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Case Report

Combined Anti-Fungal Therapy with Liposomal Amphotericin B and Isavuconazole in a Case of Break through Disseminated Fusariosis in Acute Lymphoblastic Leukemia

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Abstract

Break through fusarium infection during antifungal prophylaxis is an emerging problem and a life-threatening condition, especially in immunocompromised hematological patients; thus, early identification of infection and appropriate and aggressive antifungal therapy are required. Here, we present the case of a 51-year-old woman with Acute Lymphoblastic Leukemia B (B-ALL) who developed a disseminated fusariosis while on Voriconazole (VOR) prophylaxis, successfully treated with a prompt combination of high-dose Liposomal Amphotericin B (L-AMB) and Isavuconazole (ISA). The treatment obtained a clinical improvement until complete resolution with no signs of infection recurrence during the following 16 months.

Keywords: Liposomal Amphotericin B; Voriconazole; Isavuconazole; Fusariosis; Leukemia

Abbreviations: B-ALL; VOR; L-AMB; ISA; MICs; CT

Introduction

Fusariosisis the second most common cause of disseminated fungal infection after aspergillosis in patients with hematological malignancies; more often involving skin, lungs and paranasal sinuses [1]. A significant risk of morbidity and mortality in these patients has been reported, especially during chemotherapy-induced prolonged neutropenia or stem cell transplantation [1]. Moreover, the choice of the best treatment is a challenging issue; reliable laboratory tests on antifungal sensitivity are lacking, susceptibility to triazole antifungal agents is not predictable and no correlation between Minimum Inhibitory Concentrations (MICs) and outcome was observed [1]. For this reason, prophylactic anti-mold therapy is strongly recommended in these high-risk patients [2]. However, cases of breakthrough fungal infection during prophylaxis with VOR have been reported [2–4] leading to a rapid progression of the infection until death. Although L-AMB is considered the election therapy for invasive fusariosis, its use as single agent showed unsatisfactory results owing to high rates of resistance. Therefore, higher doses of L-AMB or combination with VOR have been used in an attempt to overcome antifungal resistance [5]. Here, we describe a clinical case of disseminated fusariosis arising during VOR prophylaxis, successfully treated with high-dose L-AMB and ISA without recurrence after further immunosuppression.

Case Report

A 51-year-old female was diagnosed with a relapsed Philadelphia-negative B-ALL relapsed 17 years after the first diagnosis. In February 2021 she received re-induction intensive chemotherapy complicated by a fungal infection of the paranasal sinuses, classified as possible according to EORTC criteria [6]. The patient underwent surgical debridement of the nasal septum and an empirical treatment with VOR was promptly initiated leading to improvement and then resolution of the sinus infection. In March 2021 the patient received first consolidation with idarubicin, cyclophosphamide, dexamethasone and

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cytarabine and continued with VOR as secondary fungal prophylaxis. Ten days after the beginning of the chemotherapy, the patient developed febrile neutropenia, crampy pain to the lower limbs and muscular weakness associated with gait difficulties. In the meantime, painful subcutaneous nodules in the extremities, in the occipital region, at the trunk and at the left shoulder appeared (day 0). The nodules were initially homogeneous, erythematosus and well delimited, not necrotic or purulent (Figure 1A). A lower limbvenous doppler ultrasound, the microbiological and cytofluorimetric analysis on cerebrospinal fluid, echocardiography, and serologic assessments testing Borrelia burgdorferi, Bartonella henselae and Cryptococcus antigen were all negative. Blood culture tests revealed Pseudomonasaeruginosa, therefore antibiotic therapy with ceftazidime and meropenem was performed. Owing to persistent fever and worsening of cutaneous lesions tedizolid was added to the antimicrobial therapy, without benefit. On day +7 Computed Tomography (CT) chest scan showed a pseudo nodular consolidation with irregular delimitation located in the medial segment of the inferior left lobe, suggestive of opportunistic infection. Bronchoscopy, brain and abdomen CT scan, explorative lumbar puncture and fundus oculi examination, resulted all negative. On the same day the patient underwent skin lesions biopsy and empirically started L-AMB at dose of 3 mg/kg, while VOR was discontinued. Morphological pattern of the skin lesion showed a dermal lymphocyte, granulocyte infiltration with perivascular distribution and areas of steato-necrosis in the hypodermis. PAS and Gomori-Grocott histochemical stains did not detect the presence of fungi, while culture of the skin swab and skin biopsy was indicative of Fusarium genus (Figure 2 A-B).

