Post-traumatic Lethal Form of Primary Cutaneous Zygomycosis in a Healthy Young Patient and Review of the Literature

Mohamed Khalid Al Barrag1 SSCO, Abdu Hassan Al Zobydi2 SSCS, Mohamed Mohamed Al Hazmi1 ABM, Nabil Tadros Mikhail1 Ph.D, Mohamed Yahia Bakrain1 SSCO, Abdulmonem Mohamed Alsiddiky1 SSCO

Departments of Orthopedics1 and Surgery2, King Fahd Central Hospital, Jizan, Kingdom of Saudi Arabia

Abstract

Zygomycosis is an invasive disease caused by fungi in the class Zygomycetes. Primary cutaneous zygomycosis is uncommon. We report a case of post-traumatic most lethal form of cutaneous zygomycosis (gangrenous cellulitis), which closely resembles necrotizing fasciitis in a young healthy male patient with polytrauma. Multiple surgical debridements, skin grafting, and intravenous antifungal therapy were necessary to ultimately eradicate the infection. The early diagnosis by tissue culture and histopathology study is mandatory to successfully treat this condition.

Key words: Cutaneous zygomycosis, polytrauma, fungal infections.

Correspondence to:
Dr. Mohamed Khalid Al Barrag
Department of Orthopedic Surgery
Consultant Orthopedic Surgeon
King Fahd Central Hospital,
204 Jizan, Kingdom of Saudi Arabia
Tel: +966 7 3250717 Ext. 439
Email: drmohamedalbarrag@hotmail.com

Case Report

A 25-year-old male was involved in a motor vehicle accident; he was referred to the orthopedic department in our hospital (King Fahd Central Hospital, Jizan, Saudi Arabia) on 26 October 2007 with comminuted fracture of the shaft of the right femur and fracture of the lower right tibia just distal to a long broad compression plate which was fixed one year ago for comminuted fracture of the proximal part. This patient was ejected out of the car in a farm when his car rolled over; he was otherwise healthy before this accident. On arrival, the patient was found to be febrile with normal pulse rate and blood pressure, fully conscious, with normal chest and abdomen. The patient had swelling of the right thigh with intact skin. A swelling of the lower third of the leg on the medial aspect was noticed with superficial abrasions. The pedal pulses were felt and the motor function of the right foot was normal. A below knee cast was applied with a skin traction on the top of it. Radiological evaluation by plain x-ray of the right femur showed comminuted fracture of the lower third of the right femur with the junction of the upper two thirds...
Mohamed Khalid Al Barrag et al

(Figure 1), x-ray of the right tibia showed a long broad compression plate fixed on the medial border with non-union of the middle third old fracture and a fresh fracture seen below the compression plate (Figure 2). This patient was hospitalized for 73 days, during the admission period the patient underwent seven operations, the first surgery was done 3 days after admission, the right femur was first fixed successfully with an intramedullary nail, then during the draping of the right leg pus was seen leaking from a small puncture wound under the abrasions on the medial aspect of the lower part of the leg. Intra-operative decision was made to debride the leg, removal of the compression plate and screws and application of external fixation; with excision of the necrotic tissue a 4x5 cm oval shape skin defect was created. Wound swabs and soft tissue for culture were taken.

Figure 1: Plain x-ray of the right femur showing comminuted fracture.

Figure 2: X-ray of the right tibia showing compression plate fixed on the medial border with non-union (red arrow) of the middle third fracture and a fresh fracture seen below the plate.

Figure 3: Gangrenous cellulitis demonstrating a characteristic central blackened necrotic eschar surrounded by reddish-purple soft tissue induration.

The tissue culture grew pseudomonas and acinetobacter pathogens for which Ceftazidine 1 gm IV X 8 hourly and
Amikacin 500 mg IV X 12 hourly were started. Dressing on third postoperative day revealed necrotic edges of the wound surrounded by reddish-purple soft tissue induration and a central black crust covered with numerous small spores seen grossly, which raised the suspicion of both necrotizing fasciitis and fungal infection (Figure 3).

Figure 4: Large tissue defect which persisted after repeated debridements with clean base ready for skin grafting.

Tissues were sent for histopathology analysis and for fungal culture looking for zygomycetes. The histopathology report showed necrosis, suppuration and fungal hyphae with characteristic appearance of zygomycetes (Figures 5, 6, 7 and 8). The fungal cultures grew Rhizopus species.

Figure 5: Fungal hyphae and colonies (H & E X 100)

Figure 6: Necrosis, suppuration and fungal hyphae (H & E X 100)

Figure 7: Silver stained fungi of zygomycetes GMS X 200.

Figure 8: PAS Stained fungi of zygomycetes, typically they are broad, thin walled, and pleomorphic with irregular nonparallel contour, due to the little structural stability, they are often folded, twisted, or collapsed (PAS, X 1000).
Patient’s general condition deteriorated as shown by fever (39.5 °C, and WBC of 41 \( \times \) \( 10^9/L \)) which prompted the treating physician to change the antibiotics to Vancomycin IV 1 gm X 12 hourly, Imipenem IV 1gm X 8 hourly and oral Rifampicin 600 mg daily.

