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Invasive Aspergillosis Due to *Aspergillus flavus*: Report of Two Cases and Literature Review

Mtibaaa L[1,2,3*], Bergaoui H[1,4], Thabet E[1], Zakraoui M[2,5], Boughariou S[2,5], Gharsallah H[2,5], Ferjani M[2,5] and Jemli B[1,3,4]

[1]*Laboratory of Parasitology-Mycology, Military Hospital of Tunis, 1008, Monfleury, Tunis, Tunisia*
[2]*Faculty of Medicine of Tunis, University of Tunis El Manar, Tunis 1007, Tunisia*
[3]*LR 19DN03, 1008, Monfleury, Tunis, Tunisia*
[4]*Faculty of Pharmacy of Monastir, University of Monastir, Monastir 5000, Tunisia*
[5]*Intensive Care Unit, Military Hospital of Tunis, 1008 Monfleury, Tunis, Tunisia*

[*]**Corresponding author:** Mtibaa L, Laboratory of Parasitology-Mycology, Military Hospital of Tunis, 1008, Monfleury, Tunis, Tunisia. Faculty of Medicine of Tunis, University of Tunis El Manar, Tunis 1007, Tunisia; E-mail: mtibaalatifa@yahoo.fr

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Abstract

Invasive aspergillosis (IA) is a severe fungal infection classically affecting immunocompromised patients, although an increasing number of cases are being reported in intensive care units (ICU), including patients without traditional risk factors. We report two cases of IA caused by *Aspergillus flavus*. The first case involved a 24-year-old woman with stage II Hodgkin lymphoma who underwent autologous hematopoietic stem cell transplantation. During her ICU stay, she developed neurological deterioration, and brain magnetic resonance imaging showed a cerebral abscess. Despite negative non-invasive investigations, histopathological examination and culture of a brain biopsy revealed septate hyphae and growth of *Aspergillus flavus*, confirming cerebral aspergillosis. She received voriconazole but died despite combined medical and surgical management. The second case concerned a 46-year-old previously healthy man admitted after severe polytrauma with multiple injuries, including traumatic brain injury and open foot fractures. On day 9, necrosis of a heel wound occurred, and surgical biopsy demonstrated fungal hyphae with culture positive for *Aspergillus flavus*, establishing primary cutaneous aspergillosis. He was treated with liposomal amphotericin B, repeated surgical debridement, and negative-pressure wound therapy, leading to local improvement; however, he died later from ventilator-associated pneumonia complicated by septic shock. These cases illustrate the heterogeneous clinical spectrum of IA and highlight the emerging role of A. flavus in both immunocompromised and critically ill immunocompetent patients. Early mycological investigations remain essential for prompt diagnosis and appropriate antifungal therapy in atypical clinical settings.

Keywords: Invasive aspergillosis; *Aspergillus flavus*; Cerebral aspergillosis; Primary cutaneous aspergillosis

Introduction

The increasing use of immunosuppressive therapies, anticancer treatment protocols, and invasive intensive care procedures has profoundly modified the epidemiology of invasive fungal infections, making them an emerging concern in modern hospital settings [1]. *Aspergillus* spp. are ubiquitous saprophytic filamentous fungi found in soil, organic matter, ambient air, and hospital environments. They are responsible for invasive aspergillosis (IA), a severe opportunistic infection associated with high mortality despite advances in diagnosis and therapy [2]. Infection occurs mainly through inhalation of airborne conidia, leading to primary pulmonary involvement with potential hematogenous dissemination to the central nervous system, skin, and other organs [3]. Classical risk factors include prolonged neutropenia, hematological malignancies, solid-organ transplantation, and long-term corticosteroid therapy [1-3]. However, IA is increasingly reported in critically ill immunocompetent patients, particularly in intensive care units (ICU) following severe trauma, surgery, or prolonged mechanical

ventilation [4]. The genus *Aspergillus* comprises more than 300 species, with at least 60 implicated in human disease. *Aspergillus* fumigatus remains the predominant species, followed by *A. flavus, A. niger,* and *A. terreus* [5]. These species differ in epidemiology, virulence, and antifungal susceptibility profiles [6]. Diagnosis of IA relies on a combination of clinical, radiological, and mycological criteria. Despite increasing recognition, published data remain limited and are mostly based on small series and case reports. In this context, we report two cases of invasive aspergillosis due to *Aspergillus flavus* diagnosed at the Military Hospital of Tunis.

Case Presentation

Case 1: A 24-year-old woman with stage II Hodgkin lymphoma followed for 18 months was treated with multiple chemotherapy regimens and autologous hematopoietic stem cell transplantation (-1month). She was admitted to the ICU on Day 0 for acute respiratory distress secondary to transfusion-associated circulatory overload with pulmonary edema. On Day 5, she developed neurological deterioration with altered consciousness and left hemiparesis. Brain magnetic resonance imaging (MRI) performed on Day 7 showed a 56 × 36 mm right parieto-temporo-occipital lesion suggestive of cerebral abscess (Figure 1).

