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LETTER TO THE EDITOR

Possible hepatosplenic candidiasis treated with liposomal amphotericin B and caspofungin combination

Sir,

Combination anti-fungal therapy is one of the hottest topics in the infectious diseases. Recently, Nivoix et al. reported 20 cases of fungal infection treated with combination of caspofungin and an azole or an amphotericin B formulation in invasive fungal infections.[1]

Despite several developments in the quality of care and anti-microbial therapy, febrile neutropenia is still a morbid and mortal syndrome. In spite of extended spectrum anti-bacterial and anti-fungal agents, fever may persist in several situations.[2]

Hepatosplenic candidiasis (HSC) is a potentially mortal complication encountered in immunocompromised or febrile neutropenic individuals, especially, those being treated with intensive chemotherapy protocols for acute leukaemia. Immediate recognition of this complication and initiation of appropriate treatment is crucial in order to control the infection, decrease the morbidity and mortality, and avoid delays in treatment of the underlying condition.[3]

A 28 years old female patient with a diagnosis of acute myeloid leukaemia (AML-3) 5 months ago developed fever (39 °C) 13 days after receiving first consolidation chemotherapy. She was neutropenic (neutrophil count 90/mm^3). Her physical examination was unremarkable. She was considered as neutropenic fever. Blood and urine cultures were performed. Cefepime (3×2 g) and isepamicine (500 mg×2) were initiated empirically. Since, fever did not resolve, teicoplanin was added on the 4th day, amphotericin deoxycholate (1 mg/kg) was added on the 6th day. On the 8th day of antibiotherapy her neutropenic status resolved (neutrophil count 1600/mm^3) but she developed pain on her right hypocondriac region. Emergency abdominal ultrasonography and magnetic resonance imaging was in concordance with hepatosplenic candidiasis (multiple, irregular, and ill-defined hypointense lesions). Bone marrow or blood cultures did not reveal any pathogen. *Candida* and *Aspergillus* antigen tests were negative in serum. Anti-bacterial therapy was stopped, anti-fungal therapy was switched to liposomal amphotericin B (LAMB, 3 mg/kg for 1 week, 5 mg/kg for 2 weeks). Despite 3 weeks of liposomal amphotericin B, her fever did not resolve, and there was no regression in the radiologic findings. Caspofungin (70 mg/day 1st day, subsequently 50 mg/day) was added to the therapy. Her fever resolved 7 days later. There was radiologic regression in the control imaging studies on the 3rd week of combination therapy. LAMB was stopped and caspofungin was continued for an additional 5 weeks. At the end of this period her lesions had regressed to the minimal level. IV therapy was stopped. She was given oral flucanazole for 2 months on maintenance therapy. There is no recurrence on the 12th month of her follow up.

The patient was considered as 'possible hepatosplenic candidiasis' according to guidelines of the European Organisation for Research and Treatment of Cancer and the Mycosis Study Group.[4] Since, patient did not respond to a total of 25 days of amphotericin B deoxycholate or LAMB treatment clinically and radiologically, caspofungin was added to the therapy. We could not courage to switch to caspofungin alone, since the molecule was relatively new and had entered our national market, very recently. Evidence available today suggests that the combination of a polyene with an echinocandin is typically indifferent for *Candida*.[5] However, in vitro results do not always correlate with in vivo results. Barchiesi et al.[5] reported that the combination regimen with amphotericin B and caspofungin was the only therapeutic approach yielding organ sterilization in a murine candidemia model induced by a *Candida glabrata* strain indifferent to combination of these molecules. To our knowledge there is no study comparing monotherapy with combination therapy in hepatosplenic candidiasis. Biopsy was not performed because of her persistent thrombocytopenic status. Patient was followed up by radiologic imaging

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techniques.[3] Her renal and liver function tests were normal during the whole treatment period.

To our knowledge this is the first reported hepatosplenic candidiasis case treated with combination therapy. Hepatosplenic candidiasis should be kept in mind in febrile neutropenic patients who did not respond to classic anti-bacterial therapy. When clinical or microbiological failure is evident with monotherapy, combination therapy may be considered as a salvage therapy option.

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Bilgin Arda[a]
Nur Soyer[b]
Oguz Resat Sipahi[a*]
Ozcan Hüdaverdi[b]
Meltem Isikgoz Tasbakan[a]
Guray Saydam[b]
Murat Tombuloglu[b]
[a]*Department of Infectious Diseases and Clinical Microbiology, Ege University Faculty of Medicine, Bornova-Izmir, Izmir, Turkey*
[b]*Department of Internal Medicine, Ege University Faculty of Medicine, Bornova-Izmir, Izmir, Turkey*
E-mail address: sipahio@med.ege.edu.tr

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* Corresponding author. Tel.: +90 2323904510.