Leukemia Research Reports 8 (2017) 4–6

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

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

Sheenu Sheela[a], Sawa Ito[b], Jeffrey R. Strich[c], Maura Manion[c], Celina Montemayor-Garcia[d], Hao-Wei Wang[e], Karolyn A. Oetjen[a], Kamile A. West[d], Austin J. Barrett[b], Mark Parta[f,1], Juan Gea-Banacloche[g], Steven M. Holland[c], Christopher S. Hourigan[a,2], Catherine Lai[a,*,2]

[a] Myeloid Malignancies Section, Hematology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA
[b] Stem Cell Allogeneic Transplantation Section, Hematology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA
[c] Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA
[d] Department of Transfusion Medicine, NIH Clinical Center, National Institutes of Health, Bethesda, MD, USA
[e] Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
[f] Clinical Research Directorate/Clinical Monitoring Research Program, Leidos Biomedical Research, Inc., NCI Campus at Frederick, Frederick, MD 21702, USA
[g] Experimental Transplantation and Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

ARTICLE INFO

Keywords:
Acute myeloid leukemia
Fusarium solani
Allogenic transplant

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 sinopulmonary 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/m^2/day IV on days 1–3, etoposide 200 mg/m^2/day continuous IV infusion (CIV) on days 8–10, and cytarabine 500 mg/m^2/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*

* Correspondence to: Myeloid Malignancies Section, National Heart, Lung and Blood Institute, Room 10CRC 5-5142, 10 Center Drive, Bethesda, MD 20814-1476, USA.
E-mail address: catherine.lai@nih.gov (C. Lai).

[1] Supported in part by the Intramural Research Programs of the National Heart, Lung, and Blood Institute and the National Institute of Allergy and Infectious Diseases of the National Institutes of Health. This project has been funded in in whole or in part with federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. HHSN261200800001E. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

[2] These authors contributed equally.

http://dx.doi.org/10.1016/j.lrr.2017.07.001
Received 14 April 2017; Received in revised form 1 July 2017; Accepted 17 July 2017
Available online 18 July 2017

