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Case report

A case of hepatosplenic T-cell lymphoma successfully treated by HLA haploidentical stem cell transplantation

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We report a case of hepatosplenic T-cell lymphoma (HSTL) transplanted from an HLA-haploidentical daughter. A 51-year-old man was referred due to liver function test abnormalities and fever. He was confirmed to have γδ-type HSTL by bone marrow and liver biopsies. He was treated with five cycles of a CHOP regimen. Although metabolic complete response (CR), as defined by positron emission tomography, was achieved, his bone marrow still contained tumor cells on polymerase chain reaction (PCR). He underwent transplantation using unmanipulated peripheral blood stem cells from his HLA-haploidentical daughter. The preconditioning regimen consisted of fludarabine, melphalan, busulfan and antithymocyte globulin. Graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus and short-term methotrexate. Neutrophil engraftment was achieved on day 14. His bone marrow exhibited a completely female phenotype by fluorescence *in situ* hybridization, and no lymphoma cells were detected by PCR on day 30. Although he developed grade II acute GVHD on day 47, it was successfully treated by prednisolone. He has a limited type of skin chronic GVHD and still receives oral immunosuppressive therapy. He remains in CR four years after transplantation.

Keywords: hepatosplenic T-cell lymphoma (HSTL), haploidentical stem cell transplantation, graft-versus-host disease (GVHD)

INTRODUCTION

Hepatosplenic T-cell lymphoma (HSTL) is a rare subtype of lymphoma that accounts for 1.4% of mature T- and NK-cell neoplasms.[1] This disease typically presents in young men and is known to be highly aggressive, being characterized by hepatosplenomegaly, thrombocytopenia and systemic symptoms without lymphadenopathy.[2,3] Tumor cells are usually positive for CD3, CD2, CD7 and CD56, but negative for CD4, CD8 and CD5.[4] Although most cases express γδ T-cell receptor (TCR), some express αβ TCR. Both TCR αβ and γδ types present with a similar onset and clinical course, and the αβ subtype of HSTL is considered an immuno-phenotypic variant.[5] HSTL is associated with a recurrent chromosome abnormality of isochromosome 7q, and less often with that of trisomy 8.[6] Recently genomic abnormalities, including *SETD2*, *STAT5B* and *PIK3CD*, were reported to be mutated and related to the pathogenesis of HSTL.[7]

HSTL has a poor prognosis with a 5-year survival of only 7%.[1] CHOP or CHOP-like first-line regimens have been reported to be insufficient against HSTL,[4] and only allogeneic transplantation has been reported as a useful treatment associated with a cure.[8]

We report a case of γδ HSTL that was successfully treated by HLA haploidentical stem cell transplantation.

CASE REPORT

A previously healthy 51-year-old man was referred to our hospital because of abnormalities on liver function tests and thrombocytopenia found during a health examination and a 2-day history of fever. He had not received immunosuppressive medications or biological agents. His Eastern Cooperative Oncology Group (ECOG) performance status was 1. Physical examination revealed a temperature of 38.4 °C, hepatomegaly (extending 7.5 cm below the right costal margin) and splenomegaly (extending 6 cm below the left costal margin), but no superficial lymphadenopathy. Laboratory findings included a white blood cell count of 4,900/μL (including 3% abnormal lymphocytes), hemoglobin of 11.5 g/dL, platelet count of 4.9×10^4/μL, AST of 200 IU/L, ALT of 135 IU/L, ALP of 727 IU/L, LDH of 997 IU/L (normal range 110-210 IU/mL), γ-GTP of 107 IU/L, T.Bil of 1.8 mg/dL and sIL-2R of 1,858 U/mL, with no evidence of viral etiology (Table 1). ^{18}F-Fluorodeoxyglucose positron

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Table 1.

WBC	4900	/μL	TP	7.5	g/dL
meta	1	%	AST	200	IU/L
stab	9	%	ALT	135	IU/L
seg	42	%	ALP	727	IU/L
eos	0	%	LD	997	IU/L
baso	0	%	γ-GTP	107	IU/L
mo	11	%	T.Bil	1.8	mg/dL
lym	34	%	BUN	10	mg/dL
atyp. cell	3	%	Cr	0.53	mg/dL
Ebl	3	/100 WBC	UA	6.9	mg/dL
RBC	369	$x10^4$/μL	Na	136	mEq/L
Hb	11.5	g/dL	K	3.8	mEq/L
Ht	34.1	%	Cl	101	mEq/L
Plt	4.9	$x10^4$/μL	Ca	8.5	mg/dL
			Glu	146	mg/dL
PT-INR	1.11		HbA1c	5.3	%
APTT	41.4	sec			
Fbg	149	mg/dL	CRP	0.98	mg/dL
FDP	11.8	μg/mL	IgG	2439	mg/dL
DD	3.3	μg/mL	IgA	296	mg/dL
			IgM	107	mg/dL
			Ferritin	525.2	ng/mL
			β2MG	6.1	mg/L
			sIL-2R	1858	U/mL
			HTLV-1	(-)	
			HIV	(-)	
			EBV		
			VCA-IgG	x320	
			EBNA	x320	

