Successful management with urgent haploidentical-peripheral blood stem cell transplantation for a patient with severe aplastic anemia who developed disseminated fungal infection following immunosuppressive therapy

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Abstract

Urgent haploidentical hematopoietic cell transplantation may be considered in cases of severe aplastic anemia (SAA) without human leukocyte antigen-matched donor and suffering from severe infection. However, deciding on allogeneic transplantation in the setting of active systemic infection is challenging due to poor outcomes. This report presents a case of disseminated *Magnusiomyces capitatus* infection in a 5-year-old male who underwent immunosuppressive therapy for hepatitis-associated SAA. To address the critical situation, granulocyte transfusion was promptly administered from the patient's mother, followed by unmanipulated haploidentical peripheral blood stem cell transplantation from the patient's father with posttransplant cyclophosphamide, ultimately resulting in successful rescue.

BRIEF REPORT

Successful management with urgent haploidentical-peripheral blood stem cell transplantation for a patient with severe aplastic anemia who developed disseminated fungal infection following immunosuppressive therapy

Authors

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Urgent haplo-PBSCT for a refractory AA patient

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Abbreviations

SAA	severe aplastic anemia
HLA	human leukocyte antigen
IST	immunosuppressive therap
MRD	matched related donor
haplo-HSCT	haploidentical hematopoietic stem cell transplantation
rATG	rabbit anti-thymocyte globulin
CyA	cyclosporin A
L-AMB	liposomal amphotericin B
CT	computed tomography
G-CSF	granulocyte colony-stimulating factor
GVHD	graft-versus-host disease
PT-Cy	posttransplant cyclophosphamide
haplo-PBSCT	haploidentical peripheral blood stem cell transplantation

Abstract

Urgent haploidentical hematopoietic cell transplantation may be considered in cases of severe aplastic anemia (SAA) without human leukocyte antigen-matched donor and suffering from severe infection. However, deciding on allogeneic transplantation in the setting of active systemic infection is challenging due to poor outcomes. This report presents a case of disseminated *Magnusiomyces capitatus* infection in a 5-year-old male who underwent immunosuppressive therapy for hepatitis-associated SAA. To address the critical situation, granulocyte transfusion was promptly administered from the patient's mother, followed by unmanipulated haploidentical peripheral blood stem cell transplantation from the patient's father with posttransplant cyclophosphamide, ultimately resulting in successful rescue.

Severe aplastic anemia (SAA), a critical hematological disorder marked by pancytopenia and bone marrow

failure, is treated with immunosuppressive therapy (IST) when a suitable human leukocyte antigen-matched related donor (MRD) is unavailable. During severe concurrent infections in the SAA patients, rapid immune recovery is necessary, however, selecting urgent haploidentical hematopoietic stem cell transplantation (haplo-HSCT) amidst active infection presents a significant challenge.[1,2]

A previously healthy 5-year-old male with no significant past medical history, developed idiopathic hepatitis, for which he was treated with oral steroids on an outpatient basis. However, two months later, he was diagnosed with SAA (on day -55 of transplantation). At the time of the diagnosis, his blood counts were as follows; white blood cell count 0.15×10^9/L, neutrophils 0.02×10^9/L, hemoglobin 6.6 g/dL, reticulocytes 1×10^9/L, and platelets 4×10^9/L. The bone marrow aspirate smear showed markedly hypoplastic bone marrow, consistent with a diagnosis of SAA. In particular, his C-reactive protein was 1.37 mg/dL, and his β-D glucan level was 44.2 pg/mL, suggesting a fungal infection. However, a whole-body contrast-enhanced CT scan showed no infectious foci. In the absence of MRD, IST was initiated on day -32 as follows: Rabbit anti-thymocyte globulin (rATG, 2.5 mg/kg/day for five days) and cyclosporin A (CyA, 5 mg/kg/day for consecutive days). He developed a fever on day -29, immediately after the completion of rATG treatment, and a blood culture grew yeast for which liposomal amphotericin B (L-AMB, 5 mg/kg/day) and voriconazole were started empirically from day -28. The yeast was identified as *M. capitatus* ; antimicrobial susceptibilities are summarised in Table 1. Contrast-enhanced CT scans on day -29, revealed disseminated lesions in the spleen, kidney, and lungs (Figure. 1A–C). Although blood cultures were negative on day -15, fever (body temperature >38.5 *C) persisted. Administration of granulocyte colony-stimulating factor (G-CSF) failed to increase the neutrophil count. Given the critical situation with persistent pancytopenia, granulocyte transfusions from his mother were given (four times; days -11, -10, -4, and -3). Concurrently, an urgent haploidentical peripheral blood stem cell transplantation (haplo-PBSCT) from his father was planned to expedite immune cell recovery.

