

# Successful Hematopoietic Stem Cell Transplantation in AML and Hepatosplenic Candidiasis: Case Report and Review of Literature

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Received : July 21, 2020  
Accepted : January 4, 2021  
Published : March 5, 2021

## Abstract

**Background:** Hepatosplenic fungal infection in patients with acute leukemia is a rare disease. **Case Report:** We report a 33-year-old female with acute myeloid leukemia (AML) who developed probable hepatosplenic fungal infection after induction chemotherapy, underwent hematopoietic stem cell transplantation (HSCT) from matched sibling brother successfully. The patient received anti-fungal treatment for seven months and lesions tended to stabilize before transplantation. She was also treated with voriconazole and caspofungin throughout transplantation. Repeat abdominal MRI post-transplant revealed obvious regression of hepatic and splenic lesions. Eventually, she was discharged with full recovery of cell count. **Conclusion:** Complete imaging resolution of lesions is not a prerequisite for HSCT if the infection can be controlled with antifungal therapy.

**Keywords:** Acute Myeloid Leukemia, Antifungal Agents, Caspofungin, Hematopoietic Stem Cell Transplantation, Mycoses, Voriconazole.

## Introduction

Invasive fungal infections (IFIs) are one of the most relevant causes of morbidity and mortality for patients with hematological malignancies. The epidemiology of IFIs has changed from candidemia to aspergillosis over the recent decades [1], and the rate of invasive candidiasis is estimated to be less than 1% [2]. Chronic disseminated candidiasis (CDC) is a special clinical manifestation of invasive candidiasis; the most frequent form of CDC is hepatosplenic candidiasis (HSC). The incidence of HSC was between 2.0 and 7.4% in patients with acute leukemia [3-4].

Timely diagnosis of HSC is often difficult, because non-specific clinical presentations and limited sensitivity of diagnostic techniques including histopathology, tissue or blood culture [5-6]. At present, the optimal management of HSC has not been well established, such as the choice

of therapy agents, the treatment duration. Not all guidelines are in agreement on the treatment of HSC for immunocompromised patients [7-10]. The Infectious Diseases Society of America (IDSA) suggests that treatment should be continued until lesions resolved on repeat imaging, however, which usually needs several months [11].

In addition, HSC leads to a therapeutic dilemma of whether chemotherapy or HSCT protocol should be suspended until the infection is completely eliminated, which often leads to serious consequences (i.e., relapse) [12-13]. At present, there is no related guideline on transplant indication for patients with HSC. Thus, in this study, we describe a case of HSC in a woman with AML whose liver and splenic lesions improved following seven months of three anti-fungal drugs and eventually completed subsequent HSCT from matched sibling.

## Case Report

A 33-year-old female with AML received an induction chemotherapy of cytarabine and idarubicin before admission. During agranulocytosis her main symptoms were fever and persistent low back pain. Blood culture suggested *Candida tropicalis*. Abdominal ultrasound revealed multiple hypoechogenic liver and splenic lesions.

In May 2017 she was transferred to our institution. Physical examination revealed conjunctival pallor, abdominal tenderness, mild hepatosplenomegaly and generalized lymphadenopathy. Repeated blood cultures for bacteria and fungus were negative. Laboratory investigation showed slightly raised liver enzymes and inflammatory indicators including procalcitonin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), 1, 3- $\beta$ -D dextran. Bone marrow examination was normal. Chest contrast enhanced computed tomography (CT) revealed multifocal lesions, mainly small nodules. An abdominal MRI demonstrated multiple low-density liver lesions partially with enhancing walls.

Based on prior *Candida tropicalis* fungemia and multiple low-density lesions in liver and spleen, a probable diagnosis of HSF was made. Intravenous voriconazole was initiated for the first 2 weeks, followed by combined caspofungin for the ensuing 2 weeks. On 2 June, first consolidation chemotherapy with CAG (cytarabine, aclacinomycin and granulocyte colony-stimulating factor) was initiated. Two months after dual anti-fungal therapy, the patient's body temperature gradually returned to normal. She was discharged to continue voriconazole 200 mg twice daily.

