

[CASE REPORT]

Successful Cord Blood Stem Cell Transplantation for Primary Cutaneous CD8-positive Aggressive Epidermotropic Cytotoxic T-cell Lymphoma Complicated with Cerebral Infiltration

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Abstract:

A 16-year-old boy, who had been initially examined for bilateral blepharidema and slight eruption, presented with rapidly deteriorating symptoms in associating with headache and consciousness disturbance. He was diagnosed to have primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma (PCAE-CTL) by a biopsy of the skin and brain. After whole-brain radiation and some courses of chemotherapy, cord blood transplantation was performed with myeloablative conditioning. After transplantation, the cerebral dysfunction gradually improved. Disease remission was confirmed by the disappearance of any abnormal findings on electroencephalogram and magnetic resonance imaging. PCAE-CTL is reported to be an extremely aggressive disease with a poor prognosis, but the timely performance of cord blood transplantation is considered to be a promising treatment strategy.

Key words: primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma, cerebral infiltration, cord blood transplantation

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Introduction

Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma (PCAE-CTL) is a rare histopathological subtype of cutaneous T-cell lymphoma (CTCL), which was firstly reported in 1999 by Berti et al. (1), and it was given a provisional status in the WHO classification of lymphoma in 2008 (2), and recently has been described as a rare, but distinct subtype in the latest WHO classification (3). Some case series have been reported which describe the clinicopathological features of PCAE-CTL; epidermotropic infiltration of CD8-positive cytotoxic T-cells in cutaneous tissue, rapid progression, and systemic dissemination including visceral organs and central

nervous system (CNS) (4, 5). PCAE-CTL has been reported to be refractory to conventional chemotherapy and its prognosis is extremely poor. Allogeneic hematopoietic stem cell transplantation (alloHCT) is considered to be a curative option for this aggressive disease; only some cases have been reported to survive without disease after undergoing alloHCT.

We herein describe a successful clinical course of PCAE-CTL with CNS infiltration which was achieved by cord blood transplantation (CBT). To our knowledge, this is a first case report of PCAE-CTL for which CBT was successfully performed.

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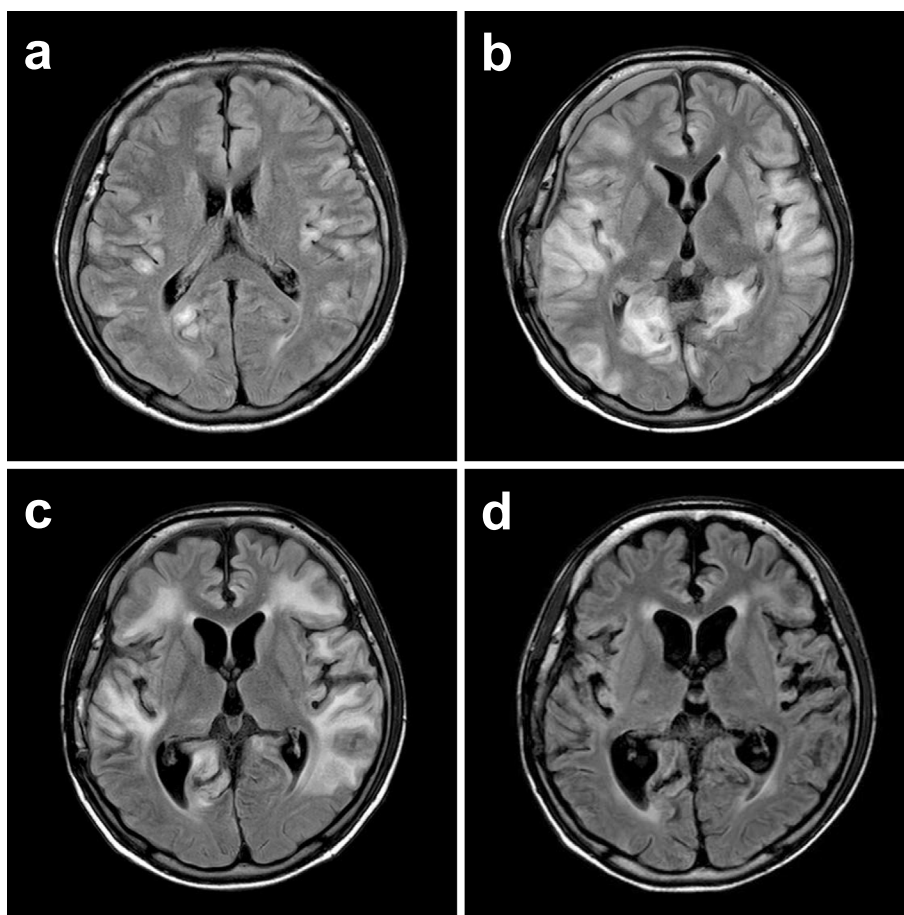


