

CLINICAL REPORT

Leukaemic Cutaneous T-cell Lymphoma Manifesting Papuloerythroderma with CD3⁻ CD4⁺ Phenotype

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The leukaemic form of cutaneous T-cell lymphoma, as represented by Sézary syndrome, exhibits erythroderma. We describe here an indolent leukaemic patient with cutaneous T-cell lymphoma, who initially had a nodulotumorous eruption with a crop of solid papules, but finally presented with papuloerythroderma. Histologically, the skin lesions showed non-epidermotropic dermal infiltration of atypical lymphocytes with lymphoid follicles and a granulomatous change. The circulating malignant CD4⁺CCR4⁺ T cells lacked the expression of T-cell receptor and did not respond to concanavalin A. The unresponsiveness of T cells to the T-cell mitogen may be associated with the non-epidermotropic behaviour of the tumour cells and the initially non-erythrodermic eruption. **Key words:** cutaneous T-cell lymphoma; papuloerythroderma; phenotype.

(Accepted September 24, 2009.)

Acta Derm Venereol 2010; 90: 68–72.

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Cutaneous T-cell lymphoma (CTCL) is a peripheral T-cell malignancy, which firstly involves the skin, then gradually the lymph nodes or other organs as the disease progresses (1). Sézary syndrome is the typical

leukaemic variant of CTCL, presenting as erythroderma and lymphadenopathy (1). However, atypical cases of leukaemic CTCL exhibiting skin eruptions other than erythroderma have been reported in relation to the aberrant surface phenotype (2). The tumour cells of CTCL usually have a CD3⁺CD4⁺ mature helper T-cell phenotype and express functional T-cell receptor (TCR). In addition, CD4⁺ Sézary cells highly express cutaneous leukocytes antigen (CLA) and chemokine receptors CCR4, CCR7, and CCR10 (3). TCR and CD3 complex interacts with antigen/major histocompatibility complex on antigen-presenting cells, inducing T-cell proliferation and cytokine production via activated T-cell signalling pathways. Therefore, an abnormality in the expression of CD3/TCR complex may lead to unresponsiveness of tumour cells to external antigenic stimuli and unique skin eruptions. We report here an unusual case of CTCL with chronic leukaemia of T cells lacking the expression of CD3/TCR complex and exhibiting a papuloerythrodermatous eruption.

CASE REPORT

In July 2004, a 74-year-old Japanese man was referred to us for evaluation of a one-year history of topical corticosteroid-resistant, pruritic eruption on his trunk. On examination, there were coalesced nodules or tumours on his lower chest (Fig. 1a) and scattered red papules on the trunk and extremities (Fig. 1b). Lympho-

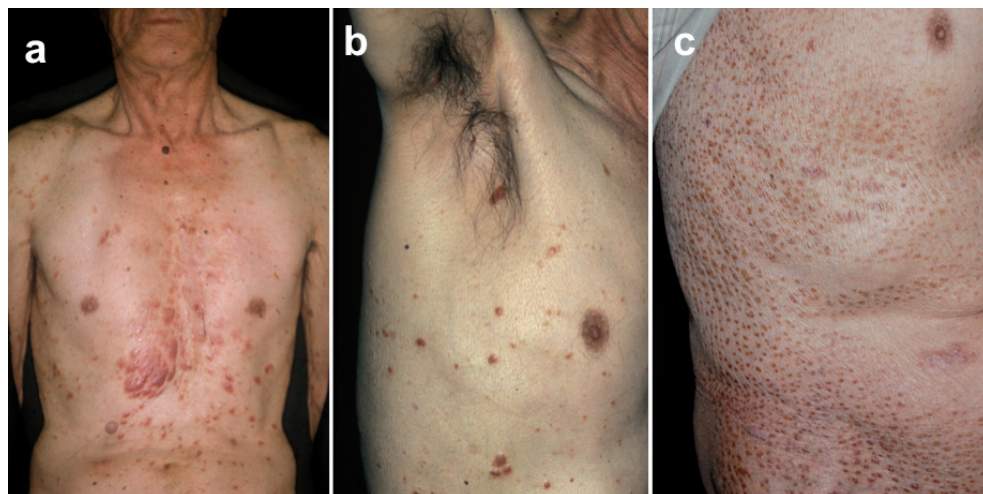


Fig. 1. Clinical appearance. (a and b) Initial well-defined, elevated nodules or tumours on the patient's trunk and extremities. (c) Evolved disseminated papular lesions forming deck-chair sign.

