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Review Article

Immunological insights into iatrogenic fungal meningitis caused by *Fusarium solani*

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ABSTRACT

Fungal meningitis has emerged as a significant public health problem, with outbreaks of the fungus *Fusarium solani* have been recorded in different locations exhibiting high pathogenicity and the serious central nervous system infections. Statistical studies demonstrate that the incidence of neuroinfections caused by *Fusarium solani* are in its majority presented in women (95%), with 88% having a history of obstetric-gynecological procedures, such as cesarean sections, or those involving intrathecal anesthesia. A literature review has been performed to elucidate the mechanisms implied in the immunological response to fungal neuroinfections caused by *Fusarium solani*. 18 articles found in different databases including PubMed, Cochrane Library and Scopus were incorporated in the present article. A critical knowledge gap regarding the evasion mechanisms employed by *Fusarium solani* to overcome the barriers of the nervous system. Further research in neuroimmunology is crucial in order to establish new therapeutic approaches to treat these infections.

Key Words: central nervous system; neuroinfection; fungus; meningitis; fusarium solani; anesthesia; iatrogenesis.

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RESUMEN

La meningitis fúngica ha surgido como un importante problema de salud pública, con brotes del hongo *Fusarium solani* registrados en diferentes regiones, exhibiendo alta patogenicidad y causando graves infecciones del sistema nervioso central. Estudios estadísticos demuestran que la incidencia de neuroinfecciones causadas por *Fusarium solani* se presenta mayoritariamente en mujeres (95%), con un 88% de casos relacionados con procedimientos obstétrico-ginecológicos, como cesáreas, o aquellos que involucran anestesia intratecal. Se realizó una revisión de la literatura para dilucidar los mecanismos implicados en la respuesta inmunológica a las neuroinfecciones fúngicas causadas por *Fusarium solani.* Se incorporaron 18 artículos encontrados en diferentes bases de datos, incluyendo PubMed, Cochrane Library y Scopus, en el presente artículo. Existe una importante brecha de conocimiento con respecto a los mecanismos de evasión empleados por *Fusarium solani* para superar las barreras del sistema nervioso. La investigación adicional en neuroinmunología es crucial para establecer nuevos enfoques terapéuticos para tratar estas infecciones.

Palabras clave: sistema nervioso central; neuroinfección; hongos, meningitis; fusarium solani; anestesia; iatrogenia.

INTRODUCTION

Meningitis is defined as inflammation and irritation of the meninges. In fungal meningitis, the meninges are infected and inflamed due to an increase in pressure secondary to the creation of an abscess, granuloma, cyst, etc. These intracranial masses increase pressure because of the subarachnoid space's obstruction, blocking cerebrospinal fluids drainage. This increase in pressure generates the symptoms that patients refer to such as severe headaches, nausea, vomiting, visual alterations, neurological deficits, or even convulsions.

Its diagnosis relies on classic clinical signs such as nuchal rigidity, Kernig's sign, and Brudzinski's sign. These signs work on the principle that by stretching the inflamed meningeal membranes, it will cause detectable irritation in the body. Positive signs increase the likelihood of a meningitis diagnosis, while their absence reduces this probability. They are most effective when combined with other historical and examination features to provide a comprehensive clinical assessment.[1]

Fungal meningitis, however, is particularly challenging to diagnose due to its nonspecific symptoms and often the absence of meningeal irritation signs. This difficulty in diagnosis results in delayed treatment, leading to higher rates of morbidity and mortality.[2] The complications from which meningitis derives have a great influence on mortality since they compromise brain tissue by generating chronic inflammation and subjects it to frequent hypoxic events. The most common and feared complication is the rupture of fungal aneurysms. A fungal aneurysm is highly mortal because of its rapid progress to hemorrhagic complications, that severely compromises patient´s lives. At the same time, one of the biggest concerns of medical personnel is that the elevation of intracranial pressure rises enough to herniate the tonsils of the cerebellum, compressing the cardiorespiratory center, resulting in respiratory failure, stupor, coma, arrhythmias, and even cardiac arrest.[3]

