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Case Report

Fungemia Due to the *Fusarium solani* Species Complex in Coinfection with *Aspergillus terreus* After Haploidentical Hematopoietic Stem Cell Transplantation for Severe Aplastic Anemia

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Abstract: Invasive fungal infections (IFIs) represent an important cause of morbidity and mortality in patients undergoing hematopoietic stem cell transplantation (HSCT), particularly in the setting of profound and prolonged immunosuppression. Among the emerging etiological agents, filamentous fungi, especially *Aspergillus* spp. and *Fusarium* spp., stand out, and although coinfection is rare, it poses a significant diagnostic and therapeutic challenge. We report the first known case of coinfection by *Aspergillus terreus* and the *Fusarium solani* species complex in a patient with severe aplastic anemia who underwent haploidentical HSCT. The patient developed a clinical presentation consistent with disseminated fungal infection, characterized by *Fusarium* fungemia and necrotic skin lesions, despite combined antifungal therapy. Graft failure and prolonged neutropenia were the main determinants of the unfavorable outcome. This case highlights the complexity and severity of invasive fungal coinfections in immunocompromised hosts, emphasizing the need for rigorous microbiological surveillance, early diagnosis, and new integrated therapeutic approaches coupled with effective immune recovery.

Keywords: Coinfection; Fusariosis; Fungemia; *Aspergillus*; Hematopoietic Stem Cell Transplantation; Immunosuppression; Aplastic Anemia.

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1. Introduction

Invasive fungal infections (IFIs) constitute one of the leading causes of morbidity and mortality in patients undergoing hematopoietic stem cell transplantation (HSCT), especially in the presence of profound immunosuppression, as seen in cases of severe aplastic anemia [1,2]. In this population, the combination of severe and prolonged neutropenia, cellular immunosuppression induced by cytotoxic agents, and disruption of mucocutaneous barriers creates a highly favorable environment for colonization and invasion by opportunistic fungi [1].

Among the emerging etiological agents, filamentous fungi stand out, particularly *Aspergillus* spp., the most prevalent pathogen in HSCT recipients, and *Fusarium* spp., whose incidence has been progressively increasing, especially in patients with underlying hematologic diseases or those exposed to intensive immunosuppressive regimens [3,4]. Invasive fusariosis is characterized by an aggressive clinical course with cutaneous, pulmonary, and hematogenous tropism. Unlike aspergillosis, *Fusarium* spp. exhibits a higher

propensity for fungemia, making positive blood cultures a marker of disseminated disease and an indicator of poor prognosis [4].

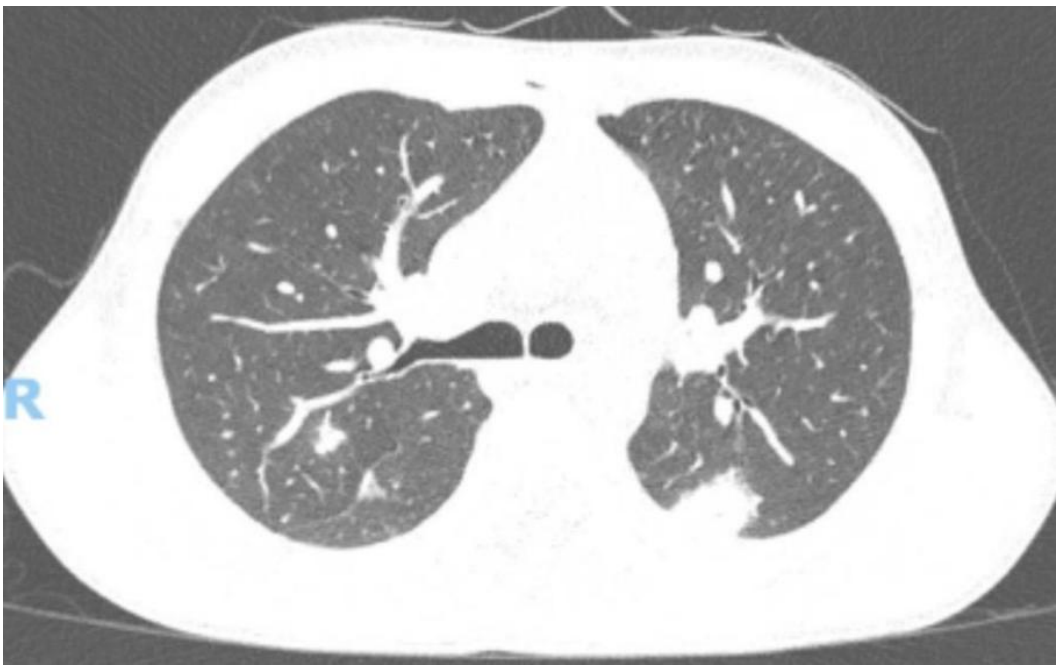
Fungal coinfections caused by distinct filamentous species, although rare, represent an additional clinical challenge, often associated with profound immunosuppression, diagnostic difficulty, and therapeutic limitations [1,2,4]. This report describes a rare case of coinfection by *Aspergillus terreus* and the *Fusarium solani* species complex in a patient with severe aplastic anemia who underwent haploidentical HSCT, illustrating the diagnostic and therapeutic complexity of such conditions in immunocompromised hosts.