The conditioning regimen comprised fludarabine (25 mg/m^2/day for 5 days), melphalan (70 mg/m^2/day for one day), and total-body irradiation (300 cGy in a single fraction). The infused cell counts were 1.3×10^9/kg for total nucleated cells and 4.6×10^6/kg for CD34-positive cells. For graft-versus-host disease (GVHD) prophylaxis, posttransplant cyclophosphamide (PT-Cy) was administered at a dose of 50 mg/kg/day on days 3 and 4. Following this, mycophenolate mofetil was given orally at a dose of 15 mg/kg/day from day 5 to day 35, along with tacrolimus administered orally or intravenously to maintain a serum concentration of 10-15 ng/mL from day 5 to day 180. Additionally, administration of G-CSF was initiated from day 5. Voriconazole was temporarily discontinued when the patient developed posterior reversible encephalopathy syndrome on day -3. On day 14, invasive aspergillosis was suspected due to a positive galactomannan antigen test and the appearance of new well-circumscribed lesions in the lungs, for which voriconazole had to be resumed. (Figure 1D). Micafungin was also added for the first two weeks of the treatment. Engraftment was successfully achieved on day 19. On day 29, the patient was diagnosed with grade 2 acute GVHD in the intestinal tract, which responded well to methylprednisolone treatment. A CT scan on day 15 demonstrated improvement of disseminated lesions in the liver and spleen (Figure 1E, F). However, on day 38, a contrast-enhanced CT scan revealed multiple pseudoaneurysms in the spleen (Figure 1G). Due to the substantial risk of splenic rupture, an open splenectomy was performed on day 45. The histopathological examination of the removed spleen revealed numerous pseudoaneurysms and epithelioid granulomas, with no pathogens isolated in the abscess culture. Contrast-enhanced CT scans on day 211 showed resolution of the renal lesions (Figure 1H), although the nodular lesions in the lungs were still present (Figure 1I). Weekly viral monitoring was performed for three months post-engraftment, with no evidence of viral reactivation or infection. The dose of L-AMB was gradually reduced and discontinued over a period of eight months after the transplantation due to kidney injury. He was discharged on day 190. At 18 months after haplo-PBSCT, he was alive with complete chimerism and no signs of secondary graft failure or chronic GVHD, although a nodular lesion persisted in the right lung.

SAA is a hematological disorder for which IST is commonly chosen as the standard treatment, particularly when suitable MRD are unavailable. In recent years, there has been an accumulating evidence supporting the use of haplo-HSCT as a salvage transplant strategy for relapsed/refractory SAA following IST.[3-8] In the

United States, a multicenter phase II trial (BMT CTN 1502) was conducted from 2017 to 2020 to evaluate the efficacy and safety of PT-Cy haplo-HSCT in 31 patients (median age 24.9 years, [interquartile range 10.4–51.3]) with relapsed/refractory SAA post-IST.[3] The one-year overall survival rate was 81%, and there were no cases of grade 3–4 acute GVHD or severe chronic GVHD; despite these promising results, graft failure occurred in 5 patients (16%; 4 primary, 1 secondary). All of them received another salvage HSCT, resulting in transplant-related death in four cases. Furthermore, a retrospective analysis by the EBMT[4], involving 16 patients with SAA who underwent PT-Cy haplo-HSCT following Baltimore conditioning regimen[9], demonstrated a two-year overall survival rate of 93% and a 28-day neutrophil engraftment rate of 69%. These findings indicate that PT-Cy haplo-HSCT is a valuable treatment option for this condition, although graft failure may be a primary concern for this approach. It is worth noting that these reports focused on planned HSCT from haplo-identical donors, and did not address urgent HSCT cases. Therefore, this strategy may not be directly apply to the case presented here. In cases of uncontrolled fatal infections, such as the current case, the primary objevtive of urgent haplo-HSCT is to achieve rapid hematopoietic recovery. Due to the longer time required for engraftment and the relatively higher risk of graft failure associated with cord blood, we opted for haplo-PBSCT. Regarding the preparative regimen, considering the organ reserve capacity due to severe infection, we extrapolated it from the BMT CTN 1502 protocol, opting for a combination of fludarabine 125 mg/m^2, melphalan 70 mg/m^2, and total-body irradiation 300 cGy. Ultimately, urgent haplo-PBSCT was effective in controlling the severe fungal infection.

Magnusiomyces species , including *M. capitatus* (formerly known as *Geotrichum capitatum*), are emerging as notable pathogens in immunocompromised hosts. A European multi-center study found that 40% of infections occurred during antifungal prophylaxis, mainly with azoles or echinocandins.[10] In our case, the patient developed a breakthrough *M. capitatus* infection with lesions in the lungs, kidneys, and spleen while on micafungin prophylaxis, treated initially with L-AMB and voriconazole as per guidelines.[11] The aforementioned study showed azoles, alone or combined, outperformed other antifungals, with a 30-day mortality rate of 43% and highlighted neutrophil recovery as crucial for reducing mortality. This finding supports our management strategy that aims for rapid immune recovery is the key to survival.

