INTERNAL MEDICINE

□ CASE REPORT □

Cord Blood Transplantation Provided Long-term Remission in a Case of Adult T-cell Leukemia-lymphoma (ATL) with Myelofibrosis

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Abstract

A 53-year-old man was diagnosed with adult T-cell leukemia-lymphoma (ATL) acute type transformed from chronic type. A bone marrow analysis showed diffuse infiltration of abnormal lymphocytes and diffuse fibrotic change. He received unrelated cord blood transplantation (CBT) following reduced-intensity conditioning with complete remission of ATL after two courses of chemotherapy and achieved neutrophil and platelet engraftment. At 99 days after CBT, a bone marrow biopsy showed apparent resolution of myelofibrosis. These results suggest the therapeutic potential of CBT for patients with chemosensitive ATL with myelofibrosis.

Key words: adult T-cell leukemia-lymphoma, myelofibrosis, cord blood transplantation

(Intern Med 55: 197-201, 2016)
(DOI: 10.2169/internalmedicine.55.6109)

Introduction

One of the characteristic features of adult T-cell leukemia-lymphoma (ATL) is its frequent multi-organ involvement (1, 2). The clinical subtype of ATL is classified according to laboratory findings and the location of the tumor lesion (1). Because bone marrow involvement is not included in these criteria, a pathological assessment of the bone marrow is not a priority for ATL patients.

Myelofibrosis (MF) is characterized by fibrosis in the bone marrow with excessive deposits of extracellular matrix proteins (3). Secondary MF has been reported in various lymphoid neoplasms, such as malignant lymphoma, multiple myeloma, and chronic lymphoid leukemia. However, there have been a limited number of case reports describing MF among ATL patients.

We herein describe a case of ATL with MF in which durable remission for both ATL and MF was achieved after umbilical cord blood transplantation (CBT).

Case Report

A 53-year-old man presented with circulating abnormal lymphocytes and positivity for anti-human T-lymphotropic virus type 1 (HTLV-1) antibody in October 2008. Clonality of HTLV-1-integrated cells was detected by a Southern blot analysis, and the patient was diagnosed with chronic type ATL. He was followed up without any specific treatment due to the absence of symptoms. After 6 months of observation, he was admitted to our hospital with hypercalcemia (corrected serum calcium 12.3 mg/dL). A peripheral blood count yielded a leukocyte count of 8.1×10^9/L, hemoglobin level of 14.7 g/dL, and platelet count of 136×10^9/L (Table).

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Received for publication July 4, 2015; Accepted for publication August 19, 2015
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Table. Laboratory Data at Time of Diagnosis of ATL Acute Type.

RBC	448	$\times 10^4$/μL	Total protein	6.8	g/dL
Hb	14.7	g/dL	Albumin	4.1	g/dL
Hematocrit	44.1	%	Calcium (corrected)	12.3	mg/dL
MCV	98.4	fl	BUN	9	mg/dL
MCH	32.8	pg	Creatinine	0.59	mg/dL
MCHC	33.3	g/dL	Total bilirubin	0.8	mg/dL
Reticulocyte	1.18	%	AST	16	U/L
WBC	8,100	/μL	ALT	11	U/L
Stab	1	%	ALP	507	U/L
Segment	41	%	LDH	132	U/L
Lymphocyte	21	%	CRP	0.02	mg/dL
Monocyte	2	%	sIL-2R	11,111	U/mL
Ab-Lym	35	%	PTHrP	110.57	pmol/L
Platelets	13.6	$\times 10^4$/μL			

Abbreviations: Stab indicates: stab neutrophil, Segment: segmented neutrophil, Ab-Lym: abnormal lymphocytes, BUN: blood urea nitrogen, sIL-2R: soluble interleukin-2 receptor, PTHrP: parathyroid hormone-related protein