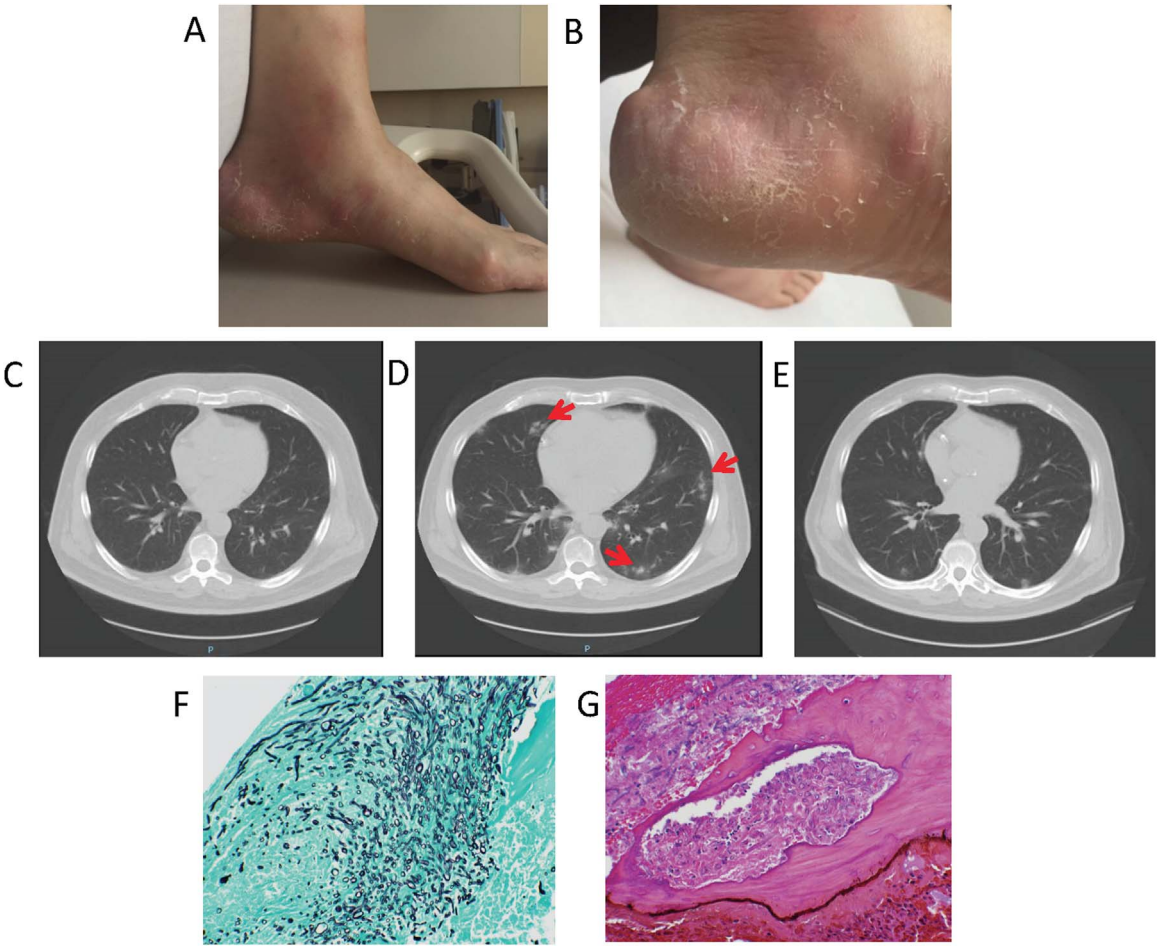

Fig. 1. A- Left foot, ankle and lower legs showing erythema, swelling and nodules. B- Enlarged view of left medial heel nodule. C- Baseline CT chest. D- Week 3 CT chest with nodules and infiltrates (arrows). E- Week 15 CT chest with resolution of nodules and infiltrates. F- GMS 20×, showing *Fusarium* hyphae and spores identified in the left middle turbinate. G- H & E 20×, showing hyphae and spores in the bone of the nasal turbinate and surrounding soft tissues.

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 2.0×10^9/L. The total duration of severe neutropenia with ANC less than 0.1×10^9/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/m^2 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/m^2, total body irradiation (12 Gy), and a donor lymphocyte infusion (2×10^8/kg CD3$^+$T cells) which was followed by cyclophosphamide 120 mg/kg prior to CD34$^+$ selected

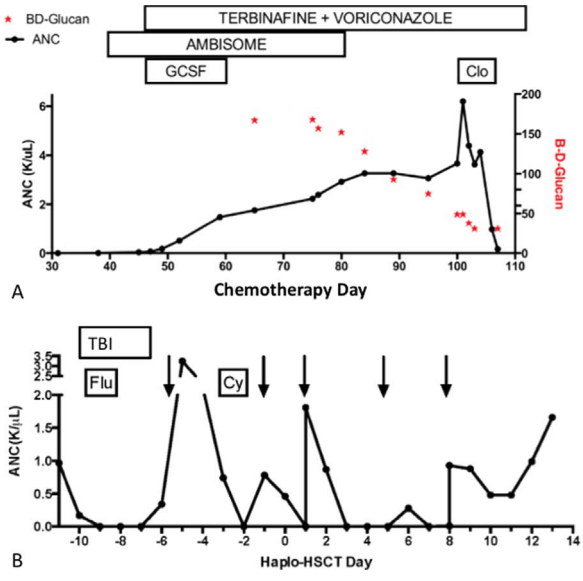

Fig. 2. A- Relationship between ANC recovery, antifungal therapy and reduction in (1→3)-β-D-glucan(B-D-Glucan) levels. Clo = Clofarabine. B- Use of granulocyte infusions to minimize neutropenia during allogeneic transplantation (SCT). Timing of granulocyte infusions shown with arrow. Note: Transplant day -11 is chemotherapy day 106. SCT conditioning done with Fludarabine (Flu), Cyclophosphamide (Cy) and Total Body Irradiation (TBI).

peripheral blood stem cell infusion. GVHD prophylaxis was with sirolimus (trough goal 5–12 ng/mL) along with ultra-low dose interleukin-2 (ULD-IL2) 100,000 international units/m2(clinical trial NCT02226861). 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 $< 0.5 \times 10^9$/L) from clofarabine consolidation 10 days prior to stem cell graft infusion, and the time to engraftment (ANC $> 0.5 \times 10^9$/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 antifungals can cause variable sensitivity to galactomannan and/or (1→3)-β-D-glucan tests [9]. Antifungal susceptibility testing is recommended, however, there is lack of clear evidence to support the relation between fungal susceptibilities and clinical efficacy [1].

Host factors that predict poor outcomes of *Fusarium* infection in patients with hematological malignancies are prolonged profound neutropenia (> 14 days and $< 100/mm^3$, respectively) and therapy with corticosteroids [6]. Colony stimulating factors have a role in the treatment of life-threatening infections due to chemotherapy-associated neutropenia, and in shortening the duration of prolonged neutropenia to reduce the incidence of febrile neutropenia [10]. However, these agents should be used with caution in patients with active AML to avoid stimulation of leukemic blast proliferation [11].