By May 2023, outbreaks of fungal meningitis had been recorded in states in the north of Mexico, such as the case of Durango, where 1,801 cases have been reported, it is of special interest that 95 % of the cases correspond to female patients, and 88 % of these cases with a history of gynecological-obstetric procedures, such as cesarean section, unfortunately there have been 39 deaths related to the outbreaks to that date. Since October 5, 2022, when the first cases were reported, and so far, it has been recorded that 31 of the cases have a positive PCR result for *Fusarium solani* fungus species.[4]

Between 1974 and 2022, 26 cases of neuroinfections caused by *Fusarium* were identified in the literature. In contrast to the recent outbreak, 60% of the individuals had underlying hematologic malignancy and 16% received immunosuppressive therapy. Given that many of the reported cases occurred before the widespread clinical use of voriconazole, most of the patients were managed with amphotericin B monotherapy.[5]

MATERIALS AND METHODS

A systematic review was carried out, based on the main globally recognized scientific databases, such as PubMed, Cochrane Library and Scopus. The terms ("Neuroinfection" AND "Fungus" OR "*Fusarium solani*"), ("Meningitis" AND

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"*Fusarium solani*"), ("Neuroinfection" AND "Anesthesia" AND "*Fusarium solani*") allowed to delimit the results with greater specificity oriented to iatrogenic meningitis by *Fusarium solani*. In addition, combinations of keywords were made that placed greater emphasis on the available treatments and on the therapeutic interventions applicable to this pathology. 18 articles from 2014 to 2024 were included in this review, focusing only on those with significant clinic and therapeutic relevance. Articles outside the temporal range, not indexed in the selected databases, or lacking a relevant focus on immunological and therapeutic approach were excluded.

RESULTS

Fungal neuroinfections

Although it is estimated that there are millions of species of fungi, only 70,000 have been identified, of which 300 have been classified as pathogenic for humans, and only 10-15 % can invade the central nervous system. Fungi need environments with organic matter and water to develop, resources that are found in hosts such as humans. How these organisms reach the body is usually due to direct contact with the skin, mucous membranes, or vascular system, the inhalation of their spores, or their direct inoculation. Generally, fungi do not tend to infect humans and in the case of an infection, the mechanisms of the immune system can prevent its dissemination; however, if these mechanisms fail to contain these agents, they can reach the meninges, cross the blood-brain barrier (BBB) and finally reach the central nervous system (CNS).

It is not common for this type of fungal infection to be transmitted from patient to patient, neither having a high incidence, however, various risk groups are more susceptible to fungal infections, such as individuals with HIV/AIDS, solid-organ transplants, hematological diseases, extensive burns or immunodeficiencies. However, in the reported outbreaks, the circumstances of the patients were different, as they were immunocompetent patients who have undergone surgical interventions of the nervous system, such as a lumbar puncture.[6-7]

Fusarium solani

Among the filamentous hyaline fungi is the genus *Fusarium*, which includes more than 200 different species, among which some agents are pathogens for humans, such as *F. solani, F oxysporum, F. verticillioides, and F. proliferatum, with F. solani* being the most resistant and lethal species of them. *Fusarium solani* can cause superficial infections such as onychomycosis and keratitis or disseminate throughout the system and generate serious pulmonary infections, meningitis, and brain or vertebral abscesses (Figure 1).

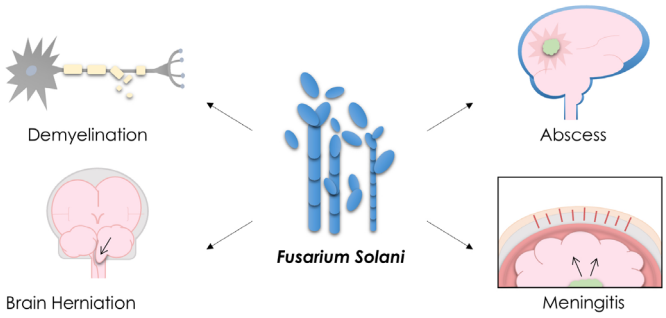

Figure 1. Impact of *Fusarium solani* at central nervous system level. The repercussions of fungal infections are mainly characterized by demyelination, abscesses, brain herniation and meningitis.

