JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
CASE REPORT

Type 1 diabetes mellitus after cord blood transplantation from an unrelated donor with a disease-sensitive haplotype

Kensuke Matsumoto[1]*, Taisuke Matsuyama[2], Ritsu Sumiyoshi[1], Matsuo Takuji[1], Tadashi Yamamoto[1], Ryosuke Shirasaki[1], Haruko Tashiro[1]

[1]Department of Hematology/Oncology, Teikyo University School of Medicine, Itabashi-ku, Japan, and [2]Department of Orthopedic Surgery, Teikyo University School of Medicine, Itabashi-ku, Japan

Keywords
CBT, Disease-sensitive haplotype, HLA

***Correspondence**
Kensuke Matsumoto
Tel.: +81-3-3964-1211
Fax: +81-3-3964-1600
E-mail address:
matsumot@med.teikyo-u.ac.jp

J Diabetes Investig 2023; 14: 344–347

doi: 10.1111/jdi.13939

ABSTRACT

Allogeneic hematopoietic stem cell transplantation (allo-HSCT), a curative treatment for hematopoietic neoplasms, often causes various autoimmune disease-like conditions. In contrast, allo-HSCT-related type 1 diabetes mellitus is extremely rare. Herein, we report a case of allo-HSCT-related type 1 diabetes mellitus in a patient who had undergone cord blood transplantation (CBT) as a treatment for acute myeloid leukemia. The patient's human leukocyte antigen was replaced with the donor type after transplantation. The donor had a disease-sensitive haplotype. To the best of our knowledge, this is the first reported case of type 1 diabetes mellitus following CBT.

INTRODUCTION

Type 1 diabetes mellitus is a type of diabetes mellitus usually characterized by insulin-dependence and preceded by an immune reaction to the islets of Langerhans[1]. Type 1 diabetes mellitus is associated with specific human leukocyte antigen (HLA) haplotypes, mostly involving DRB1*0405-DQB1*0401, and invariably shows rapid progression[2].

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been used widely as a curative treatment for hematological malignancies, with caution taken to avoid the development of graft versus host disease (GVHD). In allo-HSCT, chronic GVHD exhibits autoimmune disease-like symptoms. Although autoimmune disease-like conditions are seen frequently after allo-HSCT, HSCT-related type 1 diabetes mellitus has seldom been reported in the literature.

CASE REPORT

A previously healthy 30-year-old man presented with recent onset anemia. The patient was diagnosed with acute myeloid leukemia with myelodysplasia-related changes through bone marrow examination. Peripheral blood analysis showed that the glycated hemoglobin (HbA1c) level was at 5.5% 3 months before admission; at this point, anemia was not severe. Upon admission, the HbA1c level was at 6.5% and Hb was 8.1 g/dL (Table 2). The fasting blood glucose (FBG) level was 100 mg/dL, and glycosuria was not detected. The patient had no family history of diabetes mellitus.

He achieved complete remission after chemotherapy. Following this, the HbA1c level was 4.8%, and resolution of anemia was noted when complete remission was achieved.

We successfully performed an allogenic cord blood transplantation (allo-CBT) from an HLA-2-mismatched, unrelated, female donor 8 months after the onset of leukemia. Both the donor and patient's HLA profiles are shown in Table 1. Pre-transplant treatment included Ara-C, cyclophosphamide, and total body irradiation (12 Gy). As a prophylactic measure for acute GVHD, methotrexate and tacrolimus were administered. Trough levels of tacrolimus were maintained between 7.2 and 22.2 ng/mL following allo-CBT.

Anti-glutamic acid decarboxylase (GAD) antibody (<5.0 U/mL) and anti-insulinoma-associated protein-2 antibody (anti-IA-2 antibody) were negative 48 days before transplantation. The patient did not experience hyperglycemia before transplantation. Granulocyte engraftment was achieved 19 days after allo-CBT. The patient developed grade I acute GVHD during granulocyte engraftment.

