Case study

FUSARIUM INFECTION AFTER ALLOGENEIC STEM CELL TRANSPLANTATION WITH PROLONGED NEUTROPENIA

Abstract:
Fusarium is an opportunistic fungal pathogen which is emerging as a significant cause of morbidity and mortality in the immunocompromised host (1). This disease can be localized, focally invasive or disseminated, when two or more noncontiguous sites are involved. We present a case of disseminated fusariosis in a patient with prolonged and profound neutropenia after the third allogeneic stem cell transplantation for acute lymphoblastic leukemia.

Keywords: stem cell transplantation, fusarium infection, neutropenia

Case:

A 22-year-old male applied to university hospital outpatient clinics for fever and fatigue. He was diagnosed as T cell acute lymphoblastic leukemia and induction chemotherapy was started as methotrexate (1 gram/m^2 , on day 1) and cytarabine (3 gram/m^2, on days 2 and 3). During the maintenance therapy, relapse has occurred and induction chemotherapy was started. Induction therapy including cyclophosphamide (300/m^2, on days 1 to 3), vincristine(2 mg per day, on days 4 and 11), doxorubicin (50 mg/m^2, on day 4) and dexamethasone (40 mg per day, on days 1 to 4 and days 11 to 14) yielded to complete remission. Therefore, after 13 months of the diagnosis, an allogeneic hematopoietic stem cell transplantation (allo-HSCT) was planned. We searched his family but couldn't find full match donor and donor selection was made among from his one related brothers with two-human-leucocyte mismatched antigens. Because of HLA mismatches, autologous back-up stem cells were removed for potential graft failure. The conditioning regimen consisted of total body irradiation (TBI) 2x200 cGy on days -6,-5,-4 and cyclophosphamide 60 mg/kg on days -3, and -2. CD34+ peripheral blood stem cells on a number of 4.6x10^6/kg were collected from the donor together with T cell depletion (4 log).

During the allogeneic hematopoietic stem cell transplantation (HSCT) period, immunosuppressive medications (cyclosporine), antibiotics (carbapeneme, aminoglicoside, teicoplanin, fluconasole, caspofungin) and filgrastim were given, as a HSCT protocol. Altough we expected for an engraftment after four weeks of treatment, we did not observe neutrophil or platelet engraftment signs. We therefore assessed this clinical picture as a primary graft failure. Therefore, after one-month of the first HSCT, a second allogeneic-HSCT from the same donor without conditioning regimen was performed (5.02 x10^6 CD34+ cells /kg).

After 10 days of the second HSCT, while he was receiving broad-spectrum multi antibiotherapy (meropenem, teicoplanin, caspofungin, acyclovir) due to intractable fever over 38 ^{0}C , and immunosuppressive therapy (cyclosporine and mycophenolate mofetil) for graft versus host disease (GVHD) prophylaxis, a target-shaped, hyperemic, painful but not itchy skin lesion, 2-cm. diameters appeared on the right hand palm (Figure 1a). Laboratory examination showed white blood cell: 0x10^9/L, hemoglobin: 8,6 g/dL, platelet:5x10^9/L. Cultures taken regularly did not show any positive results. Blood, urine cultures and skin biopsy were taken from the patient and empirical oral voriconazole (200 mg two times per day) was started. The biopsy and blood cultures yielded fusarium. (Figure-2a, 2b). Persistent fever and extended skin lesions involving whole body, confirmed disseminated character of the infection under voriconasole therapy (figure-1b,1c). Then, a combination antifungal therapy with liposomal amphoterisin-B (LAmB) (5mg/kg) and intra-venous voriconazole (loading dose, 6 mg/kg/day, followed by 4 mg/kg/day intravenously every 12 h) was initiated. The graft failure as well as persisted, We used autologous back-up as doses 0.33x10^6/kg for salvage treatment, but he had no response. Than that obligated the patient for another (third) HSCT. The donor, was selected this time the other HLA two-mismatched younger seventeen-year-old brother. T-cell depletion was not preferred in order to prevent a loss in CD 34+ cell number in the graft (total number of 3,9x10^6 CD34+ peripheral blood stem cells/kg were infused after 55 day of the first transplant). The conditioning regimen included fludarabine (30 mg/m^2 on days -4,-3 and -2) and cyclophosphamide (800 mg/m^2 on days -4,-3 and -2). Antifungal and antibiotic therapies went on the whole transplantation period without breaking. Two weeks after the third transplantation, neutrophil engraftment occurred and the skin lesions related with fusarium improved remarkably (90 percent) and the fever regressed. After neutrophil engraftment his clinical condition improved to ECOG 1. The skin biopsy and blood cultures did not yield fusarium. Four weeks after the third transplantation grade 2 GVHD of skin and

