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CASE REPORT

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

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Abstract

Urgent haploidentical haematopoietic cell transplantation may be considered in cases of severe aplastic anaemia (SAA) without a 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.

KEYWORDS
aplastic anaemia, fungal infection, haploidentical peripheral blood stem cell transplantation

Severe aplastic anaemia (SAA), a critical haematological disorder marked by pancytopenia and bone marrow failure, is treated with immunosuppressive therapy (IST) when a suitable HLA-matched related donor (MRD) is unavailable. During severe concurrent infections in SAA patients, rapid immune recovery is necessary, however, selecting urgent haploidentical haematopoietic 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 haplo-HSCT) based on the following blood test results; white blood cells 0.15×10^9/L, neutrophils 0.02×10^9/L, haemoglobin 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 β-D-glucan level was 44.2 pg/mL (normal range, < 20 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 (5 mg/kg/day for consecutive days). He developed a fever on day −29, immediately after the completion of rATG treatment, and 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 *Magnusiomyces 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 (> 38.5 ∘C) persisted. 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, post-transplant cyclophosphamide (PT-Cy) was administered at a dose of 50 mg/kg/day on days 3 and 4. Mycophenolate mofetil was then given orally at a dose of 15 mg/kg/day from day 5 to day 35, together with tacrolimus administered orally or intravenously to maintain a serum concentration of 10–15 ng/mL from day 5. Additionally, administration of granulocyte colony-stimulating factor 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 2 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 after a discussion of the risks and benefits of splenic artery embolization to avoid surgery. 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 the resolution of the renal lesions (Figure 1H), although the nodular lesions in the lungs were still present (Figure 1I). Viral monitoring weekly for three months post-engraftment showed no reactivation or infection. The dose of L-AMB was gradually reduced and discontinued over a period of eight months after the transplantation. Finally, he was discharged on day 190 and remained alive with complete chimerism for 20 months after haplo-PBSCT.

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

Agent	MIC
Amphotericin B	1
5-Fluorocytosine	<0.125
Miconazole	2
Fluconazole	16
Itraconazole	0.25
Voriconazole	0.5
Micafungin	1

Abbreviation: MIC, minimum inhibitory concentration.

In recent years, there has been accumulating evidence supporting the use of haplo-HSCT as a salvage transplant strategy for relapsed/refractory SAA following IST [3–8]. A multi-centre phase II trial (BMT CTN 1502) assessed PT-Cy haplo-HSCT in 31 relapsed/refractory SAA patients post-IST, which showed an 81% one-year survival rate, no severe GVHD, but five graft failures, leading to four transplant-related deaths despite salvage HSCT [3]. A retrospective analysis by the EBMT of 16 SAA patients receiving PT-Cy haplo-HSCT with Baltimore conditioning [9]. showed a 93% two-year overall survival and 69% 28-day neutrophil engraftment rate [4]. These findings suggest planned PT-Cy haplo-HSCT for relapsed/refractory SAA patients as a beneficial treatment despite graft failure concerns, but its applicability to urgent HSCT cases, not covered in these studies, may be limited. In uncontrolled fatal infections, such as the current case, urgent HSCT aims for rapid haematopoietic recovery, favouring haplo-PBSCT over cord blood due to its faster engraftment and lower graft failure risk. 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.

Magnusiomyces species, including *M. capitatus* (formerly known as *Geotrichum capitatum*), are emerging as notable pathogens in

