Primary Cutaneous CD8+ Aggressive Epidermotropic Cytotoxic T-cell Lymphoma in a Human T-cell Leukaemia Virus Type-1 Carrier

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Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma is rare, accounting for less than 1% of all cutaneous T-cell lymphoma (CTCL) (1). We report here a case of this type of lymphoma in a human T-cell leukaemia virus type-1 (HTLV-1) carrier.

CASE REPORT

A 58-year-old Japanese woman visited our hospital in 2006. She first noticed a red plaque on her left thigh approximately ten years previously. The number and the size of the plaques gradually increased despite treatment with topical steroid. At the initial visit, dermatological examination revealed irregularly shaped elevated erythematous plaques and ulcers with pus and crusts on her right breast (Fig. 1a). She also had multiple infiltrated red plaques with scales and crusts on her trunk and thigh (Fig. 1b). No superficial lymph nodes were swollen. Her general condition was good. She was from Kyushu, Japan, an area endemic for HTLV-1, and she was seropositive for the virus. The peripheral white cell count was normal without any atypical lymphocytes. Laboratory values were within normal limits except for a slightly increased level of serum soluble IL-2 receptor (965 U/ml, normal: 167–497 U/ml). Systemic examination revealed no visceral involvement. A skin biopsy specimen from the ulcer on the right chest showed diffuse infiltration of leukocytes in the dermis and subcutaneous tissues. In the upper and middle part of the dermis, there was dense infiltrate of neutrophils, histiocytes and lymphocytes. Approximately half of infiltrating cells were $CD3^+$. These T cells were mainly $CD4^+CD25^+$, and the rest were $CD8^+$. Many $CD8^+$ cells and some $CD4^+CD25^+$ cells infiltrated the lower dermis and adipose tissues. By Southern blotting analyses, neither rearranged bands for T-cell receptor beta chain nor clonal integration of HTLV-1 were detected using DNA from the skin lesion. Considering her skin manifestation characteristic for CTCL, seropositivity of HTLV-1, and infiltration of $CD4^+CD25^+$ cells in the skin, she was first diagnosed with smouldering type of adult T-cell leukaemia (ATL). Topical corticosteroid, psoralen plus ultraviolet A (PUVA) and oral retinoid were applied. These were partially effective, and the skin lesions disappeared 3 months after initiation of oral retinoid therapy except for the ulcers on the patient's right breast (Fig. 1c) and left thigh. She was subsequently treated with methotrexate instead of retinoid, but the

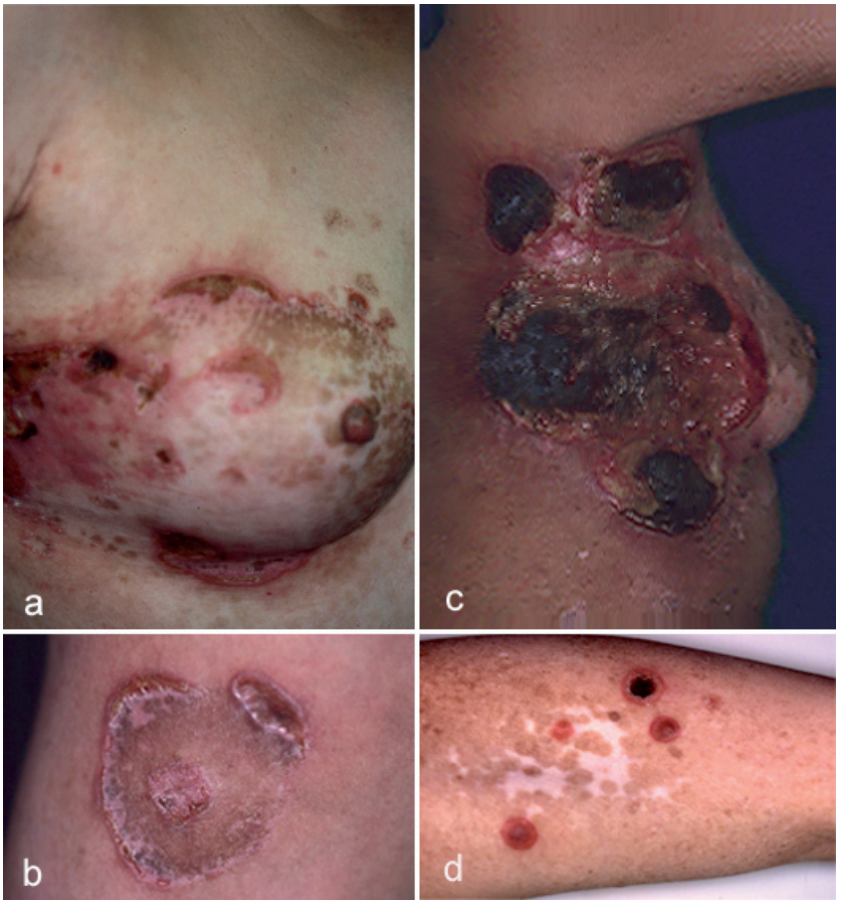

Fig. 1. (a) Multiple elevated erythematous plaques and ulcers with pus and crusts on the right chest. (b) A red plaque on the left thigh. (c) A deep ulcer in the right breast that appeared 8 months after the patient's first visit. (d) Multiple purple-red macules with central necrosis that appeared 14 months after her initial visit.