gastrointestinal tract have occured. Corticosteroid, mycophenolate mofetil, cyclosporine were given as GVHD therapy. Due to GVHD presentation we could not discharge the patient. The patient went on ambisome for 32 days and voriconasole for 81 days after fusarium infection. Also he received granulocyte-colony stimulating factor (Neupogen 48 MU) 91 times for 4 months due to profound neutropena, 72 units erythrocyte suspension and 53 units platelet suspensions transfused because of severe anemia and trombositopenia. 6 months after the first transplantation, although neutrophil engraftment has occurred, the patient did never achieve a successful platelet engraftment and has died due to massive gastrointestinal hemorrhage.

Discussion:

Fungi belonging to the genus Fusarium are ubiquitously present in soil, air, and water and are parasites of numerous plants. In humans, these microorganisms usually cause superficial or subcutaneous infections such as keratitis or onychomycosis, but they may cause severe disseminated infections in immunocompromised patients (1).

Invasive or disseminated fusariosis is a rare but severe complication in hematological diseases (2). Patients with compromised immune function are at high risk for invasive fusariosis, particularly in the setting of prolonged and profound neutropenia and/or severe T cell immunodeficiency (3). Among patients with hematologic malignancy, the infection predominates during periods of neutropenia, typically among patients with leukemia receiving induction chemotherapy (4). Invasive fusariosis also occurs with an increased frequency among HSCT recipients higher than the autologous recepients(5). Marcio Nucci et. al. presented that the incidence of fusariosis among HSCT recipients varies according to the type of transplantation. It is lowest among autologous and highest among the allogeneic.(6). The prognosis of fusariosis is directly related to the patient's immune status, with high death rates (mortality reaches to 80 to 90%) in patients with persistent immunodeficiencies (4). We described an adult allo-HSCT patient with disseminated fusariosis treated with early combination of voriconazole and LAmB. The patient underwent to the third allo-HSCT from another younger brother and we report a unique case report in this respect. The duration of the neutropenia was 68 days and engraftment occurred after the third allo-HSCT. The patient's clinical condition improved after neutrophil engraftment and did not die due to infection or complications related with infection.

In severely immunocompromised patients, two characteristics suggest the diagnosis of disseminated fusariosis: the presence of skin lesions (either cellulitis at sites of skin breakdown caused by trauma or onychomycosis, or metastatic lesions) and mold growing from blood cultures. Skin biopsies should be performed in all immunocompromised patients with suspicious skin lesions, and should be sent for both histopathology and microbiology studies. Blood cultures should also be obtained (7).

The optimal treatment strategy of patients with fusariosis remains unclear because of the lack of clinical trials and the critical role that immune reconstitution plays in the outcome of this infection. Successful outcomes have been reported with various antifungal agents including amphotericin B deoxycholate , liposomal amphotericin B (4), amphotericin B lipid complex, and the triazole antifungals, voriconazole (8) and posaconazole . Combination antifungal therapy has also been described in single case reports and a retrospective study (9). We presented treatment varieties and demographic features on table 1.

A lipid formulation of amphotericin B (3 to 5 mg/kg IV once daily) is usually the preferable first-line therapy. A combination of a lipid formulation of amphotericin B and voriconazole (6 mg/kg IV every 12 hours for two doses, followed by 4 mg/kg IV every 12 hours) is often used because of the variable susceptibility of Fusarium spp to antifungal agents and the need to ensure that at least one active antifungal agent is given.

