Continuous Amphotericin Irrigation for Cutaneous Mucormycosis in the Pediatric Patient

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CASE REPORT

Please cite this paper as: Chavanon V, Molina N, Taub DM, Taub PJ. Continuous amphotericin irrigation for cutaneous mucormycosis in the pediatric patient. Surgical Sciences Journal [2020] 2(1): 1-4.

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ABSTRACT

Mucormycosis is a life-threatening fungal infection caused by a group of molds called mucormycetes. Mucormycosis occurs in patients with less competent immune systems, including diabetes. Infected tissue is sent to a lab where it is cultured and examined under a microscope where doctors can diagnose the disease. As well, doctors do CT scans to check for damages to the facial structure. Treatment should be immediate and begin with high doses of intravenous antifungal medications such as amphotericin B, Isavuconazole or posaconazole. Surgery is required to remove infected tissue. To date, there are scant reports of the use of topical antifungal agents as an adjunct to surgery in the pediatric patient with cutaneous mucormycosis.

Key Words: pediatric; cutaneous; mucormycosis.

INTRODUCTION

Invasive infections caused by fungal organisms are a major cause of morbidity and mortality in immunocompromised pediatric patients. Mucormycosis is caused by members of the Mucoales order, of which the Rhizopus species are the most common pathogenic agents. Rhizopus species possess ketone reductase that enables proliferation in an acidic environment that is seen in poorly-controlled diabetes (i.e. ketoacidosis). Disorders like leukemia that cause a decrease in the white blood cell count predisposes the development of mucormycosis.

The Mucor fungal species are found in soil. Spores of mucormycosis enter the body through open wounds and attack host tissues. Infection can involve the sinuses and/or central nervous system (rhinocerebral), lung, gastrointestinal tract, heart, as well as the skin and soft tissues (cutaneous). The fungus is angioinvasive and causes thrombosis of vessels leading to tissue necrosis. [1]

Symptoms include fevers, sinus pain, an inflamed eye socket, and proptosis causing difficulty with vision. As well, one sign of fungal invasion is blood clotting and dead tissue due to a loss of blood flow. The latter is often associated with deep extension in the subcutis or below. [1] Patients experiencing such symptoms should managed emergently for the best outcome.

The diagnosis of mucormycosis requires a high degree of suspicious in the immunocompromised patient. Wound biopsies can be sent for culture as well as immediate staining. Since the former can take a while to grow out, immediate staining will minimize the time to treatment.

Unlike other invasive fungal infections, the prognosis and outcome of invasive mucormycosis have not

significantly improved over the past decade. Successful treatment relies on immediate eradication of the organism. A multidisciplinary approach is necessary to improve survival and should include extensive surgical debridement, antifungal therapy, and correction of the underlying metabolic or impaired immunological status. Newer modalities that improve survival would be a welcome addition to the treatment paradigm.

CASE REPORT

A 10-year-old female patient was referred with a necrotic wound over the posterior aspect of her neck (Figure 1). Her past medical history included prematurity, gastroschisis, acute and chronic kidney disease, asthma, drug-induced diabetes mellitus, essential (primary) hypertension, pericardial effusion, acute bronchiolitis due to respiratory syncytial virus, superior vena cava syndrome, and short gut syndrome requiring small bowel transplant. On account of her necessary immunosuppression, the consulting pediatric infectious disease service was suspicious for mucormycosis. After evaluation and discussion, she was emergently taken to the operating room for excision of the necrotic wound and frozen section biopsy. Several specimens were shown to have branching hyphae on hematoxylin and eosin stain (Figure 2). Serial wound margin biopsies were sent until no hyphae were noted. A negative-pressure dressing (KCI, San Antonio, TX) was applied and the patient was continued on intravenous amphotericin B.

She was taken back to the operating room when her temperature spiked above baseline and repeat biopsies showed persistent branching hyphae. Following the second return to the operating room, a decision was made to cyclically instill amphotericin B into the wound via the negative-pressure dressing. In the absence of prior dosing recommendations for either adult or pediatric patients, a 0.1% solution (1 g in 1000 cc of 5% dextrose in water) was chosen since it precipitates in normal saline. The solution was instilled four times per day and allowed to sit in the dressing for 10 minutes before being suctioned out. The dressing was changed twice weekly at the bedside for 4 weeks before she was returned to the operating room for thorough evaluation and possible coverage with a split thickness skin graft (Figure 3). At six-month follow-up, the patient was noted to be free of infection with an intact skin graft (Figure 4).