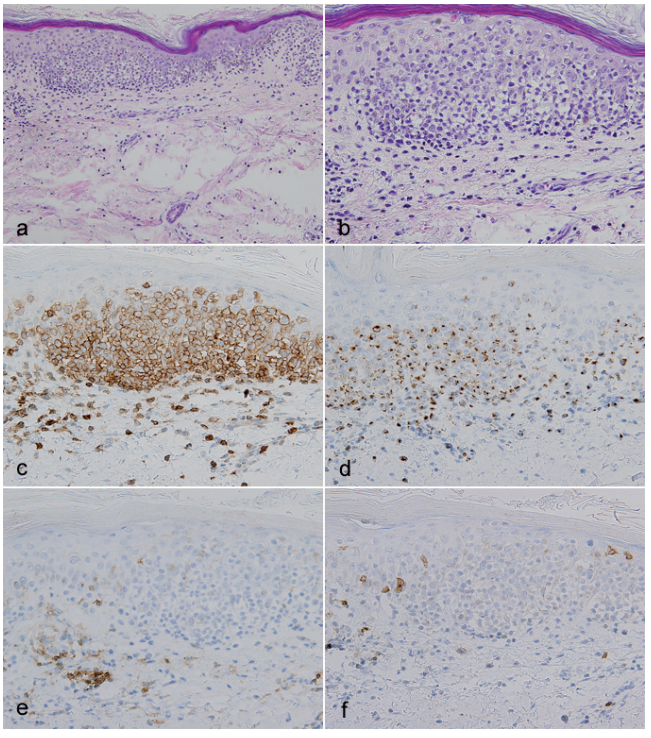

Fig. 2. Histology of the purple-red macule. Atypical lymphoid cells infiltrating in the epidermis, forming pagetoid clusters. Sparse perivascular lymphoid cell infiltration is also observed (a: ×200; b: ×400). Tumour cells are positive for CD8 (c) and granzyme B (d), but negative for CD4 (e) and CD25 (f) (×400).

ulcers remained. The ulcers responded well to radiation therapy. One month after the end of radiation therapy, however, she began to develop new macules (Fig. 1d). A biopsy specimen from the purple-red macule showed infiltration of atypical lymphocytes in the epidermis and upper dermis. Intraepidermal pagetoid spreading of atypical lymphocytes, with clear cytoplasm, and scattered necrotic keratinocytes were noted (Fig. 2a, b). Atypical cells were positive for CD3, CD7, CD8 (Fig. 2c) and granzyme B (Fig. 2d), but negative for CD4 (Fig. 2e), CD5, CD20, CD25 (Fig. 2f) and perforin. She was diagnosed with primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma based on typical clinical and pathological findings. Systemic examination revealed invasion to the pancreas and the thyroid gland. The patient refused multidrug chemotherapy. She was treated with oral corticosteroid only, and died at the age of 60 years, 16 months after her first visit. An autopsy revealed tumour cell infiltration into the heart, lung, pancreas, bone marrow, thyroid gland, abdominal para-aortic lymph nodes and peripancreatic lymph nodes. Tumour cells observed in these organs were positive for CD8, but negative for CD4 and CD25.

DISCUSSION

Primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma is characterized by a proliferation of $CD8^+$ cytotoxic T cells and has an aggressive clinical course with a median survival of 32 months (2). Clinically, this lymphoma is characterized by localized or disseminated eruptive papules and nodules showing central ulceration and necrosis, or hyperkeratotic patches and plaques. Prominent epidermotropism, forming pagetoid clusters of tumour cells, epidermal necrosis, and cell positivity for CD8 and cytotoxic molecules are pathological characteristics. Differentiation from other types of CTCL expressing a $CD8^+$ cytotoxic T-cell phenotype is based on clinical presentation and clinical behaviour. The patient showed variable eruptions during the course of the disease and an aggressive clinical behaviour consistent with the diagnosis. It was, however, not easy to reach a diagnosis because of seropositivity of HTLV-1 and mixed cell infiltration in the first biopsy specimen. This case emphasizes the importance of examining repeated biopsies from the skin lesions.

The pathogenesis of this lymphoma remains unknown. Specific genetic abnormalities and association with a specific virus, including HTLV-1, have not been described. In fact, this is the first report of a primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma in a HTLV-1 carrier. HTLV-1 is associated with various inflammatory diseases, such as HTLV-1 associated myelopathy/tropical spastic paraparesis (3) and HTLV-1 uveitis (4). HTLV-1 may not directly induce proliferation of tumour cells in our case because no HTLV-1 DNA was detected from the skin lesion, but an immunomodulatory effect of HTLV-1 might be involved in the pathogenesis. This case shows that an HTLV-1 carrier can develop CTCL other than ATL.

The authors declare no conflict of interest.

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