There are also different virulence factors in the *Fusarium* genus, such as mic toxins that suppress both cellular and antibody-mediated immune response, or other toxins such as Fumonisin B1, its mechanism of action in central nervous system infections consists of causing axons demyelination, in addition to damaging microglia by altering cellular respiration, and altered cellular respiration is a result of affecting the phospholipid membrane.[3,6] Another very relevant factor in fusariosis is their adaptability to environments with very few oxygen availability, by activating the processes of glycolysis and oxidative phosphorylation, which favor inflammation.[7]

The incidence of fusariosis varies geographically, with higher rates reported in tropical and agricultural regions. However, in recent years, outbreaks of meningitis and endophthalmitis caused by *Fusarium* have been documented in urban areas. These outbreaks have been linked to batches of contaminated parenteral drug formulations, as a result of poor aseptic manufacturing methods and the persistence of *Fusarium* within the production facilities, since this species is capable of persisting in drains and pipes, rubber sealants, cosmetics, among others.[8] Therefore, the administration of a contaminated drug can be related to an infection with this fungus, in this way, there is the hypothesis that the main entry route for *Fusarium solani* was during the epidural or spinal blockade before a cesarean section.

Recent studies found that *Fusarium solani* exhibits a concerning tropism for the cerebral vasculature, leading to severe vasculitis and arterial dissection. This predilection may contribute to an increased risk of vertebrobasilar complex vasculitis (CVC) in patients affected by the current fungal meningitis outbreak. While the ascending spread of infection from the lumbar epidural space is a possible explanation, the full extent of *Fusarium´s* angioinvasive nature remains to be elucidated.[9]

Fusarium solani infections present a significant challenge due to the inherent resistance of these fungi to many antifungal classes; it is well-documented to have intrinsic resistance to echinocandins. The intrinsic resistance of *Fusarium* likely arose in the environment as a survival mechanism; it has developed efflux pumps that effectively combat plant-produced antimicrobials and tebuconazole. Furthermore, global warming might be contributing to increased virulence in some *Fusarium* species. For example, thermotolerance has been observed in the *Fusarium graminearum* complex, threating food security and leading to increased fungicide use in agriculture, which could further exacerbate antifungal resistance in the future.[5]

Role of the immune system

When a *Fusarium* infection occurs due to direct exposure of the tissue to the agent, before entering the central nervous system, it encounters a barrier generated by the meninges, where the fungus can lead to the formation of abscess or granulomas, causing a significant elevation of the intracranial pressure.

During systemic infections *Fusarium* may disseminate through the bloodstream to the CNS. The BBB restricts the fungal entry, limiting the infection to vasculature. However, because of immunosuppression, mechanisms of immunological evasion, or a high inoculum in immunocompetent patients, the fungus can disrupt this barrier and spread to CNS parenchyma, which may result in encephalitis or brain abscesses.[10] This underscores the importance of generating therapies that reinforce central nervous system barriers.

When *Fusarium* overcomes the primary barriers of the innate immune system such as phagocytosis, it is detected by the adaptive immune system through the recognition of its cell wall of chitin and β-glucan employing specific receptors and then the antigenic presentation is carried out by microglia and dendritic cells. However, the presence of immune cells in the CNS can cause irreparable damage due to the limited regeneration capacity of the resident cells. In addition, the recruited immune cells can contribute to the spread of fungi through the "Trojan horse" mechanism. The involvement of microglia and antigen-presenting cells may offer potential therapeutic targets related to immune activation and modulation.

