Mediterranean Journal of Hematology and Infectious Diseases

Scientific Letters

Fatal Disseminated Fusariosis During Induction Therapy for Adult Acute Lymphoblastic Leukemia in a Patient with Prior Multiple Myeloma

Keywords: Acute Lymphoblastic Leukemia; Fusariosis; Fungal Infection; Multiple Myeloma.

Published: September 01, 2026 **Received: July 05, 2026** **Accepted: August 14, 2026**

Citation: Alberti S., Cavallaro G., Tebaldi A., Tebaldi P., Finazzi M.C., Grassi A., Galli M., Paris L., Stefanoni P., Valsecchi F., Rambaldi A., Lussana F. Fatal disseminated fusariosis during induction therapy for adult acute lymphoblastic leukemia in a patient with prior multiple myeloma. Mediterr J Hematol Infect Dis 2026, 18(1): e2026074, DOI: http://dx.doi.org/10.4084/MJHID.2026.074

To the Editor.

Invasive fungal infections are a major cause of morbidity and mortality in patients with hematologic malignancies, particularly during prolonged neutropenia and intensive chemotherapy. In acute lymphoblastic leukemia (ALL), prophylaxis is challenging because mold-active azoles interact with vinca alkaloids and may increase hepatotoxicity with asparaginase, whereas provide incomplete coverage against *Aspergillus* spp. and rare molds such as *Fusarium* spp. We report a fatal case of proven cutaneous invasive fusariosis with radiologically presumed pulmonary dissemination during induction therapy for Philadelphia-negative B-cell precursor ALL (BCP-ALL) in a 58-year-old man with heavily pretreated multiple myeloma (MM).

Clinical Case Description. A 58-year-old Tunisian man was diagnosed with IgAκ MM in February 2017, presenting with anemia, osteolytic lesions, and a skeletal plasmacytoma. He received bortezomib, thalidomide, and dexamethasone plus radiotherapy, followed by high-dose melphalan and autologous stem cell transplantation, achieving a very good partial response. In November 2019, because of biochemical and skeletal progression, he started daratumumab, lenalidomide, and dexamethasone, achieving a stringent complete response in January 2023, maintained through February 2025 after 63 cycles. In February 2025, the patient developed severe pancytopenia, with circulating lymphoid blasts. Bone marrow evaluation established the diagnosis of BCP-ALL, with a B-II (common) immunophenotype according to EGIL criteria. *BCR::ABL1* transcript was negative. Fluorescent in situ hybridization (FISH) analysis showed a hypodiploid clone with loss of one *TP53* allele, consistent with B-lymphoblastic leukemia/lymphoma with hypodiploidy (WHO 2022) and low hypodiploidy (ICC 2022); RNA transcriptomic analysis detected no recurrent fusion transcripts consistent with *BCR::ABL1*-like (Ph-like) ALL. Risk according to GIMEMA LAL1913 protocol was very high.[1] MM remained in stringent CR. A contrast-enhanced computed tomography (CT) scan showed a renal lesion suspicious for leukemic infiltration, whereas testicular ultrasonography was negative. The patient had ECOG performance status 0, severe obesity (BMI41 kg/m^2), and marked hypogammaglobulinemia, secondary to MM and previous therapy. The treatment was adapted from GIMEMA LAL1913 protocol for patients aged 55 to 65 years.[1] Due to hepatic steatosis and obesity, Peg-Asparaginase (PegAsp) was reduced to 500 IU/m^2.[2] Cerebrospinal fluid examination was negative. Antimicrobial prophylaxis consisted of acyclovir 400 mg q12h, ciprofloxacin 500 mg q12h, and micafungin 50 mg daily from day 1. Micafungin was preferred to avoid azole-vincristine interactions, and additive hepatotoxicity during asparaginase-containing induction. Serum beta-D-glucan and galactomannan tests were monitored weekly and remained negative. On day 7, febrile neutropenia developed and blood cultures yielded catheter-related *Escherichia coli*; piperacillin–tazobactam (4.5 gr/4 times a day) and amikacin 15 mg/kg were started. On day 12, meropenem replaced piperacillin–tazobactam after recurrent fever and recovery of an ESBL-producing *E. coli* isolate. The patient also developed grade 4 hepatotoxicity (peak bilirubin 29 mg/dL), antithrombin deficiency, hypofibrinogenemia requiring cryoprecipitate and antithrombin supplementation, and steroid-induced diabetes requiring insulin. On day 19, three painful erythematous nodules appeared on the left arm and trunk, rapidly became necrotic (**Figure 1**). A punch biopsy on day 21 showed extensive necrotizing infiltration of the dermis and hypodermis by septate hyphae and conidia (**Figure 2**). Culture yielded *Fusarium solani*, initially identified by colony and microscopic morphology using lactophenol cotton blue staining and subsequently confirmed by Sanger

