

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

Adult T-cell leukemia-lymphoma (ATL) is a hematological malignancy caused by human T-lymphotropic virus type 1 (HTLV-1) with a dismal outcome.¹ Allogeneic hematopoietic cell transplantation (HCT) is the 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 an 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 an HTLV-1 carrier.³⁻⁵ The transient proliferation of donor-derived ATL cell-like lymphocytes was also reported, but the donor was an 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 reinfection of donor cells after allogeneic HCT using anti-viral drugs are undertaken, although there is no published evidence to support this approach.¹

Here, we present 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. The patient took part in a prospective comprehensive study to analyze 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 four 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 recurrence of ATL, there was an emergence of abnormal lymphocytes in the peripheral blood (PB) (Figure 1A). The percentage and absolute number of abnormal lymphocytes determined morphologically were 4.5% and 203 cells/ μ L, respectively. At the same time, there was an elevation of serum soluble interleukin-2 receptor (sIL-2R) level (2,250 IU/mL, normal range 157-474 IU/mL) and proviral load (PVL, 8.16 per 100 peripheral blood mononuclear cells [PBMC]). In multi-color flow cytometry (FCM) analysis, we were able to detect a significant population of CD3+CD4+ CADM1+CD7^{low}-dim T cells (Figure 1B). We diagnosed 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 is 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 the FCM analysis was not a typical pattern^{9,10} that CD7 expression varied in this T-cell population. However, we were unable 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 (2,649 IU/mL) and PVL (29.1 per 100 PBMC). 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 natural killer (NK) cells. The results showed that chimerism was completely donor-derived in all fractions (Figure 2A). In order to assess the chimerism and clonality of CD4+ T cells, we sorted T cells into different fractions named D (CADM1+CD7+), P (CADM1-CD7+), N (CADM1-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 XY FISH. We additionally performed inverse polymerase chain reaction

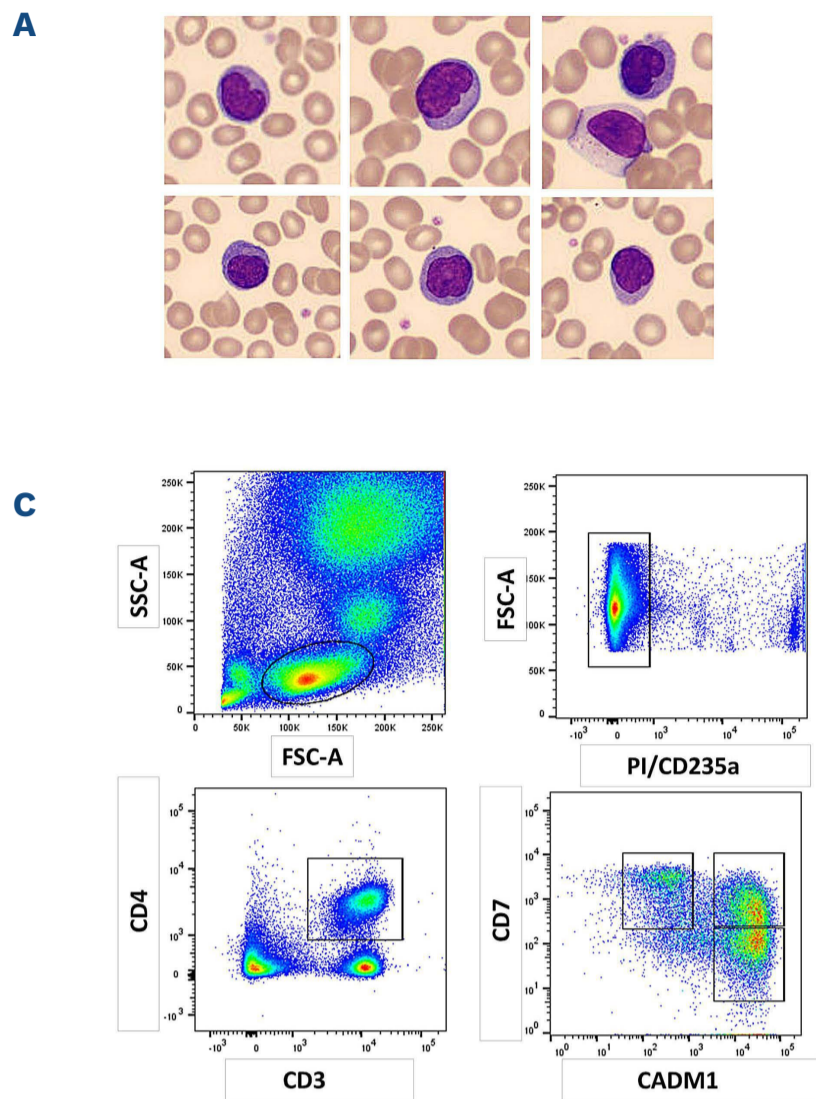


Figure 1. Morphology of lymphocytes and flow cytometry analysis in peripheral blood. (A) Example image of lymphocytes in peripheral blood obtained by CellaVision DC-1. (B) Flow cytometry analysis to assess the expression pattern of CADM1/CD7 in CD3+CD4+ T cells as previously reported. The sample was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

