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Complication of massive trauma by fungal infection and bone tuberculosis

Fatehi Elzein[a,*], Nazik Mohammed[a], Maria Arafah[b], Ahmed Albarrag[b], Rabea Habib[c], Aqeel Faqehi[c]

[a] Infectious Diseases Unit, Prince Sultan Military Medical City (PSMMC), Riyadh, Saudi Arabia
[b] Department of Pathology, King Saud University, Riyadh, Saudi Arabia
[c] Department of Orthopedic Surgery, PSMMC, Riyadh, Saudi Arabia

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ABSTRACT

We report a middle aged man who was admitted with severe necrotising fasciitis following a motor vehicle accident (MVA). Histopathology of the excised tissue suggested mucormycosis while a bone tissue culture revealed fully sensitive *Mycobacterium tuberculosis*. He received intravenous liposomal amphotericin B combined with multiple surgical debridements and ended with right shoulder disarticulation. In addition he completed a nine months course of anti-tuberculosis treatment. He remained stable one year following his admission.

We believe that trauma contributed to both conditions by direct inoculation of fungal spores and through immunological reactivation of old healed tuberculosis focus. This case highlights the importance of considering diagnosis of invasive fungal infections following MVA.

1. Introduction

Invasive fungal infection particularly mucormycosis involves immunocompromised patients, diabetics, neutropenics and patients with metabolic acidosis. Lesser known is a post traumatic necrotising infection that occurs in immunocompetent trauma victims. Overall, cutaneous mucormycosis constitutes 19% of all mucormycosis cases [1,2]. Traumatic injury contributes to 56% of primary cutaneous mucormycosis [3]. Invasive infections with or without necrotising fasciitis can follow the introduction of fungal spores present in the soil, decaying plants and plants debris. These fungi utilise trauma-induced acidic, iron-rich environments and proliferate in the tissue. Furthermore, trauma-related local immunodepression and possibly systemic immunosuppression increase their pathogenicity. In addition, angioinvasion and consequent thrombosis, which is characteristic of mucormycosis, leads to tissue ischemia and worsening necrosis [4]. Trauma can be incited by an event as trivial as a scratch or an intramuscular injection or as major as a natural disaster, such as the Joplin tornado or an Asian tsunami. Invasive fungal infections have emerged as an important combat-related illness in the Afghanistan and Iraqi wars.

2. Case

A 63-year-old man sustained a road traffic accident while in the passenger seat (D-10). He was initially admitted to a local hospital with necrotising fasciitis of the right upper limb. An initial assessment revealed a friction injury to the right upper arm complicated by a right distal humerus fracture and a degloving injury extending to the right hand. An x-ray of the right elbow revealed a severe comminuted supracondylar fracture with a subcutaneous tissue defect (Fig. 1). He was treated with broad-spectrum antibiotics including meropenem and vancomycin in addition to multiple irrigations and surgical debridement (I&D). He is known to have diabetes mellitus with HbA1C of 7.7% and well controlled hypertension.

On arrival to our hospital (D0) the vital signs were normal. Pulse rate was 86 beats/minute, blood pressure was 119/56 mmHg, temperature was 37.0 °C, RR 16 breaths/minute and oxygen saturation was 100.0%. There was a severe degloving injury of the right upper limb involving the arm, elbow and forearm with necrotic black exposed muscles (Fig. 2).

He was immediately taken to the operation room (OR) for I&D. Intravenous meropenem and vancomycin were continued. The examination in OR showed a severe crushing injury and soft tissue loss over anterior, medial and lateral aspect of the right elbow with severe necrosis of most flexors and extensor muscle of the right elbow. The radial and ulnar arteries were not felt but were audible with a doppler assessment. He underwent right above-elbow amputation on D3 and started on a negative pressure dressing vacuum assisted closure (VAC). The investigations showed white cell count 30.4 x 109/L, haemoglobin 8.0 g/dL, platelets 300 x 109/L, creatine kinase 1338 units/L, ESR 92

* Corresponding author.
E-mail address: felzein@psmmc.med.sa (F. Elzein).

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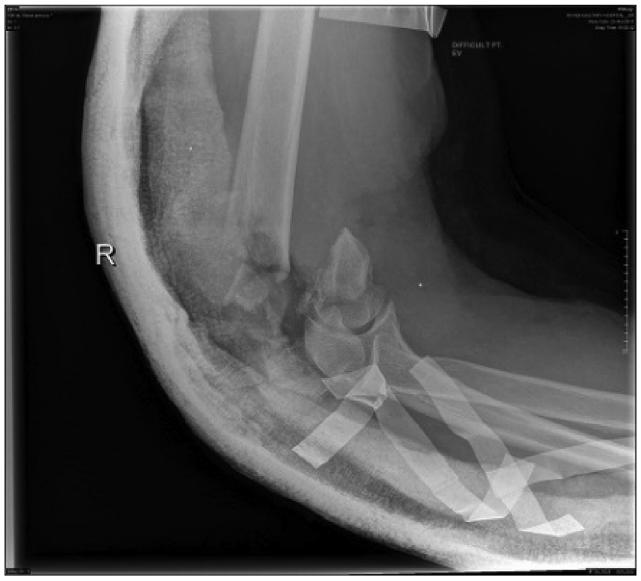

Fig. 1. X ray right elbow showing severe comminuted supracondylar fracture with subcutaneous tissue defect.

