Successful Engraftment After Repeat Cord Blood Transplantation Using an Identical Conditioning Regimen for MPS II

Sachio FUJITA, Takashi KOIKE, Mayuko SHIBATA, Ryota KANEKO, Kosuke AKIYAMA, Daisuke TOYAMA, Hiromasa YABE and Shohei YAMAMOTO

Department of Pediatrics, Tokai University School of Medicine

(Received January 23, 2026; Accepted March 10, 2026)

Graft failure remains a major complication in cord blood transplantation (CBT), particularly in patients with nonmalignant diseases, such as inherited metabolic disorders. However, optimal strategies for retransplantation after graft failure remain controversial. Here, we describe a case of mucopolysaccharidosis type II (MPS II) in which durable engraftment was successfully achieved following a second CBT using the same conditioning regimen as the initial transplantation. A 4-year-old boy with MPS II underwent unrelated CBT after undergoing a reduced-intensity conditioning regimen consisting of total abdominal irradiation, fludarabine, and melphalan. He acquired methicillin-resistant *Staphylococcus aureus*-associated sepsis early in the posttransplant period and developed graft failure on day 28, presumably due to drug-induced myelosuppression rather than insufficient conditioning intensity. Sixty-six days after the first transplantation, a second CBT was performed using the identical conditioning backbone but with antithymocyte globulin as immunosuppressant. The second course was complicated by severe hypercytokinemia with hemophagocytosis, cytomegalovirus antigenemia requiring preemptive antiviral therapy, and upper gastrointestinal bleeding. Nevertheless, donor chimerism remained high, and engraftment was confirmed on day 40 with transfusion independence on day 50. This case highlights the need for an etiological assessment of graft failure and demonstrates the viability of the initial conditioning regimen as a retransplantation strategy when inadequate conditioning is unlikely.

Key words: graft failure, second transplantation, cord blood transplantation, identical conditioning regimen, mucopolysaccharidosis type II

INTRODUCTION

Cord blood transplantation (CBT) is an established therapeutic option for inherited metabolic disorders, such as mucopolysaccharidosis type II (MPS II). However, its rapid availability and tolerance of human leukocyte antigen (HLA) mismatch [1, 2] often leads to graft failure [3]. Multiple factors have been implicated in this significant complication, including graft-related factors, such as cell dose and HLA disparity [4–6], insufficient conditioning intensity [7, 8], donor-specific anti-HLA antibodies [9], hypercytokinemia-associated hemophagocytic syndrome [10–13], and drug-induced marrow suppression [14–17]. While retransplantation is often required after graft failure, the optimal conditioning and immunosuppression strategy has not been established. Intensifying conditioning may increase regimen-related toxicity, particularly in young children. Here, we report a case of MPS II in which successful engraftment was achieved after a second CBT under the same conditioning regimen as the first transplant, following careful etiological assessment of graft failure.

CASE PRESENTATION

The patient was a 4-year-7-month-old boy, diagnosed with MPS II in infancy based on characteristic clinical findings and biochemical and genetic testing. He had undergone enzyme replacement therapy from 15 months of age and had participated in a clinical trial of a blood–brain barrier-penetrating enzyme formulation (JR-141). Following trial completion, the patient was referred for hematopoietic stem cell transplantation. The first CBT was performed using a 7/8 HLA-matched unrelated cord blood unit. The infused total nucleated cell (TNC) and CD34-positive cell doses were 5.77×10^7/kg and 1.49×10^5/kg, respectively. Conditioning consisted of total abdominal irradiation (2 Gy × 2), fludarabine (30 mg/m² × 5), and melphalan (60 mg/m² × 3). Graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus and short-term methotrexate. From day 4 after the first CBT, the patient developed high-grade fever (> 38°C). Blood cultures revealed methicillin-resistant *Staphylococcus aureus*, prompting intravenous vancomycin (VCM) treatment. Persistent fever (38°C–40°C) and a generalized rash affecting the extremities developed from day 6, raising concern for a pre-engraftment immune reaction and/or acute GVHD. The patient was started on prednisolone (PSL), which subsequently improved fever and rash. Bone marrow examination on day 14 showed a hypocellular marrow with focal hemophagocytosis. The white blood cell count was