2. Case Report

A 17-year-old male patient from Bolivia, previously healthy, was admitted with a clinical presentation of prolonged fever, weight loss, asthenia, and epistaxis. Initial laboratory tests revealed severe pancytopenia with profound neutropenia (<100/mm^3), hemoglobin of 5.8 g/dL, and platelet count of 4,000/mm^3. Bone marrow biopsy demonstrated diffuse hypocellularity without blasts, confirming the diagnosis of severe aplastic anemia. During hospitalization, under persistent neutropenia, the patient remained febrile. Chest computed tomography revealed pulmonary consolidation consistent with bacterial pneumonia, later corroborated by the isolation of *Pseudomonas aeruginosa* in bronchoalveolar lavage, in addition to multiple bilateral nodules with ground-glass halo sign (Figure 1), a finding suggestive of invasive fungal infection.

Given this scenario, complementary investigation included serial serum galactomannan testing, all of which were negative, and bronchoscopy with bronchoalveolar lavage, whose fungal culture and additional microbiological studies were also negative. Histopathological examination of lung biopsy showed diffuse alveolar hemorrhage without morphological features consistent with fungal infection. Based on these findings, targeted broad-spectrum antibiotic therapy was initiated along with antifungal prophylaxis with voriconazole.

Figure 1. Axial chest computed tomography showing bilateral ground-glass opacities with halo sign, predominantly in the left lower lobe, suggestive of angiocentric infiltrate with perilesional hemorrhage, consistent with an invasive fungal pneumopathy.

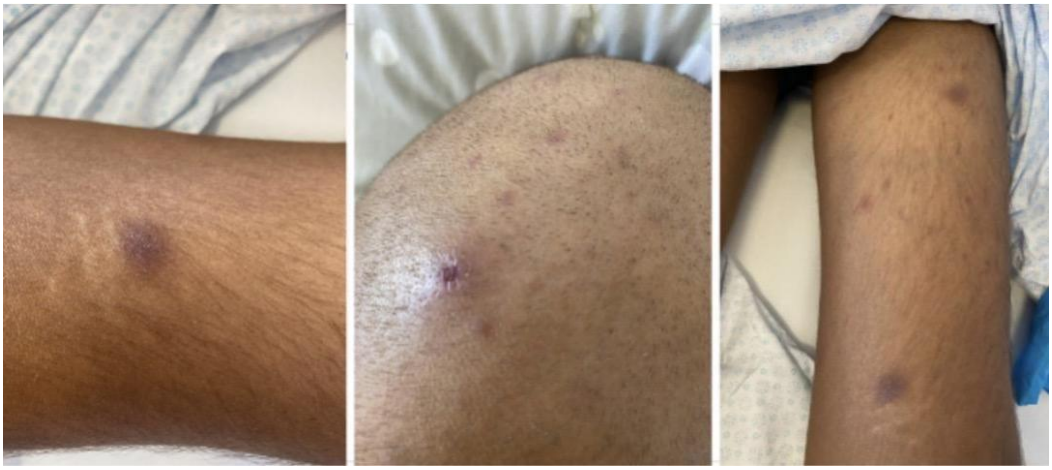


After clinical stabilization, preparation for the haploidentical hematopoietic stem cell transplant was initiated, using a myeloablative conditioning regimen consisting of cyclophosphamide (50 mg/kg/day for 4 days) and antithymocyte globulin (2.5 mg/kg/day for 3

