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CASE REPORT

Disseminated Fusariosis with Secondary Hemophagocytic Lymphohistiocytosis

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ABSTRACT

We report here a 7-year girl with B-Acute Lymphoblastic Leukemia (ALL) on Berlin Frankfurt Munster (BFM) based induction chemotherapy who presented with fever, cough, and painful necrotic skin lesions simulating pseudomonas sepsis. The patient was eventually diagnosed with disseminated fusariosis. While on combination antifungal therapy, fever reappeared with pancytopenia and hepatosplenomegaly, and she was subsequently diagnosed with secondary Hemophagocytic lymphohistiocytosis (HLH) and was treated using the HLH 2004 protocol. The child responded to treatment well. This report highlights the high index of clinical suspicion, appropriate investigations needed to diagnose fusariosis and secondary HLH in pediatric oncology practice promptly, and the successful treatment outcome despite having them both. *J Microbiol Infect Dis 2022; 11(2):69-73.*

Keywords: *ALL, Fusariosis, Hemophagocytic Lymphohistiocytosis*

INTRODUCTION

Invasive fungal infections significantly cause mortality and morbidity in immune-compromised children [1]. There is an increase in the diversity and severity of fungal infections in these children [2]. Hematopoietic Stem Cell Transplantation (HSCT) recipients and children with prolonged neutropenia are prone to disseminated fusarium infection with a significant risk for mortality [3].

CASE REPORT

A 7-year girl with B-Acute Lymphoblastic Leukemia (ALL) on Berlin Frankfurt Munster (BFM) based induction chemotherapy presented on Day 11 with fever and cough. A Contrast Enhanced Computerized Tomogram (CECT) thorax revealed patchy consolidation in both lungs with bilateral minimal pleural effusion. Her total leukocyte count was 600/cumm, her platelet count was 10,000/ cumm, and her hemoglobin was 7.6 g/dl. Blood culture revealed pan-sensitive Pseudomonas aeruginosa growth. Antibiotics were changed to carbapenems, fluconazole prophylaxis was started, and blood transfusion was given. She became afebrile and symptomatically better. On Day 17 of induction, she developed a new-onset continuous high-grade fever associated with a painful erythematous papular lesion over the left leg and right hand. These lesions started appearing on the trunk, faces, and upper and lower extremities. Within 48 hours, the center of the nodules became ulcerated and covered by eschar (Figure 1 A, B). Considering Pseudomonas sepsis, Ceftazidime was added as a second drug. Meropenem was subsequently stopped after an overlapping period of 48 hours. Cultures from skin lesions were taken in view of ongoing construction work in the hospital and prolonged febrile neutropenia. Liposomal Amphotericin was added. Culture from skin scrapings grew filamentous fungus. Hence Voriconazole was added. The fungal isolate was identified as Fusarium dimerium (Figure 2). A broth dilution antifungal susceptibility test was done for the fungal isolate. The Minimum Inhibitory Concentration (MIC) of the isolate for Amphotericin B was 0.5 µg/ml and >16 µg/ml for Voriconazole. Blood culture also revealed the same growth. Because of disseminated

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fusariosis with prolonged neutropenia, Granulocyte-Colony Stimulating Factor was added. The child was screened for disseminated fusariosis. CECT Brain and abdomen revealed no lesion. Repeat CECT chest revealed multiple cavitation lesions in lungs suggestive of fungal etiology, and CECT sinus showed Bilateral maxillary sinusitis with hyperdense content in the left maxillary sinus, possibly fungal. She responded to treatment with an improvement in total counts of blood values, and the necrotic skin lesions started ulcerating and eventually fell off (Figure 1 C, D). The remaining induction chemotherapy was modified, avoiding anthracycline, and she attained morphological remission. Liposomal amphotericin was given for five weeks. The child initially showed an excellent clinical response to Voriconazole, and Voriconazole prophylaxis continued.

Post induction, she developed fever spikes and pancytopenia with hepatosplenomegaly. The repeat blood cultures were found negative. There was no evidence of leukemia relapse, and work-up for Hemophagocytic lymphohistiocytosis (HLH) revealed hyperferritinemia (S. Ferritin = 5,910 µg/L), hypertriglyceridemia (Triglyceride = 420 mg/dl), Along with pancytopenia, fever spikes, and splenomegaly, Fusarium associated secondary HLH was diagnosed. She was started on dexamethasone as per HLH 2004 protocol, and Voriconazole was continued.

We did not administer Cyclosporine because of persistent hypertension. She needed three antihypertensives while on dexamethasone. Etoposide was avoided given the neutropenia. During this period, she took dexamethasone for eight weeks as per protocol. She was given modified consolidation chemotherapy (Cyclophosphamide & mercaptopurine) during the HLH protocol phase. Subsequently, she remained symptoms-free, completed the rest of the chemotherapy without modification, and is in the maintenance phase of chemotherapy.