Two days after CBT, the patient had a fever (body temperature >37.5°C). Test results for cytomegalovirus

Received 9 November 2021; revised 15 September 2022; accepted 19 October 2022

Table 1 | HLA typing of the patient and donor

	Sex	Blood type	HLA-A	HLA-B	HLA-Cw	HLA-DRB1	HLA-DQB1
Patient (before CBT)	M	O+	2	35	10	4	8
			0201	3501	0304	0403	0302
			26	61	8	12	9
			2602	4002	0801	1201	0303
Patient (after CBT)	M	A+	2	61	1	4	7
			0201	4006	0102	0405	0301
			2	54	8	12	4
			0201	5401	0801	1201	0401
Donor (cord blood)	F	A+	2	61	1	4	Unknown
			0201	4006	0102	0405	
			2	54	8	12	Unknown
			0201	5401	0801	1201	

The patient's HLA changed to DRB1*0405-DQB1*0401 post-transplant. This is a high-risk HLA haplotype for type 1 diabetes mellitus.

antigenemia and *Aspergillus* antigens were negative at the time of granulocyte engraftment. No other sign of infection was detected. Bone marrow aspiration on day 62 after CBT revealed that the patient maintained complete remission, and G-band analysis revealed 99.6% of female chromosomes.

Five days after CBT, we noted elevated FBG levels (130 mg/dL). After that, the FBG increased further, recording a

