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SHORT COMMUNICATION

CD4/CD8 Double-negative T-cell Lymphoma: A Variant of Primary Cutaneous CD8$^+$ Aggressive Epidermotropic Cytotoxic T-cell Lymphoma?

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The classification of cutaneous T-cell lymphoma (CTCL) is based on clinical, histological and immunohistochemical features in the 2008 WHO classification (1). However, some cases are difficult to classify under this system. Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma is a rare subtype of CTCL, characterized by widely distributed lesions with ulceration, haemorrhage, necrosis or superficial crusts, and epidermotropic infiltrates of CD8$^+$ cytotoxic T cells. This disease shows a rapid progression, with extracutaneous dissemination and unfavourable prognosis (2, 3). We report here a case of CD4/CD8 double-negative CTCL that showed clinical and pathological findings quite similar to those of primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma (PC8AEC-TCL).

CASE REPORT

A 65-year-old Japanese man had presented to our hospital for generalized asymptomatic cutaneous lesions that had first appeared on the forearms approximately 4 months previously. He had lost 10 kg in body weight over the previous few months, although no fever, malaise or anorexia were noted. Physical examination revealed indurated, erythematous, asymptomatic patches and plaques of up to 4 cm in diameter over his whole body (Fig. 1a). Annular erythemas (Fig. 1b) and indurated plaques with surface crusts (Fig. 1c) were also visible. Skin biopsy specimens from an indurated erythematous plaque showed an infiltration of atypical lymphocytes in the superficial dermis and epidermis (Fig. 2a). The atypical lymphocytes had clear and abundant cytoplasm and a prominent epidermotropism was observed. Numerous necrotic keratinocytes were detected focally in the epidermis. Immunohistochemical staining revealed that the atypical lymphocytes expressed CD3 (Fig. 2b), granzyme B, perforin, T-cell intracellular antigen-1 (TIA-l) (Fig. 2c) and T-cell receptor (TCR) β-chain (Fig. 2d), but not CD4 (Fig. 2e), CD8 (Fig. 2f), CD5, CD7, CD20, CD30, CD56, TCR γ-chain or Epstein–Barr virus-encoded early small RNAs (EBER). Clonal TCR β gene rearrangement was found to be positive by polymerase chain reaction tests, but negative by Southern blotting. Peripheral blood cell count was normal, and there were no atypical lymphocytes. The results of all other biochemical examinations, including levels of lactose dehydrogenase and soluble interleukin-2 receptor, were within normal limits. The patient's serum was negative for anti-human T-cell leukaemia virus type 1 antibody. Positron emission tomography/computed tomography showed a high uptake of fluorodeoxyglucose only in the cutaneous lesions. Neither hepatosplenomegaly nor lymphadenopathy was detected. Although bone marrow aspirations showed normocellular marrow and revealed no obvious atypical lymphoid cells in immunohistochemical examination, we detected clonal TCR β gene rearrangement by Southern blotting. Based on these clinical, histopathological and immunohistochemical features, a diagnosis of CD4/CD8 double-negative aggressive epidermotropic cytotoxic T-cell lymphoma was made. The patient was initially treated with topical corticosteroid and oral psoralen plus ultraviolet A (PUVA), which were effective to some extent in reducing the number of lesions. As bone marrow involvement was detected, the chemotherapy with cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone (CHOP) was administered. Bone-marrow transplantation was not performed, because the patient had had severe pneumocystis pneumonia before this chemotherapy and was estimated to be in poor physical condition. Almost all the lesions disappeared after the first cycle of chemotherapy, but rapid recurrence was detected on the trunk and extremities. The next regimen of chemotherapy, comprising dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide (SMILE), could not be continued due to renal damage. We attempted several therapies, including oral vorinostat, oral etoposide, total skin electron beam (TSEB), intravenous gemcitabine and intravenous anti-CCR4 monoclonal antibody (mogamulizumab). Transient improvement or inhibition of development of new lesions was seen for each therapy, but the lesions recurred rapidly and became advanced. The patient died of multiple organ failure 24 months after the initial diagnosis.

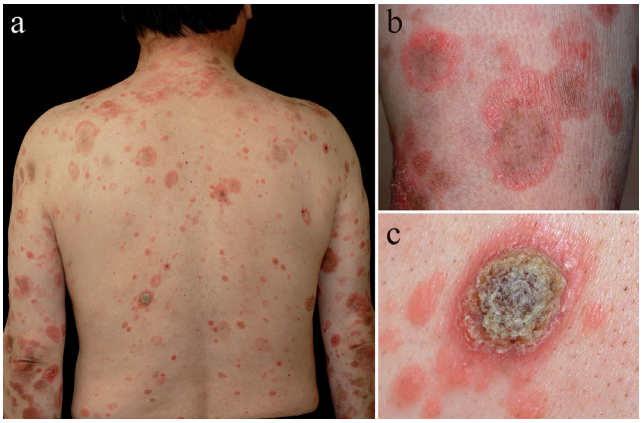

Fig. 1. (a) Erythematous patches and plaques disseminated over the whole body. (b) Annular erythemas and (c) indurated plaques with surface crusts.