emission tomography/computed tomography (^{18}F-FDG PET/CT) demonstrated marked hepatosplenomegaly with uniform uptake of FDG (standardized uptake value (SUV) max was 4.9) and no significant uptake in bone marrow (BM) (Figure 1A). BM aspiration revealed the presence of 55.2% abnormal lymphocytes (Figure 2A), which were positive for CD3, CD2, CD7, CD16 and TCR-γδ (detected by IMMU510 antibody, Beckman Coulter), but were negative for CD4, CD8, CD5, CD25, CD56 and TCR-αβ (detected by WT31 antibody, Becton Dickinson) on flow cytometry. TCR gene rearrangement was analyzed by polymerase chain reaction (PCR) using a marrow sample, which revealed clonal rearrangement of the γ chain. A normal karyotype was found by G-banding. Based on fluorescence *in situ* hybridization (FISH) analyses, 15% of cells harbored 6 to 8 copies of 7q31 (D7S486 probe with Spectrum Orange), in contrast to 2 copies of chromosome 7 centromere (D7Z1 probe with Spectrum Green), suggesting the presence of isochromosome 7q or amplification of 7q31. BM biopsy revealed the diffuse proliferation of medium-sized lymphoma cells (Figure 2B, 2C). Immunohistochemical staining of BM biopsy specimens demonstrated positivity for T-cell intracellular antigen-1, and negativity for Granzyme B and perforin. EBV-encoded RNA by *in situ* hybridization was negative. Liver biopsy revealed sinusoidal infiltration by medium-sized lymphoid cells (Figure 2D, 2E). He was diagnosed with the γδ subtype of HSTL. Staging according to the Ann Arbor system was IVB, with the involvement of the BM, liver and spleen.[9] The International Prognostic Index placed him in the high intermediate risk group,[10] and the prognostic index for peripheral T-cell lymphoma was group 3.[11] He was treated using CHOP, which consisted of cyclophosphamide, doxorubicin, vincristine and prednisolone, every three weeks. After five cycles of CHOP, he achieved metabolic complete

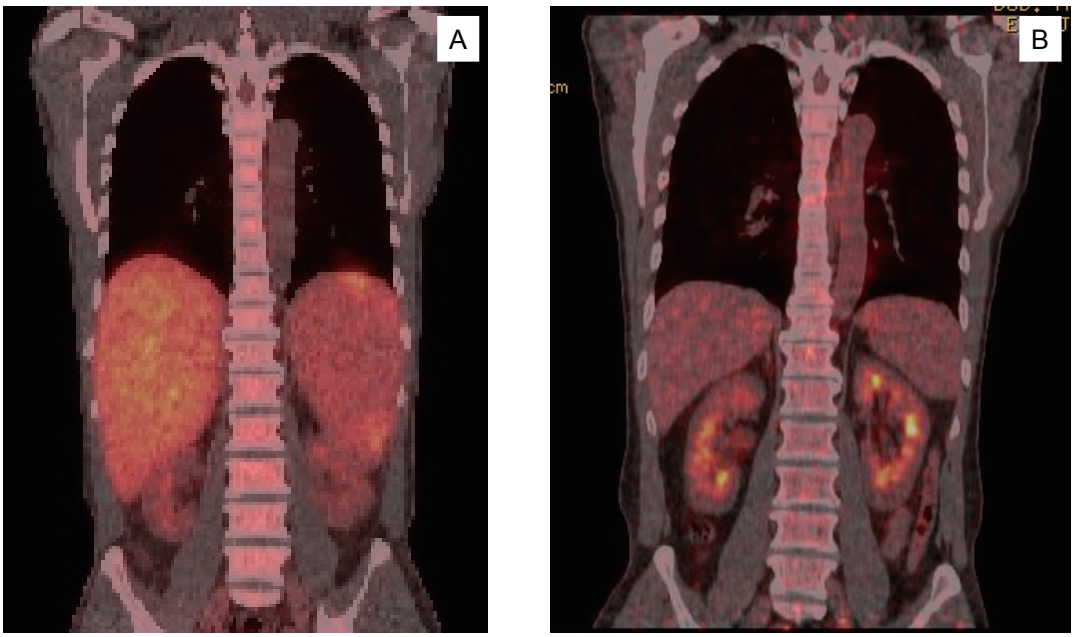

Fig. 1. (***A***) 18F-FDG PET/CT showed marked hepatosplenomegaly at the diagnosis, and (***B***) the liver and spleen normalized in size after five cycles of CHOP treatment.