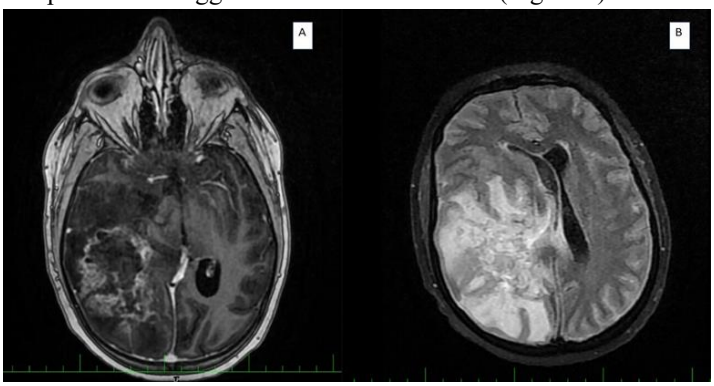

Figure 1: *(A) Axial contrast-enhanced T1-weighted MRI with gadolinium showing a right cerebral abscess. (B) Axial T2-weighted/FLAIR (Fluid-Attenuated Inversion Recovery): MRI sequence highlighting the perilesional edematous component of the abscess. The green scale indicates lesion measurements in centimeters (cm).*

Empirical antibiotics combined with dual antifungal therapy (liposomal amphotericin B and caspofungin) were initiated. On Day 12, after correction of thrombocytopenia, stereotactic brain biopsy was performed and revealed septate hyphae, with culture identifying *Aspergillus flavus*, confirming cerebral IA (Figure 2A and 2B).

On Day 14, antifungal therapy was switched to voriconazole (500 mg twice daily). On Day 28, the patient developed refractory intracranial hypertension with cerebral herniation, requiring decompressive craniectomy; however, despite treatment, her condition progressively worsened, leading to death. Patient Information (Figure 2).

Case 2: A 46-year-old previously healthy man was admitted to the ICU on Day 0 following a road traffic accident causing severe polytrauma and traumatic brain injury with a Glasgow Coma Scale score of 3/15. Initial whole-body computed tomography revealed a left fronto-temporo-parietal subdural hematoma, subarachnoid hemorrhage, bilateral hemothorax, pelvic fracture, and open fractures of the fourth and fifth metatarsals of the right foot associated with a heel wound. After hemodynamic stabilization, surgical management of peripheral injuries and pleural drainage were performed. On Day 9, he developed progressive cutaneous necrosis at the site of the right heel wound (Figure 3), for which surgical debridement and biopsy were performed.

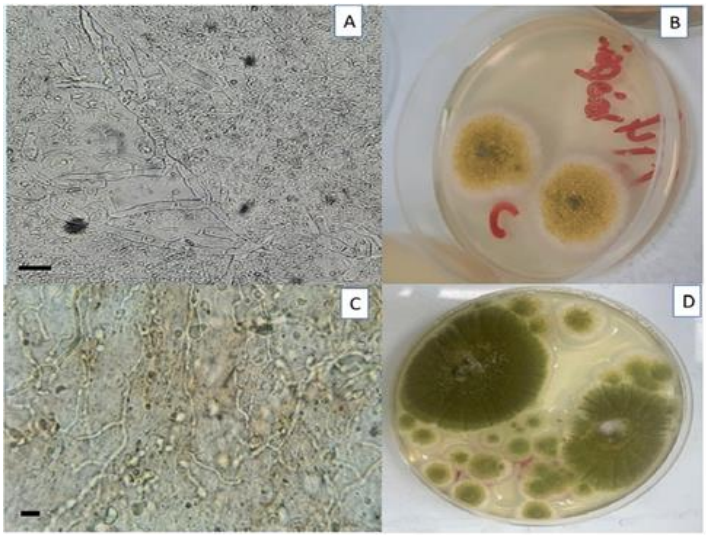

Figure 2: *A: Microscopic examination of the brain biopsy showed septate Aspergillus-type hyphae (scale bar 10µm); B: culture of brain biopsy specimens showing Aspergillus flavus; C: Microscopic examination of the cutaneous biopsy showed septate Aspergillus-type hyphae (scale bar 10µm); D: Culture of cutaneous biopsy specimens showing Aspergillus flavus.*