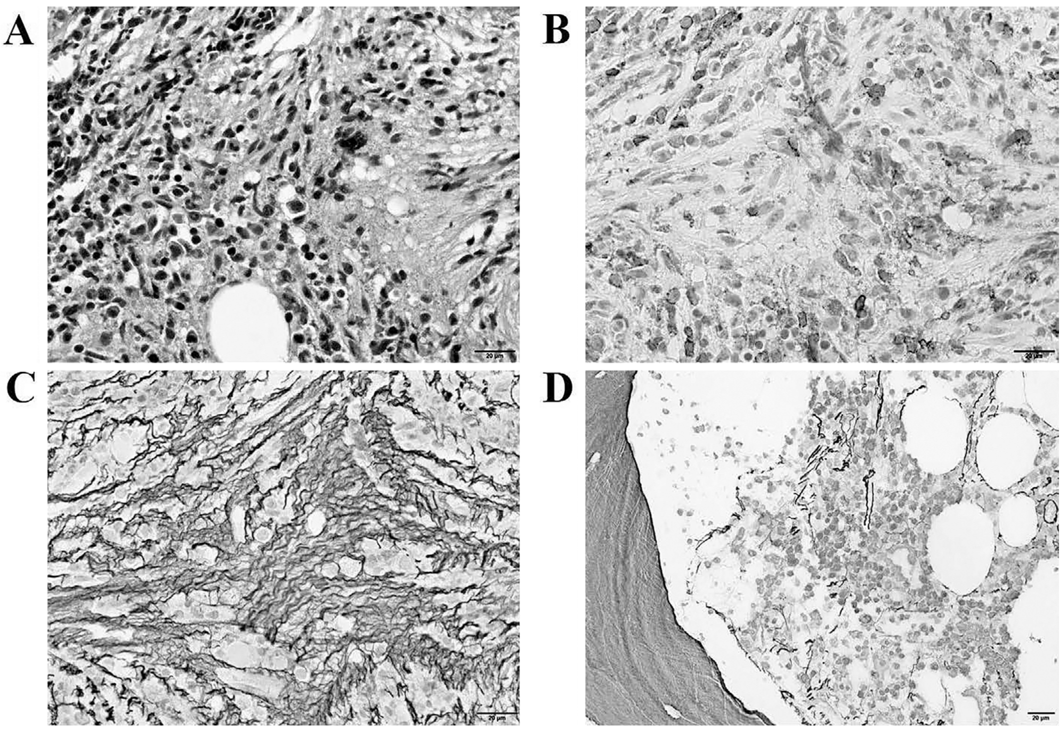

Figure 1. Pathological features of the bone marrow. The biopsy specimen of the bone marrow shows diffuse infiltration of atypical lymphocytes (Hematoxylin and Eosin staining: A, 200×). Immunohistochemically, the infiltrating atypical lymphocytes were CD4 positive (B, 200×). Reticulin staining of the bone marrow at diagnosis (C, 200×) and at day 99+ after transplantation (D, 200×).

Abnormal lymphocytes were present in the peripheral blood at 35%, and leukoerythroblastosis was not observed. Flow cytometry revealed that the abnormal lymphocytes were positive for CD2, CD3, CD4, CD5, CD25, and CCR4 and negative for CD8, CD7, CD26, CD16, CD56, and CD30. A Southern blot analysis for HTLV-1 provirus reconfirmed the monoclonal proliferation of HTLV-1-integrated cells in the peripheral blood. A real-time polymerase chain reaction (PCR) analysis using fluorescent hybridization probes and a melting curve analysis demonstrated that the patient was negative for the V617F *JAK2* mutation (exon 14). Neither lymphadenopathy nor hepatosplenomegaly was detected on computed tomography scans. The lactate dehydrogenase level was within the normal range. Soluble interleukin-2 receptor and parathyroid hormone-related protein levels were elevated to 11,111 U/mL (normal range: 145-519 U/mL), and 110.57 pmol/L (normal range: <1.1 pmol/L), respectively. A PCR analysis showed that the HTLV-1 proviral load was 5,100 copies/10^4 cells. Bone marrow aspiration resulted in a dry tap, and a bone marrow biopsy revealed diffuse infiltration of abnormal lymphocytes and diffuse fibrotic changes with a slight increase in megakaryocytes (Fig. 1A-C). The serum level of transforming growth factor-β1 (TGF-β1) was elevated to 8.36 ng/mL (normal range:

