Adult T-cell Lymphoma Complicated with Epidermodysplasia Verruciformis-like Eruptions

Adult T-cell lymphoma (ATL) was first reported by Uchiyama *et al.* (1) as a distinct malignancy of mature T cells occurring primarily in patients born in southwestern Japan (2). Patients with epidermodysplasia verruciformis (EV) present in childhood with numerous thin, pink, flat papules and plaques that resemble verruca plana (3). EV is mainly caused by the human papilloma virus (HPV) types 5 and 8, but also by HPV types 9, 12, 14, 15, 17, 19, 25, 36, 38, 47, and 50 (3). Recently, EV-like eruptions have been observed in immunosuppressed patients, especially those with human immunodeficiency virus (HIV) (3), Merkel cell carcinoma (MCC) (4-6), and renal transplantation (7,8). Herein, we report a rare case of skin eruptions of ATL complicated with EV-like eruptions.

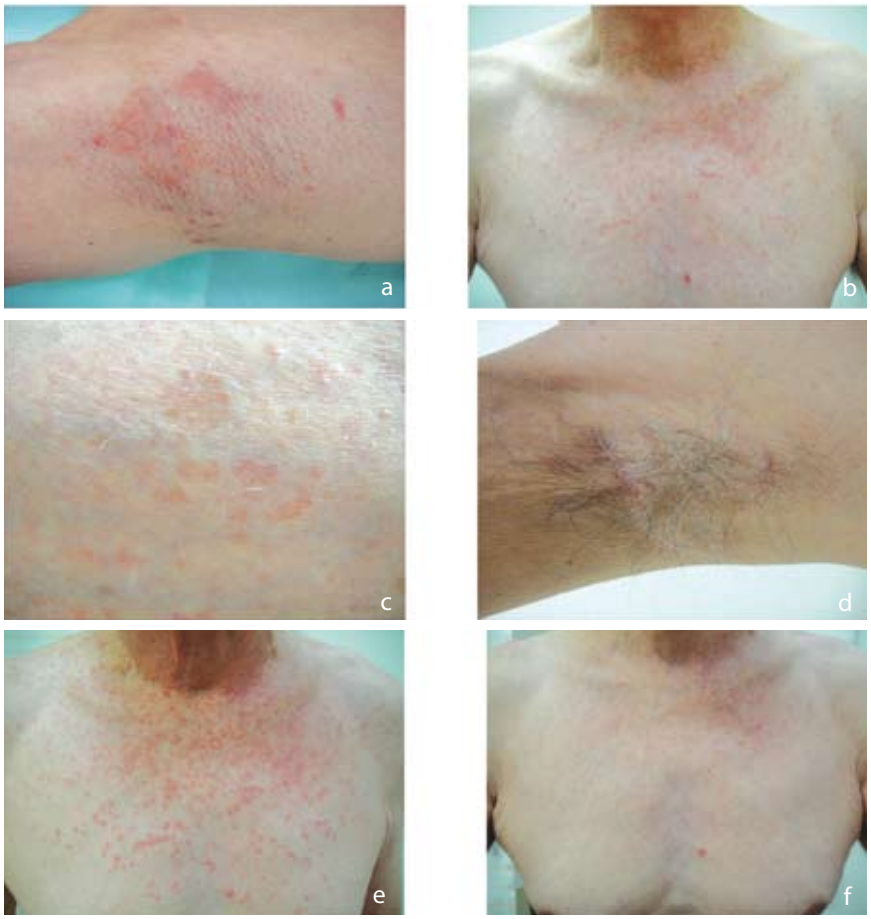

Figure 1. Clinical findings at first visit (a-c), after narrow-band ultraviolet B phototherapy (d), and at 8 months (e) and 1 year (f) after treatment with traditional Chinese medicine, yokuinin. (a) An erythema with dryness on the right axilla. (b) Pink colored, slightly raised, flat-surfaced, well-demarcated papules and plaques on the chest. (c) At a high magnification of (b). (d) Skin eruptions of ATL have disappeared. (e) The epidermodysplasia verruciformis-like eruptions increased. (f) The epidermodysplasia verruciformis-like eruptions disappeared spontaneously.