adenopathy was absent in both the axillae and groins. Peripheral blood examination showed normal counts of leukocytes ($8.1 \times 10^9/l$) with 57.0% neutrophils, 1.0% eosinophils and 24.0% lymphocytes, but 13.0% of lymphocytes exhibited a medium-sized and irregular-shaped nucleus. Notably, serum immunoglobulin E level was high (49,000 U/ml; normal $170 < U/ml$). The other blood chemistry values were normal, and circulating antibody against human T-cell lymphotropic virus type I was negative. Visceral involvement was absent as evaluated by roentgenographic examinations.

A skin biopsy specimen taken from a nodule on the chest revealed a dense infiltrate of atypical lymphocytes in the dermis (Fig. 2a). These tumour cells did not show epidermotropism. In some areas, there were lymphoid follicles (Fig. 2b) and Langhans-type giant cells surrounded by the tumour cells (Fig. 2c). The atypical lymphocytes had medium-sized convoluted nuclei (Fig. 2d). Immunohistochemical study showed that the tumour cells were positive for CD4, CD45RO, but negative for CD3. Large lymphocytes in the lymphoid follicles were CD20⁺ B cells. While histiocytes infiltrating in the upper dermis were positive for CD68, Langhans type giant cells were negative for this marker.

A flow cytometric analysis of peripheral blood mononuclear cells (PBMCs) showed 69.6% CD4⁺ cells and 13.9% CD8⁺ cells. The gated circulating CD4⁺ T cells were positive for CD45RO (84.3%) and CCR4 (94.9%), but negative for CD3, TCR $\alpha\beta$, TCR $\gamma\delta$, CD7, CD45RA, CD56, CXCR3, and cutaneous lymphocyte-associated antigen (CLA) (Fig. 3). A standard Southern blot analysis of DNA extracted from PBMCs exhibited

monoclonal rearrangement bands of TCRC β 1. Thus, the tumour cells possessed the CD3/TCR-defective helper T-cell phenotype.

The patient's condition was thus diagnosed as leukaemic CTCL. He was treated with oral administration of prednisolone, 10 mg daily, and etoposide, 25 mg daily for 7 days at a 4-week interval. Since 2004, his general and leukaemic conditions had been well controlled by the therapy, with flattened nodulo-tumours, except for transient pneumonia that was successfully treated with antibiotics. During this indolent clinical course, however, the skin eruption was gradually changed to multiple solid papules on the trunk and proximal limbs. In 2009, the papular lesions were disseminated but spared axillae, inguinal regions, antecubital and popliteal fossae, and in particular, abdominal folds, forming a deck-chair sign (Fig. 1c). We diagnosed the eruption as papuloerythroderma. His leukaemic state remained unchanged and the papuloerythrodermatous eruption persisted.

To examine the function of tumour cells, we isolated both CD3⁺CD4⁺ normal T cells and CD3⁻CD4⁺ tumour cells from the patient's PBMCs using BDTM IMag Cell Separation System with the anti-human CD3 and CD4 Particles-DM (BD Biosciences PharMingen, San Diego, CA, USA) according to the manufacturer's directions. The CD3⁻CD4⁺ tumour cells were isolated by magnetic immunoselection by sorting CD4⁺ cells followed by depleting CD3⁺ cells. The CD3⁺CD4⁺ normal T cells were obtained by sorting CD4⁺ cells from the CD3⁺ cells. The purity of each fraction was more than 90% (Fig. 4a). To confirm the monoclonal expansion of CD3⁻CD4⁺ tumour cells, we performed a