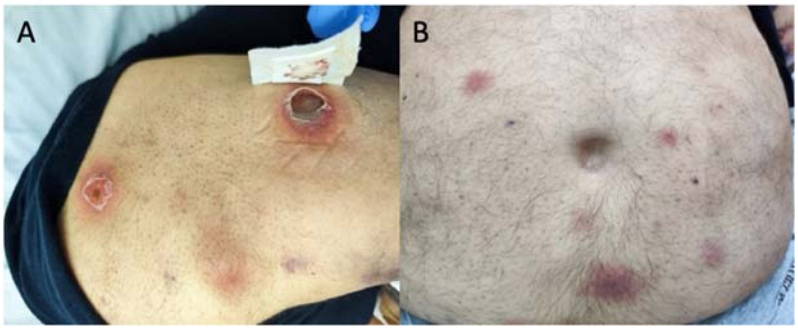

Figure 1. Painful erythematous nodular skin lesions with rapid necrotic evolution involving the left arm (**A**) and abdomen (**B**). Photographs taken on day 19, with informed consent obtained and proper de-identification.

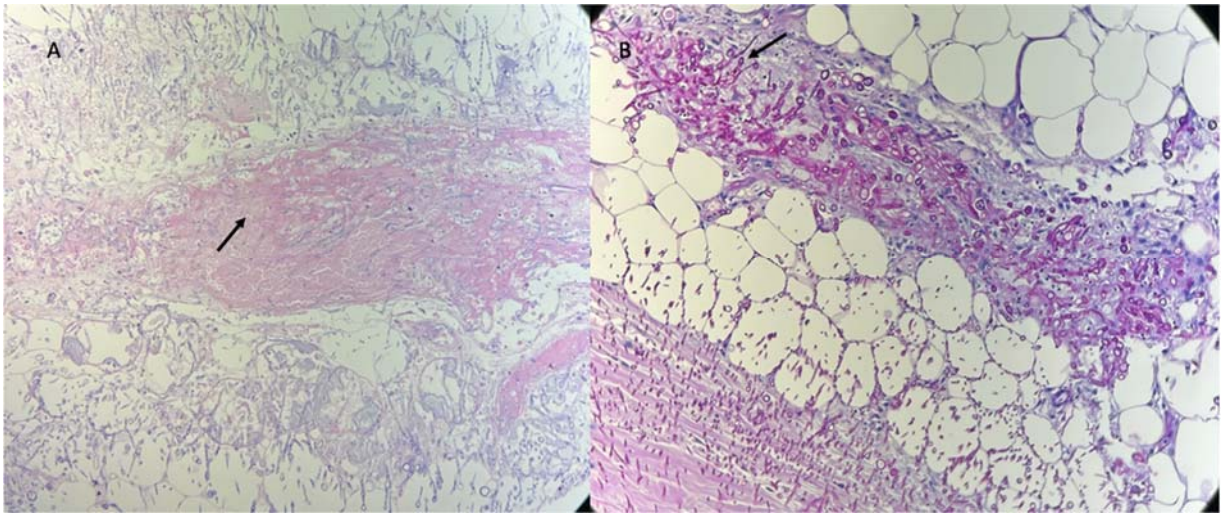

Figure 2. Skin biopsy performed on day 21 from the start of induction chemotherapy. (**A**) Hematoxylin and eosin staining; original magnification ×200. The arrow indicates fat necrosis. (**B**) Periodic acid–Schiff (PAS) staining; original magnification ×200. The arrow indicates septate hyphae.