DISCUSSION

Eradication of mucormycosis is challenging when reversal of the host's immunocompromise is not likely. The initial treatment of obvious involvement is surgical resection to negative margins. Some studies have suggested a treatment delay of more than 6 days portends a poor prognosis. [3] Frozen section of tissue margins can facilitate determining the extent of the resection. When tissues are stained with standard hematoxylin and eosin, branching hyphae are visible.

Medical treatment involves antifungal agents, of which amphotericin is the most commonly used. The medication works by interfering with the cell membrane of the fungus. [4] It binds to ergosterol and forms pores that results in rapid leakage of key functional ions (hydrogen, sodium, potassium, and chloride) leading to cell death. There is also evidence that amphotericin B causes oxidative stress within the fungal cell, but it remains unclear to what extent this oxidative damage contributes to the drug's effectiveness. Two forms of amphotericin exist, A and B, are known, but only the latter is used clinically, on account of its greater activity in vivo.

Common side effects include a reaction with fever, chills, and headaches soon after administration, as well as renal toxicity. [2] Allergic reaction may also occur. Other serious side effects include hypokalemia and cardiac inflammation.

The use of topical amphotericin has been described as primary or adjunctive treatment in patients with rhinocerebral and ocular involvement. [5, 6] Deoxycholate amphotericin B is toxic to mammalian cells. An experimental solution of 45% amphotericin in 35% sodium deoxycholate was applied to Mucor cells and human cells in culture. [7] At a concentration of 2 mg/mL, amphotericin was cytotoxic to fibroblasts, keratinocytes, and osteoblasts, and less

effective against fungi. It was rapidly fungicidal at 20 mg/mL. Clinically, Saedi, et al. report 30 patients with mucormycosis infection limited to the nose and sinuses treated with endoscopic debridement of necrotic tissue as well as placement of amphotericin-soaked pledgets. [8] The pledgets were used for an average of 32 days. Ten patients were noted to have a recurrence and 18 (60%) patients survived the infection.

The role of topical amphotericin B in the management of cutaneous mucromycosis in pediatric patients has not been well studied. One case report described the use of topical Amphotericin in a 6-month-old male with acute lymphoblastic anemia (ALL) and acute myeloid leukemia (AML). [9] Despite prophylactic fluconazole, the patient developed an area of concern around a central venous catheter. Following presumed adequate debridement and a short course of vacuum-assisted closure, a topical 0.1% solution of deoxycholate amphotericin B in D5W was applied to gauze sponges and placed onto the wound. Following 3 weeks of treatment, complete healing of the wound indicated eradication of the mucormycosis. A dose of 1 to 1. mg/kg/day was chosen based on data described above. [4] Despite persistent pancytopenia, no recurrence was described.

Another case report described the use of topical amphotericin B in a 58-year-old patient with a 47% total body surface area burn from a house fire. [10] In light of multiple pre-existing co-morbidities and the acute immunocompromise due to the large burn, she developed cutaneous mucormycosis over the torso and specifically the right breast. In addition to parenteral antifungal agents, amphotericin B-soaked pledgets were applied every eight hours at a dilution of 24 mg in 1000 mL of sterile water. Subsequent wound biopsies failed to show mucormycosis.

The use of instillation therapy has yet to be described for the treatment of cutaneous mucormycosis in either the adult of pediatric patient. One obvious concern with this mode of therapy is the amount of absorption. In patients with renal injury due to either chronic disease or the use of other nephrotoxic medications, including systemic amphotericin, there may already be existing kidney damage. The theoretical benefit of a vacuum-assisted dressing, with the potential for fluid infiltration, is that the medication is allowed to contact the wound surface and then be removed. The vacuum can be set to deliver a given amount of solution over a given time period on a given cycle. This could be regulated based on the patient's renal function.

It is doubtful that invasive disease can be managed with topical treatment alone, but the combination can serve to better manage the disease as a whole.

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FIGURES:

Figure 1. Intraoperative appearance of posterior neck wound positive for mucormycosis.

