Open Forum Infectious Diseases

PERSPECTIVES

Fusariosis in the Sphere

Daniel Aguilar-Zapata[1]

[1]Hospital Médica Sur, Infectious Diseases and Hospital Epidemiology, Mexico City, Mexico

In 2012, the US Centers for Disease Control and Prevention reported a fungal meningitis outbreak due to *Exserohilum rostratum*, caused by methylprednisolone administration. Twelve years later, an iatrogenic outbreak of *Fusarium* meningitis was documented in Mexico after epidural anesthesia.

Keywords. antifungals; fungal meningitis; fusariosis; Mexico; outbreak.

Mexico has been in the spotlight regarding fusariosis over the past 2 years. First, a serious epidemiologic outbreak of iatrogenic meningeal fusariosis occurred in 2 Mexican states (Durango and Matamoros) [1, 2]. Then, the first fusariosis case series in Mexico was published following an ambitious 10-year clinical-epidemiologic project that allowed us to monitor the status of this serious invasive fungal infection [3]. Within this context, several authors have presented communications, reviews, and experiences that have raised awareness about the clinical implications and complications of *Fusarium* species.

Fusarium species are ubiquitous fungi distributed throughout the environment. They are considered pathogenic in small grain cereals and maize, and they cause global losses [4, 5]. In humans, immunocompetent keratitis and onychomycosis are the most frequently caused diseases; however, in individuals who are immunocompromised (eg, prolonged neutropenia, hematologic malignancy), fusariosis presents as a disseminated disease in which fungal pneumonia, skin invasion, and fungemia are the most common clinical presentations [4].

THE OUTBREAK

The outbreak timeline began in September 2022 (Figure 1). The first patient was a woman who received epidural anesthesia for a cesarean section. She presented at Hospital Regional No. 1 in Durango, Mexico, with clinical meningitis syndrome [1, 6]. Alarms were raised when the General Epidemiology Office in Mexico added 3 more cases sharing the following characteristics: history of epidural anesthesia, signs of meningeal infection, and hospitalization at the same private clinics in Durango. Seven months later, in April 2023, a young Hispanic woman received epidural anesthesia at a small clinic in Matamoros, Mexico. Days later, she developed meningeal symptoms that were determined, via cerebrospinal fluid (CSF), to be caused by rare fungal forms and high levels of β-D-glucan [2]. A cascade of cases then occurred, leading to the US Centers for Disease Control and Prevention releasing an outbreak alert [7] through which >185 residents were informed that they were at high risk for fungal meningitis [2]. This became the second wave of *Fusarium* meningitis cases in Mexico within 10 months (Figure 2).

Beyond the catastrophic nature of a neurologic fungal outbreak, 3 important aspects can be highlighted to allow a better understanding of this central nervous system (CNS) fungal infection for future outbreaks: measuring β-D-glucan in the CSF, change in imaging in the CNS, and new treatment options.

CSF β-D-GLUCAN TEST

1,3-β-D-glucan, a cell wall component of many fungi, is detected by the Fungitell commercial assay [8]. This test has been validated as an aid to diagnose invasive fungal infection. Invasive candidiasis, aspergillosis, and fusariosis are clinical entities for which this biomarker has high sensitivity. In invasive fusariosis, β-D-glucan appears to have greater value as a screening assay rather than a diagnostic assay because of its low positive predictive value [9]. This is mainly a serum test, with use under special circumstances as a diagnostic tool with CSF samples. A systematic review of studies in which β-D-glucan was tested in CSF to detect fungal meningitis showed good performance in different scenarios of fungal pathogens affecting the CNS. It is important to highlight that >95% sensitivity was reported in the cortisol injection–related outbreak of *Exserohilum rostratum* with a cutoff of 80 pg/mL. Sensitivity and specificity were 100% and 98%, respectively, based on a cutoff of 138 pg/mL [10].

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Correspondence: Daniel Aguilar-Zapata, MD, Hospital Médica Sur, Infectious Diseases Department, Puente de Piedra 150, Tlalpan, CP. 14050, Mexico City, Mexico (daniel_aguilar@hotmail.com).

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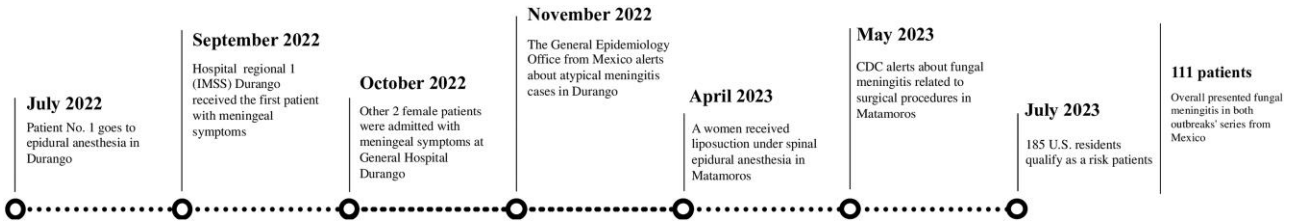

Figure 1. Timeline of cardinal events from the iatrogenic meningeal *Fusarium* infection outbreaks in the cities of Durango and Matamoros in northern Mexico. From July 2022 to July 2023, 111 patients were considered as having possible, probable, and confirmed infections. IMSS, National Institute of Social Security (Mexico); CDC, Centers for Disease Control and Prevention (USA).

