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Exserohilum rostratum fungal meningitis associated with methylprednisolone injections

Arturo Casadevall[1,*] and **Liise-anne Pirofski**[1]

[1]Departments of Microbiology & Immunology & Medicine (Division of Infectious Diseases) of the Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, USA

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In October 2012, the CDC reported an outbreak of fungal meningitis associated with methylprednisolone injections [1]. Although the index case had *Aspergillus fumigatus* meningitis [2], subsequent reports indicated that the majority of affected patients had meningitis caused by *Exserohilum rostratum*, an extremely rare cause of human fungal disease [1,3,4]. The outbreak is presumably the result of direct inoculation of *E. rostratum*-contaminated methylprednisolone into human tissue, and the cause appears to be a manufacturing mishap. This is not the first instance of fungal meningitis resulting from contaminated steroid preparations. It was 10 years ago when several cases of fungal meningitis caused by *Exophiala* (*Wangiella*) *dermatitidis* occurred in patients receiving injectable steroids [5]. Further back in time, epidemics of zygomycosis occurred from the use of bandages and wood depressors, among others, that were contaminated with fungal spores [6]. Each of these outbreaks was characterized by high mortality and morbidity, thereby illustrating the potential of certain fungal species to cause life-threatening disease when they interact with human hosts in whom integument and mucosal defenses have been compromised by iatrogenic procedures.

The foregoing fungal outbreaks notwithstanding, it is clear that the *E. rostratum* meningitis epidemic is a new clinical entity for which there is little or no previous clinical experience. A search of the PubMed database using the words '*Exserohilum rostratum*' revealed only a dozen or so cases of human disease, the majority being keratitis and cutaneous infections. Despite several cases of invasive disease in patients with severely impaired immunity, what is most striking is the apparent rarity of human disease caused by *E. rostratum*. The fact that *E. rostratum* can cause human disease indicates that the fungus does have pathogenic potential. On the other hand, the rarity of disease implies that there is a high level of resistance to disease caused by this organism. The fact that the majority of the cases presented as meningitis suggests that we are dealing with a new disease that could reflect the potentially synergistic combination of previously unrecognized *E. rostratum* neurotropism

[*]Author for correspondence: Tel.: +1 718 430 3665 arturo.casadevall@einstein.yu.edu.

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and local immunosuppression (in the CNS). However, it is also important to recognize that the foregoing scenario came to light in the setting of iatrogenic introduction of the fungus, suggesting that the size of the inoculum was a major contributor to disease development. Notably, cases of cutaneous mucormycosis occurred following the Joplin tornado [7], highlighting the fact that the combination of a large number of fungal organisms and a breach in barrier immunity can result in fungal disease in persons in whom it would not normally be suspected.

The current *E. rostratum* epidemic and other unsuspected outbreaks of fungal disease provide many new lessons and raise many questions, perhaps the most compelling of which are why 'new' fungal diseases occur and whether they can be anticipated and/or prevented. One approach to understanding the current epidemic is to consider it based on the tenets of the 'damage-response framework' (DRF) of microbial pathogenesis [8]. According to the DRF, the ability of a microbe to cause disease depends on both the host and the microbe, which must interact, with resulting host damage reflecting the outcome of the host–microbe interaction. New diseases and new microbes often raise the question of whether the microbe is really a pathogen or whether it only causes disease in certain patients. However, from the vantage point of the DRF, there is actually no need to consider whether or not *E. rostratum* (or any other microbe) is a pathogen, because it focuses on the outcome of the host–microbe interaction, rather than categorizing microbes based on their pathogenic potential. Thus, the DRF makes it easy to understand how organisms that are not pathogenic in some hosts can cause disease as a function of the immune status of the host and the intensity of the immune response. Since the *E. rostratum* epidemic has already killed over two dozen individuals, it is clear that the *E. rostratum*–human interaction can result in massive damage to the human host, with the caveat that, to date, this has only been observed after the direct deposition of fungal cells into tissue laden with steroids, which are immunosuppressive agents.

The DRF posits that host damage can come from the host, the microbe or both, and that disease occurs when the host damage stemming from the host–microbe interaction affects homeostasis [9,10]. At this time, we know very little about how *E. rostratum* damages human tissues, but given that this is a soil saprophyte associated with vegetation, we can expect that, similar to other environmental fungal pathogens, it is could express enzymes that could potentially directly damage human tissues. *E. rostratum* is a black mold by virtue of the fact that it can synthesize melanin, a pigment that has been associated with both virulence and resistance to polyene- and echinocandin-type antifungal agents [11]. The most prevalent type of human fungal meningitis is currently cryptococcal meningoencephalitis. This disease is very common in patients with AIDS, in whom meningitis can present with minimal inflammation in the setting of increased intracranial pressure resulting from tissue edema and a blockade of cerebrospinal fluid flow. However, the early indications are that *E. rostratum* meningitis is a very different clinical entity. In contrast to HIV-associated cryptococcal meningitis, which is often associated with few leukocytes in the cerebrospinal fluid, patients with *E. rostratum* meningitis presented with average neutrophil counts of 648 cells/mm^3 [4], suggesting that the inflammatory response in the CNS could have contributed to host damage. A similar mechanism has been proposed in bacterial meningitis, and has led to consideration of the use of steroids, along with antimicrobial agents in certain types of meningitis, in the treatment of bacterial meningitis [12].

At the time of writing, the epidemic of *E. rostratum* meningitis is abating, as the contaminated lots have been identified and removed from clinical use. It is hoped that with improved manufacturing practices and vigilance, fungal contamination will not occur and this tragic episode will not repeat itself. However, the emergence of human disease with *E. rostratum* has demonstrated that, when provided with the opportunity for bypassing cutaneous and mucosal barriers, which normally restrict *E. rostratum* access to human

tissues, this fungus can cause devastating disease. The history of infectious diseases is ripe with examples of human diseases caused by microbes that were once considered to be 'nonpathogens'. These instances often share the commonality that the causative microbes breached a barrier that enabled them to enter a niche in which their interactions with host tissues resulted in damage and disease. In some instances, such microbes emerged as pathogens in concert with a susceptible population. For example, cryptococcal meningitis was once a very rare disease that has become distressingly common as a result of large numbers of immunocompromised patients worldwide [13]. Similarly, the emergence of *Candida albicans* as the cause of catheter-associated bloodstream infection was the result of an opportunity provided by the loss of barrier immunity caused by the insertion of a catheter, which in many instances is amplified by the use of broad-spectrum antibacterial drugs that can facilitate fungal (*Candida*) overgrowth. In recent years, other emergent fungal pathogens have caused devastating loses to amphibian species, bats, corals and other ecosystems [14]. Although fungi are frequent causes of disease in plants, amphibians and insects, they are relatively rare causes of invasive disease in mammals, a fact that has been attributed to a combination of elevated body temperatures and adaptive immunity [15]. However, this protection may erode with climate warming as the thermal gradient between mammal core temperatures and the environment narrows, and this has been suggested to raise the threat of new fungal diseases [16]. Regardless of its future as a human pathogen, *E. rostratum* is an example of an emergent fungal disease, and this fungal meningitis outbreak warns us of the pathogenic potential inherent in the fungal kingdom.

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