QUIZ SECTION

Rapidly Progressive Multiple Skin Plaques and Nodules: A Quiz

Hikari BOKI[1], Tomomitsu MIYAGAKI[1,2], Hiraku SUGA[1], Hanako OHMATSU[3] and Shinichi SATO[1]
[1]Department of Dermatology, Graduate School of Medicine, the University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8655, Japan, [2]Department of Dermatology, St Marianna University School of Medicine, Kawasaki, Kanagawa and [3]Department of Dermatology, National Hospital Organization Sagamihara National Hospital, Sagamihara, Kanagawa Japan. E-mail: asahikari1979@gmail.com

A 71-year-old Japanese male was referred to the dermatology department with a history of rapidly developing and growing nodules with occasional ulceration. Four months previously, a 4-cm sized nodule, which eventually ulcerated, had developed on his buttock (Fig. 1A). He had no preceding skin symptoms. Similar nodules continued to appear over his entire body. Physical examination revealed multiple well-demarcated red nodules and indurated plaques of various sizes, scattered over his whole body (Fig. 1B). Some of the nodules were ulcerated with thick crust (Fig. 1C). He had no constitutional symptoms. Standard haematological and biochemistry tests, including white blood cell counts in peripheral blood, serum lactate dehydrogenase level and serum soluble interleukin-2 receptor level, were normal. Antibodies to human T-cell leukaemia virus type 1 and human immunodeficiency virus were negative. Positron emission tomography-computed tomography showed no involvement of lymph nodes or internal organs. The patient's medical history included diabetes mellitus, hypertension, and vasospastic angina. He had no history of being immunocompromised.

What is your diagnosis? See next page for answer.

a. Mycosis fungoides
b. Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma
c. Extranodal natural killer/T-cell lymphoma
d. Primary cutaneous diffuse large B-cell lymphoma, leg type
e. Blastic plasmacytoid dendritic cell neoplasm

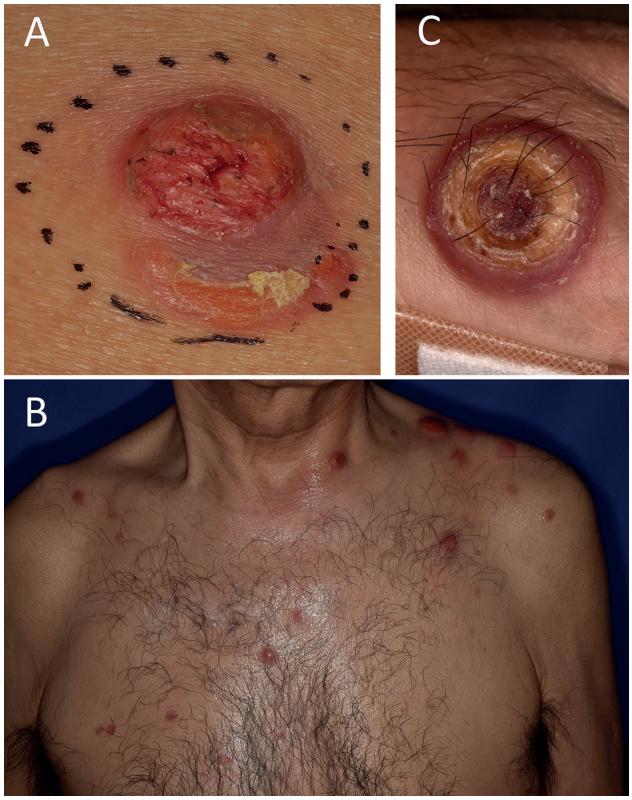

Fig. 1. Clinical presentation. (A) A 4 cm-sized erythematous nodule with ulceration on the left buttock, (B) red nodules of variou sizes scattered on the chest, and (C) a 2cm-sized indurated erythematous plaque with thick crust on the left hand.

ANSWERS TO QUIZ

Rapidly Progressive Multiple Skin Nodules: A Commentary

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Diagnosis: **Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma**

Skin biopsy revealed the infiltration of medium-sized atypical lymphoid cells from superficial to deep dermis with marked epidermotropism (Fig. 2A, B). No angiocentricity or angiodestruction was found. Immunohistochemical staining showed that atypical cells were positive for CD3, CD7, CD8, granzyme B, TIA-1, and T-cell receptor (TCR) beta chain and negative for CD4, CD5, CD30, CD45RO, CD56, and TCR delta chain (Fig. 2C–F). Epstein-Barr virus-encoded RNA in situ hybridization was negative. The MIB-1 index was 90%.

