Successful treatment of severe aplastic anemia following acute hepatitis with liver fungal abscess by haploidentical peripheral blood stem cell transplantation: a case report

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A 34-year-old man presented with fever 3 months after developing acute hepatitis of unknown etiology. Laboratory analyses revealed pancytopenia, and bone marrow biopsy confirmed the diagnosis of aplastic anemia (AA). He developed severe AA, becoming neutropenic, which led to invasive infections with liver abscesses that was possible to have been caused by *Aspergillus* species. Micafungin was not effective, and treatment with liposomal amphotericin B (L-AMB) and voriconazole (VRCZ) did not alter the size or activity of the lesion, but the patient's body temperature returned to normal. He was referred to our hospital for emergent allogeneic hematopoietic stem cell transplantation (HSCT). However, a human leukocyte antigen (HLA)-identical donor was not found, and peripheral blood HSCT using a reduced-intensity conditioning regimen with post-transplant high-dose cyclophosphamide from an HLA-haploidentical sibling donor was considered. L-AMB was discontinued before the conditioning for HSCT, but VRCZ was continued. Neutrophil engraftment was obtained after 13 days from HSCT. No adverse events due to the graft versus host disease or recurrence of liver abscess occurred. Haploidentical HSCT using peripheral blood stem cells mobilized by granulocyte colony-stimulating factor may be a treatment option for severe AA patients with invasive fungal infections if an HLA-matching donor cannot be found. (Journal of Hematopoietic Cell Transplantation 8(3): 97-101, 2019.)

Introduction

Aplastic anemia (AA) is characterized by bone marrow failure and marked decreases of all marrow elements. Hepatitis-associated AA (HAAA) most often affects adolescent and young men who present with severe pancytopenia two to three months after an episode of acute hepatitis.^{1,2} The marrow failure can be precipitous and severe, and is usually fatal if untreated. Furthermore, the hepatitis can be clinically undistinguishable from typical viral hepatitis, but with no specific cause identified.

It is well-known that AA is a potentially fatal condition if there is no response to immunotherapy and/or if there is progression to severe pancytopenia. In particular, invasive fungal infections (IFI) are reported to have very poor prognoses.³ While the role of hematopoietic stem cell transplantation (HSCT) in these AA patients is evolving, even now there are some patients with HSCT-related mortality. However, it is recommended that early allogeneic HSCT (allo-HSCT) should be done in younger severe AA patients with concerns about the risk of severe infections. Patients with AA who lack a matched sibling or unrelated donor and who have a severe

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Figure 1A. Clinical course of the patient at the time of liver dysfunction. (Abbreviation) mPSL, methylprednisolone; PSL, prednisolone; SNMC, stronger neo-minophagen C; WBC, white blood cell; Hb, hemoglobin; Plt, platelet; T. Bil, total bilirubin; D. Bil, direct bilirubin; ALT, alanine transaminase; AST, aspartic aminotransferase.

Figure 1B. Clinical course of the patient after the diagnosis of HAAA. (Abbreviation) CRP, C-reactive protein; WBC, white blood cell; Hb, hemoglobin; Plt, platelet; MRSA, methicillin-resistant *Staphylococcus aureus*; GAL, galactomannan test; CFPM, cefepime; MEPM, meropenem; MCFG, micafungin; VCM, vancomycin; VOR, voriconazole; LVFX, levofloxacin; ST, sulfamethoxazole/trimethoprim; PIPC/TAZ, piperacillin/tazobactam; L-AMB, liposomal amphotericin B; Flu, fludarabin; CY, cyclophosphamide; TBI, total body irradiation; PBSCT, peripheral blood stem cell transplantation.

infectious condition that cannot wait for immunosuppressive treatment to take effect are at increased risk of death from infection. Haploidentical HSCT (haploHSCT) can successfully rescue these refractory severe AA (SAA) patients.^{4,5}

We present an HAAA patient with liver abscesses of serious fungal infection who successfully received haploHSCT.