Patient was therefore diagnosed with disseminated fusariosis and antibiotic treatment was discontinued. On day +17, L-AMB was increased to 5 mg/kg and oral ISA at 200 mg/die was added in the attempt to better overcome any possible resistance. This treatment achieved stable apyrexia after 24 hours. On day +24, after 7 days since the start of high-dose L-AMB and ISA, the nodules gradually improved, becoming less numerous, sized-reduced, less erythematous and not painful (Figure 1B). After further twenty days, chest CT scan showed a dimensional reduction of the pulmonary nodule, a necrotic and a minimal ground glass component. On the other side, the skin lesions became dyschromic, flat and almost completely resolved. Due to renal toxicity, we decided to discontinue L-AMB after a total dose of 7400 mg and to continue anti-fungal therapy with ISA as single agent.

The patient received the third consolidation cycle with high doses of methotrexate and cytarabine and after that, due to the persistence of measurable residual disease, she was switched to monoclonal anti-CD22 antibody, Inotuzumab-ozogamicin, as bridge to allogenic stem cell transplantation, obtaining deep molecular response at the time of the transplant. Chest CT scan before transplant was negative and only dyschromic skin changes on lower limbs were present. ISA was maintained throughout the whole peri-transplant period. Sixteen months after the onset of skin lesions and ten months after allogeneic transplant, the patient is in good general condition, without any signs or symptoms of recurrence of the infectious disease (Figure 1C).

Discussion

Fusarium species are hyaline filamentous fungi widely distributed in soil, plant debris, air and water [1,7]. The mainly entry routes are airways, through damaged mucous membranes or skin and nails injuries [1]. Most frequently species causing

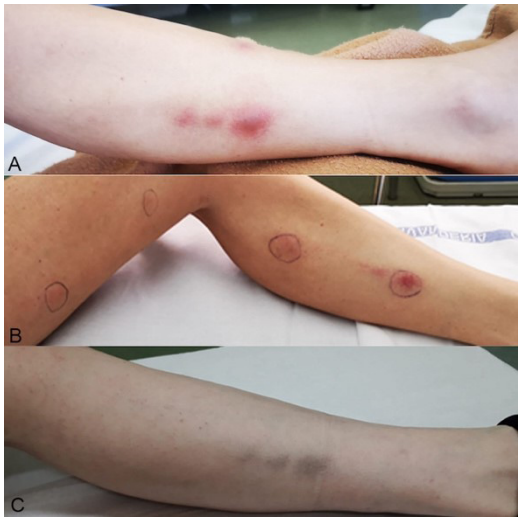

Figure 1: Fusarium, clinical picture. **1A**: On day 0, both lower limbs presented with erythematous and painful subcutaneous nodules, diffusely infiltrated, following venous course. **1B**: On day 24, cutaneous lesions gradually recovered, present slight reduction in size, flat and less erythematous. **1C**: After 16 months of fusarium spp. infection, the skin lesions generally healed and the scar remained.

