is warranted in this patient population as it may offer therapeutic benefit via a different mechanism of action.

While we may wish to attribute the patient's success to the topical dAmB, the confounding role of salvage micafungin merits analysis. Based on the reviewed literature, current evidence for adjunctive echinocandins is conflicting and not robust. Traumatic inoculation with soil can lead to mixed infections with multiple fungal organisms, the most common of which are Mucorales and *Aspergillus*. [19] Both contain low concentrations of the beta-D-glucan target, which provides microbiological rationale for adding echinocandin therapy, particularly in severe or refractory cases [20]. Although Mucorales as a whole are not considered susceptible to echinocandin therapy, combination therapy with L-AMB has been shown to improve survival in mice infected with *Rhizopus oryzae*, the most common species causing invasive mucormycosis [21]. Clinical data to support combination therapy are limited to retrospective examinations. Reed and colleagues observed a survival benefit in rhino-orbital mucormycosis patients receiving combination polyene-caspofungin therapy compared to polyene monotherapy without controlling for species [22]. Although the exact species isolated in our patient remains unknown, echinocandin therapy may have played an important role in his recovery and its use merits further study.

Lastly, the role of immunocompetence in his recovery warrants discussion, but the significance is uncertain. Factors associated with improved survival of rhino-orbital-cerebral mucormycosis (ROCM) include prompt recognition and initiation of medical treatment by day 12, reversal of modifiable risk factors such as hyperglycemia, and aggressive surgical debridement [23,28]. Of interest, the survival rate of ROCM in patients with diabetes (60–84%) is numerically higher than in patients without any form of underlying disease (55–67%) [24,28]. This may be due to the reversibility of hyperglycemia and more prompt diagnosis in patients with diabetes. Comparatively, however, those with

