

BRIEF REPORT

Talimogene laherparepvec resulting in near-complete response in a patient with treatment-refractory Merkel cell carcinoma

Michael A. Cilento MBBS^{1,2}  | Oliver Klein MD, FRACP³  | Elizabeth Egan RN¹ | Rachel Roberts-Thomson MBBS, FRACP^{1,2}

¹Department of Medical Oncology, Queen Elizabeth Hospital, Woodville, South Australia, Australia

²Adelaide Medical School, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, South Australia, Australia

³Olivia Newton-John Cancer Research Institute, Heidelberg, Victoria, Australia

Correspondence

Michael A. Cilento, Department of Medical Oncology, Queen Elizabeth Hospital, Woodville, SA, Australia.
Email: michael.cilento@sa.gov.au

Abstract

Merkel cell carcinoma (MCC) is a rare and aggressive cutaneous tumour of neuroendocrine cell origin, which can grow rapidly and metastasise early. Localised disease is treated with surgery and radiotherapy. Disease that reaches a more advanced stage can be treated with a variety of different treatment modalities including surgery, radiotherapy, chemotherapy, radionuclide therapy, immunotherapy, and intralesional therapy. We report a case of a patient who had exhausted all local and systemic treatment options and who subsequently had an exceptional response to intralesional injection of Talimogene laherparepvec (TVEC).

KEYWORDS

cancer intervention, chemotherapy<oncology, dermatology, immunology, skin cancer<oncology

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare and aggressive cutaneous tumour of neuroendocrine cell origin, which can grow rapidly and metastasise early.¹ The pathogenesis of MCC is associated with either chronic exposure to ultraviolet light (UV) or the presence of Merkel cell polyomavirus (MCPyV).² In the Australian population, the predominant aetiologic factor is sun exposure.

We report a case of a 75-year-old man with treatment-refractory MCC, who had an impressive and durable response to intralesional therapy with Talimogene laherparepvec (TVEC).

CASE

A 75-year-old Caucasian man from rural South Australia presented to his local doctor with a relatively small skin

lesion on the dorsal aspect of his left hand that was increasing in size. Past medical history was significant for cigarette smoking, chronic obstructive pulmonary disease (COPD), type 2 diabetes mellitus, hypertension, hypercholesterolaemia, and multiple previous excisions of cutaneous squamous cell carcinomas and basal cell carcinomas of the face.

The patient underwent excisional biopsy revealing a diagnosis of MCC. The tumour was 13 × 11 mm, the depth of invasion was 5 mm, with a mitotic rate of 14 mitoses per square millimetre. A focus of perineural invasion was identified. Immunohistochemistry showed the tumour cells to be positive for neuroendocrine markers CD56, chromogranin, and synaptophysin. CK20 was strongly positive with a paranuclear dot pattern. TTF-1 and p63 were negative. The proliferative index as measured with Ki-67 was high at 80%–90%. The MCPyV status of the tumour was not known. While the detection of virus by real-time polymerase chain reaction (PCR) or immunohistochemistry

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is possible, this has not been a standard practice for all patients given it does not alter management.³ This tumour had arisen in a background of sun-damaged skin.

Computed tomography (CT) scans showed some patchy nodular ground-glass lesions in the lower lobes; there was no evidence of metastatic disease. 18-Fluorodeoxyglucose positron emission tomography (FDG-PET) scan confirmed no evidence of metastatic disease.

The patient subsequently underwent wider local excision, skin graft and sentinel lymph node biopsy, which was negative. Pathology revealed clear surgical margins.

Following successful surgery, the patient completed 5 weeks of adjuvant radiotherapy to the affected area. However, soon after completion, a new nodule was detected proximally in the upper limb; this area was proximal to the skin graft and proximal to the field of adjuvant radiotherapy. Local excision of the nodule confirmed MCC, and the patient received further adjuvant radiation to this area.

When another in-transit lesion was subsequently detected on excisional biopsy, the patient went on to commence systemic therapy with the anti-PD-L1 immune checkpoint inhibitor avelumab, given by intravenous infusion every 2 weeks under the care of a medical oncologist. The patient remained on this treatment for 6 months; however, there was ongoing development of further in-transit metastases, some of which were ulcerating and required palliative external beam radiotherapy. He was then referred for radionuclide therapy in a tertiary cancer centre, with a nuclear medicine department experienced in this treatment modality.

Investigations prior to radionuclide treatment included a repeat FDG-PET scan along with a Gallium Dotatate PET scan. This revealed multifocal moderately avid cutaneous lesions along the left forearm to the distal elbow. There was low-grade activity in a left axillary node, but no distant metastatic disease. He subsequently went on to receive peptide receptor radionuclide therapy (PRRT) with Lu-177 DOTA octreotate (LuTate) concurrent with immunotherapy in an attempt to control his locally progressive disease. The initial induction cycle of treatment resulted in prompt symptomatic improvement with visible reduction in the size of all lesions, and a further cycle was administered 6 weeks later. The response to this therapy was short-lived. Intravenous carboplatin chemotherapy was pursued, with no meaningful response after 2 cycles.

Further local disease progression resulted in large symptomatic lesions in the affected area (Figure 1). The next line of treatment was the introduction of intratumoural injection of TVEC, an oncolytic viral immunotherapy; although not reimbursed for this indication, the patient was able to obtain individual compassionate access from the pharmaceutical company. The patient tolerated the treatment well and had a number of lesions injected over a treatment duration of 6 months.



FIGURE 1 Photograph of left upper limb showing large, ulcerated mass in the dorsal forearm and a smaller localised tumour recurrence on the hand.