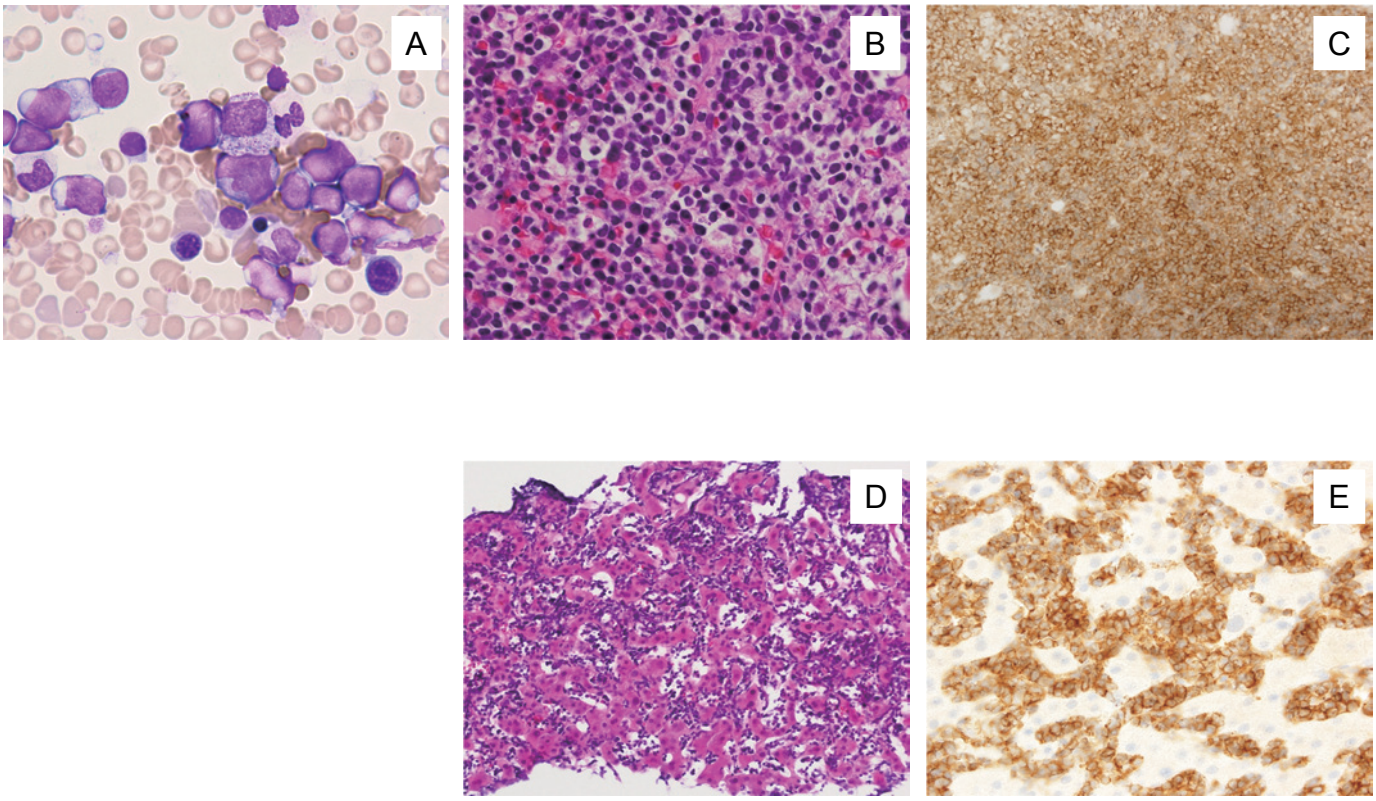

Fig. 2. (***A***) A bone marrow smear revealed 55.2% abnormal lymphocytes at the diagnosis. (***B***) Bone marrow biopsy showed diffuse proliferation of medium-sized lymphoma cells with pale cytoplasm and (***C***) CD3 staining. (***D***) On liver biopsy, the liver sinus was filled with lymphoma cells with the same morphological features and (***E***) CD2 staining.

response (CR), as defined by PET (Figure 1B). Although there were no lymphoma cells observed on microscopic examination, TCR-γ rearrangement was still detected in BM by PCR.

