Autologous recovery with chromosomal abnormalities after unrelated umbilical cord blood transplantation with myeloablative conditioning in a case of pediatric acute lymphoblastic leukemia

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Abstract

Detailed case reports of autologous recovery of hematopoiesis after hematopoietic stem cell transplantation with myeloablative conditioning (MAC) are scarce. We present a rare case of a 3-year-old male with relapsed KMT2A-rearranged acute lymphoblastic leukemia (ALL) who experienced autologous recovery following secondary engraftment failure after cord blood transplantation (CBT) with MAC. Similar to previous reports, we detected unusual chromosomal abnormalities, which differed at each bone marrow examination. He remains alive without relapse of ALL 12 months after CBT. As the rate of recurrence or late occurrence of secondary malignant neoplasm remains unclear, careful follow-up is required, especially in pediatric patients.

1 Introduction

Hematopoietic stem cell transplantation (HSCT) is an important treatment approach that has been used to cure a wide range of malignant and non-malignant diseases; however, various early and late complications can occur following HSCT[1,2]. A proportion of patients experience primary or secondary graft failure after receiving HSCT[3]; however, reports of autologous hematopoietic recovery after graft failure following application of a myeloablative conditioning (MAC) regimen are rare. Some case reports of adult patients experiencing autologous recovery have been published[4,5,6,7]. In pediatric populations, such autologous recovery was retrospectively reported through a questionnaire survey based on the Japan Society for Hematopoietic Cell Transplant (JSHCT) registry data[8]; however, there have been no detailed case reports.

Herein, we report a case of a patient with acute lymphoblastic leukemia (ALL) who experienced autologous hematopoietic recovery after cord blood transplantation (CBT) with total body irradiation (TBI)-based MAC, despite once achieving a neutrophil engraftment, who also showed different complex chromosomal abnormalities, without any disease relapse, on repeatedly conducted bone marrow (BM) examination.

2 CASE DESCRIPTION

A 3-year-old male presented at the referred hospital with chief complaints of fever and subcutaneous bleeding. Blood tests showed bicytopenia, with a white blood cell count of 7.34×10^9/L (blasts 42%, neutrophils 22%), hemoglobin 7.3 g/dL, and platelet count of 57×10^9/L. He was diagnosed with ALL, with no abnormal karyotype, based on findings of 94.8% $CD19^+$ $cyCD79a^+HLA\text{-}DR^+$ $CD38^+$ blasts on BM examination.

KMT2A rearrangement was detected by fluorescence in situ hybridization (FISH) analysis, but no partner genes were identified.

He received induction therapy, including vincristine, L-asparaginase, prednisolone, and doxorubicin, and achieved first complete remission (CR) at the molecular level; however, a very early relapse occurred, with 30% BM blast cells. After admission to our hospital, he received reinduction therapy using the ALL-REZ BFM 90 protocol[9], leading to achievement of second CR, negative for minimal residual disease (MRD) by *KMT2A* FISH analysis. He underwent unrelated CBT from a human leukocyte antigen 6/8 allele-matched male donor, containing 4.9×10^7/kg total nucleated cells and 1.7×10^5/kg $CD34^+$ cells, following a MAC regimen consisting of TBI (total dose, 12 Gy at 2 Gy/fraction) twice daily from day –3 to –1, 60 mg/kg/day of cyclophosphamide on days –5 and –4, and 60 mg/kg/day of etoposide on day –7 (Fig. 1). As prophylaxis for graft versus host disease (GVHD), tacrolimus was continuously administered from day –1, with short-term methotrexate at 10 mg/m^2/day on day 1 and 7 mg/m^2/day on days 3 and 6. He had fever on day 9 and a rash, expanding to his whole body on days 9–11. We diagnosed engraftment syndrome and started 2 mg/kg/day methylprednisolone twice daily. Neutrophil engraftment was achieved on day 20, as the first of 3 consecutive days of neutrophil count >0.5 x 10^9/L; however, his absolute neutrophil count (ANC) gradually decreased shortly after the engraftment and reached a nadir on day 26. BM examination on day 27 showed apparent hypocellularity with no myeloblasts but macrophages, a proportion of which exhibited hemophagocytosis (Fig. 2), suggesting secondary engraftment failure, despite 49–62% recipient-derived cells on chimerism analysis of short tandem repeat (STR) sequences. We planned a salvage transplantation, but white blood cells and neutrophils showed upward trends on days 33 and 39, respectively. BM chimerism analysis on day 41 revealed that recipient-derived cells accounted for more than 95%, suggesting autologous hematopoietic recovery. His BM achieved CR at MRD levels by*KMT2A* FISH and showed a complex karyotype of 46,XY,t(7;8)(q11.2;q11.2) in five cells; 46,XY,t(1;4)(p32;q21),t(5;10)(p15;p11.2) in five cells; 46,XY,t(9;19;12)(p24;p13;q13) in two cells; 46,XYadd(1)(p34),add(3)(p21),add(5)(q31) in one cell; 46,XY,-1,-2,+add(3)(q11.1),-7,der(8)t(7;8)(q11.2;p23),-11,-12,+4mar in one cell; and 46,XY in six cells at cytogenetic examination.