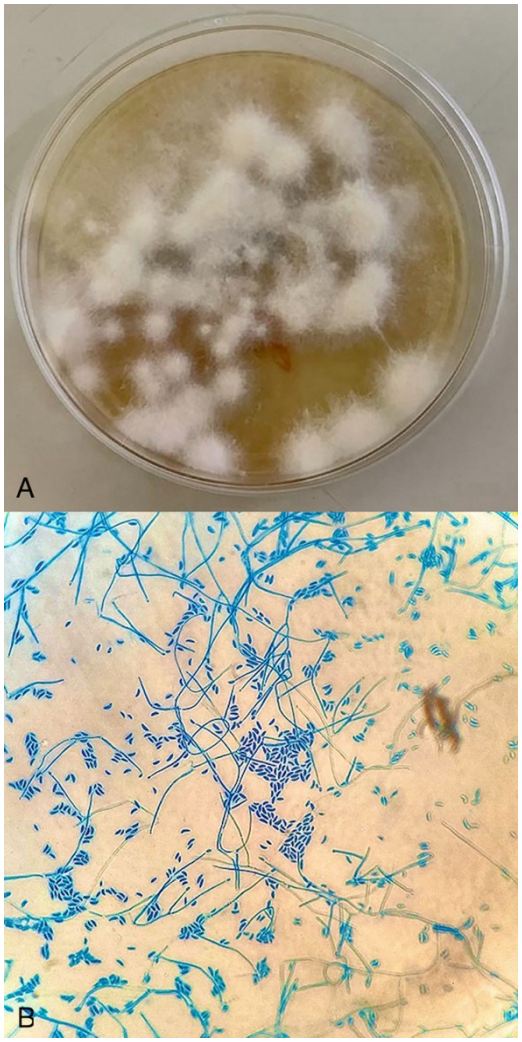

Figure 2: Fusarium spp. from skin culture. **2A**: The morphologic image in Sabouraud Dextrose Agar showed the growth of clear colonies of moulds after 4 days at 37°C. Colonies expanding changed to yellow with aging. **2B**: The microscopic image of fusarium spp. showing visible banana-shaped hyaline septate hyphae and branched at right angle. The examination was performed using lactophenol cotton blue staining [15].

infection in humans are Fusarium solani (50%), Fusarium oxysporum (20%) and Fusarium verticillioides (10%) [4]. Patients affected by acute leukemia and those who undergo bone marrow transplantation carry the highest risk to develop disseminated fusariosis due to prolonged neutropenia and cellular secondary immunodeficiency related to aggressive and chronic immunosuppressive therapies [1].

Skin lesions are the most common clinical manifestation [8], appearing in about 70% of cases, are often the only sign of disease and frequently appeared as painful, purulent and necrotic nodules [9]. The muscle involvement is quite rare and has been described in 15% of cases [7]. Lung involvement is frequent in immunocompromised patients, in our case it was attributed to Fusariumspp. Due to the concomitant appearance with skin lesions and the optimal response to the antifungal treatment. Our patient presented painful subcutaneous nodules lacking the described necrotic and purulent aspect [8,9] and associated with myalgias and gait difficulty.

Given the aggressiveness and the rapidity of infectious dissemination, a prophylactic anti-mold treatment is recommended in high-risk patients [2]. However, breakthrough Fusarium infections during prophylactic antifungal therapy have been described and represent a challenging issue [2], associated with high mortality rates, since Fusarium spp. have shown intrinsic resistance to antifungal agents [1]. Recent studies have reported several cases of breakthrough fungal infection during VOR [2,3], possibly related to immunological host factors, intrinsic resistance of pathogens against the molecule or low bioavailability of the drug at the infection site [4,10]. In vitro antifungal susceptibility tests have shown that some Fusariumspp. Exhibit high MICs for agents such as VOR and L-AMB [9,11], however, VOR or L-AMB monotherapy often obtain modest results [12], since no correlation between MICs and clinical outcome was reported [1]. The choice of a combination therapy between a broad-spectrum antifungal agent with a high bioavailability such as ISA [13] with high doses of L-AMB to reach all possible sites of infection had the aim to adequately and rapidly face a such severe life-threatening complication; ISA could be effective in a wide range of rare invasive fungal diseases, including those caused by Fusariumspp. and in vitro shows the ability to inhibit Fusariumspp growth [13,14]. In addition, low toxicity profile has been reported with ISA compared to VOR [14] making this an attractive drug for combination treatments. Our approach allowed us to obtain consistent lesions improvement both in the skin and in the lung and to continue the treatment for a long time with ISA mono therapy to contain the toxic effect by high doses of L-AMB and to prevent possible recurrence during following immunosuppression.

Conclusions

Early diagnosis of Fusarium infection requires a highly clinical suspicion since clinical picture may differ. As seen in this case report, the skin lesions were not as usual as in the literature. To the best of our knowledge, this is the first report on the combination therapy of ISA and L-AMB successfully employed in a case of disseminated Fusariosis while on triazole prophylaxis; we provide a valid therapeutic option that may be an effective therapeutic strategy for this severe infection in immunocompromised patients. Physicians should consider to promptly starting this combined antifungal treatment when Fusariosis has been diagnosed.

Conflict of Interest

The authors declare that they have no conflict of interest

Author Contributions

Patrizia Zappasodi and Luca Arcaini conceived, designed, and supervised the study; Claudia Patricia Tobar Cabrera and Caterina Cristinelli collected data and wrote the manuscript; Claudia Patricia Tobar Cabrera, Caterina Cristinelli, Eugenio Santacroce, Eleonora Gelli, Gianluca Martini, Ludovica Calabretta, Elisa Bono, Roberta Sciarra, Manuel Gotti, Patrizia Zappasodi, Elisa Roncoroni, Marianna Rossi and Angela DiMatteo discussed and analyzed the data; Caterina Cavanna performed microbiological analyses and provided pictures; and all authors revised and approved the final version of the manuscript.

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