Pseudo-progression of adult T-cell leukemia-lymphoma after cord blood transplantation

by Shigeo Fuji, Jun-ichirou Yasunaga, Eri Watanabe, Masao Matsuoka, Kaoru Uchimaru, and Jun Ishikawa

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Case report

Title: Pseudo-progression of adult T-cell leukemia-lymphoma after cord blood transplantation

Shigeo Fuji¹, Jun-ichiro Yasunaga², Eri Watanabe³, Masao Matsuoka², Kaoru Uchimaru⁴, Jun Ishikawa¹

1. Department of Hematology, Osaka International Cancer Institute, Osaka, Japan
2. Graduate School of Medical Sciences, Faculty of Life Sciences Kumamoto University, Kumamoto, Japan.
3. IMSUT Clinical Flow Cytometry Laboratory, The University of Tokyo, Tokyo, Japan
4. Laboratory of Tumor Cell Biology, Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences, The University of Tokyo, Tokyo, Japan.

Corresponding author
Shigeo Fuji, M.D., Ph.D.
Department of Hematology
Osaka International Cancer Institute
3-1-69, Otemae, Chuo-ku, Osaka-shi, Osaka 5418567, Japan
E-mail: fujishige1231@gmail.com
Fax: +81 (06) 6945-1900  Tel: +81(6)6945-1181

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Data sharing statement
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.
Mainbody

Adult T-cell leukemia-lymphoma (ATL) is a hematological malignancy caused by human T-lymphotropic virus type I (HTLV-1) with a dismal outcome (1). Allogeneic hematopoietic cell transplantation (HCT) is a standard of care in transplant-eligible patients to improve the long-term clinical outcome in patients with aggressive ATL (1). Early allogeneic HCT is generally recommended as conventional chemotherapy does not achieve long-term disease control. Allogeneic HCT using alternative donor such as cord blood or haploidentical related donor is emerging. Although allogeneic HCT could reduce the risk of relapse or progression significantly, relapse or progression remains one of the major causes of failure in patients with ATL (2). Anecdotal reports showed that donor-derived ATL could occur, but donor-derived ATL was rarely reported, and in these cases, the stem cell donor was HTLV-1 carrier (3-5). The transient proliferation of donor-derived ATL cell-like lymphocytes was also reported, but the donor was HTLV-1 carrier (6). Theoretically, de novo donor-derived HTLV-1 infected T cells could expand polyclonally or even progress to monoclonal ATL after allogeneic HCT. The actual risk for developing ATL in patients with polyclonal HTLV-1-infected T cells is unclear. In some countries, strategies to minimize the neo-infection of donor cells after allogeneic HCT using the anti-viral drugs are undertaken, although there is no published evidence to support this approach (1).

Here, we experienced a case of pseudo-progression of ATL after cord blood transplantation (CBT): polyclonal expansion of de novo-infected cord blood-derived HTLV-1 infected T cells. This patient took part in a prospective comprehensive study to analyze the molecular markers including surface markers and other molecular markers in HTLV-1-infected individuals. The study has been approved by a formally constituted review board (Osaka International Cancer Institute, Osaka, Japan, No. 1707259142). The study was conducted in accordance with the Declaration of Helsinki.

A 58-year-old female was diagnosed with acute-type ATL at our institute. She received VCAP-AMP-VECP regimen as induction chemotherapy (7). VCAP-AMP-VECP regimen was effective, but myelosuppression persisted. Thus, chemotherapy was changed to CHOP
regimen. She received 4 cycles of CHOP regimen, and achieved complete remission. There was no HLA-matched related or unrelated volunteer donor available. Therefore, she received CBT following a reduced-intensity conditioning regimen containing fludarabine, melphalan and low-dose total body irradiation. Neutrophil engraftment was achieved at day 17 after CBT. Complete donor chimerism was confirmed. She had grade 2 acute graft-versus-host disease (GVHD, skin stage 2, gut stage 1), which was resolved by systemic corticosteroid.

Around 6 months after CBT, although there was no clinical signs or symptoms concerning for recurrence of ATL, there was an emergence of abnormal lymphocytes in peripheral blood (PB, Figure 1A). The percentage and absolute number of abnormal lymphocytes determined morphologically were 4.5% and 203/μL, respectively. At the same time, there was an elevation of serum soluble interleukin-2 receptor (sIL-2R) level (2250 IU/mL, normal range 157-474 IU/mL) and proviral load (PVL, 8.16 per 100 peripheral blood mononuclear cells [PBMCs]). In multi-color flow-cytometry (FCM) analysis, we were able to detect a significant population of CD3+CD4+CDM1+CD7low-dim T cells (Figure 1B). We diagnosed that it was relapse of ATL after CBT. There was no other lesion of relapse except for PB. Once progressed, the clinical outcome of relapsed ATL after allogeneic HCT was dismal (8). Therefore, we urgently administered mogamulizumab as CCR4 was highly expressed. Following the administration of mogamulizumab, abnormal lymphocytes in PB disappeared immediately. We reviewed the results of this case, and we thought that the result of FCM analysis was not a typical pattern (9, 10) that CD7 expression varied in this T cell population. However, we were not able to perform the additional test due to the complete disappearance of abnormal cells in PB after the administration of mogamulizumab.