Because a recovering immune system is essential for the successful outcome of fusariosis, every effort should be made to enhance immunity; this includes decreasing the dose of immunosuppressants when possible and the use of adjunctive immunotherapy such as granulocyte or granulocyte-macrophage colony-stimulating factors (G-CSF or GM-CSF), G-CSF-stimulated granulocyte transfusions, or interferon-gamma adjunctive therapies. The efficacy of these therapies for fusariosis has not been established (10).

In conclusion, Fusarium infections have been reported with increasing frequency. Due to Fusarial infection may reappear after immunosuppression, cautious use of antifungal agents after receipt of a patient with Hematopeotic stem cell transplantation is important. In an immunocompromised patient, even an harmless lesion needs to be addressed with the start of immediate treatment.

References:

1. Nucci M, Anaissie E. Fusarium infections in immunocompromised patients. Clin Microbiol Rev 2007; 20:695.

2. Liu K, Howell DN, Perfect JR, Schell WA. Morphologic criteria for the preliminary identification of Fusarium, Paecilomyces, and Acremonium species by histopathology. Am J Clin Pathol 1998; 109:45.
3. Boutati EI, Anaissie EJ. Fusarium, a significant emerging pathogen in patients with hematologic malignancy: ten years' experience at a cancer center and implications for management. Blood 1997; 90:999.
4. Nucci M, Anaissie EJ, Queiroz-Telles F, et al. Outcome predictors of 84 patients with hematologic malignancies and Fusarium infection. Cancer 2003; 98:315.
5. Nucci M, Marr KA, Queiroz-Telles F, et al. Fusarium infection in hematopoietic stem cell transplant recipients. Clin Infect Dis 2004; 38:1237.
6. Marcio Nucci, Kieren A. Marr, Flavio Queiroz-Telles, Carlos A. Martins, Plı´nio Trabasso, Silvia Costa, Julio C. Voltarelli, Arnaldo L. Colombo, Alexander Imhof, Ricardo Pasquini, Angelo Maiolino, Ca´rmino A. Souza, and Elias Anaissie; Fusarium Infection in Hematopoietic Stem Cell Transplant Recipients Fusariosis in Stem Cell Transplantation • CID 2004:38 (1 May)
7. Grigis A, Farina C, Symoens F, et al. Nosocomial pseudo-outbreak of Fusarium verticillioides associated with sterile plastic containers. Infect Control Hosp Epidemiol 2000; 21:50.
8. Perfect JR, Marr KA, Walsh TJ, et al. Voriconazole treatment for less-common, emerging, or refractory fungal infections. Clin Infect Dis 2003; 36:1122.
9. Córdoba S, Rodero L, Vivot W, et al. In vitro interactions of antifungal agents against clinical isolates of Fusarium spp. Int J Antimicrob Agents 2008; 31:171.
10. Dignani MC, Anaissie EJ, Hester JP, et al. Treatment of neutropenia-related fungal infections with granulocyte colony-stimulating factor-elicited white blood cell transfusions: a pilot study. Leukemia 1997; 11:1621.

Table 1. Demographic and clinical characteristics of HSCT recipients with fusariosis

	Gulsum Tezcan et. al.	Isabelle Durand-Joly et. al.	Marta Stanzani et. al.	Erturk et al. (Reported Case)
Underlying condition	ALL	ALL	AML	ALL
Underlying condition not in complete remission	-	+	-	-
Type of stem cell transplantation	Allo-HSCT	-	Allo-HSCT	Allo-HSCT
Conditioning regimen	Busulfex, Etoposid, Cyclophosfamid	-	Fludarabine, BCNU, Alcaran	TBI,Cyclophosphamide, and Fludarabine and Cyclophosphamide (for the second HSCT)
Immunosuppressive Agents	ATG + Mycophenolate Mofetil		ATG, Cyclosporin A, Methotrexate,	Cyclosporine and Mycophenolate Mofetil,Steroid)
Culture	Blood Synovial fluid	Skin	Skin, Blood	Skin, Blood
GVHD	-	-	-	+
Graft failure	+	-	-	+ (first and second HSCT)
Duration of neutropenia (day)	95	15	30	68
Antibiotherapy for fusariosis	LAmB + Voriconasole	LAmB + Voriconasole (Voriconasole after dissemination)	LAmB + Voriconasole	LAmB + Voriconasole
Death because of fusariosis	-	-	-	-
Disseminated Infection	+	+	+	+