The patient started oral bexarotene 300 mg/m^2/day in combination with narrow-band ultraviolet B phototherapy and local electron beam irradiation (8 Gy/1 fraction) was given to intractable lesions. The development of new nodules continued, and 6 months after bexarotene administration, a tumour developed in his right nasal cavity, which showed the same histopathological findings. Since tumours were also scattered in the head and neck region, head and neck X-ray irradiation (20 Gy/10 fractions) was added. Oral bexarotene was administered in total for 8 months and, due to the increase in refractory nodules (Fig. 3A), the systemic therapy was switched from oral bexarotene to oral etoposide at a dose of 50 mg/day for 21 days of a 28-day cycle. The skin lesions then rapidly improved and the development of new nodules stopped, resulting in complete remission after 4 months (Fig. 3B). The patient maintained complete remission for 4 months with etoposide. Subsequently, occasional recurrence of the solitary nodule was observed, but could be recovered with local electron beam therapy (8 Gy/1 fraction). The patient had been under good control with oral etoposide and occasional local electron beam therapy for 14 months in total. Subsequently, involvement of the pharynx and oesophagus developed and the patient received 2-cycles of CHOP therapy, followed by 1-cycle of ESHAP therapy. After 5 months he died, due to lung invasion.

Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma (PCAECTCL) is a rare subtype of cutaneous T-cell lymphoma, representing less than 1% of all cases (1). It is characterized by an aggressive clinical behaviour, resistance to conventional therapies, and

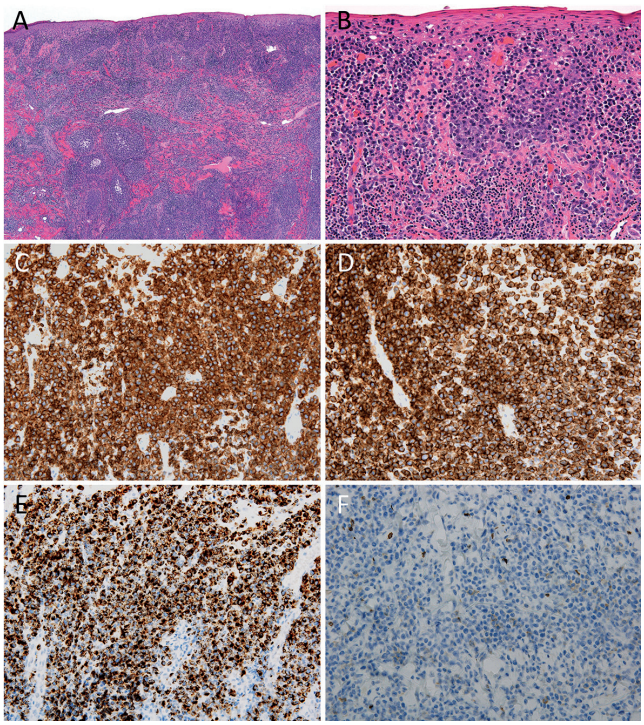

Fig. 2. (A, B) Histological findings of a red nodule from the neck. The dense infiltration of medium-sized atypical lymphoid cells from superficial to deep dermis and marked epidermotropism (haematoxylin-eosin, original magnification (A) ×40, (B) ×200). (C–F) Immunostaining of CD3 (C), CD8 (D), granzyme B (E), and CD5 (F) (original magnification ×200). Atypical lymphoid cells were positive for CD3, CD8, and granzyme B and negative for CD5.