DISCUSSION

Children with cancer are immunocompromised due to chemotherapy and prolonged neutropenia and are susceptible to infection with unusual molds and yeasts. According to adult literature, human fusariosis as a known entity has only a short history but a high mortality rate of >50% [4]. The first human case reported was keratitis in 1958 [5]. In a review of analysis done by Jieni et al. on 62 cases of ALL were having concomitant fusarium infection, failure to attain ALL remission significantly impacted mortality [6]. Our patient was a case of ALL on induction chemotherapy with neutropenia and hence was at high risk of mortality.

Clinical presentation can range from superficial to locally invasive to disseminated presentations. Skin lesions characteristic of fusariosis include multiple papulonodular lesions which develop central necrosis. However, necrosis is less likely in an immunocompetent host [7,8].

This child had generalized papules and nodules, which immediately developed central necrosis (Figure 1 A, B). Initial clinical suspicion was pseudomonas sepsis, addressed with broad-spectrum antibiotics along with Liposomal Amphotericin B, which was empirically added due to the ongoing construction work. Cultures from the scrapings of the lesion grew filamentous fungus fusarium, clinching the diagnosis of fusariosis. Initiation of Liposomal Amphotericin B early in the course of the disease may have resulted in favorable outcomes in our patient.

Fusarium species are resistant to most of the currently available antifungals. There are also no standard guidelines on the management of disseminated fusariosis. Approaches include combination antifungals, boosting innate immune systems, and novel antifungals [9]. Amphotericin B is the most used agent both in the pre and post-broad spectrum triazoles era, alone or in combinations. Combinations tried to include Amphotericin B with Voriconazle/ Echinocandins/ 5-Flucytosine / Terbinafine / even with Rifampin [9]. The increased use of combination therapy and Voriconazole has probably improved survival during the last decade [10-12]. European Society of Clinical Microbiology and Infectious Diseases and European Confederation of Medical Mycology Organization Joint Guidelines recommend a combination of voriconazole and lipid formulation of amphotericin B [13]. Considering the highMIC, most of the reports use doses in the higher range. Approaches to boost innate immunity include granulocyte transfusion, colony-stimulating factors (G-CSF), and cytokines like IFN-Ɣ [9]. The role of surgical debridement is limited to localized infections.