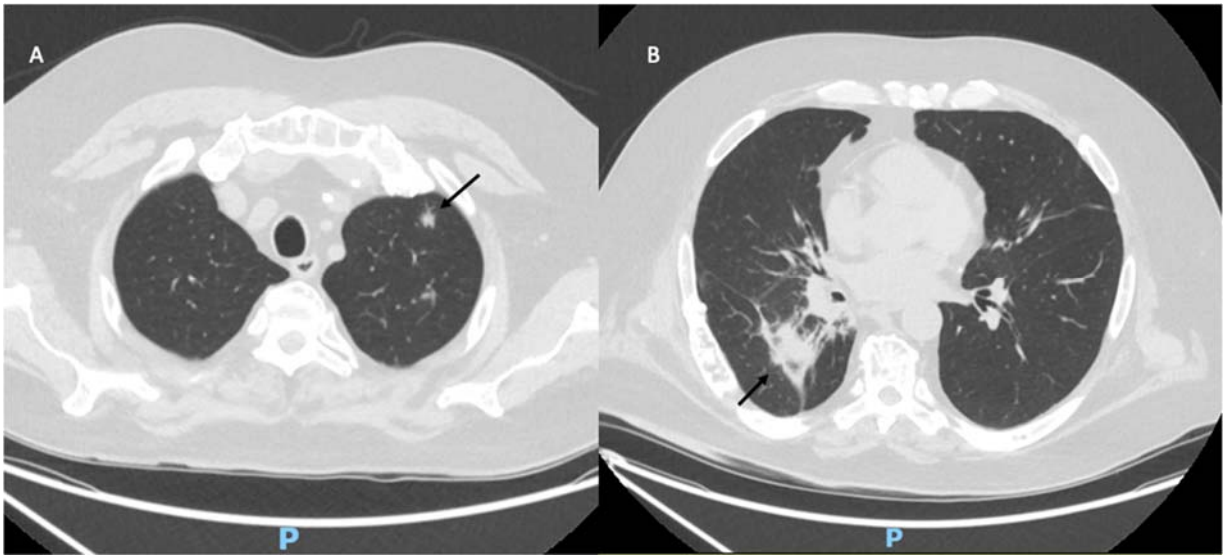

Figure 3. Chest CT performed on day 21 of induction therapy, axial sections, lung window. (**A**) Left upper lobe: the arrow indicates non-cavitated peribronchial pseudonodular consolidation, consistent with an infectious process. (**B**) Right lower lobe: the arrow indicates an area of consolidation with bronchiectasis. Images are displayed according to standard radiological convention (patient's left on the viewer's right). P = posterior.

sequencing of the D2 region of the large subunit rDNA. Minimum inhibitory concentrations (MICs) were determined, although no clinical breakpoints are available for this species.[3] Blood cultures remained negative, consistent with data in the literature reporting only a minority (40%) of disseminated fusariosis with blood cultures isolates.[4] Chest CT showed multiple nodules and parenchymal consolidations (**Figure 3**). Bronchoalveolar lavage was contraindicated by severe thrombocytopenia and coagulopathy, so pulmonary