Multiple surgical debridements were done till the wound became clean and ready for split skin grafting (Figure 4), which was done by the plastic surgeon 40 days from the first surgical intervention, the graft was taken nicely and postoperative recovery was smooth, the femur fracture and tibia fracture united well (Figures 9, 10, and 11). The patient was followed in the clinic for 18 months with complete recovery and no signs of recurrence of Zygomycosis.

**Figure 9:** The patient’s right leg after complete healing.

**Figure 10:** Plain x-ray of the right femur showed union of the fracture fixed with Intramedullary nail.

**Figure 11:** Plain x-ray of the right tibia showed union of the fractures just before the removal of external fixator.
Lethal form of primary cutaneous zygomycosis

Discussion

The zygomycetes are divided into two orders: the Mucorales and the Entomophthorales. The order Mucorales is made up of species from the genera Rhizopus, Mucor, Rhizomucor, Absidia, Apophysomyces, Saksenaea, Syncephalastrum, Cunninghamamella, and Cokeromyces. The Zygomycetes are saprophytic fungi that are ubiquitous in soil or decaying organic material. The clinical manifestations of zygomycosis are rhinocerebral, pulmonary, cutaneous, gastrointestinal, cardiac and the rarely isolated cerebral disease. Zygomycosis is often life-threatening, and hosts are usually compromised by diabetes mellitus, malignancy or immunosuppressive therapy. It has also been reported in neonates, burn patients, drug abusers and patients with hepatic or renal insufficiency. Most of these conditions are associated with impairment of normal leucocyte immune function. In the setting of normal immunity, fungal infections are contained by the concerted effort of monocyte/macrophages and neutrophilic granulocytes. Macrophages are primarily responsible for suppression of spore germination by phagocytosis and oxidative killing, whereas neutrophils are able to actively mediate hyphal destruction and fungal killing by similar mechanisms.

Cutaneous mucormycosis may develop from contamination of a preexisting surgical or traumatic wound or burn site, hematogenous dissemination, or via direct extension from adjacent infected subcutaneous tissues, manifesting in two clinical presentations; a subacute "superficial" form and a "gangrenous" form. In a review of 117 cases of cutaneous zygomycosis, no underlying illness was present in 50% of patients. In particular, cutaneous involvement was the presented pattern (19%) in a review of all English language reports of zygomycosis. Penetrating trauma was reported to be the etiological factor in 34% of these patients. Infections due to Rhizopus species have been described in solid organ transplant patients who are chronically immunosuppressed and in immunologically normal patients with traumatic or surgical wounds that become exogenously contaminated. Also different species were reported in leukemic cases and in post-traumatic healthy children and adults. Nosocomial Rhizomucor cellulitis and osteomyelitis complicating post-traumatic multibacterial infection were reported to be caused by the use of broad spectrum antibiotics, hypoalbumenemia and anemia which was treated with liposomal amphotericin B and surgical debridement. The present case was complicated with bacterial infection, perivious tibia fracture non union with plate fixation and scarring tissues in addition to the invasive nature of the fungal infection with the behavior of necrotizing fasciitis. Inoculation of an existing wound with fungal spores produces a localized infection with signs of acute inflammation, including tissue swelling, erythema, pus, and abscess formation. The initial stage may mimic a necrotizing bacterial infection; however, black eschars and deep ulcerations ensue as the disease advances. Necrotizing fasciitis due to zygomycosis is often potentially limb- and life-threatening infection. Current case is that of primary cutaneous zygomycosis infection because of the presence of the skin abrasion and soil contamination, which is reported to occur rapidly and become invasive in up to 50% of cases involved in extensive soil contamination. Rhizopus species was cultured being the most commonly recovered 47% in human zygomycosis. However, culture was positive in only 52% of the autopsy cases found to have fungal infections and only 30% of surgical specimens in which fungi were identified by direct examination. Aggressive surgical approach was followed with immediate and repeated surgical debridements in the operating theater. Usually this approach leaves a large soft tissue defect that should be covered by the plastic surgeon. A review of the literature yields a survival rate of only approximately 33% after "radical surgical excision" or amputation and amphotericin B administration.
The antifungal Amphotericin B was well tolerated by the patient which has classically been the agent of choice for zygomycosis, based on in vitro and clinical studies. However, in the current era, lipid formulations of amphotericin B are the mainstay of antifungal therapy against zygomycetes. Treatment with lipid-based amphotericin B formulations have fewer toxic side effects, especially on renal function. Posaconazole seems a promising antifungal drug especially in disseminated forms of zygomycosis. Rifampicin was given in addition to amphotericin B to create synergistic effect but there is no in vitro conclusive clinical data to recommend the routine use of such combination.

In conclusion, post-traumatic primary gangrenous cellulitis zygomycosis, can occur in healthy individuals, early diagnosis with high index of suspicion, deep tissue biopsy for culture and histopathology study can change the prognosis. Aggressive surgical approach with combination of antifungal therapy is the choice of treatment, the need for skin coverage by plastic surgeon is almost universal in all cases due to the large skin defect.

References

Lethal form of primary cutaneous zygomycosis


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