Figure 2. Map of Mexico and Texas, USA. The state of Durango is shown with diagonal stripes, within which the pin indicates the location of the city of Durango. The state of Tamaulipas is shown with dots, within which the pin indicates the location of the city of Matamoros, at the border with Brownsville in southern Texas. There are 900 miles separating these locations, in which the outbreak waves were also separated by 10 months. The solid field represents Mexico City and the zigzag area represents Texas—both of which collaborated, in coordination with the US Centers for Disease Control and Prevention, to restraint this iatrogenic outbreak.

CSF β-D-glucan measurement in the series reported by the Fungal Meningitis Response Team (from the Matamoros wave) served as a diagnostic marker in 10 probable and confirmed cases, with a mean 454 pg/mL. Monitoring CSF β-D-glucan also helped with the treatment for these patients. Decreased CSF β-D-glucan levels suggest improvement for patients who are infected [2, 11].

CNS IMAGING

CNS damage from molds can cause cerebrovascular complications, including ischemic/hemorrhagic stroke, venous thrombosis, and mycotic aneurysm [12, 13]. The incidences of these cerebrovascular complications have been estimated at ∼4% to 35% [14]. In their series, Kleinfeld et al [15] reported 3 cases of ischemic stroke and 1 case of hemorrhagic stroke with cerebral vasculitis due to an outbreak of *E rostratum* in the CNS.

Although secondary damage caused by *Fusarium* species has not been reported, Strong et al [16] and Becerril-Gaitan et al [12] observed head computed tomography and magnetic resonance imaging of patients from Matamoros who were treated in southeastern Texas, among whom vasculitis, ischemic infarction, and intracranial hemorrhage were the most frequent complications. A hypothesis concerning *Fusarium* pathophysiology in the CNS relates to the ascending model of infection, in which the membrane of Liliequist serves as a barrier; nevertheless, more physiologic studies are needed to confirm this mechanism of damage [12].

Although the diagnostic approach in meningitis syndrome typically involves routine head imaging, neurovascular findings can now be considered a possible cause of fungal meningitis. However, significant experience must be gained to define strong radiologic patterns of meningeal fusariosis.

TREATMENT

Treatment options are limited to managing invasive fusariosis. For example, fluconazole and the echinocandins show no activity against *Fusarium* species. The global guideline for the diagnosis and management of rare mold infections recommends combination therapy based on liposomal amphotericin B plus voriconazole [17]. Most patients in both waves received this recommended combination treatment.

Manogepix displays good in vitro activity against *Fusarium* species. The minimum effective concentration was ≤0.015 μg/mL, and the minimum inhibitory concentration (MIC_{50}) range was ≤0.015 to 0.25 μg/mL for *F solani*. For *F oxysporum*, the manogepix minimum effective concentration range was ≤0.015 to 0.03 μg/mL, similar to the range for the MIC_{50} at ≤0.015 to 0.125 μg/mL [18]. The compassionate use of the antifungal drug fosmanogepix must be highlighted: this outbreak demonstrated that fosmanogepix had a low MIC_{50} (≤0.008 μg/mL) for these *Fusarium* species; under its administration, 3 of the 4 patients exposed to fosmanogepix survived [2, 16].

INVASIVE FUSARIOSIS FROM MEXICO

In 2023, Mexico published a 10-year retrospective invasive fusariosis case series across 8 hospitals [3], unrelated to the outbreak described here. In that patient cohort (adult and pediatric), the predominate characteristics were invasive fusariosis related to burn injuries (49%), followed by hematologic malignancies (37%). Interestingly, 67% of patients received monotherapy and 12% had no antifungal treatment. Some patients had a late diagnosis and others had a postmortem diagnosis, emphasizing the complexity of diagnosing invasive fungal infections in Mexico.

Clearly, more needs to be learned about this fungus among the patient population in Mexico.

NEW OPPORTUNITIES

Despite concerns generated in Mexico and the United States over the most recent outbreak, achieving patient survival was the result of binational efforts in which >100 health care workers participated. However, there are many caveats surrounding these devastating cases from which we can learn. First, in Mexico and many other countries, deficiencies in diagnostic tools are an obstacle in this context. The inability to obtain quick, simple measures of CSF β-D-glucan delayed the approach in patients in Durango. As a Mexican infectious disease physician, I have always been proud of the many decades of achievements by our National Institute of Epidemiological Reference and Diagnosis and the Clinical Microbiology Laboratory at the National Institute of Medical Sciences and Nutrition Salvador Zubirán. These groups run many patient samples and have developed and standardized novel techniques for detecting pathogens that affect our population [1]. Nevertheless, in a dynamic situation such as an outbreak, a centralized laboratory has shortcomings. This may be an opportunity to expand laboratory tools in our country.

Second, although fungal pathogens such as *Fusarium* species are a significant threat to public health, they have received little attention. With the development of the World Health Organization's Fungal Priority Pathogens List [19], we must all—governments, global organizations such as the International Society for Human and Animal Mycology, the private sector, and the pharmaceutical industry—collaborate to improve the availability of routine and new antifungal drugs to medium- and low-income countries, including drugs under development in the pipeline such as fosmanogepix.

Finally, science can build bridges; catastrophic situations can create working bonds; and the digital era can make it easier to coordinate and act remotely to restore patient health. All these elements helped us react as effectively as possible to this crisis in our country.

Ultimately, 1986 patients at high risk were evaluated for fungal meningitis from both outbreaks, among which, there were 113 meningitis cases (ie, possible, probable, and confirmed). Many of these patients were compared in a report by Hoenigl et al [11], who identified 26 past cases of *Fusarium* infection in the CNS. Future fungal outbreaks will occur. We must have enough strength and confidence to face them.

Notes

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