

Complete clinical response to intralesional talimogene laherparepvec injection in a patient with recurrent, regionally advanced Merkel cell carcinoma



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INTRODUCTION

Merkel cell carcinoma (MCC) is a rare cutaneous neuroendocrine malignancy that is highly aggressive and considered incurable upon distant metastasis. The incidence rate in the United States has significantly increased in the last 30 years and is estimated to be 0.79 per 100,000.¹ The prognosis for advanced MCC is poor, with a 5-year overall survival rate of 0% to 18%.² Although MCC is chemotherapy sensitive, responses are not durable, and most patients with advanced MCC succumb to the disease.

Avelumab and pembrolizumab are the only treatments approved by the US Food and Drug Administration for patients with MCC thus far. A phase II study found a 1-year progression-free survival rate of 30% compared with 0% with chemotherapy.^{3,4}

Talimogene laherparepvec (T-VEC) is a modified oncolytic herpes simplex virus that replicates in tumor cells and expresses granulocyte-macrophage colony-stimulating factor, promoting local and systemic antitumor response. T-VEC treatment was approved by the US Food and Drug Administration for treatment of advanced melanoma. In a phase III study, intralesional T-VEC injection had superior durable and overall response rates compared with subcutaneous granulocyte-macrophage colony-stimulating factor in patients with advanced melanoma.⁵ However, the clinical benefit of T-VEC in patients with advanced MCC is not known. Here we report on a patient with surgically incurable, recurrent MCC who had a complete response to intralesional T-VEC.

Abbreviations used:

CT:	computed tomography scan
MCC:	Merkel cell carcinoma
PET:	positron emission tomography
T-VEC:	talimogene laherparepvec

CASE REPORT

A 66-year-old white man had a 6.5-cm MCC invading into the subcutaneous fat of his left buttock diagnosed in July 2014. He underwent wide local excision of the primary MCC, 2 adjacent satellite lesions, and left inguinal sentinel lymph node, which found one 13-mm positive node. Subsequently, he underwent complete left inguinofemoral lymph node dissection with negative nodes for metastasis. He received adjuvant radiotherapy to the primary site. Subsequently, he received 4 cycles of adjuvant cisplatin/etoposide. In March 2015, his MCC recurred with in-transit metastases in the left thigh and lower back. He then received pembrolizumab. After 1 dose, severe myocarditis developed, which resolved with high-dose prednisone treatment. He achieved nearly 2 years of a complete response after the 1 dose. In March 2017, the MCC recurred with 4 in-transit subcutaneous metastases in his left calf, which grew rapidly by June 2017 (Fig 1, A and B). Starting June 2017, he received T-VEC injection into 3 of the lesions at a dose of 2 mL of 10^6 plaque-forming units/mL followed by 4 mL of 10^8 plaque-forming units of T-VEC injected into the 3 lesions every 2 weeks. His disease regressed within 5 weeks. The

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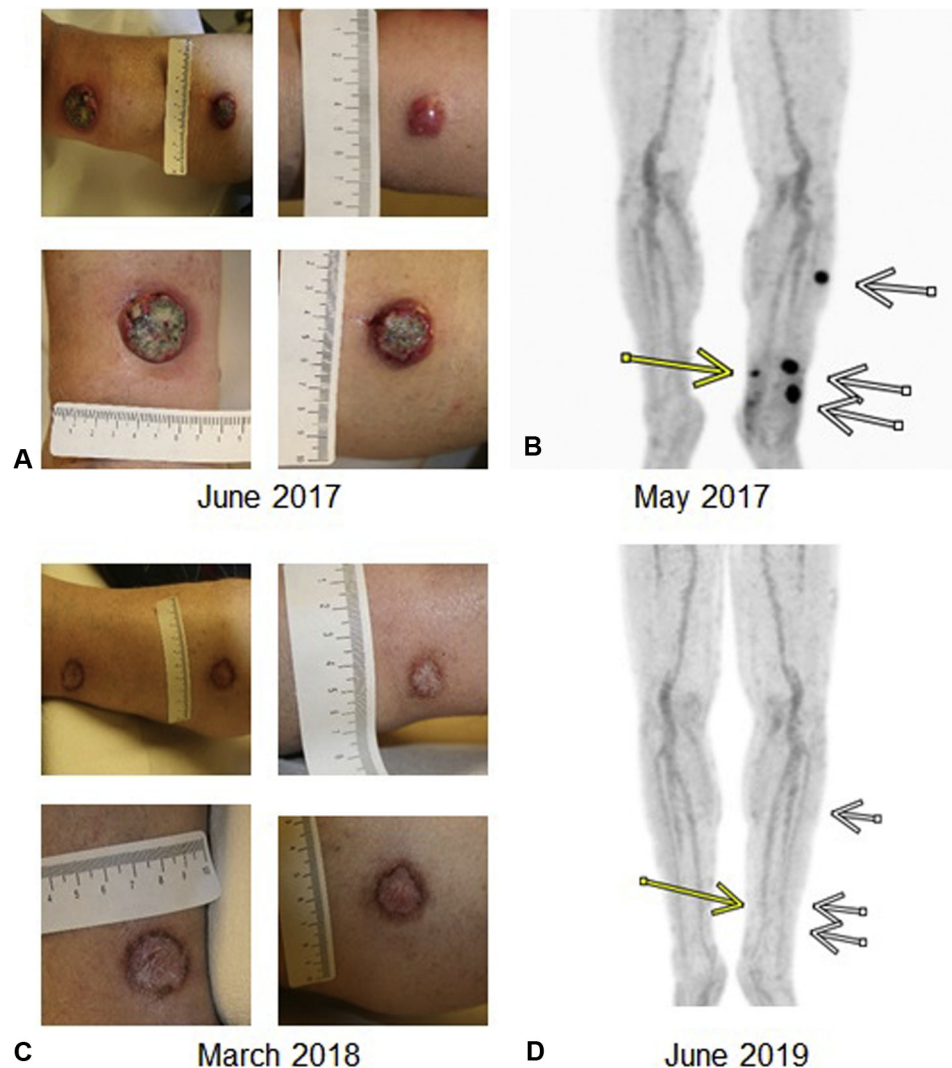