involvement remained radiologically suspected but microbiologically unconfirmed. Micafungin was discontinued while intravenous voriconazole (loading dose 6 mg/kg q12h on day 1, followed by 4 mg/kg q12h) together with liposomal amphotericin B (5 mg/kg/day) was initiated on day 21, in line with current recommendations.[3,4] Despite PegAsp-related hepatic dysfunction, full doses were maintained given the infection severity. After seven days, voriconazole was reduced to 2 mg/kg q12h because of QTc prolongation. Trough levels, measured twice weekly, remained within the therapeutic range. The last vincristine dose on day 21 was omitted due to its interaction with voriconazole. Despite adequate antifungal treatment, new necrotic lesions appeared daily without improvement in previously affected areas. Hematologic recovery did not occur after completion of induction. Severe pancytopenia, hepatotoxicity, coagulopathy, and dysproteinemia persisted. Because of the refractory course of disseminated fusariosis, compassionate use of fosmanogepix was requested.[5] On day 31 from the beginning of treatment, the patient deteriorated and was transferred to the intensive care unit (ICU) for ventilatory and hemodynamic support. Blood cultures again yielded ESBL-producing *E. coli*, documenting a superimposed bacterial infection. Bone marrow aspirate on day 35 showed no residual blasts in a severely hypocellular marrow, consistent with morphologic leukemia-free status. The patient died eight days after ICU admission from multiorgan failure, before fosmanogepix use could be authorized. **Figure 4** summarizes the patient's clinical course and the main treatments administered.

Discussion. Invasive fungal infections (IFI) are a major complication in patients with haematological malignancies.[6–8] Evidence supporting antifungal prophylaxis in adult ALL is weaker than in acute myeloid leukemia and reported incidence rates of proven or probable IFD range from 4.3% to 18.3%, likely reflecting differences in treatment intensity, local epidemiology, and diagnostic approaches.[8] The European Conference on Infections in Leukemia (ECIL) supports anti-mold prophylaxis during intensive ALL treatment, but recommendations for non-azole alternatives are limited by low-quality evidence.[6] Mould-active azoles inhibit vincristine metabolism through CYP3A, increasing the risk of neurotoxicity, and may compound asparaginase-related hepatotoxicity.[8] Echinocandins and liposomal amphotericin B are therefore frequently preferred during induction, although ECIL assigns only a C-III grade recommendation and no strategy has clearly reduced IFI incidence or mortality.[3,6,9] In this patient, micafungin was a pharmacologically reasonable choice, but it has no intrinsic activity against *Fusarium* spp. The *Fusarium solani* species complex, which accounts for the majority of invasive infections, is among the most resistant groups within the genus. Voriconazole and posaconazole often show elevated MICs, isavuconazole has limited activity, echinocandins are inactive, and amphotericin B has the most consistent in-vitro activity.[3,4] However, MICs correlate imperfectly with clinical outcome, and no clinical breakpoints are available.[3,10] Thus, the prophylactic dilemma in ALL extends beyond drug interactions: no currently licensed agent that can be safely combined with vincristine-based induction provides dependable coverage against this pathogen. Diagnosis is equally problematic. In profoundly immunocompromised hosts, fusariosis typically disseminates to the skin, lungs, and bloodstream.[3,8,10,11] Painful erythematous papules or nodules with central necrosis may be an early clue, and diagnosis relies on histology and culture of involved tissue.[8,10] Galactomannan and β-D-glucan may remain negative and cannot exclude the diagnosis.[3] Prognosis remains poor because of rapid dissemination and intrinsic multidrug resistance.[3] Outcome in invasive fusariosis largely depends on immune recovery, with persistent neutropenia and corticosteroid exposure representing major adverse prognostic factors.[12] In the absence of randomized trials, liposomal amphotericin B or voriconazole are recommended as first-line therapy, while combination treatment may be considered for disseminated disease.[3,4] Our patient progressed despite prompt combination therapy and documented therapeutic voriconazole levels, underscoring that adequate antifungal exposure may be insufficient without hematologic recovery. Several additional factors probably worsened infection risk and outcome, including MM-related immunoparesis, prolonged previous therapy, severe hypogammaglobulinemia, obesity, steroid-induced diabetes, hepatic dysfunction, coagulopathy, and bacterial sepsis.[10,12–17]

Alternative preventive strategies remain unsatisfactory. In AmBiGuard, the only randomised trial addressing this question in adult ALL, intermittent liposomal amphotericin B did not significantly reduce proven or probable IFD compared with placebo (7.9% versus 11.7%; P = 0.24).[18] Inhaled antifungals may not protect against disseminated infection or a possible cutaneous portal of entry.[5] Fosmanogepix, a first-in-class agent with activity encompassing *Fusarium* spp., remains investigational.[5]