Our case report provides further evidence that pre-existing fungal infections should not preclude SCT for hematologic malignancies [12]. For this patient, the short time to engraftment, in combination with granulocyte infusions minimized the duration of post-transplant neutropenia, which helped control the *Fusarium* infection. A multi-disciplinary approach with involvement of the Hematology, Infectious Disease and Transfusion Medicine services to maintain adequate neutrophil counts prior to engraftment was successful in this case. Granulocyte infusions have become less complicated and more effective using HLA- matched donors [13]. Mobilization regimens including G-CSF and dexamethasone have increased granulocyte yield to more than 0.6×10^9/kg [12].

Disseminated *Fusarium solani* in immunocompromised patients has a high mortality rate, is typically refractory to anti-fungal treatment, and adequate neutrophil counts appear to be an important determinant of survival [1]. Successful outcomes, as in the case, are underreported in the literature. This case illustrates the early detection, successful interventions and outcome for a systemic invasive fungal infection that is typically fatal. We used thorough skin examinations, early diagnostic interventions, (1→3)-β-D-glucan serum monitoring during treatment, serial CT scans, G-CSF to expedite neutrophil recovery and granulocyte infusions to minimize duration of peri-transplant neutropenia. Adequate neutrophil counts were critical to the management of this invasive fungal infection and allowed for successful definitive treatment of relapsed AML.

Authorship

S.S. wrote the paper and was involved in patient care. S.I. was the transplant physician involved in patient care. J.S. and M.M are infectious disease fellows involved in patient care. C.M.G. is a transfusion medicine fellow involved in patient care. H.W.W. is a hematopathology fellow and provided the pathology pictures. K.O. is a hematology fellow involved in patient care. K.A.W. is a transfusion medicine attending involved in patient care. J.A.B. is a senior investigator in the transplant department involved in patient care. M.P., J.G.B., and S.M.H. are infectious disease attendings involved in patient care. C.S.H. and C.L. wrote the paper and are leukemia attendings involved in patient care. All authors contributed assistance with editing the final version of the manuscript.

Conflict-of-interest disclosure

Authors report no relevant conflict of interest.

Acknowledgements

The authors would like to thank the patient and his family for giving us permission to publish this case.

References

[1] A.M. Tortorano, et al., ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: Fusarium spp., Scedosporium spp. and others, Clin. Microbiol. Infect. 20 (Suppl 3) (2014) S27–S46.
[2] M. Caira, et al., Uncommon mold infections in hematological patients: epidemiology, diagnosis and treatment, Expert Rev. Anti Infect. Ther. 9 (7) (2011) 881–892.
[3] D. Grosso, et al., A 2-step approach to myeloablative haploidentical stem cell transplantation: a phase 1/2 trial performed with optimized T-cell dosing, Blood 118 (17) (2011) 4732–4739.
[4] L. Pagano, et al., The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study, Haematologica 91 (8) (2006) 1068–1075.
[5] M. Nucci, E. Anaissie, Cutaneous infection by Fusarium species in healthy and immunocompromised hosts: implications for diagnosis and management, Clin. Infect. Dis. 35 (8) (2002) 909–920.
[6] E.I. Boutati, E.J. Anaissie, Fusarium, a significant emerging pathogen in patients with hematologic malignancy: ten years' experience at a cancer center and implications for management, Blood 90 (3) (1997) 999–1008.
[7] E.M. Marom, et al., Imaging of pulmonary fusariosis in patients with hematologic malignancies, Am. J. Roentgenol. 190 (6) (2008) 1605–1609.
[8] E.M. Marom, D.P. Kontoyiannis, Imaging studies for diagnosing invasive fungal pneumonia in immunocompromised patients, Curr. Opin. Infect. Dis. 24 (4) (2011) 309–314.
[9] A. Sulahian, et al., Use and limits of (1-3)-beta-d-glucan assay (Fungitell), compared to galactomannan determination (Platelia Aspergillus), for diagnosis of invasive aspergillosis, J. Clin. Microbiol. 52 (7) (2014) 2328–2333.
[10] S. Amadori, et al., Use of glycosylated recombinant human G-CSF (lenograstim) during and/or after induction chemotherapy in patients 61 years of age and older with acute myeloid leukemia: final results of AML-13, a randomized phase-3 study, Blood 106 (1) (2005) 27–34.
[11] E. Vellenga, et al., The effects of GM-CSF and G-CSF in promoting growth of clonogenic cells in acute myeloblastic leukemia, Blood 69 (6) (1987) 1771–1776.
[12] T.H. Price, et al., Phase I/II trial of neutrophil transfusions from donors stimulated with G-CSF and dexamethasone for treatment of patients with infections in hematopoietic stem cell transplantation, Blood 95 (11) (2000) 3302–3309.
[13] S.S. Kadri, et al., Role of granulocyte transfusions in invasive fusariosis: systematic review and single-center experience, Transfusion 55 (9) (2015) 2076–2085.