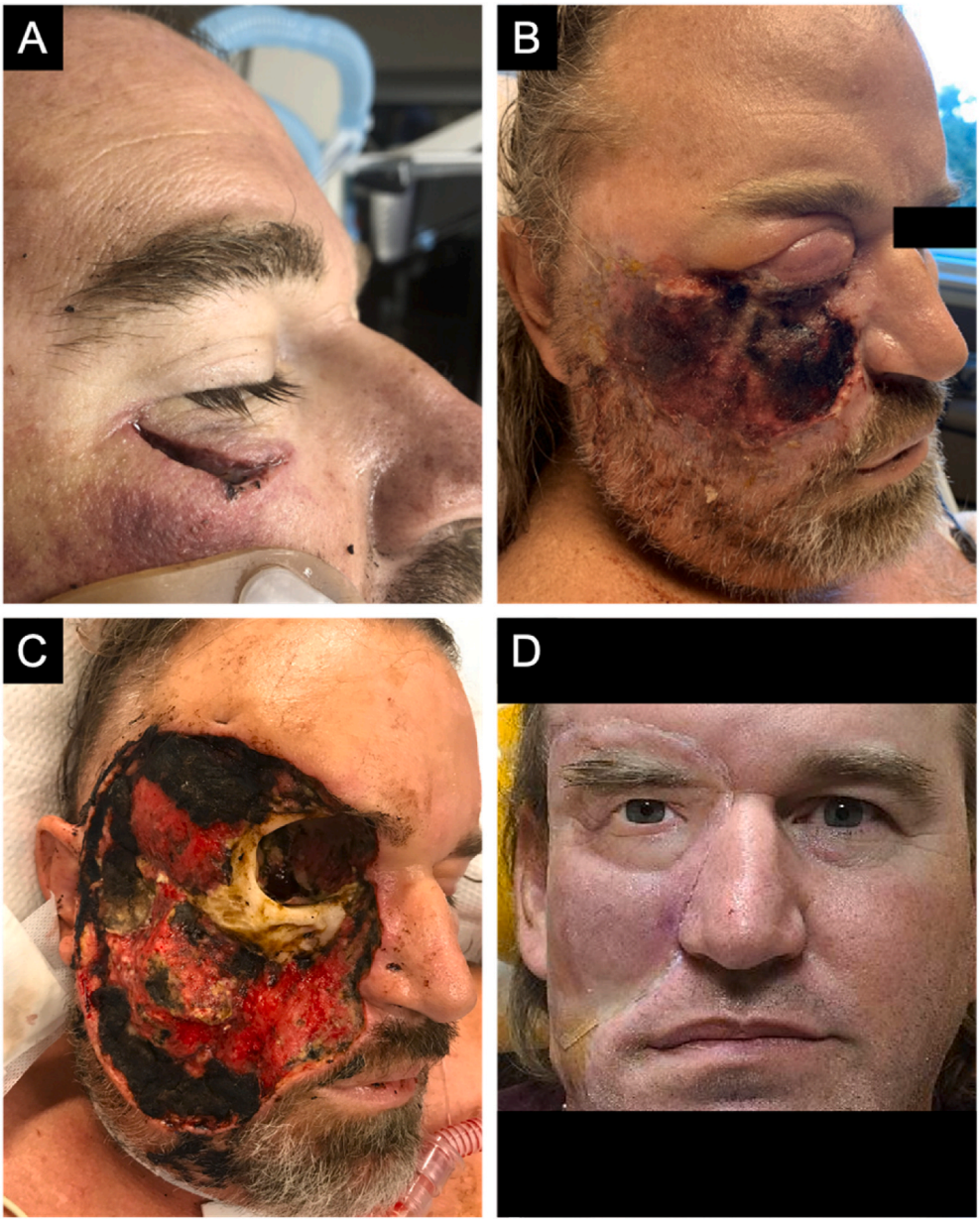

Fig. 2. A. Initial laceration upon ER arrival (HD2).
B. Pre-operative wound (HD17) with periorbital edema, facial cellulitis, and necrosis. Histopathology and culture results returned with invasive mucormycosis on HD19.
C. Ongoing necrosis and persistently positive fungal margins despite multiple debridements. Topical amphotericin started from this point (HD27).
D. Successful engraftment and ocular implantation one year later.

Table 1
Published cases using adjuvant topical amphotericin following surgical exenteration, enucleation, or craniotomy for rhino-orbital-cerebral mucormycosis (ROCM).

Reference	Age/ Sex	Risk Factors	Species	IV Therapy	Topical Route	Topical Solution	Frequency	Outcome	Final Margins
Mohsenipour 1996, Austria [12]	65 M	Immuno-suppression	*Rhizomucor* spp	dAMB, then L-AMB	Pack with absorbable gelatin sponge	dAMB 2.5 mg/cm^3	Once	Lived	n/a
Seiff, 1999, USA [23]	34 M	Diabetes, Immuno-suppression	*Mucor* spp	dAMB	Irrigation catheter into orbit	dAMB 0.25–1 mg/ mL	TID-QID x 5–14 days	Lived	n/a
Farooq, 2015, USA [24]	59 F	Diabetes, Immuno-suppression	n/a	dAMB + Micafungin	Drip into orbit	n/a	n/a	Died	n/a
Uğurlu, 2015, Turkey [25]	59 M	Diabetes	n/a	L-AMB	Direct Irrigation into socket	n/a	n/a	Lived	n/a
Liu, 2019, China [26]	50 F	Immuno-suppression	*Cunninghamella*	L-AMB + Posaconazole	Nasal irrigation	dAMB 0.08 mg/mL	BID	Died	n/a
Navarro-Perea, 2019, Spain [27]	50 F	Immuno-suppression	*Rhizopus oryzae*	L-AMB + Andulafungin	Impregnated gauze	L-AMB	BID x 7 days, then daily	Lived	n/a
Navarro-Perea, 2019, Spain [27]	52 F	Diabetes	*Rhizopus oryzae*	L-AMB + Andulafungin	Impregnated gauze	L-AMB	BID x 7 days, then daily	Lived	n/a

leukemia or hematologic disorders experience a modestly lower survival (50–63%) [28]. Surgical margin data is so far absent from meta-analyses, or when reported, lacks mortality stratification by underlying disease state. The authors believe his immunocompetence played a much smaller role in our patient's immediate survival given his delayed diagnosis, the repeated clinical failures prior to starting salvage therapies, and the reversal of his clinical course thereafter. We do, however, believe his immunocompetence has a significant role in his long-term outcome after flap surgery.

The mortality of rhino-orbital mucormycosis hinges on effective surgical debridement and concurrent polyene antifungal therapy. We believe that adjunctive topical dAmB likely played a role in abating the progression of mucormycosis in a severe refractory case that could not be contained with surgical debridement and standard systemic antifungal therapy, despite orbital exenteration. Due to the low risk of topical antifungal application relative to the potential benefit, topical dAmB deserves further therapeutic and investigative consideration, particularly in salvage scenarios.

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None.

Consent

Written informed consent was obtained from the patient or legal guardian(s) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Declaration of competing interest

There are none.

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