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A 76-year-old Japanese man visited our Department for diagnosis of eruptions that had been present on his right axilla for 6 weeks and on his neck, chest, upper back, and upper extremities for 10 years. At his first visit to our Department, an erythema with dryness on the right axilla (Figure 1, a) and pink colored, slightly raised, flat-surfaced, well-demarcated papules and plaques on the neck, chest, upper back, and upper extremities (Figure 1, b, c) were seen. He had no cervical, supraclavicular, axillary, or inguinal lymphadenopathy. Laboratory data were normal, including a complete blood count and tests for liver and kidney function. Slightly elevated serum lactic acid dehydrogenase (LDH) levels (250 U/L) were seen, but the level was less than 1.5× the upper limit of normal. Hypercalcemia was not seen. Abnormal peripheral blood lymphocytes were not detected. The serum anti-HIV antibody test was negative, but the anti-human T-lymphotropic virus type-I (HTLV-1) antibody level was over 256 times normal as determined using a particle agglutination test. The serum soluble interleukin-2 receptor levels were elevated (3120 U/mL). Positron emission tomography and computed tomography showed no nodal disease or systemic involvement. Skin biopsy of the erythematous lesion on the right axilla showed a dense superficial dermal infiltrate of hematoxylin-stained cells (Figure 2, a). At higher magnification, large convoluted lymphocytes predominated in the dermal infiltrate. Pautrier microabscesses and the presence of atypical lymphocytes within the epidermis were seen (Figure 2, b). Immunohistochemically, the convoluted lymphocytes were positive for CD3, CD4 (Figure 2, c), and CD5, and negative for CD20. Skin biopsy of the pink colored papule on the chest showed hyperkeratosis and acanthosis of the epidermis, and cytoplasmic vacuolization with eosinophilic inclusion bodies in the keratinocytes of the granular and upper spinous layers of the epidermis, and consistent with EV (Figure 2, d). T-cell receptor gene rearrangements were not observed, but monoclonal integration of human T-lymphotropic virus type 1 (HTLV-1) proviral DNA of the erythematous