Shohei YAMAMOTO, Department of Pediatrics, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan
Tel: +81-463-93-1121 Fax: +81-463-94-3426 E-mail: shohei-y@tokai.ac.jp

stable, and short tandem repeat (STR) analysis showed a donor chimerism of 75.7%. Serum ferritin was 193 ng/mL without marked elevation. Delayed hematopoietic recovery was attributed to VCM-associated hematologic toxicity. Thus, VCM was discontinued once bacteremia clearance was confirmed. On day 21, peripheral blood STR decreased to 35.6%. Tacrolimus was discontinued, and PSL was tapered. Nevertheless, bone marrow STR on day 27 decreased to 2.2%, and graft rejection was diagnosed. Autologous hematopoiesis subsequently recovered, and the patient became transfusion-dependent. Because graft failure after the first CBT was considered unlikely due to insufficient conditioning intensity, a second unrelated CBT was performed 66 days after the first transplantation, using the identical conditioning regimen but with the addition of rabbit antithymocyte globulin (ATG) to intensify immunosuppression. The second CBT used a 5/8 HLA-matched cord blood unit. The infused TNC and CD34-positive cell doses were 5.43×10^7/kg and 1.78×10^5/kg, respectively. Preemptive antiviral therapy with ganciclovir was started on day 4 due to cytomegalovirus (CMV) antigenemia. Nevertheless, persistent bone marrow suppression was observed, and antiviral treatment was subsequently switched to foscarnet. Early after the second CBT, the development of fever and rash raised concern for hypercytokinemia. PSL was initiated but provided limited benefit; thus, liposomal dexamethasone palmitate was started on day 9, resulting in clinical improvement. Serum ferritin increased to approximately 30,000 ng/mL on day 11, and bone marrow analysis on day 14 demonstrated hypocellularity with hemophagocytosis. Although no clear hematopoietic recovery was observed on day 27, donor chimerism assessed by STR analysis remained in the high 90% range. Given the stable donor chimerism and gradual hematopoietic recovery, engraftment was confirmed on day 40, and the patient became transfusion-independent after day 50.

DISCUSSION

Graft failure remains a significantly challenging complication of umbilical CBT, particularly in patients with inherited metabolic disorders. The incidence of graft failure in this population ranges from 10% to 20%, reflecting the complex interactions among graft characteristics, recipient immune status, inflammatory burden, and conditioning intensity [3–5]. In the present case, donor chimerism was transiently established (STR, 75.7%) on day 14, suggesting that the conditioning regimen was adequate to permit initial engraftment [4, 5]. However, progressive cytopenia and rapid loss of donor chimerism occurred with hemophagocytosis [10–13], prolonged antimicrobial exposure [14–17], and the chronic inflammatory milieu associated with MPS II, all of which can impair hematopoietic recovery and engraftment [3].

Immune-mediated mechanisms, particularly hypercytokinemia and macrophage activation, are commonly implicated in graft failure following CBT [10–13]. In the current patient, bone marrow hemophagocytosis was consistent with a cytokine-driven inflammatory state, and hemophagocytosis may have caused graft failure. Although the hypercytokinemic state was clinically more severe during the second CBT, durable donor-derived hematopoiesis was successfully achieved. One possible explanation is that the addition of ATG during the second CBT more effectively suppressed residual host alloreactivity. Mallhi *et al.* demonstrated that intensified immunosuppression during retransplantation after graft failure improves engraftment rates [3]. Similarly, Uchida *et al.* reported that enhanced immunosuppressive strategies in CBT contribute to improved engraftment outcomes [18]. Therefore, despite more pronounced hypercytokinemia, host-mediated graft rejection may have been more adequately controlled during the second transplantation. In addition, prompt anti-inflammatory intervention with liposomal dexamethasone palmitate may have prevented sustained bone marrow injury despite marked hyperferritinemia. In the present case, HPS became more severe after the second CBT despite the use of ATG. Two potential explanations may account for this observation. First, the second transplantation was performed in a host who had already been exposed to alloantigens and systemic inflammation. Inflammatory priming associated with graft rejection during the first transplantation, together with residual host immune activation, may have created a cytokine-responsive bone marrow microenvironment. Such inflammatory state has been reported to be associated with the development of HPS following CBT [10]. Second, early CMV antigenemia observed after the second CBT may have further amplified macrophage activation. Viral reactivation is a well-recognized trigger of post-transplant HPS and has been associated with hyperferritinemia and bone marrow hemophagocytosis [11].