Figure 1. MRI after transplantation. Fluid attenuated inversion recovery images taken at the onset of CNS symptoms (day -69) (a), before transplantation (day -18) (b), at the onset of HHV-6 encephalitis (day 64) (c), and just before discharge from hospital (day 126) (d).

Case Report

A 16-year-old boy with facial edema was initially speculated to have an autoimmune disease, and he was transferred to our department in early February 2016. At this time, he was in good general condition without fever or systemic symptoms. Laboratory findings revealed an elevation of transaminase (aspartate transaminase, 130 IU/L; alanine transaminase, 83 IU/L) and lactate dehydrogenase (578 IU/L). Myogenic enzymes were also elevated [creatinine phosphokinase (CPK), 956 IU/L; aldolase, 31.7 IU/L]. There were no abnormalities in a complete blood test, coagulatory function, or renal function. Computed tomography (CT) revealed no pulmonary lesions or hepatosplenomegaly. He gradually developed muscle pain and weakness during the 3-week period after admission, and the administration of corticosteroid was started. His symptoms, however, did not improve within 2 weeks, and tacrolimus was also administered. In mid-March, mild induration was observed on his nasolabial sulcus and forehead, for which a skin biopsy was performed. He also suffered headache and fever around this time, and magnetic resonance imaging (MRI) revealed multiple abnormal signals in the cerebral cortex (Fig. 1). Posi-

tron emission tomography detected no other lymphoma lesions. Cerebrospinal fluid (CSF) revealed no apparent abnormal cell infiltration, and no bacterial or fungal infection. The administration of dexamethasone and acyclovir resulted in a temporary partial remission of symptoms; however, his consciousness level rapidly deteriorated after 1 week, and a higher brain dysfunction emerged. At this time, the pathology of the previously performed skin biopsy revealed hyperplasia of atypical lymphoid cells in the dermis, subcutaneous tissue, and epidermis (Fig. 2). These cells were immunohistochemically CD2⁺, CD3⁺, CD4⁺, CD8⁺, CD5⁺, CD7⁺, CD30⁺, CD56⁺, TIA-1⁺, and Granzyme B⁺ (Fig. 2). Epstein-Barr virus-encoded RNA (EBER) was judged to be negative by *in situ* hybridization. The Ki-67 index was around 70%. Clonal rearrangement of T-cell receptor genes was detected. A diagnosis of PCAE-CTL was confirmed based on the above findings. Brain biopsy was also performed and apparent infiltration of abnormal lymphocytes within the cerebral cortex was detected. The immunohistochemical findings were the same as those for the skin lesion. Therefore, he was finally diagnosed to have PCAE-CTL with cerebral infiltration.

Soon after performing brain biopsy, we administered high-dose methotrexate (MTX, 3.0 g/m²); however, his con-

