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Letter to the Editor

A case of merkel leptomeningeal evolution after complete remission upon anti–PD-1 treatment

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To the Editor,

Merkel cell carcinoma (MCC) is a rare malignant neuroendocrine skin tumour [1]. The five-year survival rate is 51% for local disease and dramatically decreases to 14% for distant disease. Neurometastatic involvement is very rare in MCC [2].

MCC carcinogenesis involves either the clonal integration of the Merkel cell polyomavirus (MCPyV) into the host genome or UV-induced mutations [1], both with high immunogenic environment. Indeed, antigen-specific T cells detected in patients are frequently dysfunctional with an exhausted phenotype; and the T-cell inhibitory ligand, programmed-death-ligand 1 (PD-L1), is often expressed on MCC tumour cells [3]. Clinical trials involving programmed Death - 1 (PD-1)/PD-L1 pathway blockade in advanced MCC have shown significant improvement in the prognosis of the disease [4–6], and PD-L1 inhibitor avelumab has recently been approved by the US Food and Drug Administration in first-line treatment for metastatic MCC.

We report the first case of Merkel meningitis occurring after initial complete remission with nivolumab. To the best of our knowledge, leptomeningeal evolution of MCC is poorly described and has never been reported after PD-1/PD-L1 inhibitor therapy.

A 77-year-old patient was diagnosed in June 2015 with MCC of the left lower limb; he underwent enlarged excision of the tumour with sentinel lymph node biopsy (SLNB). Positron-emission tomography–computed tomography (PET–CT) was normal, and SLNB showed microscopic involvement without capsular effraction. Adjuvant radiation therapy was performed on the tumour site and lymph nodes (50 Gray in 25 fractions).

Three months later, PET–CT revealed a disease progression involving the lymph nodes, pancreas, bones and skin and also revealed peritoneal carcinomatosis.

Off-label treatment with anti–PD-1 antibody (nivolumab) was initiated (3 mg/kg every two weeks). After six months, tumour evaluation showed a complete response on PET–CT. Nivolumab was maintained without adverse events and finally stopped 12 months after beginning.

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Six months later, the patient was transferred to our department for bradypsychia, slurred speach and mnesic disorders. A magnetic resonance imaging (MRI) scan of the brain showed a global ventricular and meningeal contrast enhancement; cerebrospinal fluid (CSF) analysis showed hyperproteinorachia (1.66 G/L) and elevation of lactate dehydrogenase (234 UI/L) and identified small round CK20+ and CD56 + tumour cells (Fig. 1 a–c).

PET–CT showed no additional hypermetabolism. The diagnosis of MCC meningitis was made, and nivolumab was resumed. After two infusions, the patient presented with severe clinical worsening. Nivolumab was interrupted, and chemotherapy was initiated with carboplatin (area under the curve: five) and etoposide (100 mg/m^2 during three days), every 21 days. After six weeks, a clinical improvement was observed with a subtotal recovery of all symptoms, improvement of CSF parameters and decrease of MRI leptomeningeal contrast enhancement. Unfortunately, three weeks after, the patient displayed rapid neurologic worsening and died.

We report the case of a patient with MCC leptomeningeal involvement after complete response with nivolumab for metastatic MCC. Leptomeningeal involvement occurred after 12 months of complete remission obtained with an anti–PD-1 monoclonal antibody and was not associated with extracranial recurrence of the disease.

MCC is a rare but aggressive skin cancer. Most common metastatic locations are the skin, lymph nodes, liver, lungs, bones and adrenal glands [1]. To the best of our knowledge, central nervous system (CNS) involvement in the course of an MCC is not frequently reported [2,7]; it is usually observed in patients with systemic spread of the disease and associated with multiple extracranial metastases. Leptomeningeal involvement was previously reported in six cases [2,7]. In almost all cases, leptomeningeal involvement was associated with CNS metastasis and systemic spreading of the disease and was observed from one to three months after systemic spreading. All cases had a poor prognosis with a survival from one to eight months, after leptomeningeal involvement was diagnosed.

In our case, leptomeningeal involvement occurred after a 12-month period of complete remission upon anti–PD-1 therapy and was not associated with extracranial metastasis.

The search of PD-1/PD-L1 expression in the SLNB was negative in the tumour cell and positive in the tumour microenvironment but without peritumoural overconcentration. In addition, the detection of MCPyV in the tumour sample was positive. Unfortunately, we could not perform the PD-1/PD-L1 expression study on CSF smear because of insufficient material.