There was a dramatic response to TVEC therapy after 6 months. There was resolution of a significant number of the dermal metastases in the forearm, with small, pigmented nodularity remaining at the sites of treated disease (Figure 2a). The dorsal aspect of the left hand showed only residual pigmentation (Figure 2b). Post-treatment FDG-PET scan showed only minor uptake in a small area of the left forearm. The patient remained well with durable benefit a further 6 months after cessation of TVEC as illustrated in Figure 3 detailing his overall treatment course.

DISCUSSION

Immune checkpoint inhibitors such as avelumab, used in this case, or the anti-PD1 antibody pembrolizumab have become the mainstay of treating advanced MCC. While only around half of the patients treated have objective responses, there is a small subset of patients who can have long-term disease control.^{4,5} However, a significant portion of patients will experience disease progression after receiving immunotherapy; in this situation, the treatment approach is less clear, as little is known about the mechanisms of resistance to immune checkpoint blockade.

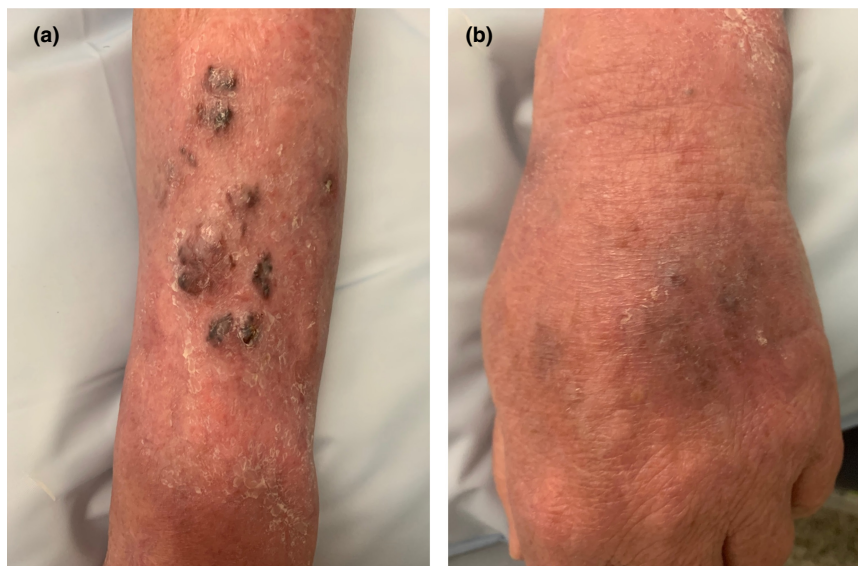


FIGURE 2 (a) Left upper limb forearm response to TVEC. (b) Left hand dorsal aspect response to TVEC.

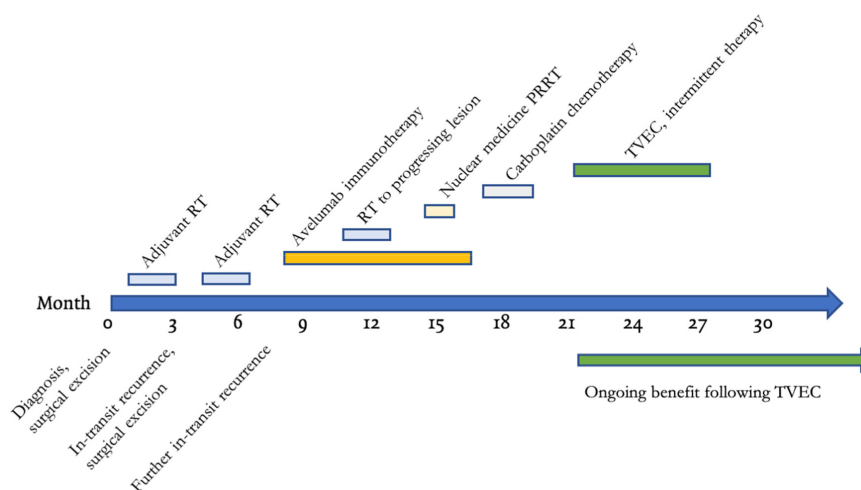


FIGURE 3 Visual schematic of patient's treatment history. Abbreviations: RT, radiotherapy; PRRT, peptide receptor radionuclide therapy; TVEC, Talimogene laherparepvec.

TVEC is an oncolytic virus, based on a modified herpes simplex virus (HSV) type 1, designed to selectively replicate in and lyse tumour cells while promoting regional and systemic antitumour immunity.⁶ In our patient, the introduction of TVEC appears to have augmented the immune response in some way, possibly through the local release of tumour antigens from the injected site, either leading to or combined with induction of systemic immunity.

While the initial experience of the use of TVEC focussed predominantly on cutaneous melanoma, there have now been a small number of cases described in the literature of durable benefit from TVEC in patients with MCC, either used following an immune checkpoint inhibitor or concurrently in combination with a checkpoint inhibitor.^{7,8}

Clinical trials including patients with MCC are underway including a study through the Memorial Sloan Kettering Cancer Center looking at TVEC with or without radiotherapy for melanoma, Merkel cell carcinoma, or other solid tumours (NCT02819843). Further studies will be required to better define the optimal sequencing and use of TVEC with immunotherapy for patients with advanced disease. This case highlights the utility of intratumoural TVEC in not only providing palliative symptomatic benefit, but for some patients a meaningful and durable tumour response as well.

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CONFLICT OF INTEREST

The authors declare no relevant conflicts of interest.

CONSENT

The patient has provided written informed consent for publication.

DECLARATION

We confirm that this manuscript contains original unpublished work that is not being considered for publication elsewhere at the same time.

ORCID

Michael A. Cilento  <https://orcid.org/0000-0003-2216-5650>

[org/0000-0003-2216-5650](https://orcid.org/0000-0003-2216-5650)

Oliver Klein  <https://orcid.org/0000-0003-0022-9553>

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