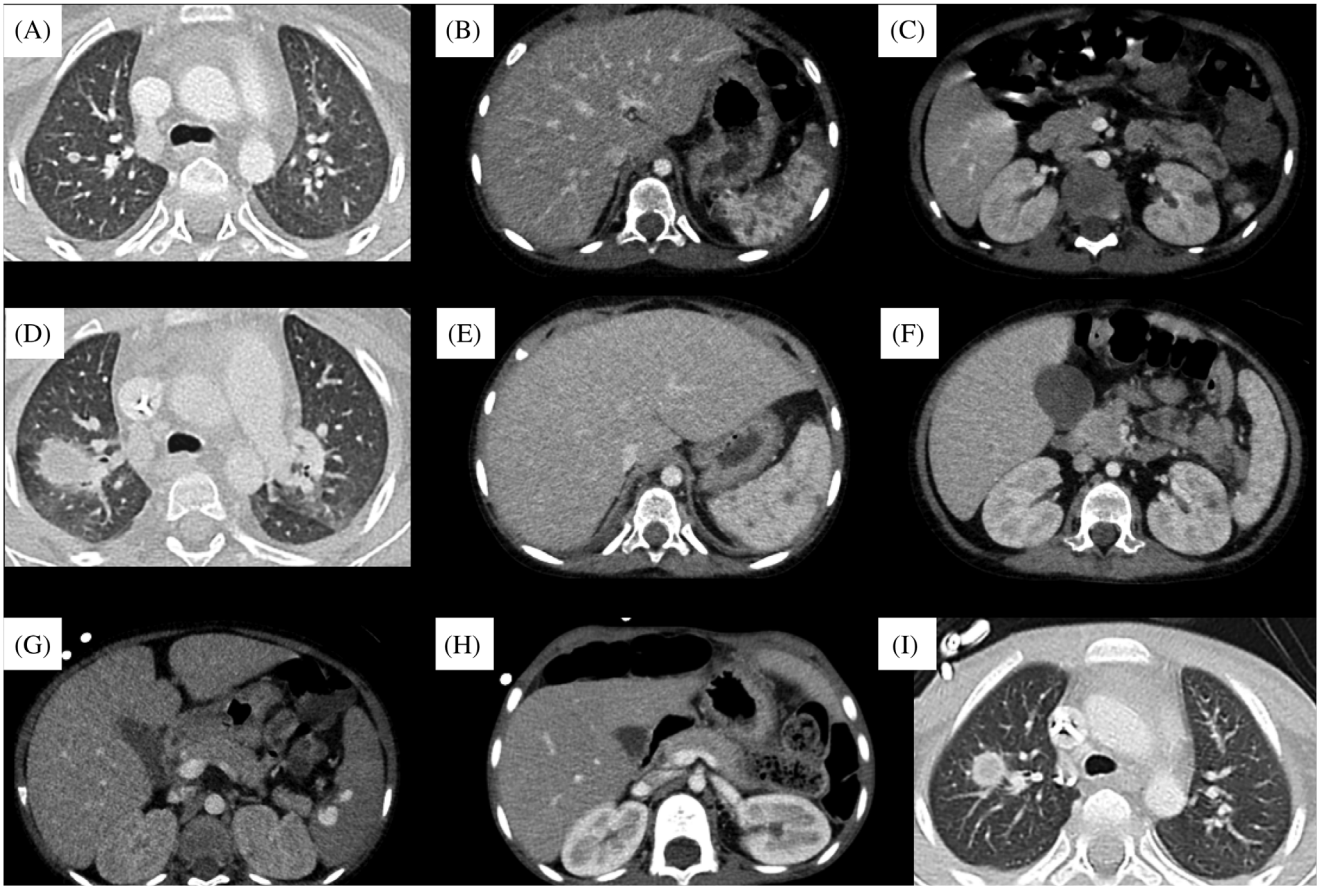

FIGURE 1 Computed tomography (CT) scan findings. (A–C) Contrast-enhanced CT scans on day −29 revealed disseminated lesions in the lung, spleen, and kidney. (D) Contrast-enhanced CT scans on day 14 demonstrated a new well-circumscribed lesion in the right lung. (E, F) Contrast CT on day 15 showed the 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.

immunocompromised hosts. A European multi-centre 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.

The present case highlights haplo-PBSCT as a critical urgent treatment for severe infections in SAA patients, pointing to the need for research on its indications for immunocompromised hosts needing quick immune recovery.

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 no conflict of interest.

DATA AVAILABILITY STATEMENT

For original clinical data, please contact the corresponding author.

ETHICS STATEMENT

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

PATIENT CONSENT STATEMENT

The patient's guardian provided written informed consent.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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