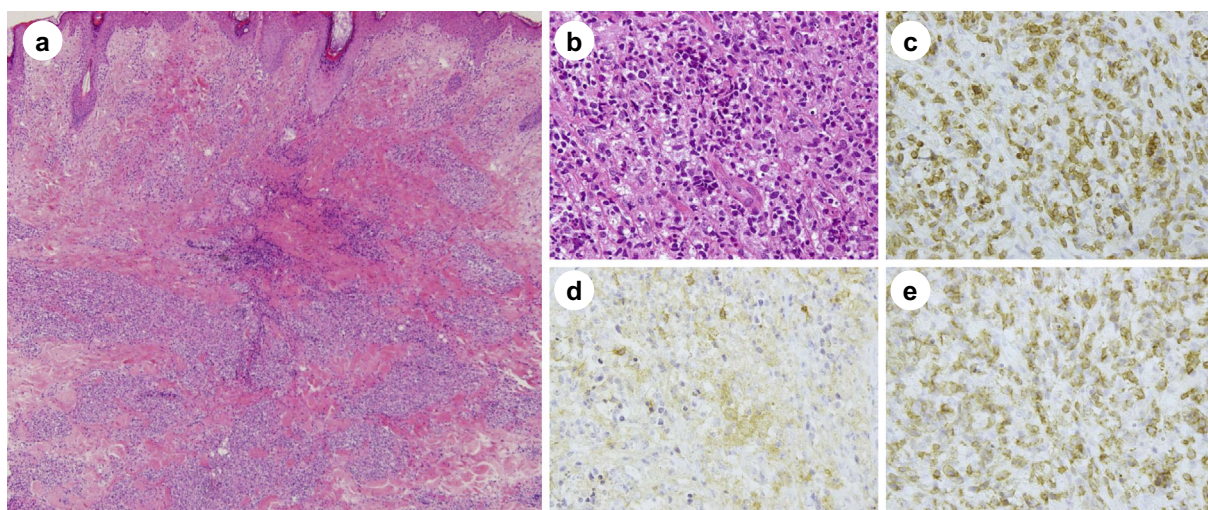


Figure 2. Histopathological findings of the epidermis. (a, b) Hematoxylin and Eosin staining, indicating. (c-e) Immunohistochemical staining for CD3 (c), CD4 (d), and CD8 (e).

consciousness level and fever did not improve within a few days. Moreover, thrombocytopenia and leukocytopenia progressed and a bone marrow examination revealed hemophagocytosis (with no evidence of lymphoma infiltration). The therapeutic strategies for both cerebral and systemic lesions were urgently required to save his life. Therefore, we initiated whole-brain irradiation (WBI; 30 Gy/15 fr), with the simultaneous administration of relatively intensive chemotherapy (EPOCH regimen; etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin), considering the aggressiveness of tumor. After the initiation of therapy, his disturbed consciousness level gradually improved. Higher brain dysfunction, however, did not change, which was also reflected in a severe abnormality on an electroencephalogram (EEG). Bicytopenia improved after the period of bone marrow suppression. Mild skin induration also disappeared. We then performed cord blood transplantation (CBT) as there were no human leukocyte antigen (HLA)-matched sibling donors.

After a conditioning regimen consisting of total-body irradiation (TBI; 12 Gy/6 fr), high-dose cyclophosphamide (60 mg/kg/day, for 2 days), and high-dose cytarabine (2 g/m², every 12 hours, for 2 days), the infusion of 1.5×10⁵/kg of CD34⁺ cells was performed in late May. HLA antigen and transplanted cord blood alleles were mismatched at three of eight loci. Tacrolimus and short-term MTX were used as prophylaxis for graft-versus-host disease (GVHD). As the risk of encephalopathy associated with human herpes virus-6 (HHV-6) was considered to be high, we prophylactically administered foscarnet (80 mg/kg/day) from day 5 until an increase in neutrophils was observed (day 21). Febrile neutropenia was established on day 10, which was well controlled with antibiotic therapy. Neutrophil, reticulocyte, and platelet engraftment were confirmed on day 30, day 27, and day 39, respectively. Fever and mild systemic eruption developed on day 30. We initially thought that this had been caused by an immunological reaction around neutrophil engraftment, and

administered 2 mg/kg/day of methylprednisolone from day 31. On day 33, somnolence and seizure developed, and brain MRI showed abnormal signals in the bilateral limbic areas. At this time, we considered the patient to have HHV-6 encephalopathy, and resumed the administration of foscarnet (180 mg/kg/day). The diagnosis was later established by the detection of HHV-6 DNA in CSF. HHV-6 DNA was not detected in the peripheral blood. His consciousness level improved within a few days, and the administration of foscarnet was continued for 1 month. There were no apparent signs of acute GVHD, and tacrolimus was tapered gradually from around day 60. After CBT, his higher brain dysfunction showed apparent improvement, and the normalization of EEG was established on day 70. On MRI, cerebral lesions that were enhanced by gadolinium continued to decrease and later became undetectable (Fig. 1). He continued to recover successfully, and was discharged to home on day 136, and the patient is currently doing well without any disease relapse or additional difficulties for more than a year.

