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Post-traumatic fatal disseminated *Apophysomyces elegans* infection

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ABSTRACT

Mucorales infections typically occur in immunocompromised hosts. We describe a case of disseminated post-traumatic Apophysomyces elegans in an immunocompetent patient status-post soil inoculation. Fungi introduced at a deep arm laceration leads to neurovascular invasion and dissemination prior to amputation and systemic treatment. We specify strict post-traumatic wound surveillance protocol and roles of novel tissue tests to improve time to diagnosis and prognosis of frequently fatal post-traumatic Mucorales infections.

1. Introduction

Mucorales are a group of environmental fungi that traditionally cause infection in the immune compromised host. Patients with uncontrolled diabetes mellitus, Human immunodeficiency virus, and/or have undergone bone marrow and solid organ transplant are at increased risk for Mucorales infection. In addition, these species are prevalent in the environment, allowing them to opportunistically infect immune competent hosts through traumatic entry. A recent literature review highlights increasing prevalence of post- traumatic mucormycosis [1]. Risk factors and mycology differ based on whether the trauma is civilian or military. Species of fungi that are commonly associated with civilian traumatic exposure are *Apophysomyces, Lichtheimia, Rhizopus* and *Mucor* [2]. Post-motor vehicle accidents (MVA) mucormycoses make up a subset of post-traumatic reports. In 2014, Australia reported that nearly 50% of reported mucormycoses cases occurred in MVA victims without any predisposing immune compromisations [3].

Apophysomyces elegans is a particularly ubiquitous environmental Mucormycotic species. It was first reported in 1979 when it was isolated from soil in a mango orchard in northern India [4]. Unlike infection with other mucorales, *Apophysomyces elegans* infection is not usually associated with immune compromising conditions [5]. Rather, this species predominates zygomycetes infections associated with trauma and disruption of the cutaneous barrier. It tends to invade vascular and non-vascular tissue like other species of zygomycetes infection, despite its unique prevalence in immune healthy individuals [1–3,6,7]. Here we report a case of disseminated *Apophysomyces elegans* infection in a immunocompetent patient injured in a MVA.

2. Case

A 60-year-old African American woman presented to the emergency department (ED) following a roll-over motor vehicle collision (MVC). She had traumatic avulsions to the front mandibular teeth, multiple bone-exposing abrasions of the forehead, superior scalp, and left superior orbit, and three deep tissue lacerations of the right upper extremity (RUE). Her past medical history was significant for non-insulin dependent type II diabetes mellitus (last hemoglobin A1C was 5.8%) and hypertension. After arrival, she was intubated for airway protection. On physical exam, patient had a significant number of abrasions and lacerations of her face, head, arms, legs, and trunk. She had multiple open wounds of the RUE including two 3 × 3 cm lacerations over the distal anterior arm, a 10 × 5 cm anteromedial distal arm laceration, and a 7 × 4 cm wrist laceration. All of these wounds extended beyond the fascia and into the deep tissue. Neurological and motor exams were not feasible due to the patient's mental state. Radial pulses were brisk and palpable. All of the lacerations required surgical closure and stabilization.

On Hospital day 0 (date of admission), the patient underwent full body CT scan, which was significant for multiple traumatic injuries including fractures of the facial bones and sinuses, C7 fracture at the transverse foramen, right upper lung contusion, grade 1 hepatic and splenic lacerations, and displaced pelvic fractures. Patient underwent interventional radiology assisted embolization of the right superior gluteal artery which was causing active extravasation into right retroperitoneum. Patient suffered comminuted, open fracture of the right midshaft humerus and multiple open, comminuted fractures of the distal radius. Significant soft tissue swelling was visualized throughout

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the upper extremity with multiple foreign bodies entrapped within subcutaneous tissue. Patient underwent vigorous washouts of the wounds in the RUE with external fixation of the humerus.

On Hospital day 1, She underwent repeat RUE washout, debridement and external fixation with wound vacuum placement. On Hospital day 3, the patient was started on empiric antibiotics with ampicillin – sulbactam intravenously (IV) 2 g Q6 hourly for possible infection in the sinus spaces due to facial bone fractures. Post-op patient spiked 100.4 F temperature. Fever work-up with blood, sputum, and urine cultures were ordered. On Hospital day 4, she underwent irrigation and debridement of the RUE wounds again. Anaerobic bottles in 2 sets of blood culture grew a gram-positive rod. Antibiotics were broadened to piperacillin-tazobactam 4.5 g IV Q6 hourly. Repeat blood cultures were negative. During morning rounds on hospital day 7, the patient's RUE was found to be cold and pulseless. Patient was rushed to the operating room (OR) and underwent extensive thrombectomy of brachial, ulnar, and radial arteries which resulted with complete return of pulses. Six hours post-operatively, patient's pulses again were undetectable with ischemic changes of the proximal radius and ulna and distal humerus. She was rushed to the OR and was found to have occlusion of the brachial artery at the right humeral fracture location. A distal upper arm and proximal forearm amputation and debridement with muscular flap was performed. Positive blood cultures from anaerobic bottles obtained on hospital day 3 were finalized as *Clostridium bifermentans*.