Subsequently, both an inflammatory response is activated, as well as an anti-inflammatory response mediated by the type and number of cytokines produced by microglia and perivascular macrophages, the predominance between these types of response depends directly on the genetic susceptibility of the patient.[5,11] Also, T cells, astrocytes, and endothelial cells inhibit fungal growth by producing cytokines (IFN- γ, TNF-α, IL-1β, IL-6, and IL-12), chemokines, nitric oxide and superoxide anion, and by the expression of MHC I and II molecules.[12]

Neutrophils have a critical role in controlling inflammatory cellular reaction, as they provoke damage to hyphae of Fusarium by phagocytosis enhanced by G-CSF and IL-15, also enhanced by IL-8 and direct damage mediated by *Fusarium´s* hyphae. Patients with prolonged neutropenia, graft-versus-host disease and corticosteroid use exhibit increased risk for fusariosis. This observation highlights the relevance of neutrophil recruitment in combating these infections. Moreover, it suggests the potential applications of neutrophils to targeted drug delivery as shown in Figure 2.[13]

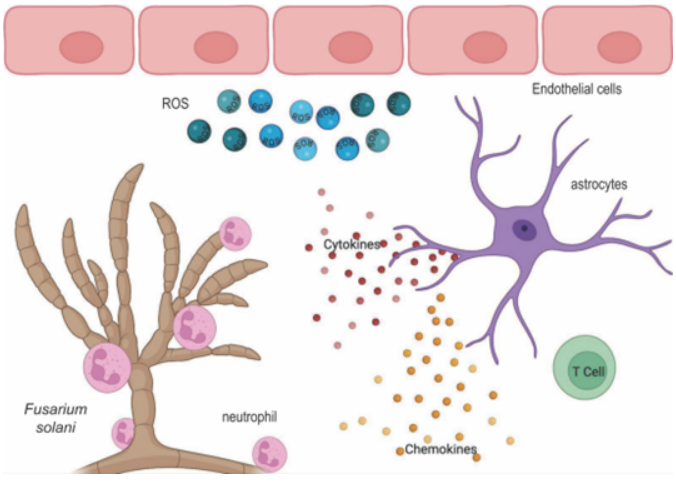

Figure 2. Immune response to *Fusarium solani*. Multiple cells are involved in the response to *F. Solani* neuroinfection, such as neutrophils, dendritic cells, endothelial cells and T cells.

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TREATMENT

Fusarium species frequently show resistance to antifungal drugs, which is one of the reasons why localized infections often spread into the bloodstream. To date, the pharmacological therapy with the greatest evidence against systemic fusariosis is the use of voriconazole, either alone or in combination with other drugs such as amphotericin b in its lipid formulation, this combination aims to broaden the antifungal activity against these highly resistant pathogens as they have shown an acceptable distribution either in CSF or brain parenchyma.[14] Species-specific antifungal recommendations remain elusive due to limited data. Novel antifungals nowadays appear as promising agents such as fosmanogepix and olorofim, with good CNS penetration, offering hope for future treatment options.[9]

Cytochrome P450 enzymes are important for ergosterol synthesis and virulence, important for Fusarium´s membrane function. Recent study groups are now evaluating the role of ERG5 and ERG6 for these fungi as a possible therapeutic target or to know their involvement in antifungal resistance. Also, to determine if mutations in ERG3, ERG6 and ERG11 are linked to anfotericin and azole resistance.[15]

Compressive and medullary syndromes caused by abscess or granulomas need prompt neurosurgical decompression, drainage, and resection tailored to characteristics of the lesion. In comparison with localized meningitis or radiculopathies are treated conservatively.[16] In case there is the possibility of surgical or endovascular therapy, that is, lesions such as abscesses are located in a cortical or subcortical area, not in places of greater care such as the brain stem, deep locations, or that are of multiple foci, the lesions can be removed also continuing with pharmacological therapy since it has been shown that this improves the survival of patients significantly.[4]

DISCUSSION

Even if there are a small number of species of fungi that can cause infections at the level of the nervous system, measures to prevent their proliferation must be implemented, since the neuroinfections caused by these agents can have fatal results. The problem of contaminated drug batches by *Fusarium* in previous outbreaks highlights the importance of ensuring adequate aseptic practices in the production of drugs. In addition, a hypothesis is raised about the entry route of the fungus during epidural or spinal blocks before gyneco-obstetric procedures.