About one week after discharge, the patient was readmitted for fever. Because of financial constraints, her treatment was switched to intravenous caspofungin and liposome amphotericin-B (L-AmB) for one month. Due

to recurrent fever, we raised a differential diagnosis of fungus versus tuberculosis. Then except for anti-fungal drugs (caspofungin and liposome amphotericin-B), the patient received the combination of anti-tuberculosis therapy including isoniazid, rifampicin, and ethambutol. Unfortunately, after more than two months, the patient still experienced recurrent fever. Then, the patient had to receive two percutaneous fine-needle aspiration under ultrasound guidance. However, pathological examinations revealed chronic granulomatous inflammation, no fungal hyphae. Fortunately, five months after dual anti-fungal treatment (caspofungin and liposome amphotericin-B), repeat abdominal MRI demonstrated reduced splenic and liver lesions. She eventually underwent allo-HSCT from matched sibling brother. Intravenous voriconazole and caspofungin were given in the course of transplantation. At twenty-eight day after allo-HSCT, follow-up abdominal MRI revealed reduced liver and splenic lesions and bone marrow smears indicated complete remission. She was discharged with oral voriconazole 200 mg twice daily.

At the time of writing this paper, the patient remained stable. Her subsequent MRI revealed gradual decrease in the size of hepatic and splenic lesions.

## Discussion

Invasive candidiasis infection remains the most frequent in neutropenic patients. CDC is a rare complication [14], often affecting liver, spleen, kidney and other organs. Prolonged neutropenia, glucocorticoid therapy, the existence of central venous catheters and mucositis are the most frequent risk factors of CDC for patients with hematological malignancies [15-16]. HSC incidence is uncertain. Some studies reported HSC rate ranged from 3% to 7% in acute leukemia [17], and 9% in transplant recipients in Europe and North America [18]. With the use of anti-fungal prophylaxis, HSC incidence in acute leukemia may have declined below 3%

[19]. HSC is linked to high mortality ranging from 10% to 25% [20].

The definitive diagnosis of HSC is on the basis of tissue pathology or culture, however, with low positive rate [21]. Thus, HSC is one of the few infections where we prefer to treat rather than diagnose. In this case, antifungal treatment before biopsy may contribute to the negative pathological results. If CDC cannot be proven by microbiological examination, imaging examination is important to define probable HSC [22]. Clinically, for many patients, the presumptive diagnosis of HSC is based on imaging abnormalities. Typical imaging findings on ultrasound, CT or MRI include nodules, micro-abscesses (“bull-eye” lesions), hypoechogenic foci or fibrosis [23-24]. For this patient, documented *Candida tropicalis* and multiple hepatosplenic lesions on CT scan were sufficient to diagnose probable HSC according to the EORTC/MSG study group definition criteria [22].

There is no consensus on the drug of first choice, and the required duration of anti-fungal treatment. Most international guidelines suggest fluconazole for stable patients, and L-AmB for severely ill patients [7-9]. But Infectious Diseases Working Party of the German Society of Hematology and Oncology for hematologic patients with HSC suggested echinocandins or L-AmB as initial therapy in unstable patients, and voriconazole is considered a second-line choice [10]. In this case, for kinds of reasons, the patient was rendered subsequently three anti-fungal agents including voriconazole, echinocandins and L-AmB. Clinically, specific therapeutic drugs depend on a variety of factors including severity of infection, host immune state, previous anti-fungal regimen, patient's tolerance and economic capability. Hence, it is difficult to answer the question: what is the best treatment for patients with HSC. Another, we should be aware that fever can persist for several weeks, even several months; and it is not usually considered as a failure of treatment during the evolution of HSC [25-26].

The Infectious Diseases Society of America advises that treatment should be continued until radiologic lesions are calcified or resolved, which usually needs several months. However, others consider anti-fungal therapy should be continued throughout chemotherapy course or HSCT [27]. In this case, the patient received anti-fungal therapy throughout transplantation.

But no consensus on the transplant time for patients with HSC was reached. Historically, uncontrolled fungal infection was considered a relative contraindication to HSCT. However, improvement in transplant method and post-transplant supportive technology have made HSCT possible for patients with disseminated fungal infection [28]. In the case, reduced intensity transplant (RIT) and HSC in a stable state before HSCT prevented fungal progression after transplant. CDC was not an absolute contraindication to stem cell transplantation [3,29]. One study reported 22 of the sixty-one patients with HSC underwent allogeneic transplantation successfully after HSC was controlled [30].

## Conclusion

HSC remains a challenging issue for patients with hematological malignancies. Timely diagnosis of HSC is challenging due to the low yield rate of positive microbiological and histological findings. In case of patients with persistent and unexplained fever and hepatic and splenic lesions, HSC should be considered when lesions are not characterized by metastasis. The encouraging outcome confirms HSC is not an absolute contraindication to chemotherapy schedule and HSCT, if the lesions are stable.

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