On hospital day 9, she was found to have black necrotic eschar and white moldy growth over her right humeral stump (Fig. 1). Further debridement of the necrotic tissue was performed such that ¾ of the humerus had been resected. Tissue biopsy was obtained and sent for histopathology and fungal and bacterial cultures. Frozen section was suggestive of mucormycoses infection (Fig. 3). The fungal cultures grew non-septate broad hyphae (which was identified later as *Apophysomyces elegans*) [8,9]. Patient was started on intravenous liposomal amphotericin B 5 mg/kg daily. Twelve hours later on hospital day 9, patient's stump showed new necrotic growth around the ligated neurovascular bundle (Fig. 2). She was rushed to the OR and underwent further debridement.

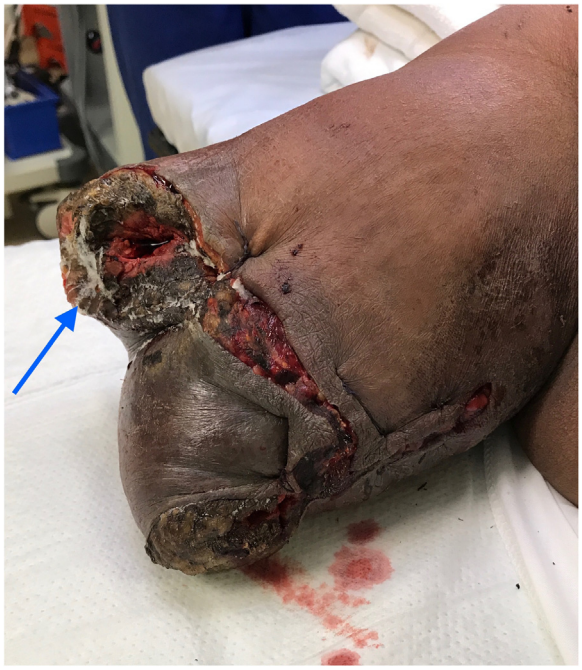

Fig. 1. Right upper extremity stump site with wound dehiscence, necrosis, and eschar formation. Blue arrow points to the growth of white “cotton wool” like material. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

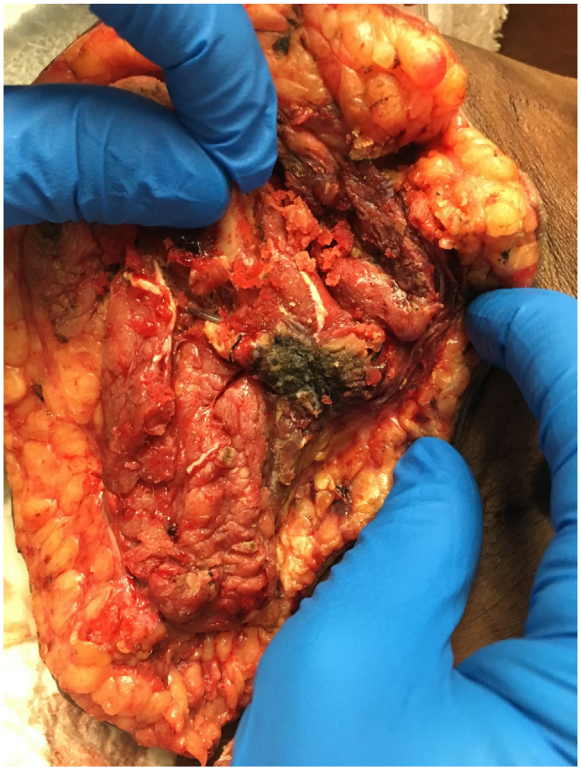

Fig. 2. New necrotic growth around ligated neurovascular bundle in the right upper extremity stump site.