General rate associated with fungal meningitis is notably high, with approximately 50% mortality rate comprising different agents, and specifically of 51% in outbreaks of *Fusarium solani.* Even though the mortality of fungal meningitis during pregnancy is not well established, given these numbers it is reasonable to infer that mortality could potentially be exacerbated by inmunological and physiological changes associated in pregnant patients.[17]

Even if the species of fungi demonstrate resistance to pharmacological therapy, it still represents the most viable alternative for contributing to patient's outcome, in some cases during the outbreak in Mexico patients who did not receive antifungal therapy had multiple complications such as vertebrobasilar thromboses, necrosis, granuloma formation and infarcts which ended with patient´s life. Endovascular therapy faces its limitations, as they are performed based on the clinical course of the infection.[18] Voriconazole alongside lipid-based amphotericin B are considered the primary treatment option. And, finally, it is necessary to correlate the relationship between the MIC and treatment effectiveness.

While the CNS was previously considered immune-privileged, recent studies have revealed that resident cell types within the CNS, particularly glial cells, possess the capability to recognize and react to invading pathogenic fungi through pattern recognition receptors (PRRs). These responses initiate immune reactions during fungal infections. Furthermore, it has been established that immune cells can be recruited to the CNS from the bloodstream during fungal infections within this region.[19] Neutrophil-mediated drug delivery strategies offer potential applications for erradicating fusariosis, while simultaneously preserving innate immunity.

Neuroimmunological mechanisms that are implicated during an infection with *Fusarium solani* are not fully determined, in comparison with other fungal species and with other sites of infection. It is important to carry out in-depth research on the interaction at the cellular and molecular that there are new therapies that help combat such neuroinfections, specially focusing on neutrophil interaction and cytochrome activity.

Also, in order to prevent fungal neuroinfections derived from gyneco-obstetric interventions, it is crucial to follow rigorous aseptic techniques during neuraxial procedures, such as maintaining good hand hygiene, wearing sterile gloves, hat and mask, and preparing the skin with antiseptic solutions. In addition, prophylactic antifungal therapy may be considered in pregnant patients at high risk of fungal infections.

CONCLUSIONS

The crucial role of the immune system in the response to infection is emphasized, especially in how the fungus overcomes natural immunity and can reach the CNS, patient´s immune state significantly influences the outcome of the disease, being neutropenia the most negative factor. The complications associated with fungal meningitis, such as the formation of fungal aneurysms, show the severity of the disease and the importance of effective management.

Fusarium infections are challenging to treat due to drug resistance and limited therapeutic options. Pharmacological research is nowadays the most promising alternative for fighting infections caused by *Fusarium solani,* while voriconazole remains the most effective drug, novel antifungals like fosmanogepix and olorofim shows promise. Targeting enzymes involved in ergosterol synthesis, such as ERG5 and ERG6, could provide new therapeutic avenues. Neurosurgical intervention is often necessary for compressive or medullary syndromes, but conservative management is suitable for localized meningitis or radiculopathies. A combination of surgical and pharmacological treatment can significantly improve survival rates in patients with fusariosis.

Additionally, general infection control measures, such as minimizing the use of invasive devices and hand hygiene, are essential to reduce the risk of fungal infections and prevent them from becoming a cause of maternal mortality.

Fusarium solani mycoses are serious infections that can cause significant disease, especially in people with immune deficiencies. While the brain was once thought to be immune-privileged, recent research shows that resident immune cells respond to fungal infections. There still exists a big knowledge gap about how the brain responds to *Fusarium solani* infections, due to the unique environment of the CNS and technical challenges in studying it. This knowledge gap needs to be addressed to improve treatment and reduce the impact of CNS mycoses.

CONFLICTS OF INTEREST

The authors declare that they do not have conflicts of interest.

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