

SHORT COMMUNICATION

Merkel Cell Polyomavirus-positive Merkel Cell Carcinoma in a Patient with Epidermodysplasia Verruciformis

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Epidermodysplasia verruciformis (EV) is a rare autosomal recessive disease characterised by abnormal susceptibility to disease-specific human papillomaviruses (HPVs), possibly due to suppressed cellular innate immunity. *EVER1/TMC6* or *EVER2/TMC8* gene mutations are often found in EV (1). All patients with EV usually have similar skin lesions from their childhood, involving disseminated flat warts or pityriasis versicolor. Elderly patients with EV have a high risk of developing carcinomas *in situ* and invasive squamous cell carcinoma (SCC) associated with HPV infections, mainly on sun-exposed skin. On the other hand, Merkel cell polyomavirus (MCPyV) is detected in most Merkel cell carcinomas (MCC) (2), which arise from Merkel cells, neuroendocrine cells in the skin. We present here a rare occurrence of MCPyV⁺ MCC in a patient with EV.

CASE REPORT

An 82-year-old Japanese man with chronic obstructive pulmonary disease and repeated occurrence of bacterial pneumonia

noticed a rapidly growing tumour on his left cheek one month earlier. He had noticed flat verrucous papules and brown macules on the neck, face and chest in his twenties. He had a 25-year-history of various skin conditions, including seborrhoeic keratosis, actinic keratosis, Bowen's disease, basal cell carcinoma, and SCC on the skin of the scalp, face, and neck that had been treated with various surgical operations and cryotherapy. Infection with HPV 16 was detected when the patient was evaluated for Bowen's disease and SCC. Although we recommended check-up every 6 months for recurrence of SCC and new skin neoplasms, he did not visit us regularly.

On the patient's return 2 years later, a hard, pink tumour (3.5 × 3.3 cm in size; height 1.4 cm) was noted on the left cheek. At the base of the tumour, there was a hard induration area (size 4 × 6 cm) with undefined borders (Fig. 1a). In addition, the left cervical lymph node was swollen. Histological study of the biopsy specimen from the tumour showed massive tumour nests from the dermis to the subcutaneous tissue, which were composed of small, oval, basophilic tumour cells with poor cytoplasm (Fig. 1b, d). Several tumour cells appeared to be in stages of mitosis. Immunostaining showed that the tumour cells were positive for cytokeratin 20 (Fig. 1c), synaptophysin, chromogranin A, and AE1/AE3, but negative for cytokeratin 7 and thyroid-transcription factor-1 (TTF-1). The MIB-1/Ki-67 labelling index was 75%, indicating the proliferation of tumour