days. In the early post-transplant period (Day +6), the patient developed necrotizing ulcerative gingivitis, and culture of the oral mucosa isolated *Aspergillus terreus*. Considering the prior use of voriconazole for prophylaxis and repeatedly subtherapeutic serum drug levels, therapy was switched to isavuconazole in order to broaden antifungal coverage and optimize plasma exposure.

In the following days (Day +10), the patient progressed with extensive fungal sinusitis and the appearance of ulcerated and necrotic skin lesions on the lower limbs and scalp (Figure 2). Histopathological and microbiological evaluation of skin and paranasal sinus samples confirmed infection by the *Fusarium solani* species complex, with clear angioinvasion. Surgical debridement of the paranasal sinuses was performed to reduce fungal burden and obtain diagnostic material, while antifungal therapy with isavuconazole was maintained.

Figure 2. Nodular, erythematous-violaceous skin lesions on the lower limbs (A and C) and scalp (B), with necrotic or ulcerated centers. Biopsy and fungal culture confirmed infection by the *Fusarium solani* species complex, consistent with invasive fungal disease.



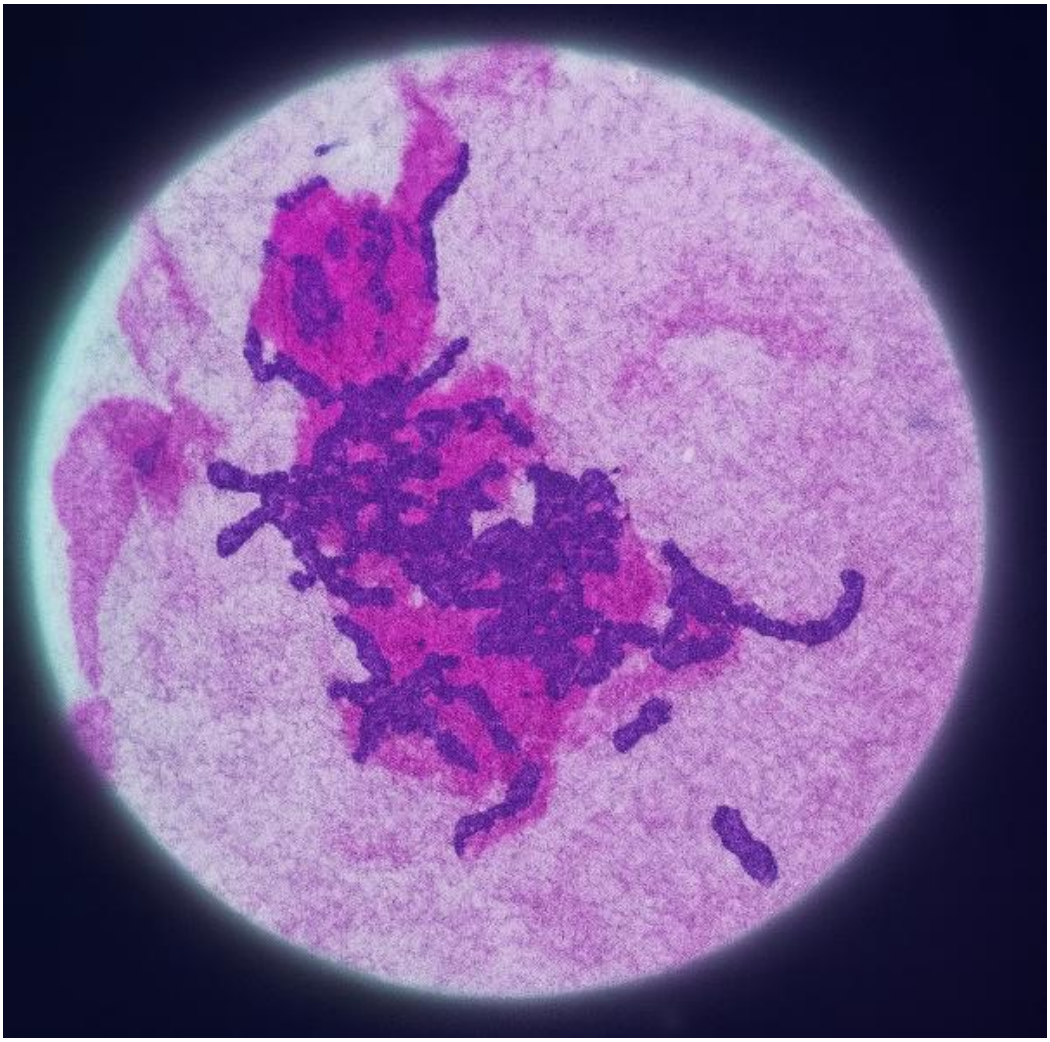
Given the patient's progressive clinical deterioration and refractory fever, liposomal amphotericin B (5 mg/kg/day IV) was initiated in combination with isavuconazole, with subsequent dose escalation to 7.5 mg/kg/day IV as a therapeutic rescue strategy in the setting of disseminated fusariosis. The patient developed hypotension, hypoxemia, and hematochezia, and peripheral blood cultures were positive for the *Fusarium solani* species complex (Figure 3), confirming active fungemia. He remained in persistent hematopoietic aplasia despite the use of granulocyte colony-stimulating factors and intensive supportive care. There was no evidence of marrow engraftment, and the clinical course progressed to refractory multiorgan failure, culminating in death on Day +30 post-transplant.

