SHORT COMMUNICATION

Coincident Metastatic Melanoma and Merkel Cell Carcinoma with Complete Remission on Treatment with Pembrolizumab

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Patients with metastatic melanoma or Merkel cell carcinoma (MCC) share a poor prognosis (1, 2). In recent years, immune checkpoint inhibitors have significantly advanced the treatment of immunogenic tumours (3). The anti-programmed cell death protein 1 (PD-1) antibodies pembrolizumab and nivolumab have been approved for the treatment of advanced melanoma. Clinical trials have provided evidence that pembrolizumab (4) as well as the anti-programmed death-ligand 1 (PD-L1) antibody avelumab (5) are effective in the treatment of advanced MCC, with avelumab approved by the US Food and Drug Administration. We report here on a patient presenting with both metastatic melanoma and MCC who experienced complete remission of both on treatment with pembrolizumab.

CASE REPORT

In July 2012, a 70-year-old man was diagnosed with a metastatic melanoma. A swelling of the right axilla was removed by surgery. Based on morphology and immunohistochemistry (IHC), an amelanotic lymph node metastasis, 5 cm in diameter, with occult primary was diagnosed (**Fig. 1** A–C). Level I/II lymph node dissection (0/23 nodes positive) was conducted, and he received adjuvant radiotherapy of 50 Gy. Computed tomography (CT) scans performed initially showed no additional metastases. Follow-up was carried out in accordance with national guidelines. In April 2016 CT revealed newly enlarged right inguinal and iliac lymph nodes.

A systematic lymphadenectomy was conducted. To our surprise, initial pathological review of the dissected tissue detected infiltrates of neuroendocrine carcinoma in 7 of 20 inguinal and 8 of 20 iliac lymph nodes (Fig. 1D). IHC revealed "dot-like" positivity for pan-cytokeratin (AE1/3) and CK20, while TTF1, MITF, MART1 and HMB45 were negative (Fig. 1E). Finally, diagnosis of MCC was made and further sustained by strong positive immunolabelling for Merkel cell polyomavirus (MCPyV) Large T antigen (clone CM2B4; Fig. 1F). No primary MCC was recorded in the patient's medical history or found on clinical examination. Endoscopy of the upper and lower intestine did not reveal an internal neuroendocrine primary. However, a suspicious pancreatic lesion (Fig. 1J) was biopsied and a melanoma metastasis diagnosed based on morphology and IHC (MART-1- and HMB45-positive; nuclear