The occurrence of BCP-ALL after prolonged MM therapy was biologically noteworthy but of uncertain causal significance. Previous melphalan and lenalidomide exposure may increase the risk of second hematologic malignancies, although B-ALL is rare (<1%)[19] Reported B-ALL cases after lenalidomide therapy appear clonally distinct from the underlying plasma cell disorder, supporting an independent leukemogenic event.[20] In our patient, no shared clonal origin was demonstrated, although this could not be

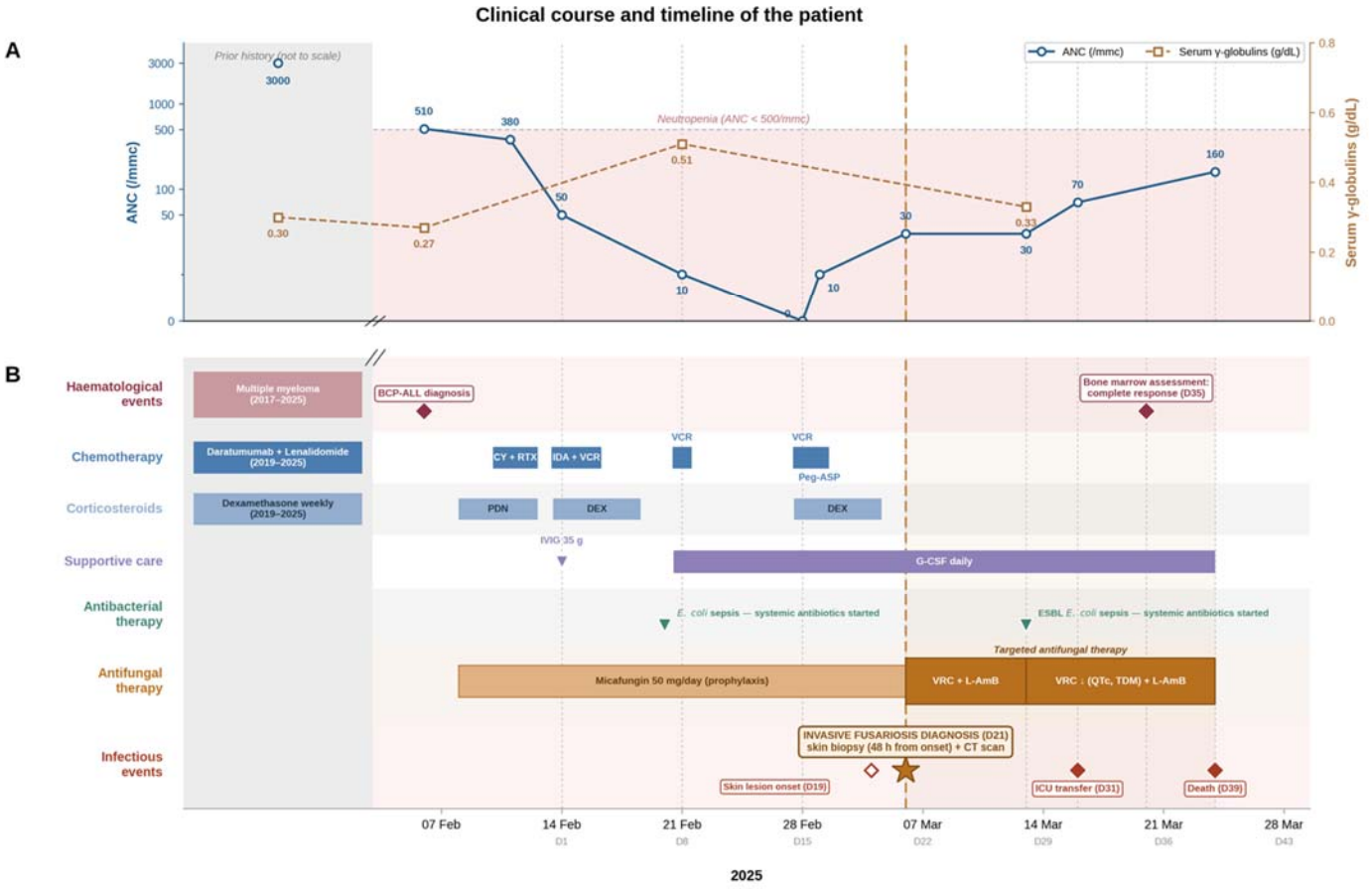

Figure 4. Clinical course and timeline of the patient. **(A)** Laboratory course throughout the disease trajectory. The solid blue line shows the absolute neutrophil count (ANC, left axis, symmetrical logarithmic scale); the dashed brown line shows serum γ-globulins measured by protein electrophoresis (right axis). The shaded pink area denotes neutropenia (ANC < 500/mmc). The grey band on the left represents the patient's prior haematological history and is not drawn to scale; it contains the baseline values recorded before the onset of the current illness. (**B)** Treatment and event timeline over the same period, aligned to the time axis of Panel A. Seven horizontal lanes summarise, from top to bottom: haematological events, chemotherapy, corticosteroid exposure, supportive care, antibacterial therapy, antifungal therapy, and infectious events. Bars indicate the duration of continuous treatments, whereas single markers indicate one-off administrations, treatment initiations, or discrete clinical events; downward triangles denote single administrations and the start of systemic antibacterial therapy, and diamonds denote clinical milestones, labelled above or below the lane. Within the antifungal lane, the lighter outlined bar represents mould-active prophylaxis and the solid bars represent targeted therapy. The diagnosis of invasive fusariosis (D21) is highlighted by a star and by a vertical orange dashed line spanning both panels, with the open diamond indicating the onset of skin lesions two days earlier (D19); the shaded orange area delimits the interval of targeted antifungal therapy. The grey band on the left, again not to scale, summarises long-term therapy and diagnoses predating the current admission. Vertical dashed lines and the labels below the time