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Journal of Hematology and Clinical Research

Heighten Science PUBLICATIONS Corporation

ISSN 2640-2823

Case Report

Successful management of disseminated Fusarium infection in a patient with acute myeloid leukemia

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Submitted: 14 August 2018
Approved: 14 September 2018
Published: 17 September 2018

Keywords: Acute myeloid leukemia; Disseminated *Fusarium* infection; Febrile neutropenia; Combined antifungal therapy

Abstract

Background: Invasive fungal infections cause significant morbidity and mortality in patients with hematologic malignancies and in recipients of hematopoietic stem cell transplantation.

Case: We report a patient with relapsed acute myeloid leukemia who developed disseminated *Fusarium* infection during the neutropenic period following the salvage cycle of chemotherapy given at King Fahad specialist Hospital in Dammam, Saudi Arabia. The invasive fungal infection was successfully managed with a combination of voriconazole and liposomal amphotericin-B.

Discussion: *Fusarium* species can cause invasive infections that may become disseminated and life-threatening in patients with acute myeloid leukemia.

Conclusion: Combined antifungal therapy and recovery of neutrophil count are essential to control invasive *Fusarium* infections.

Introduction

Invasive fungal infections (IFIs) represent a major complication in patients with acute myeloid leukemia (AML) and in recipients of hematopoietic stem cell transplantation (HSCT) [1-3]. Although invasive aspergillosis is the most frequently reported IFI in AML patients and in recipients of HSCT, infections caused by other molds such as *Fusarium* species have been increasingly reported [1,2]. Studies have shown that fusariosis is the second major cause of fungal infections in immunocomromised patients [2,4]. However, one study showed that *Candida* sp. particularly *Candida tropicalis* is a leading cause of IFIs in certain geographic locations such as Taiwan [3]. Fungal infections have the following portals of entry: skin, respiratory tract through inhalation, mucous membranes and central venous catheters (CVCs) [1-3,5,6].

Invasive or disseminated fusariosis occurs almost exclusively in immunocompromised individuals [2,5]. Disseminated *Fusarium* infection (DFI) is common in patients with hematologic malignancies (HMs), particularly those with acute leukemia [7]. The risk factors for invasive or disseminated fusariosis in patients with HMs are: (1) the HM itself, (2) neutropenia following induction treatment or subsequent cycles of chemotherapy, and (3) HSCT with its immunosuppression related to conditioning therapy, and prophylaxis as well as treatment of graft versus host disease (GVHD) [1,5,7-9].

Case Presentation

A 51 year old Saudi lady was diagnosed to have AML at King Fahad Specialist

How to cite this article: AlShammasi S, AlNujaidi D, Bakhit K, Algarni A, Al-Anazi KA. Successful management of disseminated Fusarium infection in a patient with acute myeloid leukemia. J Hematol Clin Res. 2018; 2: 015-020. https://doi.org/10.29328/journal.jhcr.1001007

Hospital (KFSH) in Dammam in early March 2016. She presented with fever, fatigue and bleeding from mucous membranes. Her physical examination revealed: pallor, clear chest, no external palpable lymphadenopathy, no abdominal tenderness or palpable organomegaly, and normal cardiovascular and neurological examinations. Her complete blood count (CBC) showed: white blood cell count (WBC): 40.05×10^9/L, hemoglobin (Hb): 9.0 g/dL, and platelet count (PLT): 19×10^9/L. Peripheral blood film (PBF) revealed thrombocytopenia and 38% blast cells. Bone marrow examination (BME) showed cellular marrow with diffuse infiltration with myeloblasts. Cytogenetic analysis showed normal cytogenetics with negative BCR/ABL, FLT3-ITD, MLL, RUNX1 and CBFB. Renal, hepatic, bone and coagulation profiles were all normal. Chest X ray (CXR), electrocardiogram and echocardiogram did not reveal any abnormality.

After establishing the diagnosis of AML, the patient was commenced on 3+7 induction cycle of chemotherapy composed of daunorubicin and cytosine arabinoside. Day 14 BME revealed hypocellular marrow without excess of blast cells. Thereafter, there had delayed recovery of blood counts so BMEs were repeated on days 35 and 53 of induction chemotherapy and the findings were similar to those obtained on day 14. As the patient continued to be clinically frail, requiring prophylactic antimicrobials and frequent blood product transfusions due to persistent pancytopenic and in the absence of donors for allogeneic HSCT, she remained unfit for a new cycle of chemotherapy, but she did not encounter any serious infection.