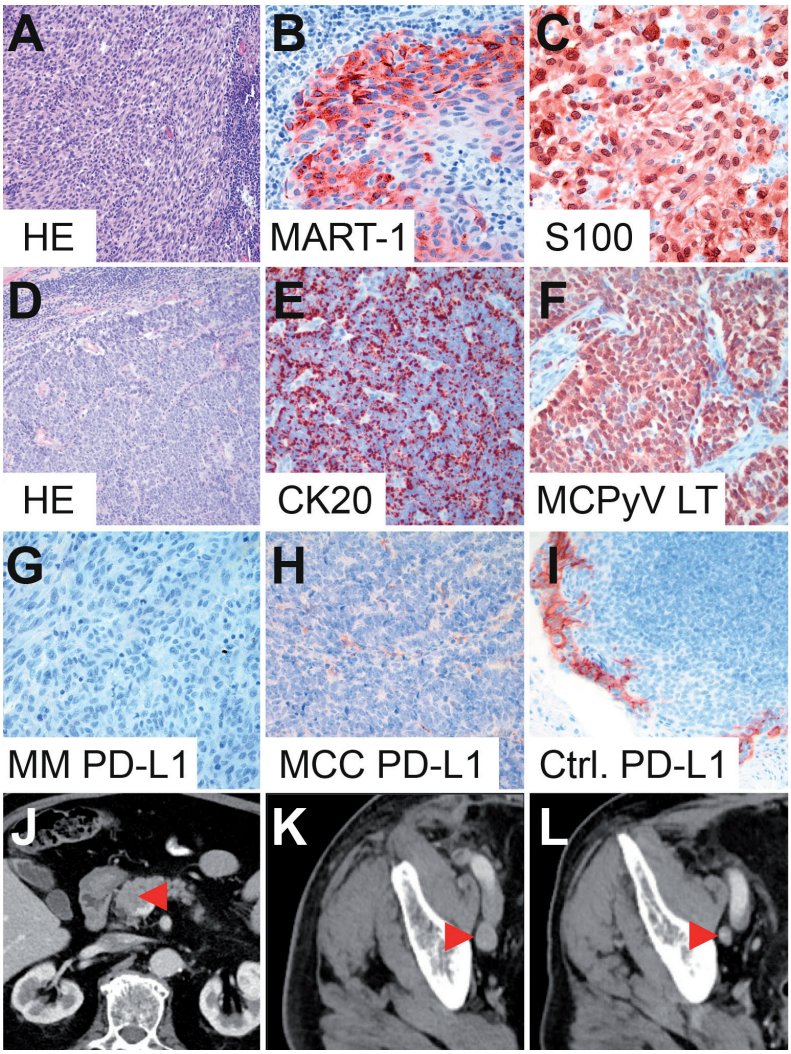

Fig. 1. (Immuno-)histological and radiological findings. (A–C) Amelanotic lymph node melanoma metastasis from the right axilla. (A) Haematoxylin and eosin (H&E) staining with atypical melanocytes positive for (B) MART-1 and (C) S100. (D–F) Iliac MCC lymph node metastasis with round oval tumor cells containing (D) sparse cytoplasm and granular chromatin on H&E staining with (E) „dot-like"-positivity for CK20 and (F) expression of Merkel cell polyomavirus Large T antigen (MCPyV LT, stained with antibody clone CM2B4). (G-I) Both the axillary lymph node metastasis (G) as well as the iliac MCC metastasis (H) are negative for PD-L1 (immunolabelled with antibody clone E1L3N, tonsillar tissue served as positive control for PD-L1 (I)). Magnification H&E 200x (A, D), all others 400x). (J–L) CT scans demonstrating pancreatic melanoma metastasis (J) as well as an parailiac MCC metastasis before (K) and after 7 applications of pembrolizumab (L). Arrow heads indicate metastases.

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expression of S100; synaptophysin, chromogranin, CAM5.2- and CD56-negative).

In July 2016, CT scans revealed a new parailiac lymph node metastasis, adjacent to the previously excised MCC metastases (Fig. 1K).

In September 2016, therapy with pembrolizumab (2 mg/kg body weight every 3 weeks) was initiated to treat both metastatic melanoma and MCC. Before treatment, the melanoma tumour marker S100ß was elevated significantly (2.30 µg/l; ULN=0.15 µg/l). After 4 infusions of pembrolizumab, CT scans demonstrated a partial response with size reduction of the right parailiac lymph node (from 18 mm to 12 mm), and a decrease in the S100ß melanoma tumour marker (to 0.52 µg/l) was observed. The pancreatic melanoma metastasis remained stable. After 3 further infusions of pembrolizumab, the patient was admitted to an intensive care unit for autoimmune pancreatitis with associated ketoacidosis and diabetes mellitus. In addition, persistent diarrhoea led to the diagnosis of autoimmune colitis. With anti-inflammatory and symptomatic treatment (insulin, loperamide, analgetics) both autoimmune disorders resolved clinically after 4 weeks. New CT scans in February 2017 demonstrated a complete response with a normalized right parailiac lymph node (Fig. 1L). In addition, the pancreatic melanoma metastasis was no longer detectable. S100ß was within normal range (0.12 µg/l). Pembrolizumab therapy remains paused since January 2017 after a total of 7 infusions. At the last follow-up, in April 2017, the patient reported significantly improved well-being and no adverse events.

DISCUSSION

We report here the rare coincidence of 2 metastatic tumours, melanoma and MCC, which both showed an outstanding response to anti-PD-1 immunotherapy. Compared with melanoma, MCC is less frequent, usually occurs in elderly patients, and immunosuppression is an important risk factor (6). In our patient, the diagnoses of melanoma and of MCC were only made in the metastatic stage, both with unknown primary tumour. Tumours with unknown primary account for approximately 2.3–3.2% of all melanomas (7) and approximately 5% of all MCCs (8). Interestingly, melanoma and MCC with unknown primary, have better survival outcomes compared with the same entities with known primary (7, 9). One explanation for this phenomenon is regression of the primary tumour as the result of a host immune response. It is not known whether the therapeutic effects of immunotherapies in metastatic solid tumours with unknown primary are improved, as large studies of melanoma or MCC have not separately reported those with an unknown primary (4, 10). A clinical trial (NCT02834013) evaluating a combination of nivolumab and ipilimumab is ongoing in patients with rare tumours, including metastatic malignant neoplasms with unknown primary origin, and may provide an answer to this question.

In melanoma, pre-treatment positive PD-L1 expression is associated with a better response rate to anti-PD-1 therapy (10). In MCC, a correlation between PD-L1 positivity and better response was not evident (4, 5). In our patient, neither the tumour cells of the right axillary melanoma metastasis nor those of the right inguinal/iliac MCC metastasis were positive for PD-L1 by IHC (Fig. 1 G–I).

In approximately 80% of MCC tumours MCPyV is clonally integrated (11). It is notable that the metastasis in our patient belongs to this group. So far, studies investigating MCPyV status as a marker of response to anti-PD-1 or anti-PD-L1 immune therapy have reported similar responses independent of MCPyV status (4, 5).

Of note, pembrolizumab was discontinued due to 2 severe immune-related adverse events (irAEs) after 7 infusions (12). Robert et al. (13) reported, in their phase III melanoma trial Keynote-006 for pembrolizumab therapy, an incidence of approximately 10–13% of ≥ grade 3 treatment-related adverse events.

The case of our patient supports data from Hauschild et al. (14), who have recently described a 51-year-old male patient with xeroderma pigmentosum, who experienced regression of melanoma metastases and multiple non-melanoma skin cancers by pembrolizumab therapy. A prospective study (NCT02834013) is ongoing, which might verify the outstanding response of our patient with 2 coincident metastatic tumours with unknown primary to anti-PD-1 immunotherapy.

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