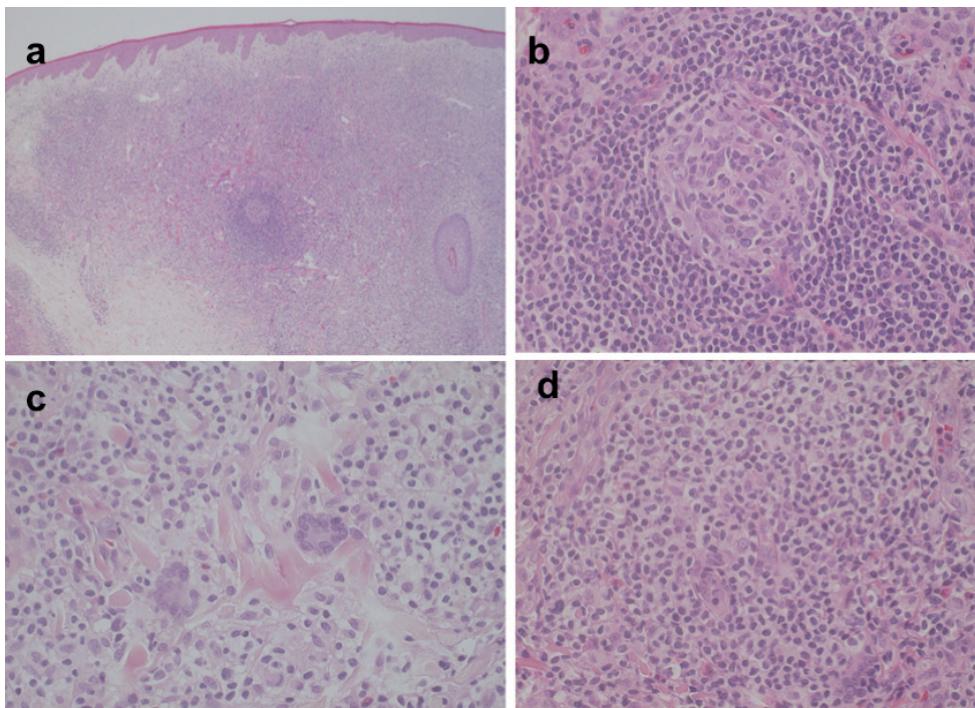


Fig. 2. Histological appearance. (a) Dense infiltrate of atypical lymphocytes in the dermis without epidermotropism. (b and c) Lymphoid follicles and Langhans-type giant cells surrounded by the tumour cells. (d) Atypical lymphocytes with medium-sized convoluted nuclei.

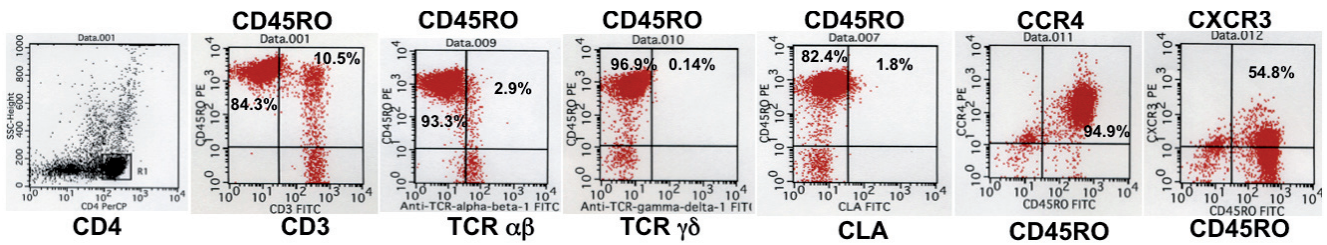


Fig. 3. Flow cytometric analysis of peripheral blood mononuclear cells. Circulating CD4⁺ T cells were positive for CD45RO (84.3%) and CCR4 (94.9%), but negative for CD3, TCR $\alpha\beta$, TCR $\gamma\delta$, CD7, CD45RA, CD56, CXCR3, and CLA.

