

## SHORT COMMUNICATION

Primary Cutaneous CD4/CD8<sup>-/-</sup> TCRαβ T-cell LymphomaNoriki Fujimoto<sup>1</sup>, Katsuyuki Kito<sup>2</sup>, Takashi Yoshida<sup>3</sup> and Toshihiro Tanaka<sup>1</sup>*Departments of <sup>1</sup>Dermatology, <sup>2</sup>Hematology, and <sup>3</sup>Clinical Laboratory Medicine, Shiga University of Medical Science, Setatsukinowa, Otsu, Shiga 520-2192, Japan. E-mail: noriki@belle.shiga-med.ac.jp**Accepted Apr 24, 2014; Epub ahead of print Apr 25, 2014*

The CD4/CD8<sup>-/-</sup> phenotype has been reported to be associated with poor prognosis in cutaneous T-cell lymphoma (1). The majority of cases of cutaneous CD4/CD8<sup>-/-</sup> T-cell lymphoma are T-cell receptor (TCR) γδ type, which is classified as primary cutaneous γδ T-cell lymphoma in the latest WHO/EORTC classification (2). Cutaneous TCRαβ T-cell lymphoma with CD4/CD8<sup>-/-</sup> phenotype is rare, and its origin has not been widely researched (3–5). We present here a case of cutaneous TCRαβ T-cell lymphoma with CD4/CD8<sup>-/-</sup> phenotype with a unique clinical presentation, massive epidermotropism, and aggressive clinical course. We speculate that the origin of the neoplastic cells in this case is the recently recognized T-cell subset “CD4/CD8<sup>-/-</sup> TCRαβ T cells”, also referred to as double negative T cells (DNTs) (6).

## CASE REPORT

A 58-year-old Japanese woman noticed an asymptomatic nodule on her head approximately 3 months prior to her initial visit to our hospital. The nodule rapidly enlarged and erythematous lesions appeared on her trunk. She had no history of autoimmune disease, malignancy including lymphoproliferative disorders, or immunosuppressive treatment. She presented with a solitary tumour measuring 7×6 cm with central necrosis on the occipital region (Fig. 1A) and several indurated erythematous patches on her chest and back. Only the cervical lymph nodes were palpable. Atypical lymphocytes were not detected in the peripheral blood, and there were no abnormal findings on laboratory examination, including lactate dehydrogenase (189 U/l) and soluble interleukin-2 receptor (396 U/ml). Anti-HTLV-1 antibodies were not detected. Computed tomography (CT) imaging of the whole body showed normal findings despite cervical lymphadenopathy. Fluorine-18-fluorodeoxyglucose positron emission tomography (FDG PET)/CT and gallium scan of the whole body showed abnormal uptake only on the scalp. Histopathological examination of biopsy specimens from the tumour revealed perifollicular predominant infiltration of small to intermediate-sized lymphocytes with cellular pleomorphism showing epidermotropism and folliculotropism (Fig. 1B, C). Immunohistochemical study demonstrated that the neoplastic cells expressed CD3 (Fig. 1D), TIA-1, and granzyme B, but not CD4, CD8 (Fig. 1E), CD16, CD20, CD30, CD56, Foxp3 and PD-1. *In situ* hybridization for Epstein-Barr virus encoded RNA was negative. Clonal rearrangement of TCR-β and TCR-γ chain using Southern blot analysis was detected. Biopsy specimens from cervical lymph nodes and bone marrow showed no tumour cells. Flow cytometric analysis of tumour-infiltrating cells revealed that all CD3<sup>+</sup> lymphocytes expressed TCR-β not TCR-γ chain, and approximately one-third of CD3<sup>+</sup> lymphocytes expressed neither CD4 (Fig. 1F) nor CD8 (Fig. 1G).

The tumour on the patient's head disappeared after 3 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy regimen; however, the erythematous patches

increased and bullae and ulcers appeared within the erythema. Histopathological examination of biopsy specimens from the erythema revealed superficial mild perivascular infiltration of lymphocytes, subepidermal blister, epidermotropic infiltration of lymphocytes, and marked dyskeratotic cells (Fig. 1I). Most of the epidermotropic cells expressed CD3, but not CD4 and CD8. Direct immunofluorescence microscopy revealed no deposits of globulin and complement on the basement membrane zone. Although 4 cycles of DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin) chemotherapy regimen, 1 cycle of cytarabine and carboplatin chemotherapy, and total skin electron beam were also performed, there was only a transient response. Widespread erythema with superficial necrosis and ulceration appeared over the patient's entire body surface during the interval between sessions of chemotherapy (Fig. 1H), and the disease aggravated without complete remission. The patient died approximately 14 months after her initial visit, but no autopsy was performed.

## DISCUSSION

We used flow cytometry to evaluate the expression of the surface molecules CD4 and CD8. Since 2 distinct positive and negative groups regarding CD4 and CD8 expression were observed among CD3<sup>+</sup> cells shown in Fig. 1F and G, this clearly confirmed the distinct CD4/CD8<sup>-/-</sup> populations bearing TCRαβ in our case.