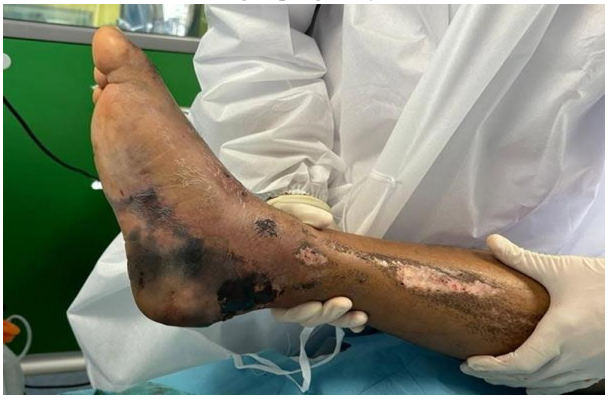

Figure 3: *Cutaneous necrosis of the right foot.*

Direct microscopic examination of the tissue showed septate fungal hyphae, and cultures on Sabouraud media identified *Aspergillus flavus*, confirming post-traumatic cutaneous aspergillosis (Figure 2C and 2D). Liposomal amphotericin B was immediately initiated, combined with repeated surgical debridement and negative-pressure wound therapy, resulting in favorable local wound evolution. However, despite local control of the fungal infection, his ICU course was complicated by ventilator-associated pneumonia progressing to septic shock, leading to death on Day 54.

Discussion

Invasive fungal infections represent a growing global burden, with more than 1.8 million cases estimated in 2017, including approximately 250,000 cases of IA [7]. Although mold-active prophylaxis has reduced IA in high-risk populations, an epidemiological shift toward critically ill non-neutropenic ICU patients, solid-organ transplant recipients, and patients exposed to corticosteroids is increasingly recognized [7]. Among *Aspergillus species*, *A. fumigatus* remains predominant, but *A. flavus* is increasingly reported, particularly in tropical regions and immunocompetent hosts [8]. In a systematic review, it accounted for 18.6% of IA overall and up to 76% in tropical areas [8]. Cerebral aspergillosis, as illustrated in our first case, most commonly results from hematogenous dissemination from a pulmonary focus, or less frequently from contiguous sinus disease. Its angioinvasive behavior leads to vascular thrombosis, infarction, and abscess formation. Despite advances in imaging, diagnosis remains challenging due to nonspecific clinical manifestations and is associated with extremely high mortality rates, ranging from 85% to 99% [9]. Brain MRI typically shows hemorrhagic, ring-enhancing lesions with diffusion restriction. However, definitive diagnosis relies on histopathological and microbiological evidence obtained from brain biopsy or cerebrospinal fluid (CSF) culture [10], which is feasible in fewer than 20% of cases [8].

Primary cutaneous aspergillosis, as observed in our second patient, is a rare entity caused by direct inoculation of fungal spores into disrupted skin, particularly traumatic wounds, burns, or surgical sites [11]. In contrast, secondary cutaneous aspergillosis reflects hematogenous dissemination in severely immunocompromised hosts [12]. Severe trauma with open fractures likely represented the portal of entry in our patient. The wide clinical variability of cutaneous lesions may delay diagnosis, highlighting the importance of early mycological investigation. ICU acquired IA is increasingly recognized even in patients without immunosuppression. Meersseman et al. reported that up to 70% of ICU associated IA cases occurred in patients without hematological malignancy, with mortality approaching 80% [13]. Early combined surgical and antifungal management significantly improves outcomes compared with delayed therapy [12], as illustrated by the favorable local control achieved in our second case despite fatal overall outcome. Microscopy remains essential, classically demonstrating septate hyaline hyphae with acute-angle branching (45°), while culture confirms species identification. However, sensitivity is limited, particularly in critically ill patients. Non-invasive biomarkers, including serum and CSF galactomannan, as well as PCR assays, provide complementary diagnostic support, although their performance varies according to host immune status and antifungal exposure [7,9]. CSF galactomannan appears particularly useful in cerebral aspergillosis, with higher negative predictive value in low-prevalence settings. Voriconazole remains the first-line treatment for IA and is the drug of choice for cerebral involvement due to excellent central nervous system penetration [8]. Isavuconazole represents an alternative with similar efficacy and improved safety profile [14]. Liposomal amphotericin B is generally reserved for refractory cases or azole resistance and was used in our second patient, associated with initial local improvement.

Conclusion

Despite therapeutic advances, the prognosis of invasive aspergillosis remains poor, particularly in cases with delayed diagnosis or central nervous system involvement. These two cases highlight the broad and expanding clinical spectrum of *Aspergillus flavus* infections, occurring in both immunocompromised and immunocompetent critically ill patients, and emphasize the need for early clinical suspicion and prompt diagnostic strategies. Histopathological and microbiological confirmation remains the diagnostic gold standard. Early recognition and timely initiation of appropriate antifungal therapy are crucial to optimize management and improve patient outcomes.

Declaration of Interests

The authors declare no conflicts of interest related to this article.

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