In July 2016, the patient was seen at the outpatient clinic. She was unwell clinically, but vitally stable. Her CBC showed: WBC of 8.87×10^9/L, Hb of 13.8 g/dL, and PLTs of: 22×10^9/L. PBF revealed thrombocytopenia and 36% circulating myeloblasts. BME was repeated and it showed cellular marrow with diffuse infiltration by myeloblasts. The patient was readmitted for salvage chemotherapy. She received fludarabine, cytosine arabinoside in addition to granulocyte-colony stimulating factor (G-CSF) in order to control her disease.

During the pancytopenic period following the salvage cycle of chemotherapy, the patient developed recurrent episodes of fever which did not respond to the following antimicrobials: piperacillin-tazobactam, amikacin, vancomycin, acyclovir, fluconazole and micafungin. Meanwhile she developed the following complications: (1) multiple indurated skin lesions involving the limbs and trunk that became ulcerated, (2) dyspnea, pleuritic chest pain with clinical evidence of consolidation and pleural effusion, and (3) gradual unilateral reduction in vision followed by loss of vision in one eye. Consequently the patient underwent extensive investigations that revealed: negative serology for viral infections, autoimmune disorders, brucella and syphilis; negative cultures of eye swabs; negative aspergillus gallactomannan test, negative blood cultures and negative BM cultures for tuberculosis, brucellosis and fungal infection. CXR and computerized axial tomography (CAT) scan of the lungs showed bilateral infiltration with airspace consolidation, pulmonary nodules and cavity formation in addition to a right-sided pleural effusion (Figure 1). Skin biopsy showed subcorneal pustular dermatitis as well as fungal hyphae that were branching at acute angles (Figure 2). The fungus was

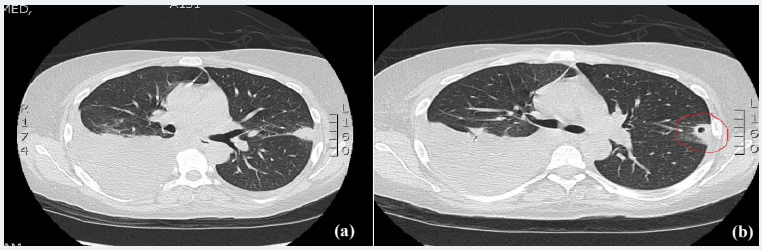

Figure 1: CAT scan of lungs showing: **(a)** Consolidation, pleural effusions and pulmonary nodules. **(b)** Consolidation, pleural effusions, pulmonary nodules and cavity formation.

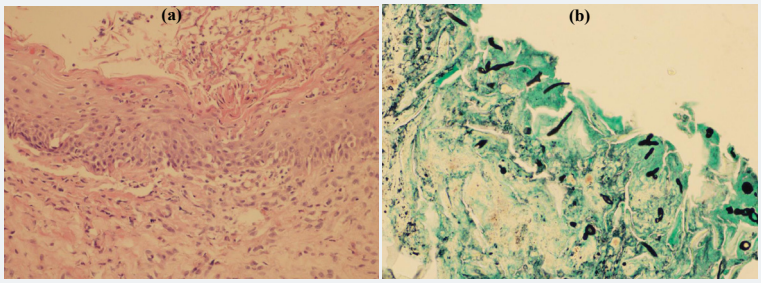

Figure 2: Skin biopsy showing: **(a)** Follicular dermatitis. **(b)** Hyphae of Fusarium species branching at acute angles.

identified as *Fusarium* sp. by electron microscopy and this was confirmed by nested polymerase chain reaction (PCR). CAT scan as well as magnetic resonance imaging (MRI) of the brain revealed no abnormality. MR arteriography of intracranial and extracranial arteries showed no vascular abnormality.

After confirming the presence of disseminated infection caused by *Fusarium* sp., micafungin was discontinued and the patient was commenced on both liposomal amphotericin-B and voriconazole intravenously (IV) in addition to subcutaneous granulocyte colony stimulating factor (G-CSF). The CVC was removed. Few days later, fever subsided. Later on, the patient started to improve clinically and more improvement was encountered after the recovery of her blood counts. Four weeks after starting combined antifungal therapy, the DFI became under control and the patient regained her vision so she was discharged on oral voriconazole. Six weeks later the patient received a consolidation cycle of chemotherapy composed of intermediate dose cytosine arabinoside (1500 mg/m^2 IV twice daily for 3 days) in order to keep her AML under control. She received voriconazole prophylaxis so as not to reactivate her previous Fusarium infection. Later on, the patient was followed up regularly in the outpatient clinic.

