

LETTER

Lack of efficacy of radiation therapy plus PD-L1 blockade for Merkel cell carcinoma arising in a patient with chronic active Epstein-Barr virus infection

Dear Editor,

Merkel cell carcinoma (MCC) is a rare and aggressive skin cancer that occurs in elderly patients.¹ The risk of MCC is increased by immunosuppression due to conditions such as human immunodeficiency virus infection, hematological malignancies, and organ transplantation.² These risk factors can also be associated with a poor prognosis in MCC. Chronic active Epstein-Barr virus (CAEBV) infection is a rare Epstein-Barr virus (EBV) infectious disease characterized by persistent infectious mononucleosis-like symptoms. Recently, programmed cell death ligand 1 (PD-L1) blockade using avelumab was approved as the first-line therapy for patients with metastatic MCC.³ Here, we report a case of extremely hyperprogressive MCC occurring in a patient with CAEBV.

A 42-year-old Japanese man presented with a 6-month history of a rapidly growing 2-cm red nodule on the dorsum of his right hand (Figure 1). He had been diagnosed with EBV-induced hepatitis at the age of 17, which was resolved with symptomatic treatment. After the subclinical stage, pancytopenia with prolonged fever developed at the age of 34, and he was diagnosed with CAEBV. Subsequently, he was administered rituximab, cyclophosphamide, doxorubicin

hydrochloride, vincristine, and prednisone (R-CHOP). After that, he had been carefully followed up by periodic monitoring of his peripheral blood EBV DNA levels. Another antecedent included tuberculous osteomyelitis at the age of 41. He was treated with rifampicin plus isoniazid, but the treatment was discontinued due to pancytopenia. Histological examination of a tissue specimen biopsied from the center of the nodule showed dense infiltration of atypical lymphocyte-like chromatin-rich cells with round mitotic nuclei and scant cytoplasm (Figure 2A). Immunohistochemical staining showed that these cells were positive for cytokeratin AE1/AE3, synaptophysin, Merkel polyomavirus (CM2B4), and Ki67, and they showed paranuclear dot-like positivity for cytokeratin 20 (Figure 2B). Computed tomography revealed no regional or distant metastases. Forty days after his first visit, the tumor had grown to 5 × 4 cm (Figure 3). The tumor was resected with a 1-cm surgical margin. A sentinel lymph node biopsy was positive from both the axilla and antecubital fossa; however, complete node dissection revealed no other nodal involvement. Four months after surgery, multiple recurrences and metastases were observed on the skin and in the muscle of the right arm. He had no response to two courses of radiation therapy (RT) with a dose of more than 100 Gy in total, employing avelumab five times (10 mg/kg every 2 weeks), and resection of several cutaneous lesions. The metastatic lesions progressed rapidly (Figure 4), and the patient died 15 months after the first operation.

Postoperative RT is reported to increase the 3-year disease-specific survival ratio from 48.1% to 76.2% in lymph node-positive patients with MCC.⁴ Moreover, the release of tumor antigen from damaged tumor cells by RT, together with PD-L1 blockade, can sometimes activate antigen-presenting dendritic cells and antitumor T cell responses. The treatment with avelumab combined with RT has been suggested to have an abscopal effect.⁵

However, this combination of RT plus PD-L1 blockade was not effective in our case. Although EBV is reportedly not associated with MCC,⁶ CAEBV is a specific EBV infection status. Patients with CAEBV have a high EBV DNA load in peripheral blood cells, B cells, T cells, and natural killer cells,⁷ potentially altering antitumor immune function. In addition, our patient had been treated with R-CHOP approximately 8 years earlier, which might have led to ongoing immune dysfunction and been related to hyperprogressive MCC.

To the best of our knowledge, this is the first case of MCC occurring in a patient with CAEBV, and it is unclear whether this was



FIGURE 1 Clinical manifestations of the patient at his first visit

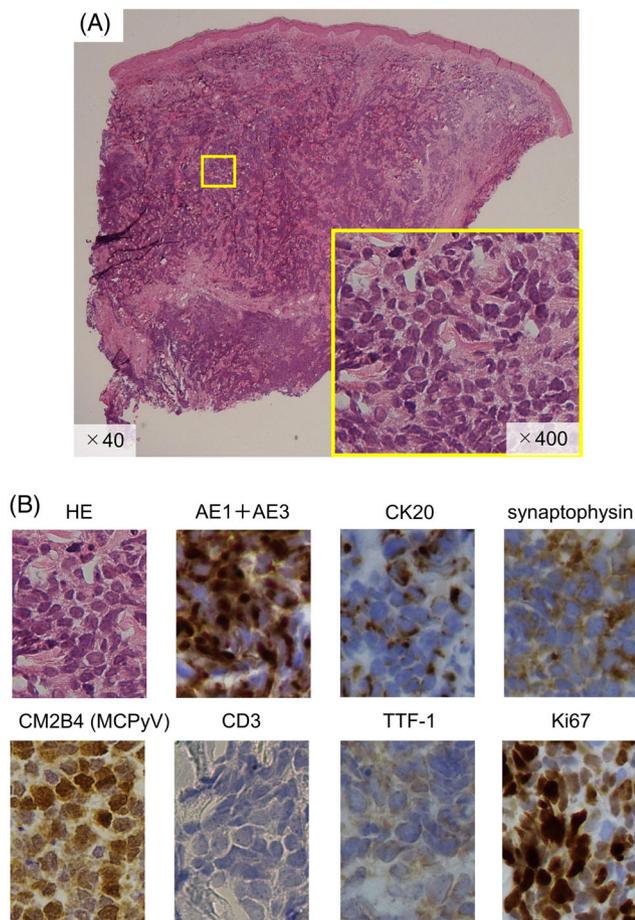


FIGURE 2 A, Histological features (hematoxylin and eosin staining, $\times 40$ and $\times 400$). B, Immunohistochemical staining for cytokeratin AE1/AE3, cytokeratin 20 (CK20), synaptophysin, CM2B4 (MCPyV: Merkel cell polyomavirus), CD3, thyroid transcription factor-1 (TTF-1), and Ki67 (original magnification, $\times 400$)



FIGURE 3 Clinical manifestation at the time of surgery (40 days after his first visit)



FIGURE 4 Clinical manifestation of the right upper arm after the first course of radiation therapy. Multiple metastatic nodules were observed. Tumors had shrunk slightly, but recurred soon thereafter

associated with a more general immune dysfunction or a more specific link between MCC and CAEBV.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Ayaka Okazaki, Nao Kusutani, Riei Kamo, and Yoshie Fukunaga cared for the patient. Ayaka Okazaki and Kozo Nakai were responsible for acquisition and analysis of data. Ayaka Okazaki, Kozo Nakai, Kotaro Nagase, Paul Nghiem, and Daisuke Tsuruta were responsible for interpretation of data and drafting the manuscript. All authors gave their final approval of the version to be published.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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