Case report

A 34-year-old man was admitted to a university hospital with general fatigue and yellowish skin (day-268). The patient had been diagnosed as having acute hepatitis, because the laboratory evaluation revealed abnormalities in the liver panel, with total bilirubin (T-Bil) of 5.0 mg/dL, alkaline phosphatase (ALP) 608 IU/dL, and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) of 4,359 and

Figure 2. Bone marrow biopsy showed hypocellular marrow, consistent with aplastic anemia

2,335 IU/dL, respectively. The complete blood count (CBC) and coagulation panel were normal at that time. Serologic test was negative for HIV-1/HIV-2 antibody, anti-HAV immunoglobulin M (HAV IgM), HB surface antigen, HCV IgG, HEV IgA, cytomegalovirus IgM, and Epstein-Barr virus IgM. Anti-nucleic and antimitochondrial antibodies were also negative. He denied any known history of liver disease among any family member. He denied any recent contact with sick people, animal exposure, or travel outside Japan. He reported drinking alcohol only on occasion, and denied any history of tobacco, drug usage, or blood transfusion. During hospitalization, the AST and ALT levels gradually decreased, although the T-Bil level remained markedly increased. High-dose methylprednisolone (mPSL) therapy was administered and successfully resolved severe bilirubinemia. However, 3 months later, the AST, ALT, and T-Bil levels were again increased. Moreover, CBC showed WBC of $500/\mu\text{L}$, Hb level of 12.1 g/dL , and Plt of $6,000/\mu\text{L}$, indicating the development of pancytopenia (**Figure 1A**). Bone marrow examination showed fatty bone marrow (**Figure 2**), a nucleic cell count of $4,000/\mu\text{L}$, and no abnormal karyotype.

Within 2 weeks after pancytopenia occurrence, he developed persistent high-grade fever despite initiation of treatment with broad-spectrum antibiotics and antifungal agent micafungin (MCFG) 300 mg/day from day-170. Etiological testing proved negative until blood culture yielded methicillin-resistant *Staphylococcus aureus* (MRSA) on day-170. Total body contrast-enhanced computed tomography scans (CT) showed multiple isolated lesions in the lung and the liver on day-154. Contrast-enhanced magnetic resonance imaging (MRI) of the liver showed the nodular mass was hypointense on T1-weighted image and hyperintense on fat suppression on

T2-weighted image on day-126 (**Figure 3**). The diagnosis was multiple liver abscesses diagnosed by MRI. We attempted to perform culture and histopathological examination by liver abscess puncture on day-117, but the pathogenic bacteria or fungus from the culture could not be identified, and the level of serum β -D-glucan was not elevated. Disseminated MRSA infection was considered as a differential diagnosis, we considered that the liver abscesses were due to an possible invasive *Aspergillus* infection because of the clinical course and positive serum ELISA tests for galactomannan (GAL) test (0.6 , reference range <0.5). MCFG was changed to voriconazole (VRCZ) from day-154, first intravenously (6 mg/kg twice daily on day 1, then 4 mg/kg twice daily thereafter), and then orally (200 mg twice daily). Even after that, high levels of C-reactive protein (CRP) and fever persisted, in combination with intermittent bacteremia, and the infection showed continued activity (**Figure 1B**). Liposomal amphotericin B (L-AMB) (2.5 mg/kg/day) was added on day-92. While MRI showed a stable state or slight shrinking in the size and activity of the lesion on day-75 (**Figure 3**), the patient's body temperature returned to normal and he was referred to our hospital for emergent allo-HSCT.

We had a plan of early allo-HSCT, but were unable to find a human leukocyte antigen (HLA)-identical donor. Nonmyeloablative peripheral blood HSCT from an HLA-haploidentical sibling donor (elder sister) was considered after approval for this procedure from the institutional review board of our institution and obtaining informed consent from the patient. We performed haploHSCT with Hopkins regimen,⁴⁻⁶ which was composed of conditioning with fludarabine ($30\text{ mg/m}^2/\text{day}$, days-6 to-2), cyclophosphamide (CY) (14.5 mg/kg , days-6 and-5), and total body irradiation (TBI) (2 Gy , day-1). Granulocyte-colony stimulating factor (G-CSF)-mobilized peripheral blood stem cells (PBSC) were infused at a CD34+cell dose of $3.3 \times 10^6/\text{kg}$. Graft-versus-host disease (GVHD) prophylaxis was CY 50 mg/kg/day (days+3 and+4), tacrolimus from day+5 through 5 months maintaining trough drug levels at 8 to $12\text{ }\mu\text{g/L}$ with tapering between 6 and 8 months and then stopped on day 265, and mycophenolate mofetil 45 mg/kg on days+5 through 35. L-AMB was discontinued before starting the conditioning, and VRCZ was continued up to the time of administration of hematopoietic stem cells. The patient exhibited neutrophil engraftment after 13 days (**Figure 1B**). Since the CT scan still revealed liver lesions, a liver biopsy was performed on day 41. Despite the finding that the fungal infection was histopathologically not