axis indicate days from the start of induction chemotherapy. **Abbreviations**: ANC, absolute neutrophil count; BCP-ALL, B-cell precursor acute lymphoblastic leukaemia; CT, computed tomography; CY, cyclophosphamide; DEX, dexamethasone; ESBL, extended-spectrum β-lactamase; G-CSF, granulocyte colony-stimulating factor; ICU, intensive care unit; IDA, idarubicin; IVIG, intravenous immunoglobulins; L-AmB, liposomal amphotericin B; PDN, prednisone; Peg-ASP, pegylated asparaginase; QTc, corrected QT interval; RTX, rituximab; TDM, therapeutic drug monitoring; VCR, vincristine; VRC, voriconazole.

definitively excluded without comparative sequencing. Hypodiploidy with loss of one *TP53* allele was compatible with, but not diagnostic of, a therapy-related origin.

Conclusions. Invasive fusariosis may develop despite guideline-consistent prophylaxis and prompt therapy. Since no available prophylactic agent reliably covers this pathogen, the key practical implication is early recognition: in neutropenic patients receiving echinocandin prophylaxis, new nodular or necrotic skin lesions should prompt urgent biopsy, culture, assessment for dissemination, and early mold-active treatment. In our patient, this approach was implemented within 48 hours, but proved insufficient in the absence of haematologic recovery.

Funding. This work was supported by Fondazione AIRC per la Ricerca sul Cancro (AIRC) AIRC 5X1000 under Grant AIRC-ISM ID 21147.and the Associazione Italiana Lotta alla Leucemia, Linfoma e Mieloma (AIL) Sezione Bergamo.

Authors contribution. SA and GC managed the patient, conceived the study, and wrote the manuscript; MCF, AG, MG, LP, PS, and FV contributed to patient management; AT contributed to the infectious disease management of the patient. PT performed the

histological evaluation and provided the histological image; AR and FL critically revised the paper and provided major intellectual contributions. All Authors revised the manuscript and gave the final approval before submission.

Patient's consent statement. The patient signed a privacy informed consent, which was approved by the Institutional Review Board of our Hospital.

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Competing interests: The authors declare no competing interest.

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