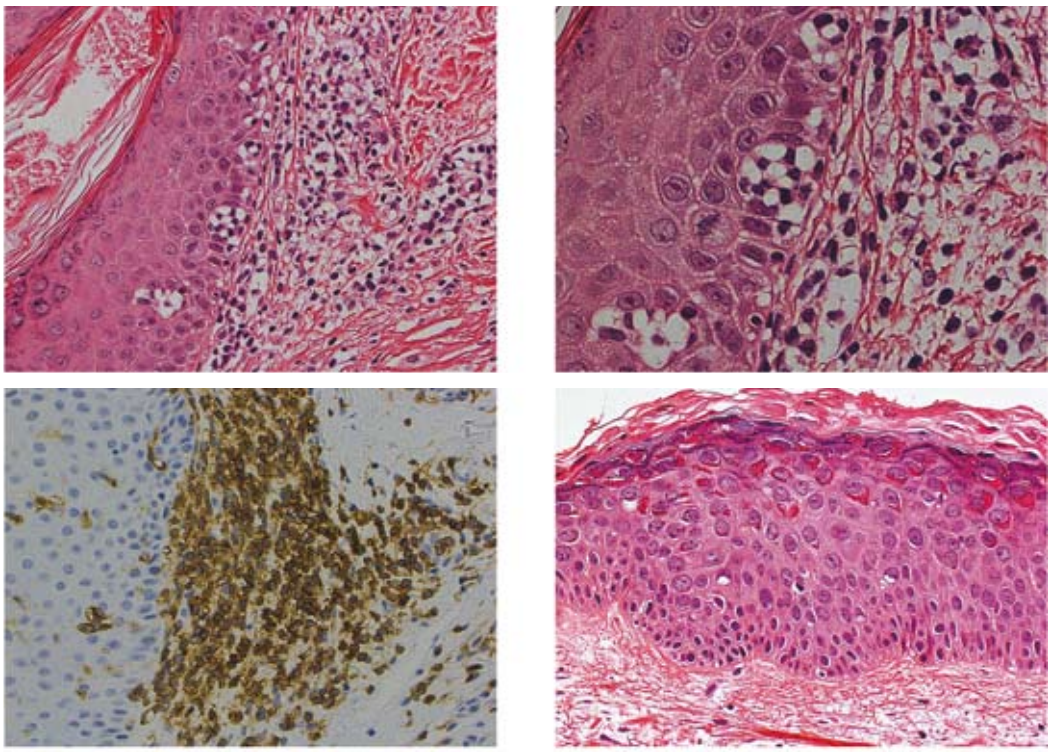

Figure 2. Histopathologic findings for the erythematous lesion on the right axilla (a-c) and the pink colored papule on the chest (d). (a) A dense superficial dermal infiltrate of hematoxylin-stained cells (hematoxylin-eosin (H&E), original magnification ×200). (b) At higher magnification, large convoluted lymphocytes predominated in the dermal infiltrate. Pautrier microabscesses and the presence of atypical lymphocytes within the epidermis were seen (H&E, original magnification ×400). (c) Immunohistochemically, the convoluted lymphocytes were positive for CD4 (original magnification ×200). (d) The eruption showed hyperkeratosis and acanthosis of the epidermis, and cytoplasmic vacuolization with eosinophilic inclusion bodies in the keratinocytes of the granular and upper spinous layers of the epidermis, which was consistent with epidermodysplasia verruciformis (H&E, original magnification ×200).

lesion on the right axilla was confirmed. However, the identification of HTLV-1 sequences in tumor DNA could not be performed because of ethical concerns. We established a diagnosis of smoldering-type ATL (9) with a patch type skin lesion (2) complicated with EV-like eruptions. Narrowband ultraviolet B phototherapy with a total dose of 10.6 J/cm^2 (initial dose 0.2 J/cm^2, maximum dose 0.95 J/cm^2) was performed to treat the lesions on the right axilla, and complete clinical remission of the lesion was obtained (Figure 1, d). The EV-like eruptions were treated orally with traditional Chinese medicine, yokuinin, for 3 months, but the treatment was ineffective, and they gradually increased (Figure 1, e). However, the eruptions disappeared spontaneously in 1 year (Figure 1, f). The patient has shown no evidence of recurrence of skin eruptions of ATL or EV-like eruptions for over 1 year and 4 months, respectively.

In the present case, HPV DNA testing for EV-like eruptions was not performed. However, based on the clinical and histopathological findings, we concluded that the eruptions were EV-like eruptions. To the best of our knowledge, this report and that of Kawai *et al.* (10) are the only two descriptions of ATL complicated with EV-like eruptions in the English language literature. In Kawai *et al.* (10), a 56-year-old patient suffering from squamous cell carcinoma of the maxillary gingiva had a 5-year history of disseminated hypopigmented macules on the chest, neck, and extremities. The patient had been diagnosed with chronic-type ATL at the age of 52 years. In this report and that of Kawai *et al.* (10), the EV-like eruptions appeared before the diagnostic confirmation of ATL. A strong association between the risk of viral infection and increased immune suppression has been suggested (11). MCC is a rare and aggressive skin cancer that primarily occurs in the elderly and immunocompromised patients (4). MCC has been linked to the newly discovered polyomavirus named Merkel cell polyomavirus (MCV) (4). Patients with EV are thought to be incapable of recognizing and targeting certain HPV-infected keratinocytes and it is possible that they also have problems clearing MCV, leading to persistent infection and ultimately malignancy (5). Oliveira *et al.* (6) suggested that the co-occurrence of pathogenic EV-HPV and MCV infections might reflect similar host-genetic susceptibility factors. Cases of acquired EV in kidney transplanted patients treated with immunosuppressive medications have also been reported (7,8).

In the present case, the patient was born in southwestern Japan, an HTLV-1-endemic area, and he grew up without being aware of the HTLV-1 infection. However, the widespread presence of EV-like eruptions for 10 years may have reflected the immunocompromised state of the patient by HTLV-1 infection. The spontaneous regression of EV-like eruptions might have been caused by transient enhancement of T cell-mediated immune responses to HPV during the clinical course of the disease. Positive results for HTLV-I antibodies and monoclonal integration of HTLV-1 proviral DNA directly contributed to the diagnosis of ATL. However, the finding of EV-like eruptions on the first physical examination provided us with an important clue to the existence of diseases associated with immunosuppression.

We reported a rare case of ATL, complicated with EV-like eruptions. This case illustrates the importance of medical practitioners paying attention to EV-like eruptions that may be clues to the existence of diseases associated with immunosuppression, including ATL.

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