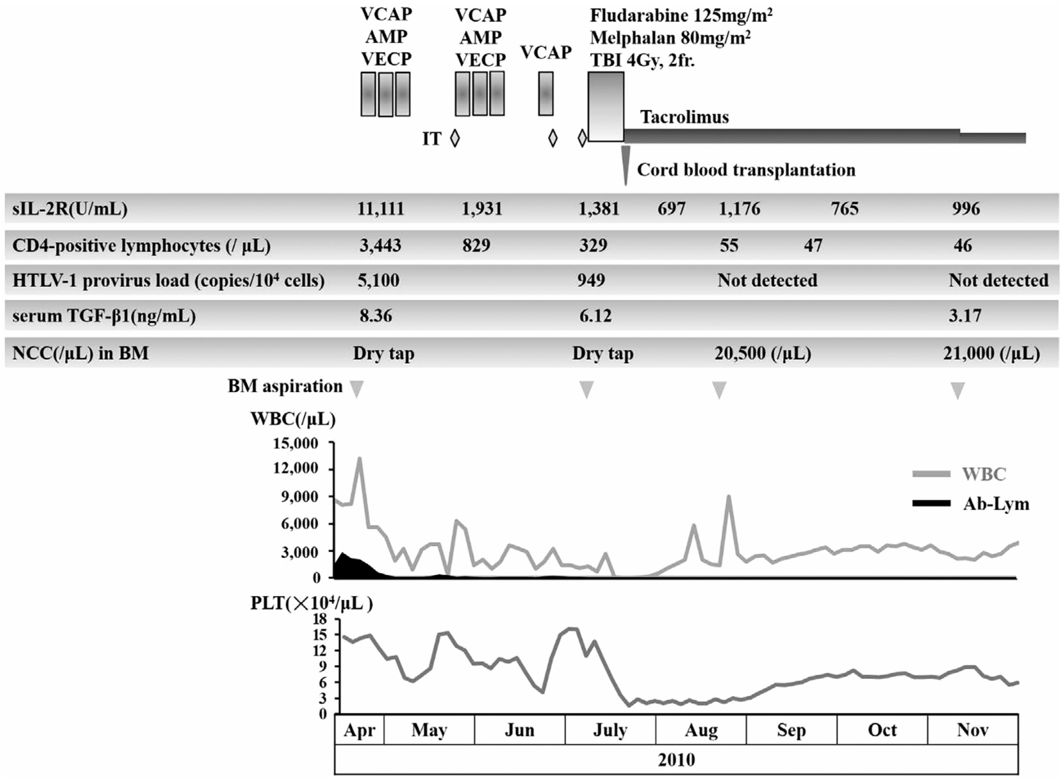

Figure 2. The clinical course from diagnosis to post-transplantation. VCAP: vincristine, cyclophosphamide, doxorubicin, and prednisone, AMP: doxorubicin, ranimustine, and prednisone, VECP: vindesine, etoposide, carboplatin, and prednisone, TBI: total body irradiation, IT: intrathecal administration of cytarabine, methotrexate, and prednisone, sIL-2R: soluble interleukin-2 receptor, TGF-β1: transforming growth factor-β1, NCC: nucleated cell count, BM: bone marrow, WBC: white blood cell, Ab-Lym: abnormal lymphocyte, PLT: platelet

1.56-3.24 ng/mL). According to these findings, the patient was diagnosed with ATL acute type with MF transformed from chronic type.