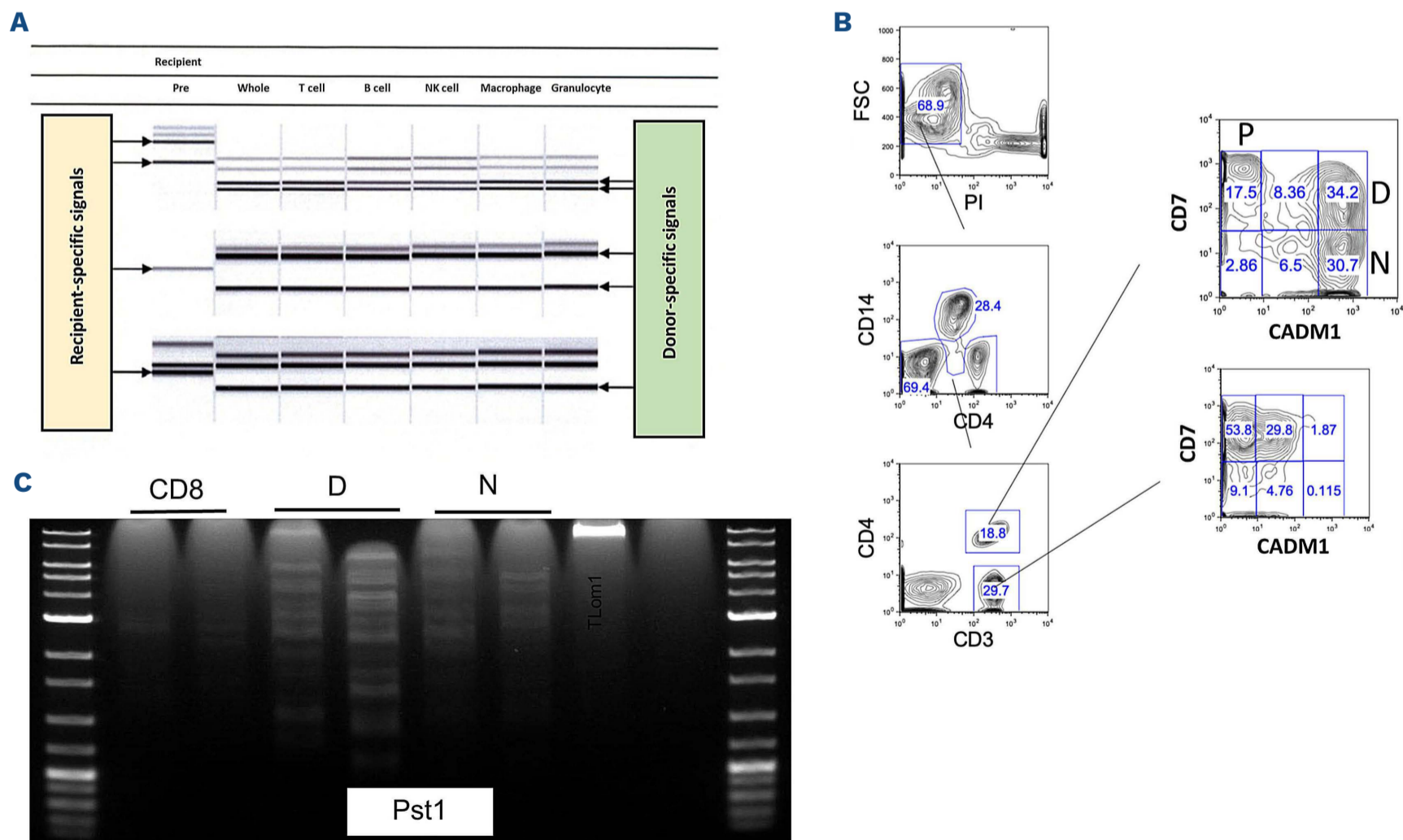


Figure 2. Chimerism and clonality analysis in peripheral blood. (A) Result of chimerism analysis using short tandem repeat in each fraction: whole blood, T cell, B cell, natural killer (NK) cell, macrophage and granulocyte. (B) Gating strategy of multicolor flow cytometry to sort P (CADM1-CD7+), D (CADM1+CD7+) and N (CADM1-CD7-) fraction. (C) Result of inverse polymerase chain reaction in the D and N fraction. CD8-positive cells were the control of polyclonal cells, and TLoM1 was a positive control of monoclonal cells.

(PCR) in the D and N fraction, and found that HTLV-1 infected cells were polyclonal in each fraction (Figure 2C). We did not have sufficient cell numbers for the analysis of the P fraction. Using inverse PCR, HTLV-1 was serially found to be polyclonal in PB. We concluded that the patient had pseudoprogression 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 carriers after allogeneic HCT. Thus, patients were followed without additional treatment. At around 4 years after CBT, the patient had neither a relapse of ATL nor had developed chronic GVHD and was free of immunosuppressive drugs, but retained the status of HTLV-1 carrier.

Here, we presented a case of pseudoprogression 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 a 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 multicolor FCM, serum sIL2R level and PVL level was consistent with the recurrence of recipient-derived ATL. However, in the multicolor FCM, the pattern of CD7 expression was not typical of 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.

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Contributions

SF designed and performed research, and wrote the paper. JY, EW, MM, KU and JI analyzed data. All authors have read the uploaded manuscript and consented to submission.

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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.

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