Around 1.5 years after CBT, there was a re-emergence of the abnormal lymphocytes in PB. The result of FCM analysis is shown in Figure 1C. The pattern was basically similar to the previous one at 6 months after CBT with elevated serum sIL2R level (2649 IU/mL) and PVL (29.1 per 100 PBMCs). In order to confirm the diagnosis of ATL progression, we performed the chimerism analysis by short tandem repeat (STR) of whole and fractionated cells in PB: granulocytes, T cells, B cells, macrophage, and NK cells. The results showed that chimerism was completely donor-derived in all fractions (Figure 2A). For assessing the chimerism and clonality of CD4+ T cells, we performed the sorting of T cells in each fraction named D (CDM1+CD7+), P (CDM1−CD7+), N (CDM1−CD7−) using FACS Aria II (Figure 2B). The sorted cells were assessed by XY Fluorescence In Situ Hybridization (FISH) as CB was male and the recipient was female. We found that all sorted cells in each fraction were male by
We additionally performed inverse PCR in D and N fraction, and found that HTLV-1 infected cells were polyclonal in each fraction (Figure 2C). We did not have sufficient cells for the analysis in P fraction. Using inverse PCR, HTLV-1 was serially found to be polyclonal in PB. We concluded that the patient had pseudo-progression of ATL after CBT: polyclonal expansion of de novo infected cord blood-derived T cells.

There is no consensus on how we manage HTLV-1 carrier after allogeneic HCT. Thus, patients were followed without additional treatment. Around 4 years after CBT, the patient had neither relapse of ATL nor chronic GVHD free of immunosuppressive drugs, but in the status of HTLV-1 carrier.

Here, we presented a case of pseudo-progression of ATL after CBT: polyclonal expansion of de novo HTLV-1-infected CB-derived T cells. As far as we know, this is the first reported case of such a clinical situation after allogeneic HCT with detailed analysis to confirm that the expanded cells were the polyclonal expansion of de novo HTLV-1-infected cord blood-derived T cells.

When we first encountered the emergence of abnormal lymphocytes in this case, we did not assess the possibility of polyclonal expansion of HTLV-1-infected cells and administered mogamulizumab, as the pattern of multi-color FCM, serum sIL2R level and PVL level was consistent with the recurrence of recipient-derived ATL. However, in the multi-color FCM, the pattern of CD7 expression was not typical in aggressive ATL as previously reported (9, 10). Thus, we added the detailed analysis to assess the chimerism and clonality when the patient had the re-emergence of abnormal lymphocytes in PB, and found that the expanded cells were donor-derived and polyclonal. As CB is always confirmed to be HTLV-1 seronegative before CBT, it is certain that HTLV-1 infected CB after CBT. As donor-derived ATL cells were reported, it would be essential to assess the chimerism and clonality when we detect abnormal lymphocytes in ATL patients after allogeneic HCT even when donor is HTLV-1 seronegative (3-6). Furthermore, it is unclear whether donor-derived HTLV-1-infected polyclonal T cells could progress to ATL. We need more data to clarify this issue in large cohorts of allogeneic HCT recipients in HTLV-1-infected individuals.

In conclusion, here we reported the first case of donor-derived polyclonal expansion of HTLV-1 infected T cells.
References


Figures

Figure 1. Morphology of lymphocytes and flow cytometry analysis in peripheral blood
Example images of lymphocytes in peripheral blood. The image was obtained by the CellVision DC-1 (A). Flow cytometry analysis to assess the expression pattern of CADM1/CD7 in CD3+CD4+ T cells as previously reported. The sample was taken around 6 months after cord blood transplant (B). Flow cytometry analysis to assess the expression pattern of CADM1/CD7 in CD3+CD4+ T cells as previously reported. The sample was taken around 1.5 years after cord blood transplant (C).

Figure 2. Chimerism analysis and clonality analysis in peripheral blood
Result of chimerism analysis using short tandem repeat in each fraction: whole blood, T cell, B cell, NK cell, macrophage and granulocyte (A). A gating strategy of multi-color flow cytometry to sort P, D and N fraction (B). Result of inverse PCR in D and N fraction. CD8 positive cells were the control of polyclonal cells, and TLom1 was a positive control of monoclonal cells (C).
Figure 1

(A) Images showing various cell types.

(B) Flow cytometry plots with SSC-A, FSC-A, FSC-A, PI/CD235a, CD4, CD7, CD3, and CADM1 axes.

(C) Expanded views of CD4, CD7, CD3, and CADM1 plots.