Neutrophil count exceeded 0.5 x 10^9/L again on day 51, reticulocyte count exceeded 1% on day 63, and platelet count exceeded 50 x 10^9/L on day 105, independent of transfusion. After careful discussion of the treatment plan with his parents, we decided to observe with caution, without another HSCT. Although BM examinations continued to reveal different chromosomal abnormalities, he remains alive 12 months after CBT without any relapse of primary disease or secondary malignant disease.

3 Discussion

We report a patient with *KMT2A* -rearranged ALL who developed secondary graft failure after CBT with TBI-based MAC and then experienced autologous hematopoietic recovery with molecular CR of primary disease. He also had complex chromosomal abnormalities in recovered autologous hematopoietic cells.

Graft failure can be classified into two groups: primary graft failure, where the patient never achieves ANC $>0.5 \times 10^9$ /L for 3 successive days, and secondary graft failure, where the patient loses donor cells after initial engraftment[10]. This case was considered to have experienced secondary graft failure, based on the above definitions. A retrospective study from Olsson et al.[11] showed that 54 of 967 patients (5.6%) experienced graft failure after HSCT. Moreover, in a report of 309 children undergoing allogenic BM transplantation[12], 11 cases (3.6%) of graft failure occurred, suggesting that graft failure is relatively uncommon. Non-malignant diseases, reduced-intensity conditioning, lower stem cell dose, viral infection, and HLA-mismatched grafts are associated with increased risk of graft failure[11,12,13]. TBI-based conditioning is considered to have sufficient immunosuppressive effects and excellent antitumor effects on malignant hematologic diseases, and can also enhance the likelihood of neutrophil engraftment in CBT, regardless of conditioning intensity[14]. In our case, secondary graft failure occurred despite the use of TBI-based MAC for malignant disorder. HLA-mismatched CBT or hemophagocytosis observed in the BM may have been factors influencing secondary graft failure.

There have been some case reports of autologous recovery following TBI-based MAC in adult patients with

chronic myeloid leukemia (CML)[4,5,6] or (acute myeloid leukemia) AML[7]. Moreover, 10 of 291 (3.4%) adult patients with CML were found to undergo autologous recovery after HSCT followed by cyclophosphamide + TBI regimen[6]. In a recent report from JSHCT[8], only 30 of 59,603 children (0.05%) receiving HSCT, who were registered to JSHCT between 1974 and 2016, experienced autologous recovery after TBI-based MAC ([?]8 Gy). Hence, autologous hematopoietic recovery after HSCT is rarely reported in pediatric patients compared with adult patients.

The persistent detection of chromosomal abnormalities in the present patient raised concerns about the development of myelodysplastic syndrome (MDS) and leukemia; however, in our case, the pattern of chromosomal abnormalities was complex, changed randomly, and did not include MDS/leukemia-related cytogenetic abnormalities such as monosomy 7 and trisomy 8. Further, only 2 of 35 children reported by JSHCT with persistent detection of chromosomal abnormalities developed MDS/AML, whereas 19 of them relapsed[8]. Absence of alloreactive response was suggested to be the reason for limited therapeutic effects.