VCM has been associated with hematologic adverse effects, including neutropenia, thrombocytopenia, and, in rare cases, pancytopenia, especially with prolonged exposure [15–17]. The possible mechanisms include immune-mediated destruction of hematopoietic cells via drug-dependent antibodies and direct suppression of bone marrow progenitor cells [15–17]. In the present case, VCM exposure temporally overlapped with progressive cytopenia and declining donor chimerism during a period of fragile donor-derived hematopoiesis and limited hematopoietic reserve. In the context of CBT, even modest drug-induced marrow suppression may have a disproportionate negative impact on graft survival. Concomitant infection-related inflammation and hypercytokinemia may have further amplified the suppressive effects on donor hematopoiesis.

Based on this etiological assessment, we implemented the same conditioning regimen for the second CBT rather than intensifying myeloablation. Escalation of conditioning intensity has been associated with increased regimen-related toxicity [7, 8]. Therefore, our retransplantation strategy focused on modulating posttransplant immune dysregulation rather than increasing cytotoxicity. To suppress host-versus-graft immune responses and cytokine-driven marrow suppression, ATG was added to the second CBT regimen. Prior reports have demonstrated improved engraftment rates during retransplantation through enhanced immunosuppression, using agents such as mycophenolate mofetil or ATG, which supports the biological rationale of this approach [3, 18]. Notably, our case demonstrates that durable engraftment can be achieved with a second transplant despite an identical

conditioning backbone, provided that the initial graft failure was not attributable to insufficient conditioning. This approach contrasts with previously reported strategies that emphasize intensified conditioning and underscores the importance of individualized, mechanism-based decision-making in retransplantation. Nevertheless, intensified immunosuppression is associated with clinically significant complications, including viral reactivation. Similar complications have been reported in studies employing strong immunosuppressive regimens, underscoring the necessity of vigilant monitoring and careful adjustment of immunosuppressive regimens on a case-by-case basis [11, 12, 18]. Although this report describes a single patient, it provides clinically relevant insights into the management of graft failure in inherited metabolic disorders. Our experience demonstrates that graft failure after CBT should not prompt the perfunctory escalation of conditioning intensity. Instead, comprehensive evaluation of graft failure etiology, including hypercytokinemia, drug-induced marrow suppression, and disease-specific factors, should guide retransplantation strategies [3, 10–17].

In conclusion, this case demonstrates that successful engraftment can be achieved after a second CBT using the same conditioning regimen when graft failure is unattributable to inadequate conditioning. Individualized retransplantation strategies that balance immunosuppression, infection control, antimicrobial selection, and toxicity may optimize outcomes in patients with inherited metabolic disorders.

DECLARATION OF CONFLICTING INTERESTS

The authors declare no potential conflicts of interest regarding the research.

authorship and/or publication of this article.

ETHICAL APPROVAL

Our institution does not require ethical approval for reporting individual cases or case series.

FUNDING

The authors received no financial support for the research, authorship, and/or publication of this article.