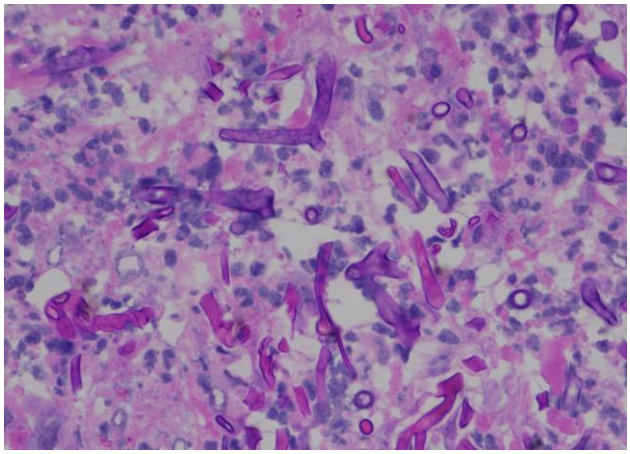

Figure 2. Histologic appearance of mucormycosis by hematoxylin and eosin stain.

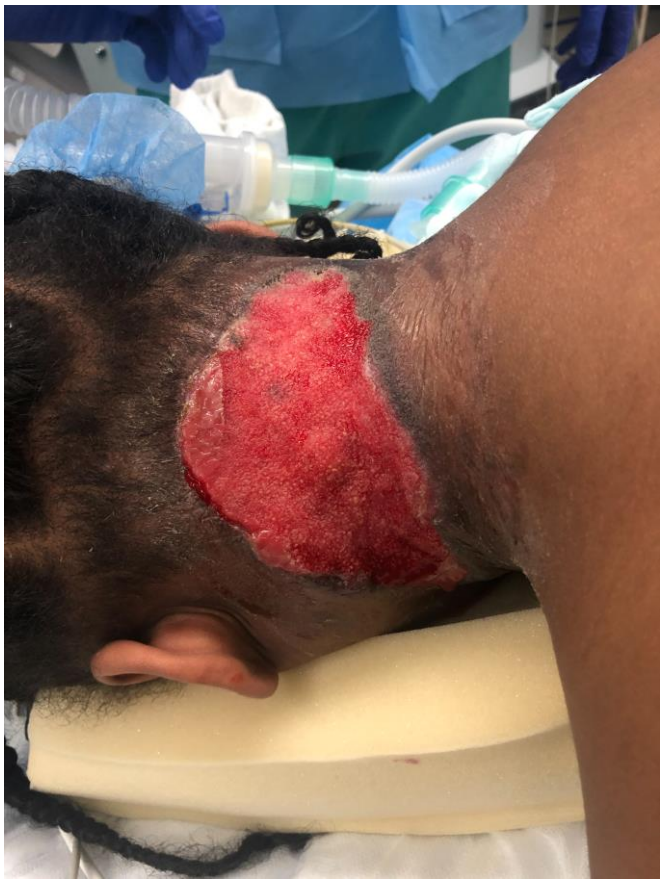

Figure 3. Intraoperative appearance of the posterior neck wound following parenteral and topical application of amphotericin B prior to coverage with a split thickness skin graft.

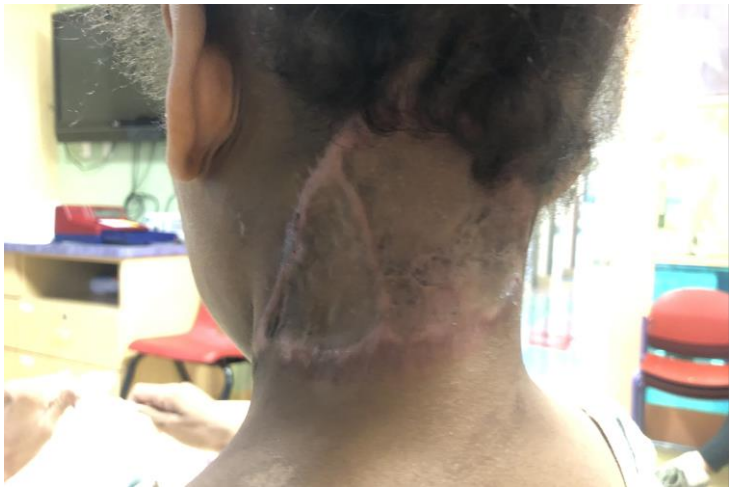

Figure 4. Postoperative appearance of the healed posterior cervical skin graft.

PEER REVIEW

Not commissioned. Externally peer reviewed.