Our patient experienced a dramatic complete response after six months of treatment with nivolumab and a 12-month period of complete response before relapse of the disease, including a six-month treatment-free period. One may hypothesise that anti–PD-1 treatment may have modified the natural course of the disease, inducing a selection pressure that has led to leptomeningeal tumour escape. Indeed, leptomeningeal metastatic involvement in MCC is unusual, often occurring together with systemic spreading of the disease and brain metastasis. Immune escape of the tumour may have been favoured in leptomeningeal environment that is commonly considered as an immune sanctuary [8,9].

Our patient has displayed clinical and biological symptoms of improvement just after treatment with carboplatin and etoposide. However, this improvement was of short duration and did not allow for additional therapeutic procedures such as radiation therapy. This observation suggests that a synergistic effect of chemotherapy and immunotherapy was obtained through an off-target effect of chemotherapy on immune system [10].

We report on an unusual exclusive leptomeningeal involvement of an MCC in a patient rendered disease free with anti–PD-1 therapy. This observation suggests that the CNS still has to be considered as an immune sanctuary and may be the location of immunotherapy-resistant disease, requiring combination therapy.

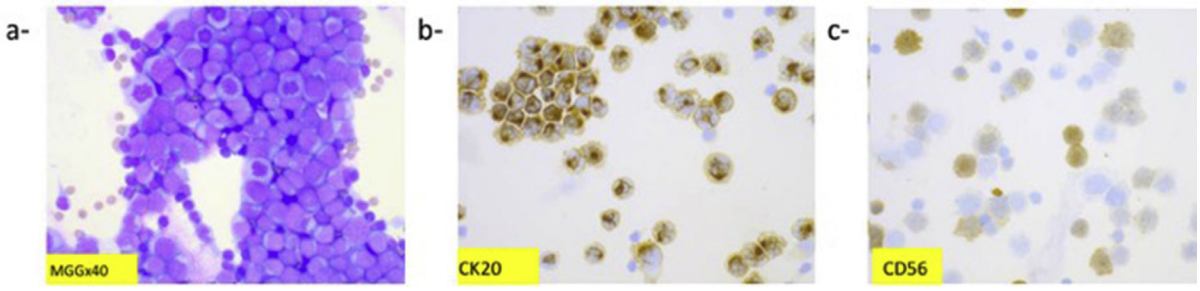

Fig. 1. Cerebrospinal fluid smear. a- MGGx40; b- CK20 immunostaining x40; c- CD56 immunostaining x40. Inflammatory cells with a high proportion of CK20- and CD56-positive malignant cells (basophilic isolated large cells with increased nucleoplasmic ratio and fine chromatin).

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Conflict of interest statement

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References

[1] Becker JC, Stang A, DeCaprio JA, Cerroni L, Lebbé C, Veness M, et al. Merkel cell carcinoma. Nat Rev Dis Primer 2017 Oct 26;3:17077.

[2] Ho KWD, Drew PA, Chuquilin M. Merkel cell carcinoma with distant metastasis to the Clivus causing symptoms Mimicking Tolosa-Hunt Syndrome: a case report and literature review. Front Neurol 2017;8:409.

[3] Walsh NM, Fleming KE, Hanly JG, Dakin Hache K, Doucette S, Ferrara G, et al. A morphological and immunophenotypic map of the immune response in Merkel cell carcinoma. Hum Pathol 2016; 52:190–6.

[4] Nghiem PT, Bhatia S, Lipson EJ, Kudchadkar RR, Miller NJ, Annamalai L, et al. PD-1 blockade with Pembrolizumab in advanced merkel-cell carcinoma. N Engl J Med 2016 Jun 30; 374(26):2542–52.

[5] Topalian SL, Bhatia S, Hollebecque A, Awada A, Boer JPD, Kudchadkar RR, et al. Abstract CT074: non-comparative, open-label, multiple cohort, phase 1/2 study to evaluate nivolumab (NIVO) in patients with virus-associated tumors (CheckMate 358): efficacy and safety in Merkel cell carcinoma (MCC). Cancer Res 2017 Jul 1;77(13). CT074–CT074.

[6] Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol 2016 Oct; 17(10):1374–85.

[7] Abul-Kasim K, Söderström K, Hallsten L. Extensive central nervous system involvement in Merkel cell carcinoma: a case report and review of the literature. J Med Case Rep 2011 Jan 26; 5:35.

[8] Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol 2002 Nov;3(11):991–8.

[9] Schadendorf D, Nghiem P, Bhatia S, Hauschild A, Saiag P, Mahnke L, et al. Immune evasion mechanisms and immune checkpoint inhibition in advanced merkel cell carcinoma. OncoImmunology 2017;6(10). e1338237.

[10] Dalgleish AG. Rationale for combining immunotherapy with chemotherapy. Immunotherapy 2015;7(3):309–16.