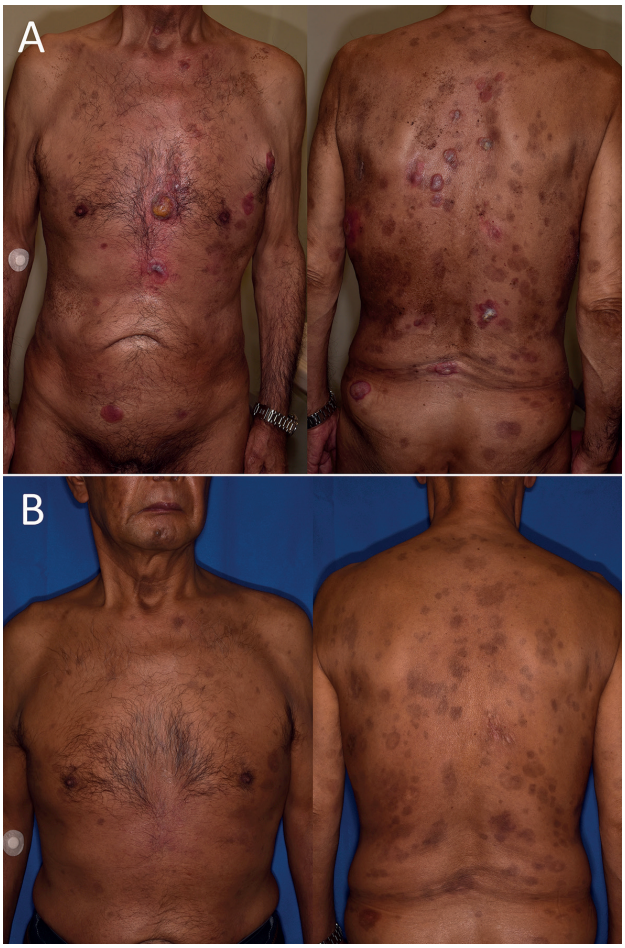

Fig. 3. (A) Multiple red tumours on the trunk before initiation of oral etoposide. (B) Complete remission of skin lesions 4 months after oral etoposide therapy. Hyperpigmentation was evident at site of previous lesions.

poor prognosis (2). PCAECTCL is included as a provisional entity in the 2018 update of the World Health Organization (WHO)-European Organization for Research and Treatment of Cancer (EORTC) classification of cutaneous lymphomas and in the 2016 revision of the WHO classification of haematopoietic neoplasms (1, 3). The main differential diagnoses of PCAECTCL are CD8-positive mycosis fungoides, primary cutaneous γδ T-cell lymphoma, and primary cutaneous peripheral T-cell lymphoma, not otherwise specified.

PCAECTCL is clinically characterized by rapidly progressing, widely distributed papules, plaques, nodules, and tumours, often with central necrosis, ulceration, or crustation on the extremities and the trunk with occasional involvement of the oral cavity (1, 4). Bone marrow and lymph node involvement are uncommon and the disease may rapidly disseminate to visceral organs (4).

Histopathology shows a prominent epidermotropism of small-to-large sized atypical lymphoid cells (3, 4, 5). There is dense infiltration of tumour cells in the superficial to deep dermis, occasionally even in the subcutaneous tissue. Tumour cells are usually positive for CD3, CD8, CD45RA, cytotoxic molecules, and TCR beta chain and negative for CD4, CD45RO, and TCR delta chain (5). In situ hybridization for Epstein-Barr virus is negative. The lack of CD5 expression, but not CD7 expression, is commonly observed.

PCAECTCL mostly occurs in elderly patients. This rapidly progressing lymphoma has a poor prognosis, with a 5-year survival rate of 31% and a median survival of 12 months (1, 5). Because of the nature of the lesions, the disease commonly impairs the usual daily activities and quality of life of patients (2, 6–8). Standard treatment for PCAECTCL has not been established and treatment of the disease is challenging. A literature review on PCAECTCL, published in 2012, reported that conventional therapies for mycosis fungoides, including phototherapy, radiation therapy, interferon, bexarotene, gemcitabine, and combination therapies were ineffective or only achieved short remission with rapid relapse (9). A recent retrospective analysis of 30 primary cutaneous aggressive epidermotropic cytotoxic T-cell lymphoma cases, most of which were PCAECTCL, revealed that allogenic haematopoietic stem cell transplantation (allo-HSCT) resulted in prolonged partial or complete remissions in 5 of 6 patients, whereas none of the chemotherapy and radiation protocols showed significant survival advantages (5). In the current case, allo-HSCT was not applicable, due to advanced age. Considering quality of life, it was decided in agreement with the patient to attempt to manage his condition with oral drugs, which can be used easily in the outpatient clinic. Although bexarotene was not effective in the current case, similar to previous reports, oral etoposide achieved relatively long remission for 14 months, longer than the reported median survival, without reduction in the patient's activities of daily living. Oral etoposide could be a choice for patients with PCAECTCL, especially for elderly patients.

The authors have no conflicts of interest to declare.

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