Discussion

PCAE-CTL is an extremely rare subtype of cutaneous lymphoma which is considered to be derived from CD8-positive cytotoxic T-cells. Since Berti et al. reported the first case in 1999 (1), less than 100 cases of PCAE-CTL have been reported in the literature. An overview of the clinicopathological features of PCAE-CTL has been described as follows; i) the relatively short history of widespread, often hemorrhagic plaques and extensive tumors, ii) epidermotropism is often prominent, particularly in the basal cell layer, iii) the presence of dermal infiltrate that consists of variably sized atypical lymphocytes with a CD8⁺/CD4⁻/EBV⁻/CD56⁻ immunophenotype, iv) common metastatic spread towards lung, testis, and CNS, v) an aggressive and dismal clinical course with refractoriness for therapy (4, 5). Although the cutaneous lesions observed in this case were rather scant

Table. Recent Reports about Allogeneic Hematopoietic Stem Cell Transplantation for PCAE-CTL.

Reference	Age/ Sex	Clinical presentations	Non-cutaneous lesions	Pathological findings	Therapy before transplant	Remission before transplant	Conditioning regimen	Donor source	Complications	Outcome
(8)	48/M	Ulcerated plaques and erythematous patches	None	CD3+ CD4- CD8+ GranzymeB+ TCR β (+) (rearrangement+)	Gemcitabine CHOP	No	TBI/CY/ATG	Matched unrelated	aGVHD (skin, gut; not severe)	Alive w/o disease (36mth)
(11)	38/M	Painful ulcerative plaques and tumors	None	CD2- CD4- CD8+ MIB-1++	PUVA, IFN- α , radiation Gem	Not mentioned	Flu/Mel Alemtuzumab	Not mentioned	Not mentioned	Died of disease
(7)	44/F	Fever Infiltrative painful plaques	None	CD2- CD3+ CD4- CD7+ CD8+ CD30- CD56- TCRy rearrangement+	CHOP CVP	No	TBI/CY	Matched unrelated	aGVHD (skin; severe)	Alive w/o disease (17mth)
(9, 10)	6/F	Disseminated skin lesions Lymph node swelling	Lymph nodes	CD3+ CD4- CD5+ CD8+ ALK- CD30- CD56- TIA1+ GranzymeB+	CHOP Neralabine L-asp, AraC, etc.	No	TBI/VP/Mel	Matched unrelated	Not mentioned	Died of disease (12mth)
This case	16/M	Myalgia Lid edema Subcutaneous induration Decline of consciousness level Seizure	Brain	CD2+ CD3+ CD4- CD5- CD7+ CD8+ CD30- CD56- TIA1+ GranzymeB+ EBER-ISH-	HD-MTX EPOCH Radiation	Not evaluable	TBI/CA/CY	Cord blood	HHV-6 encephalitis	Alive w/o disease (9mth)

aGVHD: acute graft versus host disease, ATG: anti-thymocyte globulin, CA: cytarabine, CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisolone, CVP: cyclophosphamide, vincristine, and prednisone, CY: cyclophosphamide, F: female, Flu: fludarabine, L-asp: L-asparaginase, M: male, Mel: melphalan, VP: etoposide, w/o: without

and indolent compared with those described in previous reports, it is also reported that the presentation of skin lesions in PCAE-CTL has a large diversity and its diagnosis should be done in association with the clinical and histopathological findings. The clinicopathological features in the present case were considered to be consistent with PCAE-CTL among cutaneous T-cell lymphoma; epidermotropic infiltration of cytotoxic CD8-positive T-cells with higher proliferation index, negativity for EBER, and clinically aggressive disease with a rapid deterioration of CNS lesions.

PCAE-CTL is reported to have an extremely poor prognosis. Especially, CNS infiltration is a fatal condition associated with PCAE-CTL. In the reported cases with CNS lesions, no one had survived. In this case, lymphoma lesions including CNS was considered to be sensitive to chemotherapy and radiation before transplantation; and successive CBT was thus performed. Higher brain dysfunction thereafter gradually improved after transplantation, and disease remission was confirmed by a normalization of the electroencephalograms and the disappearance of an abnormal signal area on MRI (Fig. 1). At least partially, this could be explained by the graft-versus-lymphoma effect. Brain atrophy was considered to have been caused by lymphoma infiltration as well as HHV-6 encephalitis. In addition, radiation (TBI and WBI) and high-dose MTX also might also have been partially related to cerebral damage.

