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Letter to the Editor

Successful treatment of an elderly Langerhans cell sarcoma patient by EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) chemotherapy

Keywords: Langerhans cell sarcoma, EPOCH, *BRAF* V600E mutation, Merkel cell polyoma virus

TO THE EDITOR

A 79-year-old Japanese man presented with systemic papules without itch or pain (Figure 1*a*-*b*). His Eastern Cooperative Oncology Group performance status was 2. His past medical history was unremarkable. Biochemistry testing revealed AST/ALT of 148/107 IU/L, ALP of 453 IU/L and γ-GTP of 91 IU/L. The other routine blood test and biochemistry results were within normal limits. Each cutaneous lesion was biopsied. Histologically, there was proliferation of tumor cells with abundant eosinophilic cytoplasm and atypical nuclei in the dermis. The tumor cells were positive for CD1a, CD4, CD56, CD68, CD45RO, S100 and TIA-1, and negative for CD3, CD8, CD30, ALK, granzyme B,

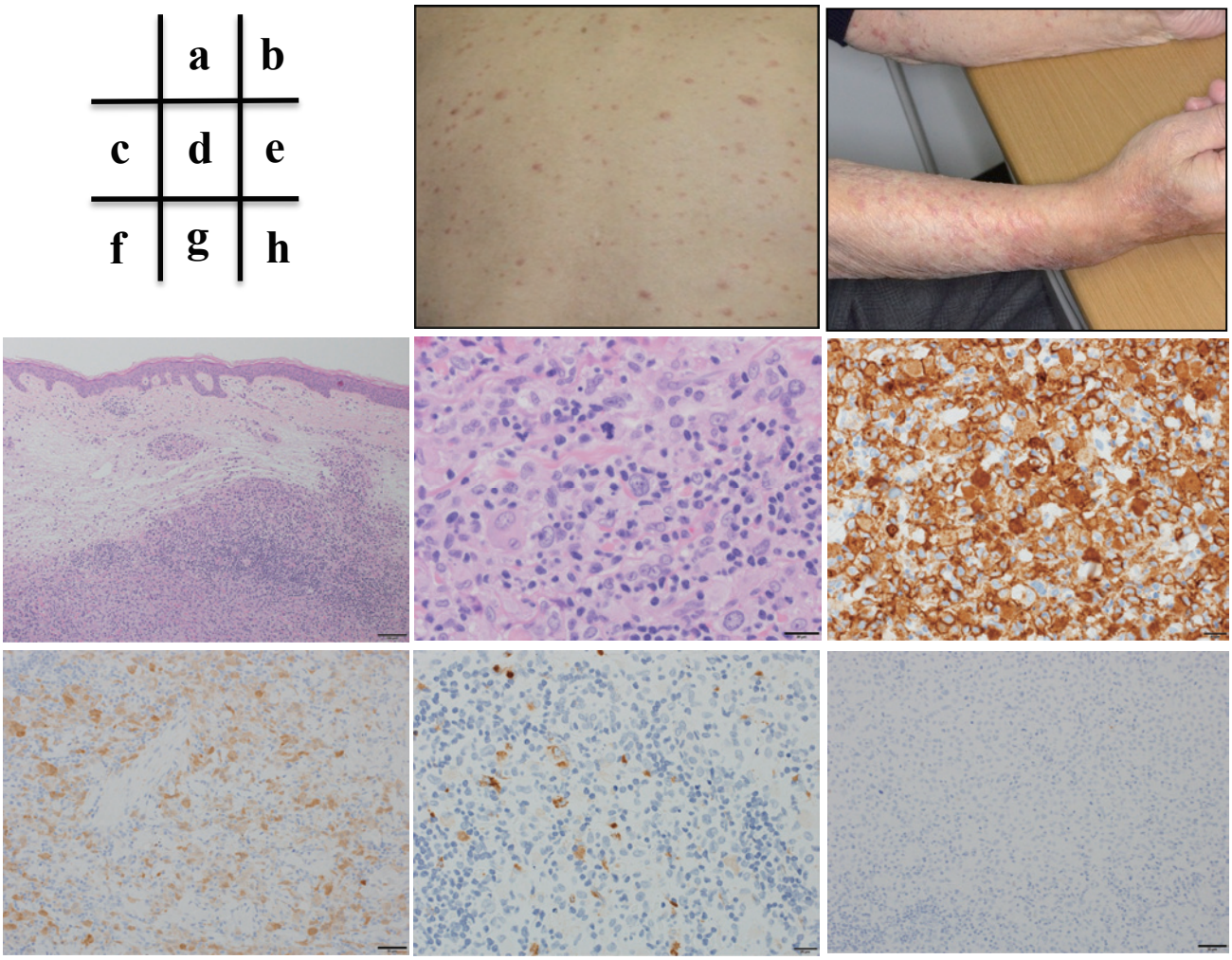

Fig. 1. Skin lesions: (***a***) back and (***b***) arm. Skin biopsy before chemotherapy: (***c***, ***d***) HE staining shows the proliferation of tumor cells with abundant eosinophilic cytoplasm and atypical nuclei in the dermis. Tumor cells were diffusely and highly positive for CD1a (***e***) and S100 (***f***). They were also partly positive for CD68 (***g***) but negative for langerin (***h***).