This case highlights the significance of haplo-PBSCT as an urgent treatment option for severe infectious complications in patients with SAA. Future research should aim to further refine the indications of urgent haplo-PBSCT for immunocompromised hosts who require rapid immune recovery to manage severe infections.

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Author contributions

Norihito Ikenobe, Kentaro Fujimori, and Hirotoshi Sakaguchi, as the primary treating physicians, managed the care of the patients and collaboratively wrote and approved the manuscript. Shota Myojin, Masaki Yamada, Chikara Ogimi, and Kenichi Imadome primarily contributed to the infection control management. Mikiko Miyasaka and Osamu contributed to radiological diagnosis, Akihiro Yoneda was responsible for surgical management, and Shotaro Matsumoto and Satoshi Nakagawa played key roles in ICU management. Yoshihiro Gocho, Takao Deguchi, Akihiro Iguchi, and Daisuke Tomizawa contributed to the diagnosis of the patients and decision-making on the treatment strategy. Kimikazu Matsumoto oversaw the entire process as a mentor, providing guidance and supervision to the team. All authors reviewed, discussed, and contributed to the improvement of the manuscript.

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Conflict of interest statement

The authors declare that they have no competing interests.

Data availability statement

For original data, please contact the corresponding author.

Ethics approval statement

This study was approved by an independent ethics committee of National Center for Child Health and Development, Tokyo, Japan.

Patient consent statement

The patient's guardian provided written informed consent.

Reference

1. Bacigalupo A. How I treat acquired aplastic anemia. Blood. 2017;129(11):1428–36.
2. Yoshida N. Recent advances in the diagnosis and treatment of pediatric acquired aplastic anemia. Int J Hematol. 2023 Mar 3. Online ahead of print.
3. DeZern AE, Eapen M, Wu J, et al. Haploidentical bone marrow transplantation in patients with relapsed or refractory severe aplastic anemia in the USA (BMT CTN 1502): a multicenter, single-arm, phase 2 trial. Lancet Hematol. 2022;9(9):e660–9.
4. Prata PH, Eikema DJ, Afansyev B, et al. Haploidentical transplantation and posttransplant cyclophosphamide for treating aplastic anemia patients: a report from the EBMT Severe Aplastic Anemia Working Party. Bone Marrow Transplant. 2020;55(6):1050–8.
5. Clay J, Kulasekararaj AG, Potter V, et al. Nonmyeloablative peripheral blood haploidentical stem cell transplantation for refractory severe aplastic anemia. Biol Blood Marrow Transplant. 2014;20(11):1711–6.
6. DeZern AE, Zahurak M, Symons H, Cooke K, Jones RJ, Brodsky RA. Alternative Donor Transplantation with High-Dose Post-Transplantation Cyclophosphamide for Refractory Severe Aplastic Anemia. Biol Blood Marrow Transplant. 2017;23(3):498–504.
7. Quintero V, Bueno-Sanchez D, Mozo-Del-Castillo Y, et al. Haploidentical Hematopoietic Stem Cell Transplantation in Pediatric Patients with Acquired Hypocellular Bone Marrow Failure. Transplant Cell Ther. 2023;29(10):621.e1–6.
8. DeZern AE, Zahurak M, Symons HJ, et al. Alternative donor BMT with posttransplant cyclophosphamide as initial therapy for acquired severe aplastic anemia. Blood. 2023;141(25):3031–8.
9. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biol Blood Marrow Transpl. 2008;14(6):641–50.
10. Del Principe MI, Seidel D, Criscuolo M, et al. Clinical features and prognostic factors of Magnusiomyces (Saprochaete) infections in hematology. A multicenter study of SEIFEM/Fungiscope. Mycoses. 2023;66(1):35–46.
11. Chen SC, Perfect J, Colombo AL, et al. Global guideline for the diagnosis and management of rare yeast infections: an initiative of the ECMM in cooperation with ISHAM and ASM. Lancet Infect Dis. 2021;21(12):e375–86.

Table 1. Antifungal susceptibility test results for *Magnusiomyces capitatus*

Agents	MIC
Amphotericin B	1
5-Fluorocytosine	<0.125
Miconazole	2
Fluconazole	16
Itraconazole	0.25

Agents	MIC
Voriconazole	0.5
Micafungin	1

Abbreviations; MIC, Minimum Inhibitory Concentration.

Figure legends

Figure 1. CT scan findings.

(A–C) Contrast-enhanced CT scans on day -29 revealed disseminated lesions in the lung, spleen, and kidney. (D) Contrast-enhanced CT scans on day 14 demonstrated a new well-circumscribed lesion in the right lung. (E, F) Contrast CT on day 15 showed the improvement of disseminated lesions in the liver and spleen. (G) Contrast-enhanced CT scans on day 38 revealed multiple pseudoaneurysms in the spleen. (H, I) Contrast-enhanced CT scan on day 211 showed the persistence of nodular lesions in the lungs, while the lesions in the kidneys disappeared.

Figure1