INFORMED CONSENT

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

REFERENCES

1) Aldenhoven M, Jones SA, Bonney B, Hughes D, De Meirleir L, Wijburg FA, *et al*. Hematopoietic cell transplantation for patients with mucopolysaccharidosis is safe and effective: Results after implementation of internal guidelines. *Biol Blood Marrow Transplant*. 2015; 21: 1106–1109.
2) Gardin A, Castelle M, Pichard S, Couzin C, De Blic J, Souillet G, *et al*. Long-term follow-up after hematopoietic stem cell transplantation for mucopolysaccharidosis type I-H: a retrospective study of 51 patients. *Bone Marrow Transplant*. 2023; 58: 295–302.
3) Mallhi K, Orchard PJ, Miller WP, Wagner JE, MacMillan ML, Davies SM, *et al*. Non-myeloablative conditioning for second hematopoietic cell transplantation for graft failure in patients with non-malignant disorders: a prospective study and review of the literature. *Bone Marrow Transplant*. 2017; 52: 726–732.
4) Laughlin MJ, Barker J, Bambach B, Koc ON, Rizzieri DA, Wagner JE, *et al*. Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors. *N Engl J Med*. 2001; 344: 1815–1822.
5) Takahashi S, Ooi J, Tomonari A, Konuma T, Tsukada N, Uchida N, *et al*. Posttransplantation engraftment and safety of cord blood transplantation with grafts containing relatively low cell doses in adults. *Int J Hematol*. 2006; 84: 359–362.
6) Kurtzberg J, Prasad VK, Carter SL, Wagner JE, Baxter-Lowe LA, Wall D, *et al*. COBLT Steering Committee. Results of the Cord Blood Transplantation Study (COBLT): clinical outcomes of unrelated donor umbilical cord blood transplantation in pediatric patients with hematologic malignancies. *Blood*. 2008; 112: 4318–4327.
7) Horwitz ME, Morris A, Gasparetto C, Sullivan KM, Chute JP, Rizzieri DA, *et al*. Myeloablative intravenous busulfan/fludarabine conditioning does not facilitate reliable engraftment of dual umbilical cord blood grafts in adult recipients. *Biol Blood Marrow Transplant*. 2008; 14: 591–594.
8) Komatsu T, Narimatsu H, Yoshimi A, Kato M, Muramatsu H, Hasegawa D, *et al*. Successful engraftment of mismatched unrelated cord blood transplantation following reduced-intensity preparative regimen using fludarabine and busulfan. *Ann Hematol*. 2007; 86: 49–54.
9) Takanashi M, Atsuta Y, Fujiwara K, Kondo T, Kato S, Taniguchi S, *et al*. The impact of anti-HLA antibodies on unrelated cord blood transplantation. *Blood*. 2010; 116: 2839–2846.
10) Tanaka H, Ohwada C, Sakaida E, Shibayama H, Tamura H, Takeuchi J, *et al*. Successful engraftment by second cord blood transplantation with reduced-intensity conditioning after graft rejection due to hemophagocytic syndrome following initial CBT. *Bone Marrow Transplant*. 2007; 40: 995–996.
11) Takagi S, Masuoka K, Uchida N, Ishiwata K, Araoka H, Wake A, *et al*. High incidence of hemophagocytic syndrome following umbilical cord blood transplantation for adults. *Br J Haematol*. 2009; 147: 543–553.
12) Nishiwaki S, Nakayama T, Murata M, Nishida T, Terakura S, Naoe T, *et al*. Dexamethasone palmitate successfully attenuates hemophagocytic syndrome after allogeneic stem cell transplantation: macrophage-targeted steroid therapy. *Int J Hematol*. 2012; 95: 428–433.
13) Kuriyama T, Takenaka K, Kohno K, Yamazaki H, Miura Y, Okada M, *et al*. Engulfment of hematopoietic stem cells caused by downregulation of CD47 is critical in the pathogenesis of hemophagocytic lymphohistiocytosis. *Blood*. 2012; 120: 4058–4067.
14) Andrès E, Zimmer J, Mecili M, Weitten T, Alt M, Maloisel F, *et al*. Drug-induced agranulocytosis and neutropenia: a review of pathophysiology, diagnosis, and management. *Am J Hematol*. 2010; 85: 694–700.
15) Von Drygalski A, Curtis BR, Bougie DW, McFarland JG, Aster RH, George JN, *et al*. Vancomycin-induced immune thrombocytopenia. *N Engl J Med*. 2007; 356: 904–910.
16) Hsieh YP, Chang CC, Kor CT, Yang YH, Chuang YC, Wu MF, *et al*. Vancomycin-induced neutropenia: a systematic review. *J Clin Pharm Ther*. 2019; 44: 665–671.
17) Segarra-Newnham M, Tagoff SS, Smith JA, Patel K, McCarthy MW, Johnson MD, *et al*. Vancomycin-induced neutropenia: case report and review of the literature. *Pharmacotherapy*. 2004; 24: 126–132.
18) Uchida N, Wake A, Nakano N, Ishiwata K, Araoka H, Taniguchi S, *et al*. Mycophenolate mofetil and tacrolimus for graft-versus-host disease prophylaxis after cord blood transplantation: a matched-pair comparison with tacrolimus alone. *Transplantation*. 2011; 92: 366–371.