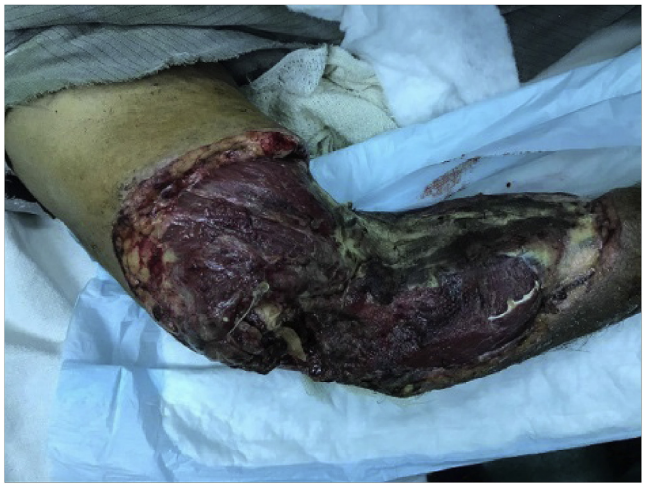

Fig. 2. Right -arm wound with areas of extensive tissue necrosis in subcutaneous tissue, with extension to the exposed muscle layer.

mm/hr., CRP 375 mg/L, procalcitonin 23.52ng/mL, serum creatinine 121 μmol/L, random blood glucose 20.3 mmol/L, HbA1C 7.7% and negative HIV serology. Tissue cultures grew multidrug resistant *P. aeruginosa, K. pneumoniae* and *C. albicans*.The culture for other fungi was negative, and tissue staining for acid-fast bacilli (AFB) was negative.

Initial tissue histopathology at our centre showed skin, subcutaneous fibroadiopse tissue, skeletal muscles and bone with ulceration, extensive necrosis and acute inflammatory exudate. These features are consistent with necrotising fasciitis. There were no fungal organisms identified by PAS and GMS stains, and no granuloma was detected.

On D5, the wound was reassessed in the OR. There was a necrotic black skin with extensively macerated fatty tissue underneath. He was started empirically on liposomal amphotericin B 5mg/kg/day. Ultimately a right shoulder tissue histopathology showed broad, ribbon-like fungal hyphae. Multiple thrombosed veins were noted among debrided tissues (Fig. 3). Although the histopathology was suggestive of mucormycosis, all the cultures for fungi were negative. Molecular testing for fungi was not available to us. Liposomal Amphotericin B was continued for a total of 70 days.

The infection was difficult to control, requiring more than 20 debridement and irrigations. Despite aggressive medical and surgical debridement, he ended up with a right shoulder disarticulation with a resection of part of the scapula. The chest wall was extensively involved and the ribs were exposed. In the end, a skin graft was successfully applied to the chest wall (Fig. 4).

A mycobacterium TB bone tissue culture sent on D22 grew fully sensitive mycobacterial tuberculosis (MTB) from the same site of fungal infection on D46. He was started on isoniazid 300mg, rifampicin 600 mg, ethambutol 1.2 g, pyrazinamide 2 g and pyridoxine 40 mg, all given once daily. A CT scan of the chest showed bilateral pleural effusion with adjacent atelectasis. A calcified granuloma was seen in the right upper lobe. Sputum smears for AFB and a polymerase chain reaction (PCR) were negative.

He completed nine months of anti-tuberculosis treatment. One year following admission, he remains stable with a fully healed wound.

3. Discussion

This patient was admitted to a local hospital with necrotising fasciitis following a road traffic accident. The patient was seated unrestrained in the passenger seat. The majority of motor vehicle accidents (MVAs) causing fungal infections involve either a motorcyclist or an unrestrained passenger, likely due to the higher risk of wound contamination [5]. In previous studies Motor vehicle accidents contributed to 37–75% of trauma-related mucormycosis [5,6]. In a review of invasive fungal infections secondary to trauma, mucormycosis is the predominant species followed by Saksenaea and Rhizopus.

Our patients had multiple bacteria and *C. albicans* isolated on tissue cultures. Co-pathogens, including other mould and bacteria, were reported in patients with cutaneous mucormycosis [3]. Enterococcus and multidrug resistant (MDR) gram-negative rods (GNR) were identified in 33%–41% of patients with skin and soft tissue fungal infection [7]. For this reason recovery of bacteria from trauma wound should not dissuade from searching for moulds in a suspected tissue. Actually presence of co-pathogens could reflect a greater wound soil contamination and hence an increased risk of mucormycosis. It is noteworthy that bacterial infection was linked to an increased risk of mucormycosis in trauma following a tornado injury [8].