Nofal et al. summarized the reported cases of PCAE-CTL, in which they refer to the clinical course and therapeutic intervention (4). Among the documented 45 cases of PCAE-CTL, only 5 patients had been reported to be alive without disease (4). Median survival is reported to be 12-32 months (1, 5, 6). Various therapeutic strategies have reportedly been tried, however, none of them is considered to be a standard therapy. The only curative method is considered to be alloHCT. There have been several reports describing cases of PCAE-TCL for which alloHCT was performed (Table). In two cases that only the skin lesions before transplantation and received myeloablative conditioning regimen including total body irradiation, both have been reported to be alive without disease for a long period of time (7, 8). They all received transplantation from matched unrelated donor, which could mean that they could have had sufficient time to coordinate the donor without disease progression. The case that had lymph node lesions is reported to have died of the disease (9, 10). In the present case, we considered that there was less time for donor coordination and performed CBT as soon as a certain disease control had been obtained with chemotherapy and whole brain irradiation. This resulted in sustainable disease remission without any additional therapy. These findings suggest that the timely performance of alloHCT from an available donor source at the time with myeloablative conditioning can be a critical point for saving the life of the cases who suffer from PCAE-CTL with organ infiltration. To our knowledge, this is a first case of PCAE-CTL in the literature for which CBT was successfully performed.

In summary, we herein reported a case of PCAE-CTL with CNS infiltration which was well-controlled by myeloablative conditioning and CBT. The timely performance of alloHCT from an available donor source, including cord blood with myeloablative conditioning, as soon as disease control is obtained, may thus be a promising treatment strategy for this extremely aggressive disease.

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

References

- Berti E, Tomasini D, Vermeer MH, Meijer CJ, Alessi E, Willemze R. Primary cutaneous CD8-positive epidermotropic cytotoxic T cell lymphomas. A distinct clinicopathological entity with an aggressive clinical behavior. *Am J Pathol* **155**: 483-492, 1999.
- Swerdlow SH, Jaffe ES; International Agency for Research on Cancer. World Health Organization. In: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. International Agency for Research on Cancer, Lyon, 2008: 439.
- Swerdlow SH, Campo E, Harris NL, et al. WHO classification of Tumors of Haematopoietic and Lymphoid Tissues. 4th ed. International Agency of Research on Cancer, Lyon, 2017.
- Nofal A, Abdel-Mawla MY, Assaf M, Salah E. Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma: proposed diagnostic criteria and therapeutic evaluation. *J Am Acad Dermatol* **67**: 748-759, 2012.
- Robson A, Assaf C, Bagot M, et al. Aggressive epidermotropic cutaneous CD8+ lymphoma: a cutaneous lymphoma with distinct clinical and pathological features. Report of an EORTC Cutaneous Lymphoma Task Force Workshop. *Histopathology* **67**: 425-441, 2015.
- Santucci M, Pimpinelli N, Massi D, et al. Cytotoxic/natural killer cell cutaneous lymphomas. Report of EORTC Cutaneous Lymphoma Task Force Workshop. *Cancer* **97**: 610-627, 2003.
- Liu V, Cutler CS, Young AZ. Case records of the Massachusetts General Hospital. Case 38-2007. A 44-year-old woman with generalized, painful, ulcerated skin lesions. *N Engl J of Med* **357**: 2496-2505, 2007.
- Wehkamp U, Glaeser D, Oschlies I, Hilgendorf I, Klapper W, Weichenthal M. Successful stem cell transplantation in a patient with primary cutaneous aggressive cytotoxic epidermotropic CD8+ T-cell lymphoma. *Br J Dermatol* **173**: 869-871, 2015.
- Kikuchi Y, Kashii Y, Gunji Y, et al. Six-year-old girl with primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma. *Pediatr Int* **53**: 393-396, 2011.
- Kato K, Oh Y, Takita J, et al. Molecular genetic and cytogenetic analysis of a primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma. *Int J Hematol* **103**: 196-201, 2016.
- Wang Y, Li T, Tu P, Wu LS, Zhu XJ. Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma clinically simulating pyoderma gangrenosum. *Clin Exp Dermatol* **34**: e261-e262, 2009.

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