EBER, langerin and CD20 (Figure 1*c*-*h*). Positron emission tomography computed tomography (PET/CT) demonstrated no significant uptake sites, including skin lesions. No significant abnormalities were found by enhanced CT scan or brain MRI. Bone marrow biopsy revealed no infiltration of tumor cells. Therefore, he was diagnosed with cutaneous de novo Langerhans cell sarcoma (LCS). Considering his age, a reduced dose of EPOCH (etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin) chemotherapy was administered, which included etoposide (50 mg/day on days 1 to 4), prednisolone (60 mg/day on days 1 to 5), vincristine (0.4 mg/day on days 1 to 4), cyclophosphamide (750 mg on day 5) and doxorubicin (10 mg/day on days 1 to 4). Etoposide, vincristine and doxorubicin were administered by continuous intravenous infusion. In total, the patient received 4 cycles of EPOCH chemotherapy. At the end of 2 cycles, skin lesions disappeared upon inspection. Biopsies of five random skin lesions were performed after 4 cycles and revealed no infiltration of tumor cells. The only therapy-related toxicity was grade 3 neutropenia. The patient was considered to have achieved complete remission (CR). Per his request, he was to be observed following CR, but he did

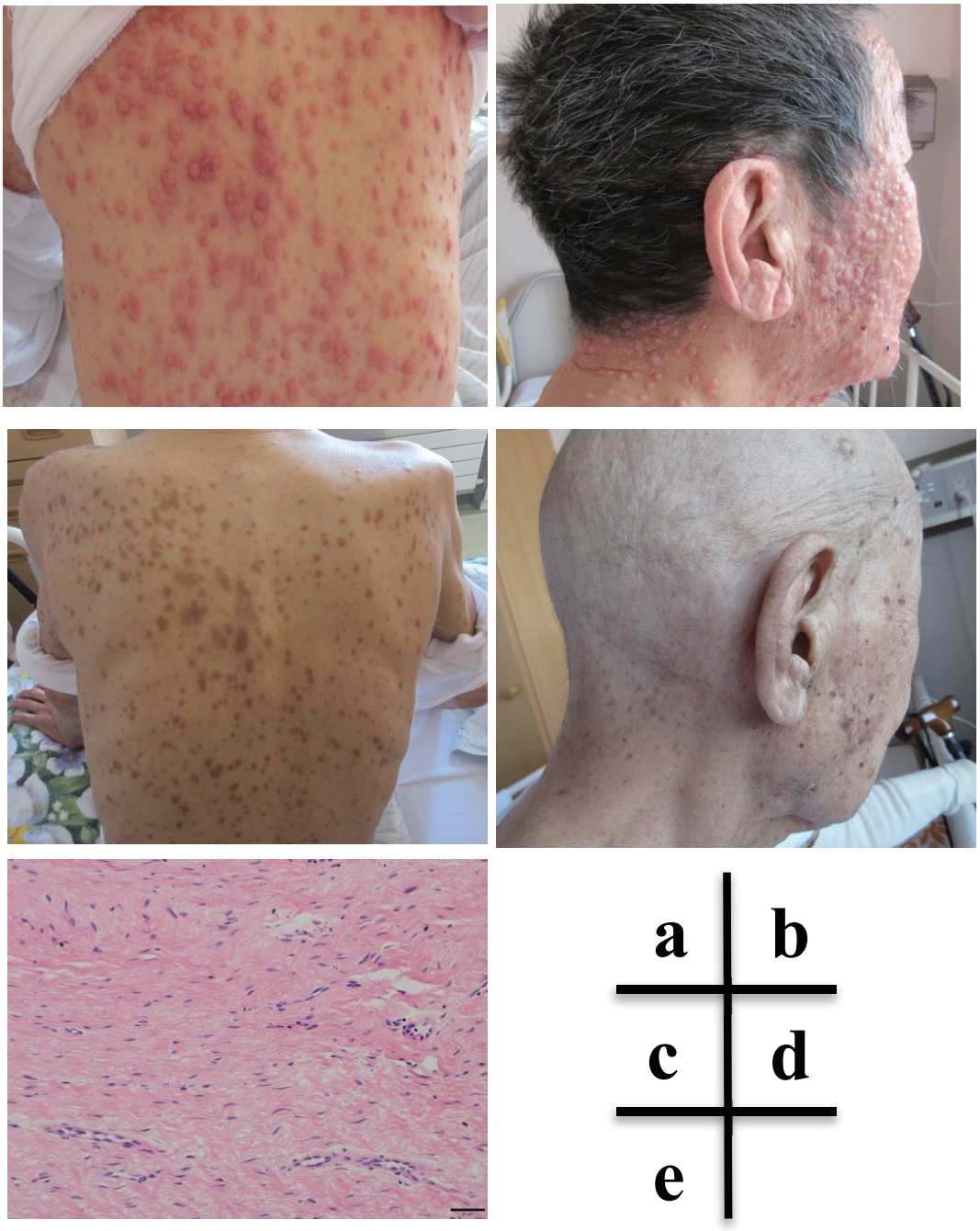

Fig. 2. Relapse after 4 cycles of EPOCH chemotherapy: (***a***) back, and (***b***) head and neck. Skin lesions in complete remission after 8 cycles of EPOCH chemotherapy: (***c***) back, and (***d***) head and neck. After 8 cycles of EPOCH, the patient achieved complete remission: HE staining of skin biopsies (***e***).