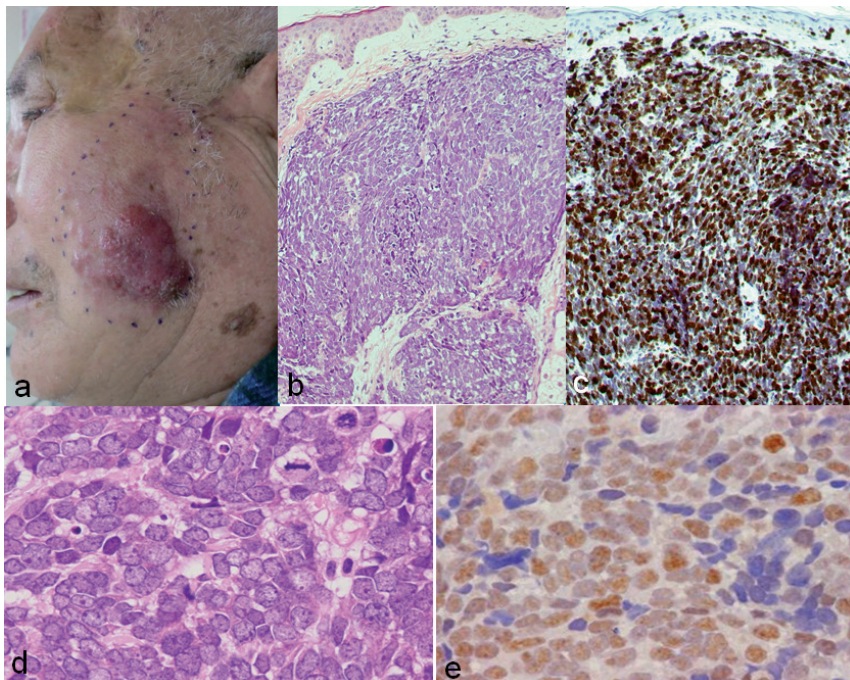


Fig. 1. A large tumour on the left cheek (a). Tumour nest with oval atypical cells from the dermis to the subcutaneous tissue (H&E stain, original magnification; b: × 100 and d: × 400). Immunopathological findings by MIB-1/Ki-67 (c) and Merkel cell polyomavirus large T-antigen (e) (c: × 100 and e: × 400).

cells. From these findings, a diagnosis of MCC was made. MCPyV large T-antigens (3) were detected in the tumour by immunostaining (Fig. 1e) and MCPyV DNA had 0.281 copies per cell, as determined by real-time PCR (4). However, HPV types 6, 11, 16, 18, 31, 33, 35, 39, 42, 43, 44, 45, 51, 52, 56, 58, 59, and 68 types and also HPV types 5, 8, and 17 types which are EV-specific HPVs, were not detected using PCR.

Mutation analysis by PCR amplification using genomic DNA derived from his blood sample revealed a homozygous mutation, c.1824-1G>A, in the *EVER2/TMC8* gene. This mutation can cause an aberrant splicing such as exon 15 skipping or activation of cryptic splice sites and therefore is a highly possible pathogenic mutation. No pathogenic mutation in the *EVER1/TMC6* gene was found. His son and daughter did not present EV symptoms. Unfortunately, we did not have an opportunity to test his family for the *EVER2/TMC8* gene mutation. We established the diagnosis of MCPyV⁺ MCC in the patient with EV on the basis of clinical features, histopathological findings, and gene mutation analysis. The patient underwent radiation therapy for MCC using 45.6 Gy to treat the tumour and 33 Gy to treat the left cervical lymph nodes, respectively. During treatment, the tumour and lymph node swelling disappeared. However, the patient decided to discontinue treatment on his own judgement. The tumour and lymph node swelling reoccurred after 5 months, and an additional round of radiation therapy was performed. It was effective for at least 4 months, but he died of unknown causes one month later.

DISCUSSION

Recently, the potential causative role of MCPyV has been suggested in the pathogenesis of MCC, because this virus is identified in approximately 90% of MCC cases (2). On the other hand, MCPyV is usually not detected in other skin tumours such as SCC (5). Patients with EV are incapable of clearing HPVs, therefore, they continue to have persistent infections that ultimately result in malignant transformation. To the best of our knowledge, only 2 EV cases with MCC and MCPyV infection have been reported (6, 7), and in one of these cases, the patient was also positive for HPVs in MCC (7). Although we did not detect the 3 types of EV-specific HPVs (as well as the mucosal HPVs that are indicative of high risk for cervical carcinoma), we cannot neglect a possibility that other HPVs are involved in MCC development. Patients with EV are susceptible to disease-specific HPVs and MCPyV infections. Thus, when physicians encounter patients with EV, they should pay attention to the possibility of SCC induced by EV-specific HPVs, as well as to MCC induced by MCPyV. In addition, we strongly recommend regular check-ups for reoccurrence and/or appearance of skin neoplasms.

Immunosuppressed patients with MCPyV infections cannot eliminate viruses after persistent infection and

may eventually develop MCC (6, 8, 9). MCPyV has been detected in non-MCC skin lesions, SCCs and common warts in EV patients (8, 9). However, HPV 5 and/or 8 (8) and HPV17 (9) have also been detected in these skin lesions. In addition, MCPyV⁺ SCC alone (10) and MCPyV⁺ SCC and MCC (11) have been reported in immunosuppressed patients. However, the association of MCPyV with SCC onset remains unclear as most SCC cases also show positivity for HPVs.

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