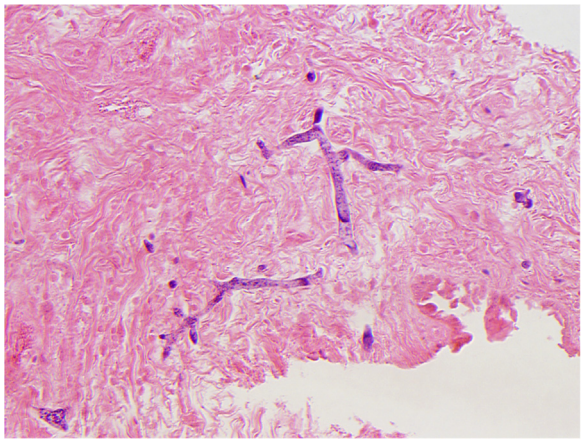

Fig. 3. Right upper extremity soft tissue shows fungal hyphae with H&E stain.

On Day 10, the patient developed left-sided maxillary necrosis concerning for disseminated mucormycoses, so intravenous micafungin 100 mg daily was added to antifungal regimen. Left buccal biopsy also grew broad-based non-septate hyphal fungi. Final species identification was made based on microscopic appearance and morphologic characteristics. Using induced sporulation, *Apophysomyces elegans* was identified via its pale-yellow color and unique unbranched ends with tear-dropped to trapezoidal shaped sporangia [9]. Oral surgeons performed complete left cheek resection. Patient's overall clinical picture continue to deteriorate on Hospital day 12 and the poor prognosis of disseminated mucormycoses was explained to the family. The patient's family made the decision to discontinue further debridements per patient's wishes, and she was made comfort care. She passed away on hospital day 13.

3. Discussion

Apophysomyces elegans is traditionally found in warm climate soils [1,2,7]. Of particular note, most documented human cases are seen in India, the United States, and Australia [3,5–7]. Our patient experienced a severe MVA with multiple traumatic injuries, including various facial and peripheral fractures and significant deep tissue lacerations. Twenty-one percent of all invasive fungal infections occur secondary to traumatic injury, and Mucorales species are responsible for 59% of these cases [2]. MVAs are the number one cause of traumatic mucor worldwide. Furthermore, two studies have shown increased incidence of traumatic mucormycoses in rural areas likely secondary to higher density of soil components conducive to fungi proliferation [2,3,10]. Most mucor cases are cutaneous and post-traumatic dissemination is rare [2,3,11,12]. Cases with rhabdomyolysis and associated acidosis (e.g. simultaneous severe crush injuries, unrestrained passengers) are at higher risk for invasive fungal infections since acidosis inhibits macrophage activity [2,6,7]. Within 30 days of injury, patients usually develop fever and leukocytosis. Necrosis is the primary physical exam finding (40–100% of cases) [6,7,12,13]. Other symptoms include visible mold growth at inoculation site, erythema, edema, purulence, and cellulitis. Estimated timing between injury/culture and symptom presentation is 10–20 days, and it generally takes up to 3 days to determine definitive diagnosis and initiate treatments once cultures are obtained [2,3,14].

Post-traumatic wounds require strict daily dressing changes and wound checks. Soiled wounds are most likely to develop mucormycotic infections [1,7]. Early detection of wound changes allows for more timely intervention and may prevent severe cutaneous and/or disseminated disease. Studies and case report review suggest that the most reliable diagnosis of mucormycoses is achieved via necrotic/moldy tissue biopsy and subsequent frozen section analysis [2,15,16]. In 2008, Wegenack et al. reported a real-time polymerase chain reaction (PCR) assay with 100% sensitivity and minimal to no cross-reaction detection with other fungal species [17]. While tissue biopsy is likely to remain gold-standard of diagnosis, optimization of screening PCR could greatly reduce time to diagnosis and treatment. Reducing turn-around time could decrease mucor-associated morbidity and mortality significantly. However, studies on PCR methods are insufficient to recommend it as a screening tool at this time [17].

Most experts agree that cutaneous mucormycosis prognosis depends significantly on source control, extent of tissue/vascular invasion at diagnosis, and potent antifungal treatments. Mucormycosis treatment should include rapid surgical debridement/source control and high-dose systemic antifungals, such as amphotericin B. Studies show significant prognostic value in early debridements. Posaconazole can be used as a salvage therapy in patients with amphotericin failure or intolerance. Ideally, patients who recover from acute mucormycoses require 1–3 additional months of oral antifungals [2,15]. Other treatment options include hyperbaric oxygen and wet to dry Dakin's dressings; however, prior investigations of these therapies are low quality, limiting support for application [2,18].

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Conflict of interest

There are none.

Ethical form

Uploaded documents include ethical form downloaded from below website. Signed informed consent has been obtained by patient's eldest child (next of kin) and will be available upon request.

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