polymerase chain reaction (PCR) analysis of the TCR β gene. A monoclonal band was detected in CD3⁺CD4⁺ cells, but not in CD3⁺CD4⁻ cells (Fig. 4b). Next, we analysed the cytokine production pattern of these two fractions. Each fraction (1×10^6 /ml in 24-well plates) was cultured along with the unfractionated samples under stimulation with concanavalin A (Con A, 2 μ g/ml) for 72 h. The culture supernatants were measured for IFN- γ and IL-4 by using enzyme-linked immunosorbent assay kits (Genzyme/Techne, Minneapolis, MN, USA) according to the manufacturer's directions. As control, healthy subject's PBMCs were used. Upon stimulation with Con A, the patient's PBMCs and healthy donor's PBMCs produced high amounts of IFN- γ . It was noted that the patient's CD3⁺CD4⁺ tumour cells secreted a low level of IFN- γ compared with CD3⁺CD4⁺ normal T cells even after Con A stimulation (Fig. 4c). On the other hand, none of them secreted detectable levels of IL-4 (data not shown). These findings suggested that the

tumour cells were unresponsive to CD3/TCR-mediated stimuli presumably because of the lack of expression of CD3/TCR complex.

DISCUSSION

The case of leukaemic CTCL described here is characterized by the unique skin manifestation and the aberrant tumour cell phenotype. The patient initially presented with nodules/tumours and a crop of solid papules on the trunk. The papular lesions gradually increased in number and spread over the trunk and other sites, but spared the abdominal creases, forming papuloerythroderma. It is known that papuloerythroderma represents a sign of internal malignancies (4, 5), or a manifestation of drug allergy (6) or CTCL (7–9). Our case documented that nodulo-tumourous lesions of CTCL may be changed into papuloerythroderma during the indolent long-term clinical course.