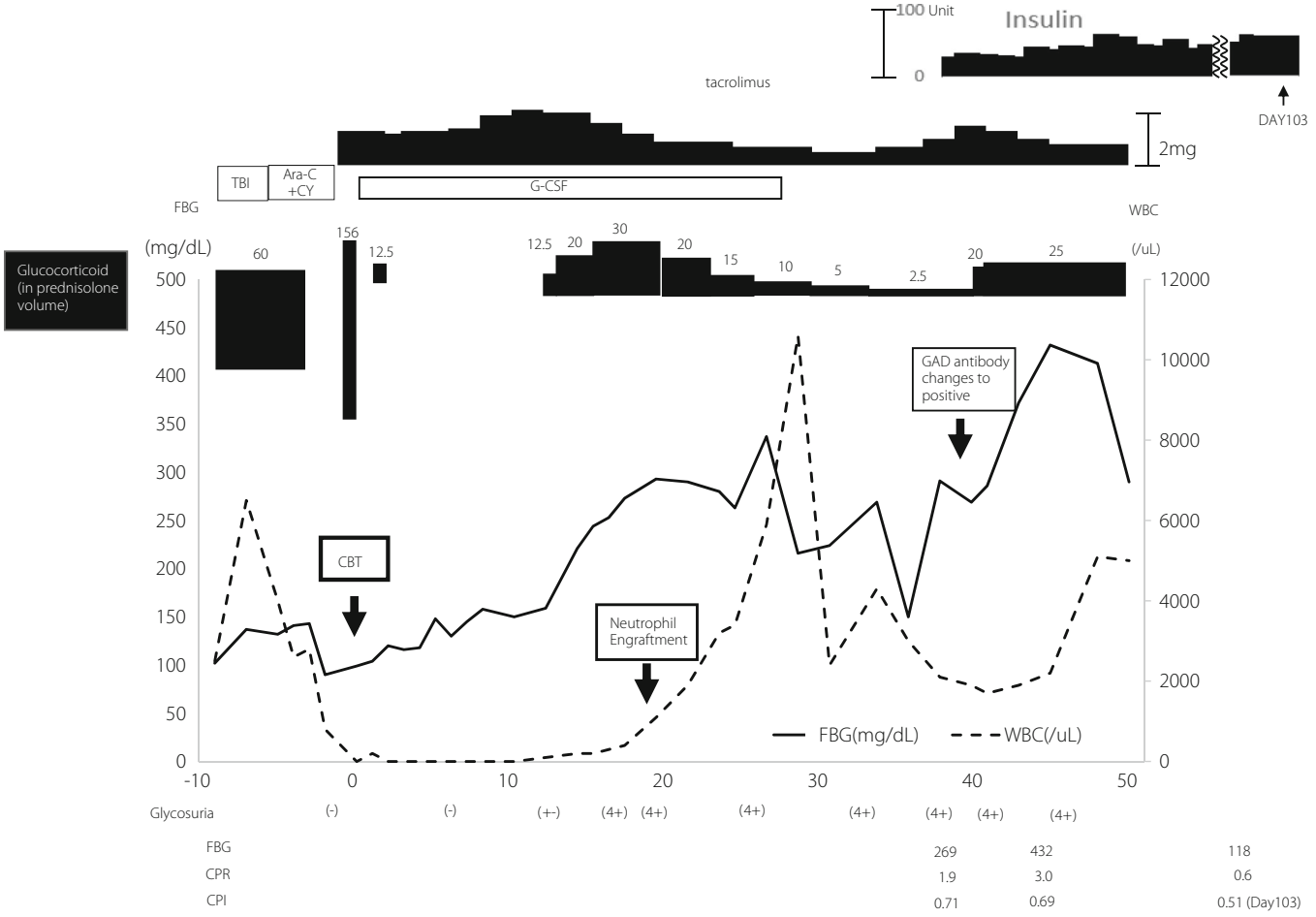

Figure 1 | Clinical course. Rapid elevation of fasting blood sugar levels 5 days after cord blood transplantation. Glycosuria was detected on day 16, and the C-peptide immunoreactivity index decreased with time.

Table 2 | The time course of RBC, Hb, and HbA1c

Days from transplantation	−281	−234	−183	−134	−83	−51	37
RBC ($\times 10^3$ μL)	353	259	246	443	398	512	275
Hb (g/dL)	11.5	9.5	8.1	13.1	11.7	14.5	8.3
HbA1c (%)	5.5		6.5	4.8	4.9	5.1	8.4

maximum of 432 mg/dL (Figure 1). The HbA1c level increased to 8.4% on day 38. Glycosuria was detected on day 16, whereas ketonuria was not. The patient was administered different steroid hormones, beginning with 125 mg of methylprednisolone on day 0. Despite steroid administration, his FBG did not exceed 126 mg/dL during days 0–4 (Figure 1). Anti-GAD antibodies (25.6 U/mL) were positive and anti-IA-2 antibodies were negative on day 38. No symptoms reminiscent of neurodegenerative disease were observed. Based on these results, GAD antibody in the residual serum 48 days before transplantation was measured, but it was negative. Abdominal computed tomography showed no remarkable findings. The patient developed an insulin-dependent state as the C-peptide immunoreactivity index decreased with time (Figure 1). We diagnosed the patient with acute-onset type 1 diabetes mellitus according to the Japan Diabetes Society[3] because he tested positive for GAD antibodies and required continuous insulin therapy from the early stage of diabetes diagnosis. The patient did not develop ketoacidosis, possibly due to the early initiation of insulin therapy.

He was administered prednisolone from day 13 to treat fever. The administered medication and FBG levels are indicated in Figure 1.

DISCUSSION

Allo-HSCT-related immune responses, such as GVHD, have become a serious complication, causing major concern. In contrast, allo-HSCT has been held with little caution regarding the development of type 1 diabetes mellitus. Only few cases of type 1 diabetes mellitus development after bone marrow transplantation have been reported, and none of them describes type 1 diabetes mellitus development following CBT[4,5].

It is well known that patients with type 1 diabetes mellitus often have a disease-sensitive HLA haplotype[2]. In our case, the CBT donor had DRB1*0405, which is a high-risk HLA allele for type 1 diabetes mellitus, whereas the recipient did not have any sensitive allele. Although there are no data regarding the DQ allele in cord blood, the patient had a 0303 DQ allele pre-transplantation, which changed to the 0401 allele post-transplantation (Table 1). Therefore, it is presumed that the DQ allele in cord blood was 0401. DRB1*0405-DQB1*0401 is a high-risk HLA haplotype for type 1 diabetes mellitus[2].

Thymus-derived T-lymphocytes appear approximately 1.5–2 years after CBT[6]. In contrast, in our case, the FBG levels increased from day 5. Therefore, we hypothesized that immune cells other than donor stem cell-derived lymphocytes were involved in the onset of type 1 diabetes mellitus in our case. Moreover, cord blood is known to contain some peripheral lymphocytes of the newborn infant[7]. Therefore, these findings suggest that lymphocytes from the cord blood may have been involved in the onset of type 1 diabetes mellitus in our case.