DISCUSSION

This case was characterized by its aggressive nature and pathological findings. Because of the pathological feature of the prominent epidermotropism of atypical lymphocytes, differential diagnoses included mycosis fungoides (MF), primary cutaneous γ/δ T-cell lym-

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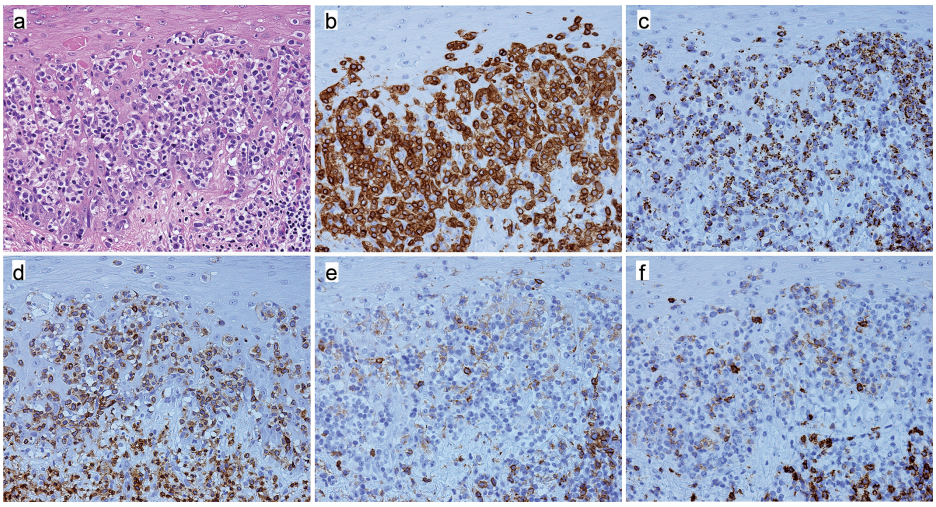

Fig. 2. (a) Skin biopsy specimens from an indurated erythematous plaque revealed infiltration of atypical lymphocytes in the superficial dermis and epidermis. The atypical lymphocytes had clear and abundant cytoplasm and prominent epidermotropism was observed. Haematoxylin-eosin staining, original magnification: ×200. Immunohistochemical staining shows the atypical lymphocytes to be positive for: (b) CD3, (c) TIA-l, and (d) TCR β-chain, but negative for: (e) CD4 and (f) CD8.

phoma (PCGD-TCL) and PC8AEC-TCL. CD4/CD8 double-negative type MF has been commonly reported, having an indolent clinical course like that of typical MF (4). However, since the present case had no long-standing precursor lesions, we ruled out the possibility of MF. Although this case had some similar features to those of PCGD-TCL (5, 6), the immunohistochemical findings of positive TCR β-chain and negative TCR γ-chain argued against that diagnosis (5).

PC8AEC-TCL, originally reported by Berti et al. (7), is rare and is still considered a provisional entity (2, 3). This disease is characterized by the proliferation of epidermotropic $CD8^+$ T cells expressing cytotoxic markers, and by aggressive clinical behaviour and an unfavourable prognosis. While the lack of CD8 expression makes a crucial difference between our case and PC8AEC-TCL, the case described here shared other features, and CD8 expression can be lost during malignant transformation; thus we consider it possible that our case is a variant of PC8AEC-TCL.

Several cases resembling the present case in terms of clinical course and immunohistochemical features have been reported. Pagnanelli et al. (8) reported a case of disseminated pagetoid reticulosis, showing the immunophenotypical features of $CD3^+$, $CD4^-$, $CD8^-$, $CD56^-$, TCR β-$chain^+$ and $TIA\text{-}1^+$. The patient did not respond to several treatments and died 18 months after the initial diagnosis. Shiozawa et al. (9) and Akkari et al. (10) also reported similar cases. According to the 2008 WHO classification, these 3 cases, like ours, do not conform to any of the existing entities.

In conclusion, it is noteworthy that CD4/CD8 double-negative cases may show features similar to those of PC8AEC-TCL. Thus, the association of these unclassified cases should be evaluated using defined entities; investigations such as transcriptome or comparative genomic hybridization analysis may lead to the establishment of a new entity in the classification of CTCL.

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