3. Discussion

Coinfections caused by invasive filamentous fungi, such as *Aspergillus terreus* and *Fusarium* spp., in HSCT recipients are rare events but are associated with extremely high mortality, particularly in the setting of profound and prolonged immunosuppression [1,2]. Among the pathogens involved, *A. terreus* stands out due to its intrinsic resistance to amphotericin B, which poses a major therapeutic challenge, especially when concomitant with filamentous fungi of variable susceptibility, such as *Fusarium* spp. [4,7]. Prolonged neutropenia remains the main risk factor and the most critical determinant of outcomes in IFIs after HSCT. Neutrophil recovery is consistently the strongest predictor of therapeutic response, surpassing even the choice of antifungal agent when aplasia persists. This observation reinforces the central message of this report: without immune reconstitution, even aggressive antifungal strategies are likely to fail [5–7].

Disseminated fusariosis, in turn, represents one of the most aggressive forms of invasive fungal infection, marked by extensive angioinvasion, rapid clinical progression, and high mortality. Unlike aspergillosis, where fungemia is uncommon, *Fusarium* spp. exhibits a remarkable hematogenous tropism, with positive blood cultures in up to 60% of cases, a finding strongly associated with disseminated disease and worse prognosis [3,4].

Figure 3. Microscopy of the peripheral blood culture showing multicellular, fusiform conidia characteristic of *Fusarium* spp. (*F. solani* species complex).



In the present report, fungal identification was performed through morphological analysis and culture, without molecular characterization or susceptibility testing. This limitation is relevant in the current context, as multilocus phylogenetic data have led to the reclassification of species within the *Fusarium solani* species complex into the genus *Neocosmospora*, including *N. keratoplastica* and *N. falciformis* [11–13]. Given this scenario, and in the absence of genetic sequencing, we opted to retain the traditional clinical nomenclature "*Fusarium solani* species complex (FSSC)," which remains widely used in medical practice. This limitation, however, carries potential therapeutic implications, since cryptic species within the FSSC may exhibit distinct susceptibility profiles and variable resistance to triazoles and polyenes, directly influencing therapeutic decision-making and prognosis [4,7,11–13].

The diagnosis of invasive fungal coinfection requires the integration of clinical, histopathological, and microbiological data. In the present case, the demonstration of septate hyaline hyphae in biopsies from multiple sites, oral mucosa, skin, paranasal sinuses, and

bloodstream, confirmed the pattern of disseminated hyalohyphomycosis. However, histopathology alone cannot reliably distinguish *Fusarium* spp. from *Aspergillus* spp., making fungal culture essential for definitive identification, particularly in settings of coinfection [3,4].