Pre-engraftment syndrome (PES) is an immune response that occurs before engraftment, similar to the onset of type 1 diabetes mellitus in our case[8]. T-lymphocytes in the umbilical cord blood are mostly naïve and therefore differ from those in adult peripheral blood. Moreover, T-lymphocytes in the umbilical cord blood change to memory cells approximately 14 days after transplantation and replace the host lymphocytes[9]. The incidence of PES is believed to be higher in the group with >90% donor-type lymphocytes in 7 days than in the group with <90% donor-type lymphocytes. Considering these factors and relating them to our patient who showed elevated FBG levels from day 5, it is also possible that umbilical cord blood lymphocytes with a type 1 diabetes mellitus-susceptibility haplotype were subjected to antigen presentation to allow expansion and memory formation until day 5; following this, they may have induced an immune response to the recipient's islets of Langerhans.

During the first medical examination at our hospital, the hemoglobin (Hb) level of the patient was 8.1 g/dL, and the Hb level recorded 1 month prior to that was 9.5 g/dL (Table 2). Therefore, anemia may have progressed over a month. The patient's HbA1c level during the first medical examination was 6.5%, which was a mildly high value. Some reports indicated that as anemia progresses, HbA1c levels are elevated due to prolonged erythrocyte survival[10]. Therefore, it is better to investigate glycoalbumin levels instead of HbA1c levels for measuring glucose tolerance in patients with anemia.

The results of this study highlight the recognition of the onset of type 1 diabetes mellitus after CBT by comparing anti-GAD antibody levels pre- and post-transplantation. As anti-GAD antibodies are known to be a predictive marker of type 1 diabetes mellitus[11], we believe that measuring anti-GAD antibody levels before HSCT will be beneficial in predicting type 1 diabetes mellitus onset after transplantation.

DISCLOSURE

The authors declare no competing financial interests.

Approval of the research protocol: N/A.
Informed consent: The patient provided written informed consent.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

REFERENCES

1. Eisenbarth GS. Type 1 diabetes mellitus. A chronic autoimmune disease. *N Engl J Med*1986; 314: 1360–1368.
2. Kawabata Y, Ikegami H, Kawaguchi Y, *et al*. Asian-specific HLA haplotypes reveal heterogeneity of the contribution of HLA-DR and -DQ haplotypes to susceptibility to type 1 diabetes. *Diabetes*2002; 51: 545–551.
3. Araki E, Goto A, Kondo T, *et al*. Japanese clinical practice guideline for diabetes 2019. *Diabetol Int*2020; 11: 165–223.
4. Vialettes B, Maraninchi D, San Marco MP. Autoimmune polyendocrine failure – type 1 (insulin-dependent) diabetes mellitus and hypothyroidism – after allogenic bone marrow transplantation in a patient with lymphoblastic leukaemia. *Diabetologia*1993; 36: 541–546.
5. Mellouli F, Ksouri H, Torjmen L, *et al*. Transmission of type 1 diabetes by bone marrow transplantation: a case report. *Pediatr Transplant*2008; 13: 119–122.
6. Koh LP, Chao NJ. Umbilical cord blood transplantation in adults using myeloablative and nonmyeloablative preparative regimens. *Biol Blood Marrow Transplant*2004; 10: 1–22.
7. Pranke P, Failace RR, Allebrandt WF. Hematologic and immunophenotypic characterization of human umbilical cord blood. *Acta Haematol*2001; 105: 71–76.
8. Frangoul H, Wang L, Harrell FEJr, *et al*. Preengraftment syndrome after unrelated cord blood transplant is a strong predictor of acute and chronic graft-versus-host disease. *Biol Blood Marrow Transplant*2009; 15: 1485–1488.
9. Gutman JA, Turtle CJ, Manley TJ, *et al*. Single-unit dominance after double-unit umbilical cord blood transplantation coincides with a specific CD8+ T-cell response against the nonengrafted unit. *Blood*2010; 115: 757–765.
10. Kilpatrick ES, Bloomgarden ZT, Zimmet PZ. Is haemoglobin A1c a step forward for diagnosing diabetes?*BMJ*2009; 339: b4432.
11. Seissler J, Hatziagelaki E, Scherbaums WA. Modern concepts for the prediction of type 1 diabetes. *Exp Clin Endocrinol Diabetes*2001; 109: S304–S316.