Number of HSCT	2	-	1	**3**

ALL: Acute Lymphoblastic Leucemia, AML: Acute Myeloid Leucemia, ATG: Anti- thymocyte Globuline, TBI: Total Body Irradiation, GVHD: Graft Versus Host Disease, HSCT: Hematopoetic Stem Cell Transplantation, LAmB: Liposomal Amphoterisin B

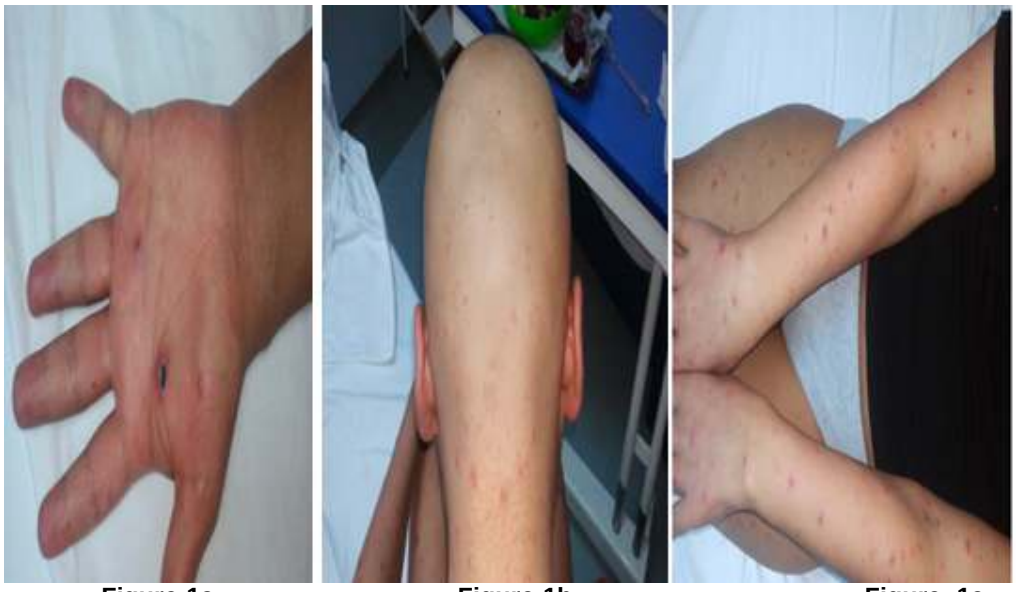

Figure-1a **Figure-1b** **Figure -1c**

Figure-1a: A target-shaped, hyperemic, painful but not itchy skin lesion, 2-cm. diameters appeared on the right hand palm

Figure-1b and 1c: Extended skin lesions involving whole body, confirmed disseminated character of the fusarium infection

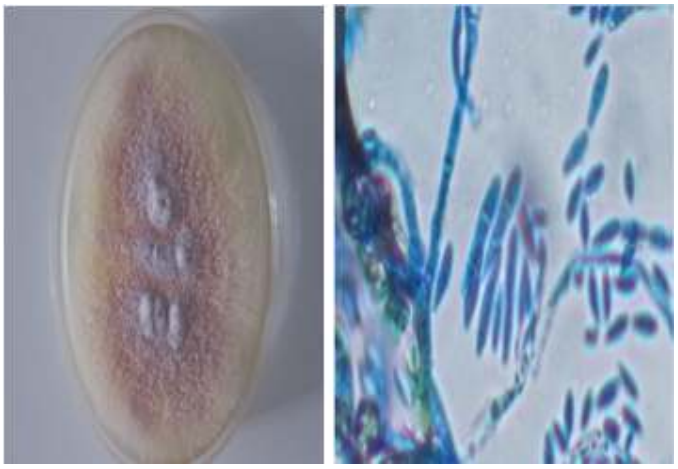

Figure -2a **Figure 2b**

Figure-2a and 2b: The biopsy and blood cultures yielded fusarium