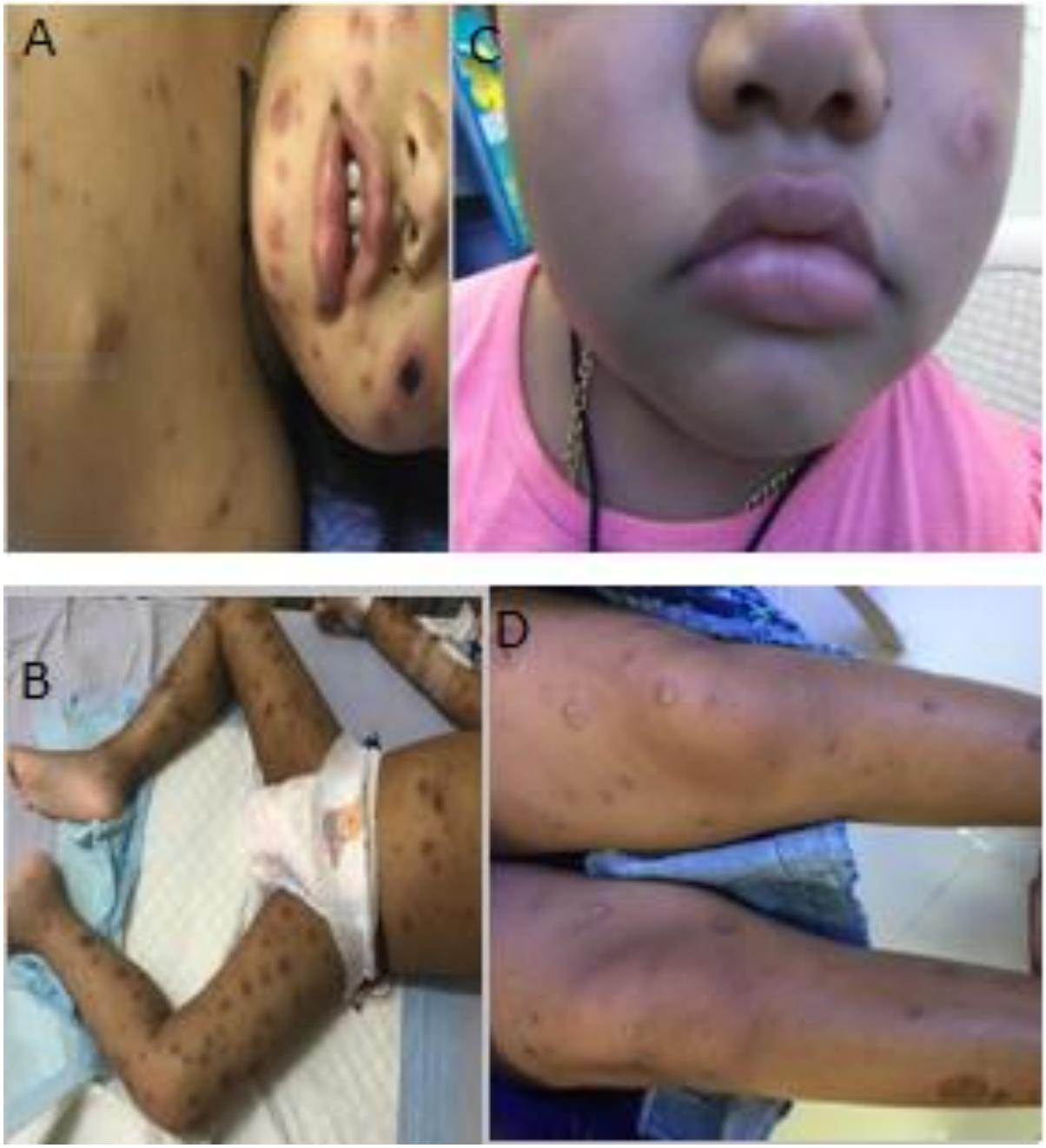

Figure 1. Cutaneous lesions A) On Day17 of steroid, papule, and black eschar on left cheek B) Papulondular skin lesions spread all over body C and D) 4 months later, complete healing of papulonodular lesions over face and throughout the body.

Based on the high mortality of Fusarium infection in immunocompromised children and inherently high MIC to antifungals, we decided to treat our patient with a combination of antifungal therapy. The child received a combination therapy of liposomal amphotericin and Voriconazole for disseminated fusariosis. It was challenging to continue the child on prolonged liposomal amphotericin due to the requirement of protracted inpatient admission and long-term toxicities. Hence after five weeks of combination therapy, Voriconazole was continued as a practical oral consolidation/ maintenance therapy, given its initial clinical response. Despite the high MIC, our patient maintained an excellent clinical response with Voriconazole. She did well on Voriconazole secondary prophylaxis and had no recurrent infection. To shorten the duration of neutropenia, G-CSF was added. All these strategies proved very effective in managing our patient.

Secondary hemophagocytic lympho-histiocytosis (sHLH) is a highly stimulated but ineffective immune response to various stimuli, including viral, bacterial, fungal, immunological disorders, and certain malignancies. Fungal infections associated with sHLH include Candida, Cryptococcus, Pneumocystis, Histoplasmosis, and Aspergillus [14]. sHLH related to fungal infections usually occur in immune suppression, disease, or therapy-related settings.

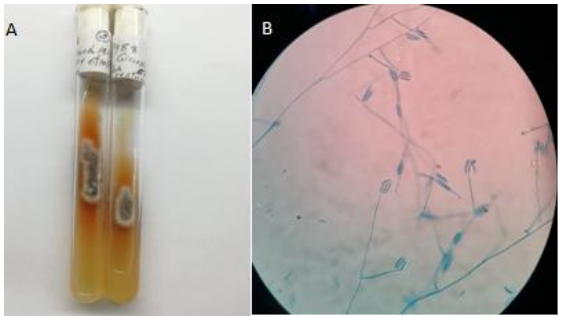

Figure 2. The Fusarium from skin scraping. (A) The morphologic image of Fusariumin on Sabouraud's agar medium (B) The microscopic image

A case report of fusarium infection in a child undergoing treatment for HLH has been reported [15]. However, we could not find any reports of sHLH associated with Fusarium in our English literature search. There are no reports of pediatric ALL with disseminated fusariosis and sHLH in published literature. We started her on HLH 2004 protocol along with antifungals. With this, HLH and fusarium infection could be controlled, and she is currently on maintenance chemotherapy for ALL along with Voriconazole prophylaxis. Secondary HLH has a dismal prognosis in adults [16].

Disseminated fusariosis in an immunosuppressed host carried a high mortality rate [4]. Although the mortality rate has decreased in the post-voriconazole era, it remains high. Therefore, a high index of suspicion is needed in the pediatric oncology setting as its cutaneous manifestations can initially mimic more common conditions like pseudomonal sepsis, especially in a sick child. Managing sHLH with immunosuppression in disseminated fusariosis is challenging and can be a double-edged sword. This case is probably the first report of an ALL child on induction having sHLH in association with disseminated fusariosis, both of which could be controlled by improvised management of sHLH and combination antifungals, followed by voriconazole prophylaxis.

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