Fig 1. Photographs and PET/CT scan imaging of metastatic Merkel cell carcinoma before and after intralesional T-VEC therapy. **A**, Cutaneous metastases on the left lower leg before initiation of T-VEC therapy. **B**, PET/CT scan image of the cutaneous metastases on the left lower leg 1 month before initiation of T-VEC therapy. **C**, Complete regression of the cutaneous metastases 9 months after the initiation of T-VEC therapy. **D**, PET/CT scan image shows complete regression of the cutaneous metastases 12 months after initiation of T-VEC therapy.

only adverse events were grade 1 fever, chills, and fatigue. A positron emission tomogram (PET)/computed tomogram (CT) scan in September 2017 found reduction in size and metabolic activity of all 4 metastatic lesions, including the un-injected lesion. In February 2018, all 3 injected lesions became flat, without evidence of active metastases (Fig 1, C), and T-VEC was discontinued. A PET/CT scan performed in June 2019 found no areas of metastasis (Fig 1, D).

DISCUSSION

This case report demonstrates a potential benefit of oncolytic virus therapy in MCC. When our patient had recurrence of MCC, he did not have effective

treatment options given his severe myocarditis with pembrolizumab. Intralesional T-VEC resulted in a dramatic durable response for ≥ 2 years even in the uninjected metastatic lesion.

Only 2 cases of intralesional T-VEC treatment in MCC exist in the literature.⁶ As in our case, these patients had regionally advanced disease with surgically incurable MCC. Intralesional T-VEC injection was given to all metastatic lesions as first-line therapy. The patients had durable complete and partial responses, respectively. Unlike these 2 cases, our case also had a complete response in uninjected lesion with T-VEC, demonstrating both an oncolytic and systemic immune response.

Table I. Currently enrolling clinical trials of intralesional T-VEC therapy in patients with Merkel cell carcinoma

Clinical trial	Treatment	Primary endpoint	Phase	Planned no. of patients
NCT02819843	<ul style="list-style-type: none"> • T-VEC with radiotherapy • TVEC without radiotherapy 	PR, CR	II	34
NCT02978625	<ul style="list-style-type: none"> • T-VEC + nivolumab • T-VEC + placebo 	ORR	II	68
NCT02890368	<ul style="list-style-type: none"> • TTI-621* monotherapy • TTI-621* + anti PD-1/PD-L1 antibody • TTI-621* + pegylated interferon-α2a • TTI-621* + T-VEC • TTI-621* + radiation 	Optimal dose finding	I	240

CR, Complete response; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; ORR, overall response rate; PR, partial response.

*TTI-621 is a soluble recombinant fusion protein consisting of CD47 binding domain of human signal regulatory protein- α linked to the Fc region of human IgG1.

One disadvantage of intralesional T-VEC treatment is that it requires injectable lesions. It is also questionable whether the intralesional T-VEC treatment is superior to checkpoint inhibitors in patients with MCC. In patients with metastatic melanoma, intralesional T-VEC therapy has only shown a positive trend of overall survival benefit, whereas the checkpoint inhibitors lead to a significant survival benefit.⁵

Growing evidence suggests that intralesional T-VEC could synergize immune stimulation by checkpoint inhibitors. A phase II study in patients with metastatic melanoma compared a combination of T-VEC and ipilimumab to ipilimumab alone and found a higher response rate (39% vs 18%).⁷ Meanwhile, in a phase IB study, a combination of T-VEC and pembrolizumab versus pembrolizumab alone had a response rate of 62% versus 34%.⁸

There are 3 clinical trials investigating intralesional T-VEC in patients with metastatic MCC (Table I). These include a phase II study of T-VEC with hypofractionated radiotherapy, a phase II study of T-VEC with nivolumab, and a phase I study of T-VEC with TTI-621 (a soluble recombinant fusion protein consisting of CD47 binding domain of human signal regulatory protein- α linked to the Fc region of human IgG1) in solid tumors, including MCC. With these investigations of intralesional

T-VEC treatment, we will better understand its place in the treatment of advanced MCC in the future.

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