After 2 courses of chemotherapy [vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP), doxorubicin, ranimustine, and prednisone (AMP), and vindesine, etoposide, carboplatin, and prednisone (VECP) regimen], he achieved complete remission. At that time, a dry tap of bone marrow aspiration persisted. His serum TGF-β1 level was also elevated (6.12 ng/mL), and the HTLV-1 proviral load remained detectable in the peripheral blood (949 copies/10^4 cells). Because he did not have a serologically human leukocyte antigen (HLA)-matched sibling donor or an unrelated bone marrow donor from the Japan Marrow Donor Program, cord blood [total nucleated cell dose, 2.0×10^7 cells/kg; CD34-positive cell dose, 0.47×10^5 cells/kg; HLA 2 loci mismatched (HLA-B and -DRB1 loci were serologically mismatched), from a female donor] from the Japanese Cord Bank Network was transplanted in July 2009, following reduced-intensity pre-transplant conditioning (fludarabine 25 mg/m^2/day for 5 days, melphalan 80 mg/m^2/day for 1 day, and total body irradiation 4 Gy, 2 fractions). Tacrolimus was used as a single agent for graft-versus-host disease prophylaxis. Neutrophil engraftment and platelet recovery (>50,000 per mm^3 without transfusions) were obtained on days 17 and 40, respectively. He achieved 100% donor chimerism, which was confirmed by a variable number in a short tandem repeat DNA analysis of the peripheral blood. On day 99, a bone marrow biopsy revealed the resolution of MF (Fig. 1D). The HTLV-1 proviral load was shown to be under the detectable levels by the PCR, and his serum TGF-β1 level decreased to normal levels. The patient remains alive in complete remission of ATL more than 5 years after CBT. The clinical course of the patient is summarized in Fig. 2.

Discussion

The incidence of peripheral T-cell lymphoma with MF is rare (4-7); only 6 cases, including the present case, have been reported in the literature. We presented the clinical course of ATL with MF and demonstrated that the use of umbilical cord blood as a transplant graft may be feasible even for patients who have ATL with MF.

Allogeneic hematopoietic stem cell transplantation has been increasingly performed as an important therapeutic option for ATL because it may provide long-term remission by the graft-versus-ATL effect (8-13). However, this approach is accompanied with a high risk of transplantation-related mortality (8, 14). In particular, a Japanese nationwide retrospective study of post-transplant patients with ATL reported a worse survival and higher treatment-related mortality following CBT than transplantation with HLA-matched related and unrelated bone marrow grafts (8, 15, 16). Moreover, MF is a persistent concern for engraftment delay and failure (17-19), although the successful engraftment of umbilical cord blood has been reported in allogeneic stem cell transplantation for the treatment of MF (20). Despite the disadvantages associated with CBT and MF concurrent with ATL, it is notable that our case achieved successful donor cell engraftment and maintained durable remission after CBT. This may be accounted for, at least in part, by transplantation during the first complete remission after initial chemotherapy, as previously reported (21, 22).

The pathogenesis of MF associated with non-Hodgkin lymphoma remains unclear. Several cytokines, such as TGF-β1, platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (b-FGF), have been reported to stimulate fibrotic changes in the bone marrow (3, 23). CD4-positive lymphocytes of patients with peripheral T-cell lymphoma and autoimmune disease have been reported to produce TGF-β1, leading to the formation of MF (7, 24). In our case, persistent MF and elevated serum TGF-β1 levels were observed even after the reduction of CD4-positive lymphocytes by chemotherapy. It has also been reported that there was no correlation between the CD4-positive lymphocyte count and the formation of MF in patients with human immunodeficiency virus/acquired immunodeficiency syndrome (25). Conceivably, it may be possible that the formation of MF was due to the presence of residual ATL cells rather than due to the total CD4-positive lymphocyte counts. Moreover, the clinical course in the present case suggested that CBT may be an effective approach to eliminate such residual ATL cells.

In conclusion, although our experience is limited to one patient, CBT may represent a potential therapeutic option for ATL patients, including those with MF. Further studies are needed to elucidate the pathogenesis and clinical features of ATL with MF.

The authors state that they have no Conflict of Interest (COI).

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