Among serum biomarkers, beta-D-glucan has limited sensitivity in fusariosis and may remain negative even in disseminated disease [4]. Galactomannan, although useful in invasive aspergillosis, may show cross-reactivity with other hyalohyphomycoses, including *Fusarium* spp., underscoring the importance of integrated interpretation of laboratory and microbiological findings [3,4,8]. In the case described, blood cultures were positive for the *Fusarium solani* species complex, confirming active fungemia and characterizing the hematogenous dissemination typical of invasive fusariosis. This finding reinforces the highly angioinvasive nature of the infection and the poor prognosis associated with this systemic pattern [3,4].

Antifungal management was established in a stepwise manner, guided by microbiological findings and clinical progression. Voriconazole was used as peri-transplant prophylaxis in accordance with first-line strategies for HSCT recipients undergoing myeloablative conditioning, particularly in institutions with a high prevalence of invasive aspergillosis [1,4,7]. Following the isolation of *Aspergillus terreus* and given the subtherapeutic serum levels of voriconazole, therapy was switched to isavuconazole, a broad-spectrum triazole with more predictable pharmacokinetics, although with variable activity against the *Fusarium solani* species complex (FSSC). This choice also considered the intrinsic resistance of *A. terreus* to amphotericin B, precluding its isolated use [4,7,9,10]. After confirmation of invasive fusariosis in skin and sinus biopsies and in the setting of refractory clinical progression, liposomal amphotericin B was added in combination with isavuconazole to broaden antifungal coverage, given the heterogeneity of susceptibility within the FSSC and the intrinsic resistance of *Fusarium* spp. to echinocandins [4,7].

In scenarios involving coinfection by fungi with contrasting resistance profiles, such as *A. terreus* and the FSSC, combined regimens may represent a rational salvage strategy, although clinical evidence of synergism remains limited. Despite aggressive therapeutic measures, the absence of neutrophil recovery remained the decisive factor in the unfavorable outcome, reinforcing its central role in the response to invasive fungal infections [4–7,9,10]. Two technical limitations should also be highlighted, as they restricted therapeutic individualization in this case: (i) the absence of susceptibility testing (MICs), which could have guided targeted selection among triazoles and polyenes for the FSSC; and (ii) the lack of molecular identification, which prevents recognition of cryptic species within the complex with potentially more or less favorable susceptibility patterns. Nevertheless, in the context of hemodynamic deterioration, angioinvasive skin lesions, extensive sinus disease, and, ultimately, fungemia due to FSSC, the decision to use broad-spectrum combination therapy was clinically justified given the severity of the disease, despite the low probability of success in the absence of engraftment.

Adjunctive measures such as optimization of hematologic support (G-CSF), surgical source control (paranasal sinus debridement), and intensive care management were implemented according to clinical evolution. In selected settings and when institutionally available, granulocyte transfusion and immunomodulation (e.g., IFN-γ) have been reported in small series and case reports; however, their effectiveness critically depends on a permissive environment for engraftment and on manageable cumulative toxicity. Their applicability in this case was limited by sustained aplasia. Regarding newly developed antifungal agents, several investigational molecules have shown promising activity against filamentous fungi, but their availability and robust clinical evidence in FSSC remain restricted; therefore, their current role is potential rather than definitive [6,7,9,10].

4. Conclusion

This case illustrates the diagnostic and therapeutic complexity of invasive fungal coinfections in HSCT recipients, particularly in the setting of prolonged neutropenia and

hematopoietic graft failure. The concomitant identification of *Aspergillus terreus* and *Fusarium solani* underscores the importance of an integrated microbiological approach combining morphological, cultural, and molecular methods for accurate diagnosis.

The case also highlights the persistent limitations in the diagnosis and management of fungal infections in high-complexity scenarios, where the absence of susceptibility testing and molecular characterization restricts individualized therapy and rational antifungal selection. Ultimately, the unfavorable outcome reinforces the crucial role of immune reconstitution as the fundamental determinant of treatment response, regardless of the antifungal regimen employed.

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Conflicts of Interest: All other authors declare no conflicts of interest.

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