Successful salvage chemotherapy and allogeneic transplantation of an acute myeloid leukemia patient with disseminated *Fusarium solani* infection

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**ABSTRACT**

Disseminated *Fusarium* infection is associated with high mortality in immunocompromised patients. Patients with acute myeloid leukemia (AML) often have an extended duration of neutropenia during intensive induction chemotherapy, consolidation chemotherapy, and hematopoietic stem cell transplantation (SCT). There is no consensus regarding management of invasive disseminated *Fusarium* infections in the setting of prolonged neutropenia (Tortorano et al., 2014) [1]. We report a case of disseminated *Fusarium* in a patient with relapsed AML who underwent successful chemotherapy and haplo-identical allogeneic SCT with administration of granulocyte colony stimulating factor (G-CSF) and granulocyte infusions.

1. Case description

*Fusariosis* in patients with prolonged neutropenia have a dismal prognosis and survival is extremely low at 4% [2]. *Fusarium* species are plant pathogens found in air and soil, and enter the human body through inhalation, ingestion, and heel or toe fissures. Early detection of *Fusarium* infections is difficult due to lack of specific laboratory assays. Management is challenging due to variability of anti-fungal susceptibilities and lack of optimal treatment strategy [1]. We report the successful treatment of a patient with relapsed AML and invasive sino-pulmonary and cutaneous *Fusarium solani* infection during a course of salvage chemotherapy and subsequent allogeneic SCT.

A 66-year-old Caucasian male with diabetes, hyperlipidemia and obstructive sleep apnea presented to the NIH Clinical Center with relapsed AML. At the time of presentation, he was noted to have firm, non-tender, erythematous subcutaneous nodules on his bilateral anterior lower limbs and painful edematous feet (Fig. 1A/B). A skin biopsy of one of these nodules was interpreted as septal panniculitis.

The patient was consented to treatment on clinical trial NCT02527447 and received treatment with salvage chemotherapy of mitoxantrone 12 mg/m²/day IV on days 1–3, etoside 200 mg/m²/day continuous IV infusion (CIV) on days 8–10, and cytarabine 500 mg/m²/day CIV on days 1–3 and 8–10 (EMA). Infectious prophylaxis with caspofungin was given during chemotherapy and oral posaconazole was started after chemotherapy as per institutional standard. During the third week after chemotherapy, new painful nodules appeared on his trunk, neck, upper arm and the plantar aspect of his foot. In addition, there was interval development of bilateral focal patchy nodular pulmonary infiltrates with ground glass and reticular appearance on chest CT imaging (Fig. 1C/D), followed by development of paranasal sinusitis. The patient underwent bronchoscopy with broncho-alveolar lavage, skin biopsy of a palpable nodule, and sinus biopsy. *Fusarium solani*...
was isolated from all three of these sites (Fig. 1F/G).

Fungal susceptibilities showed amphotericin minimum inhibitory concentration (MIC): 2 mcg/mL and terbinafine MIC: 2 mcg/mL and resistance to micafungin, posaconazole and voriconazole. The patient was initially treated with amphotericin, however, subsequent CT chest one week later showed progression of pulmonary infiltrates, and terbinafine and voriconazole were added despite fungal susceptibilities. Bone marrow examination on day 35 showed a hypocellular (5%) marrow with trilineage hypoplasia and no definitive evidence of AML. Peripheral blood neutrophils were absent. A course of filgrastim daily injections was administered for ten days, at which time his absolute neutrophil count (ANC) recovered to greater than 2.0 × 10⁹/L. The total duration of severe neutropenia with ANC less than 0.1 × 10⁹/L was 40 days. At the time of ANC recovery, the result of his Fungitell serum assay (Beacon diagnostics) was positive (167 pg/mL, positive = > 80 pg/mL), however, the appearance of his skin nodules improved, and pulmonary and sinus radiographic abnormalities stabilized during this time.

Complete remission with no evidence of minimal residual disease was confirmed on bone marrow examination on day 73. At day 100 following salvage chemotherapy, the CT showed resolution of the nodules (Fig. 1E) and Fungitell result normalized (< 60 pg/mL, Fig. 2A). He received consolidation chemotherapy with clofarabine 20 mg/m² IV on days 1–5, followed by haplo-identical SCT 10 days later. A two-step approach [3] was used as a myeloablative conditioning regimen including fludarabine 120 mg/m², total body irradiation (12 GY), and a donor lymphocyte infusion (2 × 10⁹/kg CD3⁺ T cells) which was followed by cyclophosphamide 120 mg/kg prior to CD34⁺ selected...
peripheral blood stem cell infusion. GVHD prophylaxis was with sirilumab (tough dose 5–12 mg/mL) along with ultra-low dose interleukin-2 (ULD-IL2) 100,000 international units/m2(clinical trial NC-T02226861). Micafungin was used as anti-fungal prophylaxis until day 33 following post-transplant. No other anti-fungal prophylaxis therapy was used.

The patient became neutropenic (ANC < 0.5 × 10^9/L) from clofarabine consolidation 10 days prior to stem cell graft infusion, and the time to engraftment (ANC > 0.5 × 10^9/L) was 12 days following transplant, for a total of 22 days of peri-transplant neutropenia. Due to the anticipated neutropenia, granulocyte infusions from G-CSF stimulated donors were scheduled for 5 doses during his transplant course (Fig. 2B) with average dose more than 0.6 × 10^9/kg. Granulocyte donors were selected based on negative CMV serology and to avoid any HLA class I and II antigen mismatch with the patient or haplo-identical SCT donor. Granulocyte infusions were well tolerated without complications. G-CSF was not used in the peri-transplant period. The patient is now 14 months’ post haplo-identical SCT and remains in complete remission with no evidence of infection.

The incidence of fusariosis in allogeneic-SCT ranges from 0.2% to 0.6% and in acute leukemia from 0.1% to 0.3% [1]. There is an increased incidence of Fusarium infection in immunosuppressed patients and in AML patients compared to other hematological malignancies [2,4]. In an immunocompromised host, lack of a normal immune response allows for angio-invasion of Fusarium, causing necrosis and disseminated infections.

Skin involvement is present in 68–70% of cases of fusariosis [5]. As skin is one of the primary sources of entry, thorough skin examination and biopsy of suspicious nodules should be considered. Sinus involvement occurs in 80% of cases of disseminated fusariosis, with manifestations including facial or periorbital cellulitis and sinus congestion [6]. Pulmonary nodules have been reported in 80% of patients with respiratory symptoms, with a range in diameter from 0.3cm to 2.7 cm [7]. Nodules greater than 1 cm should raise the suspicion for invasive fungal infection [8].

The role of galactomannan and (1→3)-β-D-glucan testing in fusariosis is unknown. A positive (1→3)-β-D-glucan test combined with a negative galactomannan is thought to favor diagnosis of other hyalohyphomycosis but aspergillosis [1]. Exposure to antibiotics or anti-negative galactomannan is thought to favor diagnosis of other hyalohyphomycosis but aspergillosis [1]. Exposure to antibiotics or anti-negative galactomannan is thought to favor diagnosis of other hyalohyphomycosis but aspergillosis [1].

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Conflict-of-interest disclosure

Authors report no relevant conflict of interest.

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