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Review

Invasive Fungal Infections Secondary to Traumatic Injury

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ABSTRACT

Invasive fungal infection (IFI) is a rare but serious complication of traumatic injury. The purpose of this article is to review the epidemiology, natural history, mycology, risk factors, diagnosis, treatment, and outcomes associated with post-traumatic IFI in military and civilian populations. The epidemiology of post-traumatic IFI is poorly characterized, but incidence appears to be rising. Patients often suffer from severe injuries and require extensive medical interventions. Fungi belonging to the order *Mucorales* are responsible for most post-traumatic IFI in both civilian and military populations. Risk factors differ between these cohorts but include specific injury patterns and comorbidities. Diagnosis of post-traumatic IFI typically follows positive laboratory results in the appropriate clinical context. The gold standard of treatment is surgical debridement in addition to systemic antifungal therapy. Patients with post-traumatic IFI may be at greater risk of amputation, delays in wound healing, hospital complications, and death as compared to trauma patients who do not develop IFI. More research is needed to understand the factors surrounding the development and management of post-traumatic IFI to reduce the significant morbidity and mortality associated with this disease.

Contents

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Introduction

Invasive fungal infections (IFI) are a rare but serious complication of traumatic injury characterized by fungal angioinvasion and resultant vessel thrombosis and tissue necrosis (Alonso et al., 2006; Spellberg et al., 2005). In contrast to other settings, post-traumatic IFI occurs through direct inoculation of tissue with spores at the site of injury (Bilal et al., 2016). Fungi may then take advantage of an acidemic, iron-rich environment to proliferate and invade vessels through hyphae growth. Patients with post-traumatic IFI suffer poor outcomes from the aggressive nature of the infection and from delays in diagnosis and appropriate management (Neblett Fanfair et al., 2012). Significant gaps in the literature exist, with large-scale cohorts and comparative studies curbed by the scarcity of cases. Nevertheless, a growing body of evidence drawn from case series, cohorts, and case-control studies has accumulated over the past several decades such that clinicians and researchers can begin to gain an understanding of the clinical course and consequences of developing post-traumatic IFI.

The aim of this review is to summarize the epidemiology, clinical presentation, microbiology, diagnosis, management, and clinical outcomes in military and civilian trauma patients with IFI. When possible, we will focus on IFI occurring as a direct result of soft tissue injury rather than delayed or chronic progressing infection, as the latter group likely represents a different pathogenic pathway. Additionally, we will highlight areas lacking attention in the literature to inform future research on this subject.

Epidemiology

Military

During the wars in Iraq and Afghanistan, IFI emerged as a significant complication of combat-related injury. A review of the U.S. Department of Defense Joint Theater Trauma Registry identified fungal infection by ICD-9 codes in 0.44% of combat trauma patients, although these codes were not specific to IFI and candidiasis, both invasive and non-invasive, accounted for the majority of infections (Murray et al., 2011). Subsequently, analyses of combat-injured military personnel evacuated from Afghanistan found an overall IFI incidence rate of 6.8% (Rodriguez et al., 2014a), with incidence increasing over the period of observation (Warkentien et al., 2012). These data were based on the Trauma Infectious Disease Outcomes Study (TIDOS), representing a subset of 1,133 injured soldiers evacuated from Afghanistan between 2009 and 2011. The improved sensitivity and accuracy of IFI identification afforded by TIDOS likely contributed to these starkly different incidence estimates.

Demographically, the military population affected by IFI is consistent with the underlying population of young healthy adult soldiers (Table 1). Cohort patients were all male, with a median age between 22 and 24 years old, and most had no underlying medical conditions (Paolino et al., 2012; Lloyd et al., 2014).

Civilian

The epidemiology of post-traumatic IFI in the heterogeneous civilian population is less well-defined. Observational studies have varying IFI definitions and patient characteristics, and many are confined to cases of mucormycosis only, which have an annual incidence of approximately 0.43–1.7 cases per million persons (Bitar et al., 2009; Bouza et al., 2006; Torres-Narbona et al., 2007). Traumatic injury accounts for up to 21% of these cases overall and 59% of primary cutaneous mucormycosis (Llorente et al., 2011; Skiada et al., 2011; Pagano et al., 2009; Lanternier et al., 2012; Roden et al., 2005; Skiada and Petrikkos, 2009; Skiada et al., 2012; Kaushik, 2012). Incidence of post-traumatic IFI due to all organisms, however, is poorly characterized. A prospective study in Lebanon found that the rate of fungal infection in patients injured by cluster munition explosions was 2.6% (Fares et al., 2013). Two retrospective studies found IFI to occur in 3.1% of upper extremity wounds and 15% of corn picker injuries (Moran et al., 2006a; Obradovic-Tomasev et al., 2016). These studies, however, were circumscribed to a specific injury type and are not likely to be generalizable. Vitrat-Hincky et al. (2009) identified 75 cases of post-traumatic filamentous fungal infection in the literature and their own hospital records between 1985 and 2008, most often due to either traffic accidents (41%), agricultural accidents (25%) or natural disasters (12%). Unfortunately, overall incidence from this study cannot be ascertained due to lack of a reasonable denominator.

Estimating temporal incidence trends is similarly challenging, and data is only available for post-traumatic mucormycosis, of which the frequency of published case reports has increased significantly between 1993 and 2013 (Lelievre et al., 2014). In an analysis of all-cause mucormycosis rates in French hospitals, overall IFI incidence, but not IFI in immunocompetent patients, increased between 1997 and 2006, suggesting that the rising incidence of post-traumatic mucormycosis may be attributed to an increasing proportion of immunocompromised individuals within this population. Indeed, up to 25% of patients with post-traumatic IFI may be immunocompromised to some extent (Skiada et al., 2011; Lelievre et al., 2014).

Post-traumatic IFI may exhibit seasonal and geographical fluctuations. Two case series in France and Lebanon observed higher rates of infection in rural areas (Fares et al., 2013; Bitar et al., 2009), which could be related to differences in hospital resources