In conclusion, we describe a rare pediatric case who underwent secondary engraftment failure with autologous hematopoietic recovery after CBT with TBI-based MAC. Given the limited data on autologous recovery in pediatric patients, long-term follow-up with caution, to monitor for primary disease relapse or progression to MDS or leukemia, is required.

Conflicts of interest

The authors declare no relevant conflicts of interest.

References

1. Hierlmeier S, Eyrich M, Schlegel PG, et al. Early and late complications following hematopoietic stem cell transplantation in pediatric patients – A retrospective analysis over 11 years.*PloS One* . 2018;13(10):e0204914.
2. Mohty B, Mohty M. Long-term complications and side effects after allogeneic hematopoietic stem cell transplantation: an update.*Blood Cancer J* . 2011;1(4):e16.
3. Kato M, Matsumoto K, Suzuki R, et al. Salvage allogeneic hematopoietic SCT for primary graft failure in children. *Bone Marrow Transplant* . 2013;48:1173-1178.
4. Kapoor N, Keever CA, Hsu SH, et al. Prolonged remission of accelerated phase Philadelphia chromosome negative chronic myeloid leukemia following autologous recovery of normal hematopoietic elements after busulfan/cyclophosphamide and allogeneic marrow transplantation.*Bone Marrow Transplant* . 1992;9:143-145.
5. Fouillard L, Deconinck E, Tiberghien P, et al. Prolonged remission and autologous recovery in two patients with chronic myelogenous leukemia after graft failure of allogeneic bone marrow transplantation.*Bone Marrow Transplant* . 1998;21:943-946.
6. Brunatein CG, Hirsch BA, Miller JS, et al. Non-leukemic autologous reconstitution after allogenic bone marrow transplantation for Ph-positive chronic myelogenous leukemia: extended remission preceding eventual relapse. *Bone Marrow Transplant* . 2000;26:1173-1177.
7. Gomyo A, Nakasone H, Wada, H, et al. Autologous hematopoietic recovery after unrelated umbilical blood transplantation with myeloablative conditioning for acute myelogenous leukemia. *Intern Med* . 2020;59:2409-2414.
8. Kato M, Nakasone H, Nakano N, et al. Clinical course of autologous recovery with chromosomal abnormalities after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* . 2020;55:1023-1028.
9. Tallen G, Ratei R, Mann G, et al. Long-term outcome in children with relapsed acute lymphoblastic leukemia after time-point and site-of relapse stratification and intensified short-course multidrug chemotherapy: results of trial AA-REZ BFM 90. *J Clin Oncol* . 2020;28:2339-2347.
10. Carreras E, Dufour C, Mohty M, et al. The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies. *Springer: 7th ed* . 2019.
11. Olsson R, Remberger M, Schaffer M, et al. Graft failure in the modern era of allogeneic hematopoietic

SCT. *Bone Marrow Transplant* . 2013;48:537-543.
12. Paul W, Xin T, Stacye R, et al. Etiology and outcome of graft failure in pediatric hematopoietic stem cell transplant recipients. *J Pediatr Hematol Oncol* . 2003;25(12):955-959.
13. Mattsson J, Ringden O, and Storb R. Graft failure after allogenic hematopoietic cell transplantation. *Biol Blood Marrow Transplant* . 2008;14:165-170.
14. Nakasone H, Fuji S, Yakushiji K, et al. Impact of total body irradiation on successful neutrophil engraftment in unrelated bone marrow or cord blood transplantation. *Am J Hematol* . 2017;92:171-178.

FIGURE LEGENDS

Figure 1 The clinical course and analysis chimerism in the case. VP-16, etoposide; CY, cyclophosphamide; TBI, total body irradiation; G-CSF, granulocyte-colony stimulating factor; Tac, Tacrolimus; MTX, methotrexate; mPSL, methylprednisolone; CBT, cord blood transplantation; WBC, white blood cell; Neut, neutrophil.

Figure 2 Image of hemophagocytosis in bone marrow (x1000, Wright-Giemsa stain). Hemophagocytic macrophages were scattered in bone marrow on day 27.