not present for follow-up examinations after chemotherapy for undisclosed reasons. He experienced no relapse and was in CR for 5 months after treatment. Following this period, the patient developed systemic skin lesions again. Eleven months since his last chemotherapy session, he came to our hospital with systemic skin nodules and tumors (Figure 2*a*-*b*). Skin biopsy was performed, and demonstrated LCS relapse based on morphological and immunophenotypical features. As the EPOCH regimen was successful as first-line therapy, we administered EPOCH chemotherapy again. After re-administration of 4 cycles of EPOCH, he achieved CR again (Figure 2*c*-*e*) and maintained CR for approximately 1 year. The patient is currently alive without relapse.

Langerhans cell tumor, also known as 'malignant histiocytosis X', was first reported in 1984.[1] Langerhans cells are identical to dendritic cells (DC) in the skin or mucosa, and share functions with antigen-presenting cells. The World Health Organization classifies Langerhans cell histiocytosis (LCH) among histiocytic and dendritic cell neoplasms.[2] LCH is a benign neoplasm, whereas LCS is an exceedingly rare and highly aggressive tumor that is characterized by localized- or multi-organ lesions. Regardless of numerous treatments, LCS results in a very poor clinical outcome due to its aggressive clinical course.[3] Here, we report an elderly LCS patient treated by etoposide-containing chemotherapy. LCS lesions mostly arise in the lymph nodes, skin, lung, bone and spleen.[3,4] In a relatively large study of histiocytic or dendritic cell neoplasms, the median age of patients with LCS (41 years) was older than that of those with LCH (33 years).[5] LCH, which has been difficult to distinguish from LCS because of a lack of determining factors, is diagnosed by histopathological, clinical and radiological findings.[6] Immunohistochemical features of LCS are positivity for CD1a, langerin, Birbeck granules and S100 protein, similar to LCH. In contrast, LCS exhibits higher degrees of histological atypia, a higher mitotic rate and higher MIB-1 index than LCH.[3] To our knowledge, characteristic chromosomal abnormalities or cytogenetic mutations are unknown in LCS. PET/CT is a good modality for staging and evaluating LCH,[7] and can be used to identify LCS lesions.[8] However, in this current case, the lesions were unevaluable by PET/CT.

Several treatments have been evaluated for systemic or localized LCS, with previous reports demonstrating surgical excision as the most effective treatment for localized, clear margin LCS,[5,9] and other studies found combination therapy to be effective for multi-organ lesions or progressive disease.[5,10,11] Other reports have found radiation therapy to be effective in some patients with progressive, localized LCS.[12] Patients with progressive, systemic LCS often receive chemotherapy regimens, e.g. CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) according to malignant lymphomas, as previously reported.[4,5,10,12-15] Overall, the estimated mean survival was 6.25 months with multi-organ disease.[11] This is especially true for LCS patients aged 75 years and over. Indeed, patients with progressive or multi-organ lesions did not survive after treatment, excluding those undergoing surgical excision of skin lesions.[9,16] In our case, we chose an EPOCH regimen for the patient, which lead to a favorable response and CR. EPOCH chemotherapy has been reported to be highly effective for refractory or relapsed non-Hodgkin's lymphoma.[17] Kaleem *et al.* demonstrated that EPOCH was effective for an LCS patient with multi-organ lesions.[8] We speculate that EPOCH chemotherapy was highly effective due to a pathogenic similarity with Merkel cell carcinoma (MCC). As with MCC,[18] Merkel cell polyoma virus (MCPyV) is sometimes involved in the pathogenesis of LCS. Although not every case of LCH is positive, 43% of tissues are positive for the MCPyV viral DNA sequence, and the viral load in LCS is typically higher than that in LCH.[19] MCC is considered to be sensitive to chemotherapy.[20] Carboplatin, cisplatin and etoposide comprise the first-line chemotherapy regimen for MCC.[21] It is possible that etoposide, which is effective for treating MCC, was also effective in our case, as MCPyV-induced tumorigenesis was common.

The *BRAF* V600E mutation activates the MAPK pathway, which enhances precursor Langerhans cells by triggering cytokine release and signal amplification.[22] The *BRAF* V600E mutation has been detected in LCH and LCS.[15,23] In our case, however, MCPyV was not pathologically detected and the *BRAF* V600E mutation was not analyzed. Etoposide-containing chemotherapy, EPOCH, may be efficacious for LCS due in part to the similar pathogenic mechanisms of LCS with MCC and MCPyV infection, and it may be safe for elderly patients.

CONFLICTS OF INTEREST

The authors declare no competing financial interests.

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