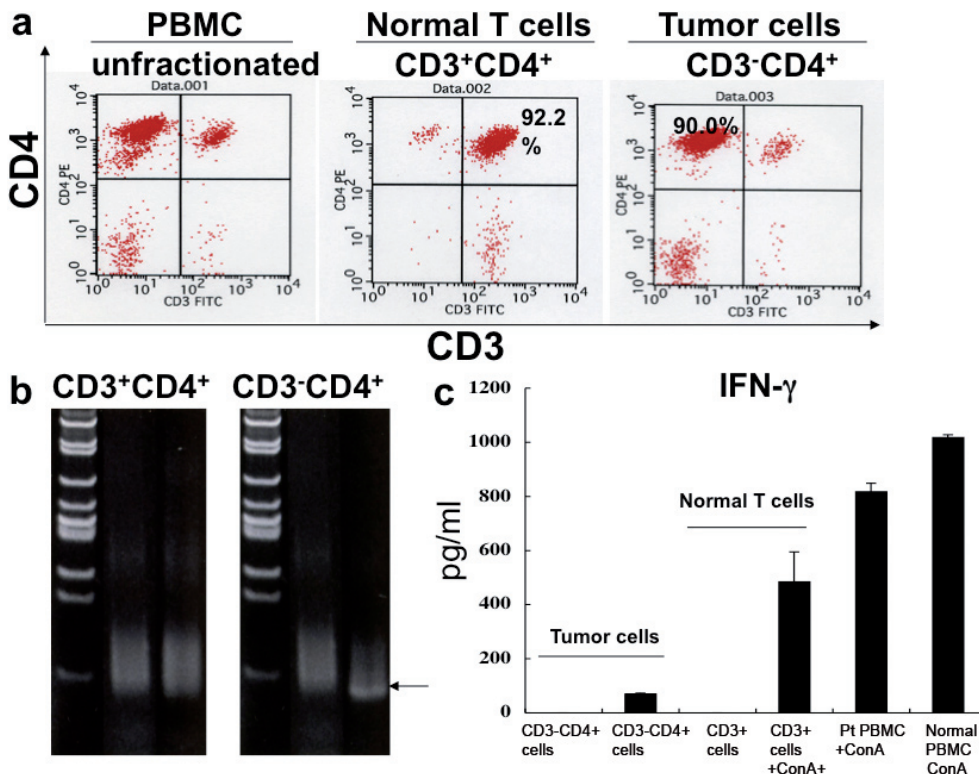


Fig. 4. Biological features of malignant T cells. (a) Flow cytometric analysis, showing successful separation of CD3⁺CD4⁺ normal T cells and CD3⁻CD4⁺ tumour cells from the patient's peripheral blood mononuclear cells (PBMCs). (b) PCR analysis of the TCR β gene. A monoclonal band was detected in CD3⁺CD4⁺ cells, but not in CD3⁻CD4⁺ cells. (c) Cytokine production pattern of tumour cells. CD3⁻CD4⁺ tumour cells, CD3⁺CD4⁺ normal T cells, patient's (Pt) PBMCs, and normal control's PBMCs (1×10^6 /well) were cultured with or without Con A (2 μ g/ml) for 72 h. The patient's CD3⁻CD4⁺ tumour cells secreted a low level of IFN- γ compared with CD3⁺CD4⁺ normal T cells even after Con A stimulation.

Papuloerythroderma histologically shows skin infiltration of eosinophils, as historically reported by Ofuji et al. (10). In drug-induced papuloerythroderma, patients have high percentages of circulating Th2 cells reacting with the causative drug as well as tissue and blood eosinophilia (6, 11). Thus it has been suggested that Th2 cells are involved in the formation of papuloerythrodermatous lesions. Since neoplastic T cells of leukaemic CTCL or Sézary syndrome usually have the cytokine expression pattern of Th2 cells (12, 13), the development of papuloerythroderma in CTCL patients may be reasonable. In the present case, the neoplastic cells expressed Th2 chemokine receptor CCR4 (14, 15) and secreted a very low level of IFN- γ even upon stimulation with Con A, compared with normal T cells. Although we could not detect IL-4 secreted from the tumour cells, their inability to produce IFN- γ may result in a Th2-preponderant condition and allows papuloerythroderma to develop. This is consistent with the finding that a significant decrease in the number of IFN- γ -producing T cells occurs with disease progression from mycosis fungoides to Sézary syndrome (16).

Cases of CTCL with CD3/TCR-lacking phenotype have rarely been reported, and the skin eruptions in those patients are varied from poikiloderma (17), nodulotumours (2), to papuloerythroderma as shown here. This aberrant expression might affect the behaviour of tumour cells. Surface expression of a fully assembled TCR/CD3 complex is required for the responses to normal mitogen and superantigen (18). Given that CTCL cells are chronically activated by some antigens in the skin milieu, the TCR/CD3-negative malignant cells could not be driven to proliferate in response to antigens indigenous to the epidermis, resulting in the non-epidermotropic, atypical erythrodermic clinical manifestation. A patient with Sézary syndrome, expressing superantigenic stimulus-transducible TCR, despite lack of CD3 expression, exhibits erythroderma (19). Taken together, the expression of functional TCR may be associated with the formation of erythroderma. In addition, the circulating tumour cells in the present case and our reported case (2) did not express CLA, whereas approximately 60% of Sézary cells bear this skin-homing molecule (20). This lack of CLA expression also may provide an explanation for development of atypical erythroderma in our patient.

In association with the atypical eruption, the histological findings are unique in this case. In addition to the absence of epidermotropism, the presence of lymphoid follicles and granulomatous change are the characteristic features, which indicate the nodulo-tumourous eruption are reactive as well as neoplastic. In fact, the patient's clinical course was indolent and not aggressive, despite having tumours. The association of these histological features with the CD3/TCR-lacking phenotype is speculative, but it is possible that the inactive state of the malignant cells might induce the various chronic

anti-tumour responses of inflammatory cells and result in pseudolymphomatous and granulomatous changes.

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