Figure 3. MRI of the liver. (A) The nodular mass is hypointense on T1-weighted image (fat suppression was used on day -75) (T1WI) on days -126 and -75. (B) The nodular mass is hyperintense on fat suppression T2-weighted image (T2WI) on days -126 and -75. On day 419, the nodular lesions of the liver were significantly absorbed and disappeared on T1WI and T2WI.

proven, VRCZ was continued. Ten months after haploHSCT, abdominal CT and MRI indicated that the lesions of the liver abscesses were significantly absorbed on day 131 and disappeared completely on day 419 (**Figure 3**). Therefore, VRCZ was discontinued. The overall clinical course was uneventful with respect to infectious complications, including liver abscess and GVHD.

Discussion

IFI, particularly those caused by *Aspergillus*, have long been recognized as a major cause of death in SAA.⁷ Herein, we report a patient with HAAA and lifesaving by haploHSCT, despite the complication of possible invasive fungal diseases due to prominent neutropenia. Early diagnosis of IFI and prompt antifungal treatment are important to improve the out-

come. Since no pathogen of the liver abscesses was identified by histological search or culture, this case was difficult to diagnose. Furthermore, empirical antifungal monotherapy with MCFG or VRCZ based on persistent or recurrent fever during neutropenia, despite broad-spectrum antibiotic therapy was ineffective. The etiology of liver abscess mainly includes infection of the liver through portal vein retrograde infection through the biliary tract, systemic blood infection, or other unknown occult infections. It has been reported that bacteria, such as *Klebsiella pneumoniae* and *Escherichia coli*, are the most common causes of liver abscess.⁸ As a result of CT and MRI examination and GAL test, the diagnosis of *Aspergillus* infection was made. While reduction of the liver abscesses was not observed using combination therapy including VRCZ and L-AMB, the fever did disappear. Therefore, it was possible to plan for the patient to undergo allo-HSCT, which is a

curative therapy for SAA.

Granulocyte transfusion may play an adjunct role in severe infections in patients with SAA.^{9,10} Fever in severely neutropenic patients is aggressively managed with the early use of broad-spectrum antibiotics and antifungal therapy, and granulocyte therapy is considered judiciously, but relatively early, in the care of the patients.¹⁰ However, granulocyte transfusion only transiently increases the granulocyte counts, and several healthy donors are needed to collect a sufficient number of granulocytes for transfusion, and repeated infusions with granulocytes from different donors over a short period of time are necessary to achieve the therapeutic goal. Recently, cord blood (CB) has also been used in the transplantation for SAA.¹¹⁻¹³ However, the use of haploidentical donors had some advantages compared with CB to abbreviate the time for HSCT in this recipient with severe infection. To improve the engraftment of CBT for SAA, and in order not to delay immune reconstitution, the selection of an optimal donor with a better HLA match and higher cell dose may be needed.^{12,13} The use of postgraft CY and peripheral blood stem cells (PBSC) guarantees engraftment with minimal GVHD in haploHSCT.^{4,5} Therefore, the current patient with SAA, who had liver abscesses that were considered to be caused by *Aspergillus* infection, chose to undergo haploHSCT using PBSC mobilized by G-CSF.

Herein, we have presented a case study in which a haploHSCT using a reduced-intensity conditioning regimen was administered to an SAA patient who had *Aspergillus* liver abscesses due to prolonged neutropenia reduction. It was suggested that haploHSCT using PBSC mobilized by G-CSF could lead to the rapid recovery of neutrophils in patients with SAA who could not find an HLA matching donor promptly and were complicated by severe infection.

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Author's contributions

KA, FT, and JS designed the study, analyzed the data, and wrote the manuscript. HM, SS, TK, and HA analyzed the data. KA, YH, and TO have followed the patient. All authors have read and approved the final manuscript.

Conflict of interest disclosure

The authors declare no conflicts of interest.

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