Discussion

Fusarium is a rapidly emerging multidrug resistant (MDR) genus of fungal opportunists that was first identified in the year 1958 [10]. *Fusarium* sp. are widely distributed in soil, plant debris, water and other organic substances [11,12]. Areas of high incidence of DFIs include: the United States of America, France, Germany, Italy, Netherland, Mexico, Australia and India [10,13]. For many years, *Fusarium* sp. have been considered as important plant pathogens [11,12]. Recently, more than 100 *Fusarium* sp. have been identified, but only 12 species are associated with human infections. The most frequent *Fusarium* sp. that cause human infections are: *F. solani*, *F. oxysporum*, *F. verticillioidis*, and *F. moniliforme*, while the less frequent F. species that cause infections in humans include: *F. proliferatum*, *F. dimerum*, *F. chlamidosporum*, *F. sacchari*, and *F. antophilum* [11-14].

In humans, *Fusarium* sp. can cause a wide range of infections ranging from local and superficial infections to disseminated, invasive and bloodstream infections [11,12,14-17]. Examples of the specific infections that can be caused by *Fusarium* sp. include: keratitis, endophthalmitis, onychomycosis, cutaneous and subcutaneous nodules, osteomyelitis, septic arthritis, sinusitis, CVC-related infections, meningitis, brain abscess, peritonitis, pneumonia, disseminated and bloodstream infections [11,12,14-17].

The risk factors for invasive or DFIs include: HMs particularly AML, acute lymphoblastic leukemia (ALL), lymphoma, and multiple myeloma; recipients of HSCT particularly those having GVHD; recipients of solid organ transplantations; solid tumors; human immunodeficiency virus patients; drugs such as corticosteroids, immunosuppressive agents and cytotoxic chemotherapy; neutropenia; hyperglycemia; burns; wounds; CVCs; active smoking; blood transfusions; pyoderma gangrenosum; and previous IFI [1,2,5-7,11,13,14,16,17,18-37]. In patients with HMs who are severely immunocompromised,

airborne transmission of invasive fusariosis may occur [38]. The sites of invasive infections caused by *Fusarium* sp. include: skin, lung, sinuses, disseminated and bloodstream infections [10,36].

The following techniques have been employed in the diagnosis of infections caused by *Fusarium* sp.: (1) microscopic identification and culture methods such as: blood cultures, tissue cultures and cultures of tissue biopsies taken from skin, sinuses, lungs and other internal organs; (2) serological assays such as galactomannan and β-glucagon tests; (3) specific nested PCR for identification and antimicrobial susceptibility testing; and (4) mass spectroscopy techniques [11,12,14,35]. Therapeutic options that are available for the treatment of infections caused by *Fusarium* sp. include: (1) single antifungal agents including: amphotericin-B, voriconazole, posaconazole and itraconazole; (2) combination therapies including either two antifungal agents such as voriconazole + amphotericin-B, voriconazole + terbinafine, caspofungin + amphotericn-B or amphotericin-B + terbinafine; or one antifungal drug + one non-antimycotic agent such as: voriconazole + metronidazole, and liposomal amphotericin-B + ciprofloxacin or ibuprofen; (3) adjunctive therapies such as: surgical debridement of infected tissues, debulking surgery such as splenectomy, removal of infected or colonized CVCs, interferon-γ, G-CSF, and granulocyte transfusions; and (4) new agents such as: MGCD290 and isavaconazole [2,4,6-11,14,18-20,34-36]. In severely immunocompromised patients who are at high-risk of having DFIs, antifungal prophylaxis is indicated [14,15].

The prognosis of fusariosis is directly related to the immune status of the affected patient and to the extent of the infection. Hence, very high mortality rates are encountered in persistently immunocompromised individuals [11,14]. Persistent neutropenia and a recent glucocorticoid therapy are the only independent factors for poor outcome [14]. In DFI, the overall mortality rate is 50% to 80% [14,15,36]. However, in patients with disseminated infection and persistent neutropenia, mortality rate may reach 100% [11].

Our patient had the following risk factors for the development of DFI: (1) AML in relapse, (2) repeated cycles of cytotoxic chemotherapy, (3) presence of a CVC at the time of infection, and (4) prolonged periods of neutropenia following the 2 cycles of chemotherapy. Unfortunately, there was no response to several antimicrobials given to control febrile neutropenia (FN) encountered after salvage chemotherapy. After confirming the presence of DFI, the patient was commenced on IV voriconazole in combination with liposomal amphotericin-B and G-CSF. Few days later, the patient started to show response and after recovery of her neutrophil count she experienced accelerated recovery and her disseminated infection was ultimately controlled. The combined antifungal therapy and the recovery of her WBC count were critical to control her life-threatening infection.

In conclusion: neutropenic patients with AML are at risk of serious fungal infections. In situations where a patient with acute leukemia develops FN that does not show favorable response to broad spectrum antimicrobials, it is essential to have comprehensive investigations in order to determine the cause of FN then to tailor antimicrobial therapy accordingly.

Acknowledgement

We are grateful to all medical, nursing and technical staff at KFSH in Dammam, Saudi Arabia who took care of the patient presented.

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