Initial presentation corresponded to mycosis fungoides (MF), but the term MF can be used only for the classical cases characterized by evolution of patches, plaques and tumours according to the WHO/EORTC classification (2). The characteristics of our case included unique clinical features that began with a solitary tumour and then became widespread necrotic erythema with histopathological findings of severe cytotoxic epidermotropic CD4/CD8<sup>-/-</sup> T cells with TCRαβ expression, and aggressive clinical course. Cutaneous T-cell lymphoma with a CD4/CD8<sup>-/-</sup> phenotype has been known to present with an aggressive clinical course, including heterogeneous subtypes, and most cases expressed TCRγδ (1). Most of these cases are now classified as primary cutaneous γδ T-cell lymphoma (2). However, CD4/CD8<sup>-/-</sup> MF has been reported to have an indolent course, part of which expresses PD-1 (7). In our case, both clinical presentation and histopathological findings were similar to primary cutaneous CD8<sup>+</sup> aggressive epidermotropic T-cell lymphoma. Since it has been postulated that the expression of CD8 is necessary in order to diagnose primary cutaneous CD8<sup>+</sup> aggressive epidermotropic T-cell lymphoma (8), and TCRγδ expression was not observed in our case, we diagnosed our patient with cutaneous peripheral T-cell

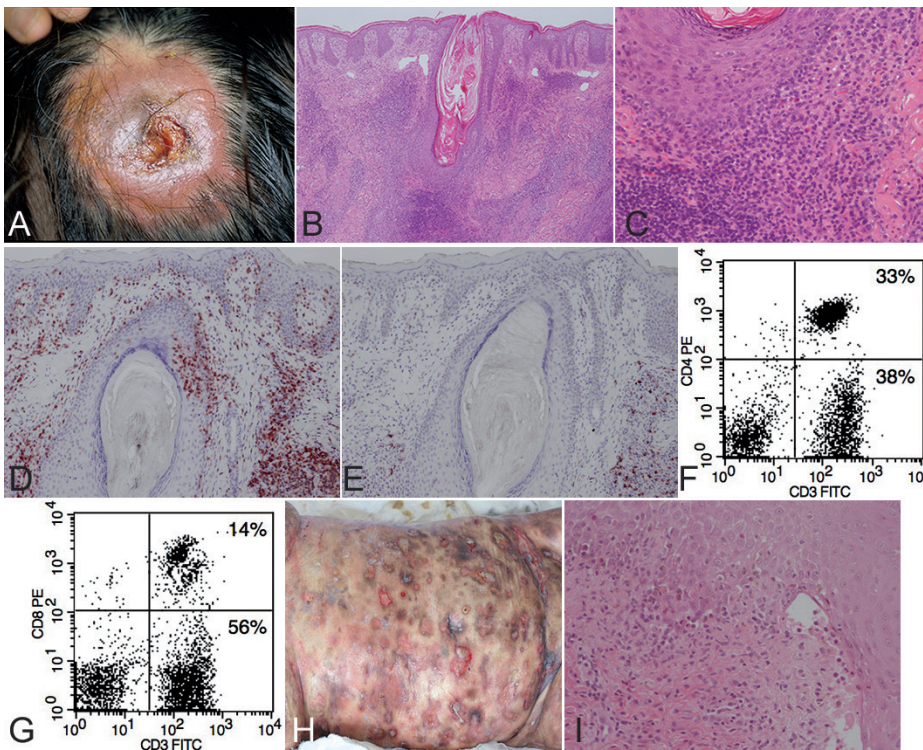


Fig. 1. (A) Clinical presentation at initial visit. A solitary tumour was observed on the occipital region. (B) Histopathological findings in a biopsy specimen from the tumour. Perfollicular predominant infiltration showing epidermotropism and folliculotropism (haematoxylin & eosin staining (H&E), original magnification  $\times 40$ ). (C) Infiltrating cells were small to intermediate-sized lymphocytes (H&E, original magnification  $\times 200$ ). (D) CD3 staining (original magnification  $\times 100$ ). (E) CD8 staining (original magnification,  $\times 100$ ). (F–G) Flow cytometry of tumour-infiltrating lymphocytes. Approximately one-third of CD3<sup>+</sup> lymphocytes neither expressed (F) CD4 (G) nor CD8. (H) Clinical presentation of the patient's trunk during the interval between sessions of chemotherapy. Widespread erythema with superficial necrosis and ulceration over the entire body surface. (I) Histopathological findings in a biopsy specimen from the erythema after 3 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy regimen (H&E, original magnification  $\times 200$ ).

lymphoma, not otherwise specified (2). Akkaria et al. (9) reported a case with similar clinical and histopathological findings to that of epidermotropic CD4/CD8<sup>-</sup> cytotoxic T-cell lymphoma, which had an indolent clinical course and which they speculated to be a variant of primary cutaneous CD8<sup>+</sup> aggressive epidermotropic T-cell lymphoma. Our case had a different clinical presentation, also in that the early lesion presented as a large solitary tumour, in contrast to the widely distributed eruption of primary cutaneous CD8<sup>+</sup> aggressive epidermotropic T-cell lymphoma (8). Therefore, our case seems to belong to an entity distinct from primary cutaneous CD8<sup>+</sup> aggressive epidermotropic T-cell lymphoma. There is one reported case of cutaneous TCR $\alpha\beta$  T cell lymphoma with CD4/CD8<sup>-</sup> phenotype that showed a localised nodule in the early phase and widespread lesions in the progressive phase (1). The same case also had an aggressive clinical course; however, details of the histopathology and clinical presentation were not available. We speculate that these 2 cases are both derived from DNTs. Based on these findings, we postulate diagnosing our case as primary cutaneous CD4/CD8<sup>-</sup> TCR $\alpha\beta$  T-cell lymphoma.

DNTs are a recently recognised subset of T cells with immunosuppressive function, which comprise 1% of peripheral T cells in humans (10). These cells express high levels of perforin and exert cytotoxic activity (6). This is the first reported case of neoplasm derived from DNTs. Loss of suppressive function of DNTs may partially explain the formation of widespread necrotic cutaneous lesions, similar to graft-versus-host diseases, as in our case. To date, CD8 expression is the only known difference between DNTs and cytotoxic CD8 T cells.

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