We planned to treat him by allogeneic hematopoietic stem cell transplantation (HSCT). However, no HLA-identical related or unrelated donors in the Japan Marrow Donor Program were found. We therefore chose his daughter, who had a haploidentical HLA, as a donor. He had no HLA antibodies. She was primed with granulocyte-colony stimulating factor (Lenograstim, 500 μg/day) injected subcutaneously for 5 days. On the fifth day, peripheral blood stem cells (PBSCs) were collected with a COBE Spectra (COBE BCT Inc., Lakewood, CO, USA). T cell depletion was not performed. The interval from diagnosis to transplantation was five months. The hematopoietic cell transplantation (HCT)-specific comorbidity index (HCT-CI) score was 0.[12] He received a non-myeloablative (reduced intensity) preconditioning regimen that consisted of 30 mg/m^2 of fludarabine for 6 days (day -7 to day -2), 3.2 mg/kg/day of intravenous busulfan for 2 days (day -5 to day -4), 50 mg/m^2 of melphalan for 2 days (day -3 to day -2) and 2.5 mg/kg of rabbit anti-thymocyte globulin (ATG) (Thymoglobuline) for 1 day (day -2), as previously described.[13] He was infused with donor PBSCs containing 2.96×10^6 CD34$^+$ cells/kg and 1.41×10^8 CD3$^+$ cells/kg. Tacrolimus (TAC) was initiated on the day before transplantation at 0.02 mg/kg/day in a continuous infusion. The target blood concentration of TAC was set at 10-15 ng/mL up to day 30 and thereafter tapered in the absence of acute graft-versus-host disease (GVHD).

Neutrophil and platelet engraftment were noted on days 14 and 22, respectively. The patient did not receive cytomegalovirus (CMV) prophylaxis. CMV antigenemia was diagnosed on day 22 (3 CMV-positive leukocytes per 50,000 white blood cells using the peroxidase-labeled monoclonal antibody, HRP-C7), and he was successfully treated with ganciclovir on days 24-30. On day 30, his BM demonstrated a normal female karyotype by G-banding and a 98.6% female type by XY FISH with no TCR-γ rearrangement on PCR. He was classified as being in molecular CR because his minimal residual disease (MRD) became negative. On day 47, small eruptions spread over his trunk and extremities. He was diagnosed with acute GVHD by skin biopsy. The grade of acute GVHD was II (skin stage 3, liver stage 0 and gut stage 0), and he was administered 0.5 mg/kg of prednisolone (PSL). He was discharged from the hospital on day 52. He continued to have limited skin lesions and was diagnosed clinically with a progressive onset type of chronic GVHD on day 118. He started to work again six months after transplantation. His skin still has a limited type of chronic GVHD, requiring 5 mg of TAC and 5 mg of PSL. He has continued to be in CR and his ECOG performance status has been 0, with his peripheral blood exhibiting a female type by FISH at four years after haploidentical transplantation.

DISCUSSION

HSTL is a rare type of T-cell lymphoma with a poor prognosis and a median survival time of < 2 years.[4] Yabe *et al*. analyzed 28 patients with HSTL, and the risk factors associated with a poor outcome included a high serum bilirubin level, trisomy 8 and the expression of αβ TCR,[14] none of which our patient had. Intensive induction chemotherapy beyond CHOP and HSCT at the first CR may improve the survival of patients with HSTL.[15] Allogeneic transplantation was reported to be potentially curative in cases of aggressive T-cell lymphoma, including HSTL, due to the graft-versus-lymphoma (GVL) effect.[16] Tanase *et al*. reported allogeneic and autologous stem cell transplantation for HSTL. Although 5 of 7 patients relapsed after autologous transplantation, only 2 of 18 allotransplanted patients relapsed. GVL activity can result in long-term survival for a substantial proportion of patients with HSTL.[8] Although most cases of HSTL express γδ-type TCR, a small subset expresses αβ TCR, which is considered an immunophenotypic variant of the same disease entity. One case with the aggressive αβ variant of HSTL was reported to have been successfully rescued by haploidentical transplantation.[5] To our knowledge, this is the first report of a case of γδ-type HSTL successfully treated by haploidentical transplantation.

The present patient had an excellent clinical course. Several reasons for this were presumed. First, he underwent allogeneic transplantation at a relatively young age and his HCT-CI score was 0. Second, his tumor burden was low at transplantation. When he achieved metabolic CR, as defined by PET, after induction therapy, his BM had a small amount of lymphoma cells only detected by PCR. Lastly, he underwent transplantation from a haploidentical donor and had a chronic limited type of skin GVHD, which may have induced the GVL effect. Our haploidentical transplantation procedure did not include post-transplantation cyclophosphamide for GVHD prophylaxis,[17] but alternatively employed a method previously reported by Hyogo College of Medicine in Japan.[18] In this approach, patients are infused with unmanipulated source stem cells from a haploidentical donor using fludarabine, busulfan, low-dose ATG and steroids. This transplantation protocol was reported to be safe and feasible if a suitable donor cannot be found in a timely manner.

In conclusion, we treated a patient with rare and aggressive γδ HSTL who achieved long-term remission, probably due to the GVL effect after haploidentical transplantation. Haploidentical transplantation may be a viable alternative technique for patients with HSTL when HLA-compatible siblings or unrelated donors are unavailable.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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