The treatment of mould infections requires urgent extensive surgery and an early commencement of antifungal therapy. Our patient required aggressive surgery with more than 20 sessions of debridement, amputation and finally disarticulation of the shoulder. The delay in the diagnosis could have contributed to this aggressive nature of the disease; however, a median of 14 days for the diagnosis was noted before the establishment of the diagnosis during a tornado in Joplin, Missouri [8]. Notably, patients usually develop symptoms after a median of 9.5 days (range 1–63 days) following trauma [6].

The rare combination of tuberculosis and fungal infection seen in this patient might have played a role as well. Additionally, the species of the mould infection, which was not identified in this patient, could have been related. Frequent agents of trauma-related mucormycosis include Apophysomes, Saksenae and licthemia [9]. Apophysomyces and Saksenae species had been reported in a number of patients with aggressive necrotising fasciitis [10,11]. An early case reports the presence of Apophysomyces in Saudi Arabia in 10-year-old girl with necrotising fasciitis following a MVA [12]. Notably, the rate of amputation in civilian trauma mucormycosis is variably reaching 12–83% [6]. On the other hand, the mortality rate (25–41%) in immunocompetent trauma patients is still high, although it is more favourable than in immunosuppressed patients [8]. Alternative strategies to improve the prognosis (e.g., hyperbaric oxygen therapy) are not of proven value and remain considered to be a salvage therapy [13].

It is possible that this patient has reactivated a latent TB infection. The CT scan of the chest showed a calcified granuloma. On the other hand, the soft tissue granuloma could have been broken up by tissue

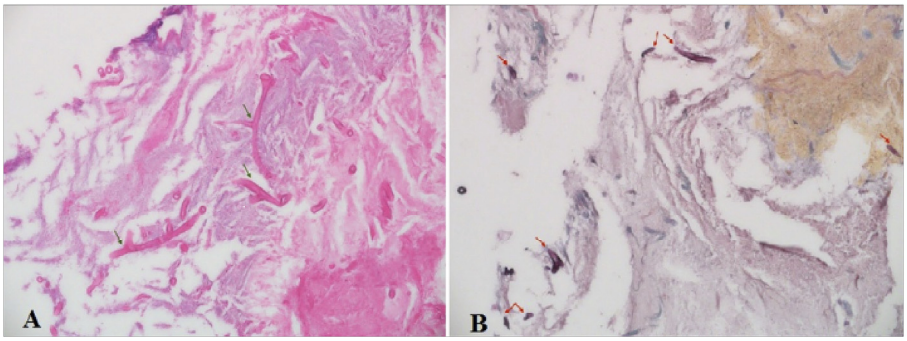

Fig. 3. A. A photomicrograph showing broad non septated fungal hyphae (green arrows) in a background of fibrous tissue (H&E stain, x400).**3B**. A photomicrograph showing few fungal elements (red arrows) staining positively with modified Gomori methenamine-silver nitrate special stain (GMS stain, x400). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

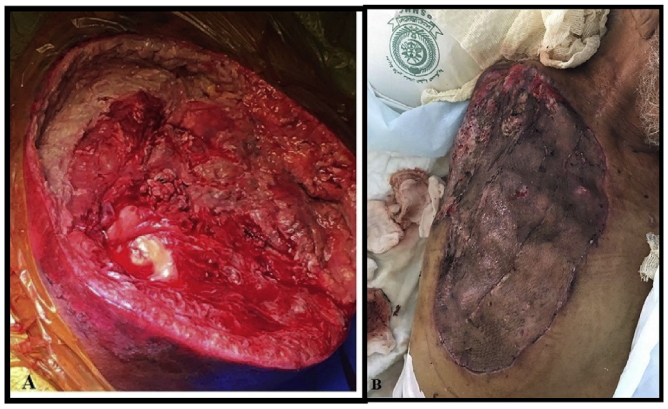

Fig. 4. Right shoulder following disarticulation before (A) and after skin graft.

destruction secondary to invasive fungal disease; nevertheless, the recovery of MTB on bone culture favours reactivation. There are previous reports of trauma-related tuberculosis. Trauma can lead to decreases in IL-2, IL-12 and IFN gamma and an increase in IL-10. Interleukin-12 is responsible for Gamma-IFN release, which is required for macrophage activation, while IL-2 results in activation and the differentiation of T-cells into T-helper 1, which secretes IFN-gamma [14]. Conversely, increased IL-10 during trauma has been reported to increase susceptibility to tuberculosis [15,16]. Interestingly, extra-pulmonary tuberculosis has been reported to occur at the same site of trauma. Haematogenous transport of mycobacteria in the monocytes recruited to trauma area is another possible explanation [17].

This case illustrates the difficulty in the diagnosis and management of cutaneous fungal infection. The diagnosis should be suspected in all cases of skin and soft tissue infections following a MVA or other civilian and combat-related injuries. Although rare, concomitant tuberculosis may need to be considered in patients with evidence of old tuberculosis at other sites.

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Ethical approval

Ethical approval was obtained from the ethical committee of PSMMC.

Declaration of competing interest

The authors declare that there are no competing interests regarding the publication of this paper.

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