



Metastatic melanoma with diffuse melanosis histologically after stable response to talimogene laherparepvec therapy

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INTRODUCTION

Talimogene laherparepvec (T-VEC) is the first oncolytic viral immunotherapy approved for treatment of unresectable recurrent melanoma metastases involving skin, subcutaneous fat, or lymph nodes after initial surgery. T-VEC has a favorable safety profile; however, use has been limited to specialized centers because of a select eligible patient population and logistical concerns.¹ A randomized phase 3 study comparing T-VEC with subcutaneous granulocyte-macrophage colony-stimulating factor in unresectable stage IIIC-IV melanoma (limited visceral disease) showed an improved durable response rate (complete and partial response ≥ 6 months) of 16.3% versus 2.1%.² We report a case of metastatic melanoma with clinically stable disease accompanied by diffuse histologic melanosis in response to T-VEC therapy to highlight important considerations regarding assessment of treatment outcomes.

CASE REPORT

A 68-year-old white man presented with lentigo maligna melanoma of the scalp, Breslow depth of 0.78 mm, microscopic satellitosis, 1/mm² mitosis, and no ulceration. He was treated with wide local excision and negative sentinel lymph node biopsy. Approximately 3 months after surgery, multiple in-transit *BRAF* V600 and *KIT* wild-type metastases

Abbreviations used:

HSV: herpes simplex virus
PPR: progression prior to response
T-VEC: talimogene laherparepvec

developed on the scalp. Whole-body imaging showed no evidence of regional or distant disease.

Given ongoing local recurrences, the patient started immunotherapy with ipilimumab, 3 mg/kg for 4 doses. His course was interrupted because of a complicated urinary tract infection secondary to nephrolithiasis unrelated to immunotherapy. Despite ipilimumab, additional in-transit lesions developed and possible distant disease versus pseudoprogression (pulmonary nodules and mediastinal, hilar, and gastrohepatic lymphadenopathy noted on imaging). Given concern for true progression, pembrolizumab was initiated. After 3 doses, he had grade 3 immune-mediated nephritis requiring a prolonged steroid course. Repeat imaging found an interval decrease in lymphadenopathy and pulmonary nodules. However, progression of the dermal metastases on the scalp continued.

Intratumoral T-VEC therapy was selected to address local disease progression in the setting of recent immune-mediated adverse events and limited alternative treatment options. T-VEC was administered according to standard dosing guidelines. Before initiation of therapy, clinical examination

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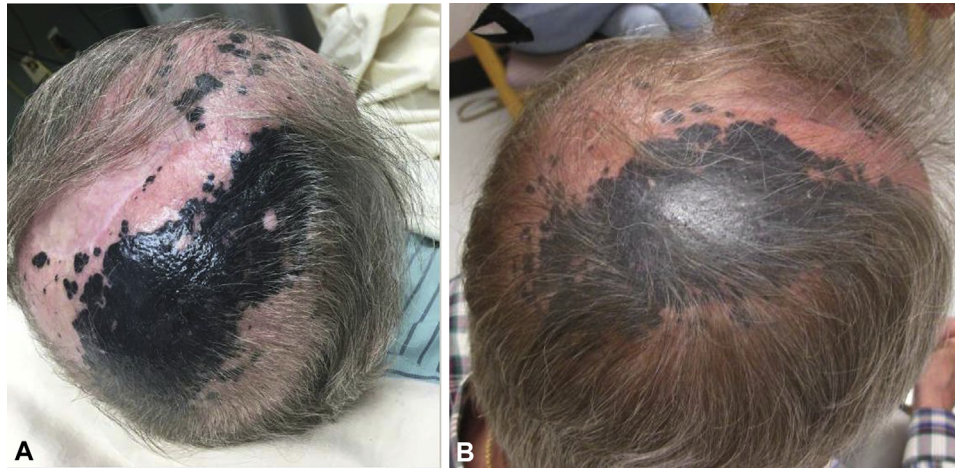


Fig 1. Pretreatment and posttreatment clinical appearance. **A**, Before treatment, numerous blue-black papules coalescing into plaques located diffusely on the scalp. **B**, After treatment, subjective mild thinning of the plaque and increased hair density noted with no appreciable change in color or surface area involvement.

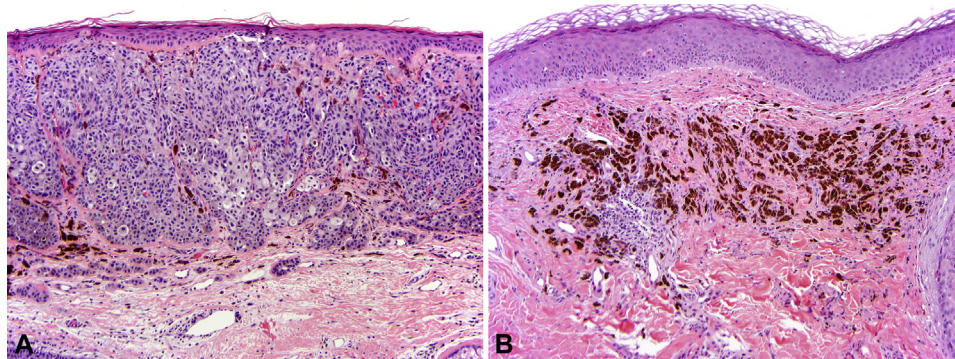


Fig 2. Pretreatment and posttreatment histopathologic appearance. **A**, Before treatment, a representative biopsy result (injected lesion) shows numerous compact nests of pleomorphic melanoma cells in the upper dermis. A few scattered melanophages filled with brown melanin pigment are also present. **B**, After treatment, a clinically darkly pigmented lesion is composed of large clusters of melanophages only. No viable melanoma cells are present. (Hematoxylin-eosin stain; original magnification: $\times 100$).

found numerous blue-black papules coalescing into plaques on the scalp without significant cervical lymphadenopathy (Fig 1, A). Representative lesions were biopsied, confirming the presence of melanoma (Fig 2, A).

Overall, the patient tolerated T-VEC well, reporting low-grade fevers and chills after initial treatment, which resolved with acetaminophen premedication. Topical lidocaine cream was used before injections to lessen pain. After 6 doses, subtle posttreatment changes were noted clinically including mild plaque thinning and slightly increased hair density but no significant color change within the treated plaque. Additional lesions were subsequently treated with similar outcomes (Fig 1, B).

Skin biopsies were performed after 9 doses to assess histologic response. Interestingly, biopsies from both treated and untreated lesions had identical findings: superficial dermal tumoral melanosis with no melanoma tumor cells consistent with disease regression (Fig 2, B). After 10 biopsies failed to find viable melanoma cells, the decision was made to transition to observation after 14 doses. After 12 months off therapy, no new cutaneous lesions concerning for in-transit melanoma developed, and staging computed tomography scans remain stable without evidence of recurrent distant disease. At the most recent evaluation, there was evidence of decrease in dermal pigment.

DISCUSSION

T-VEC is a live attenuated herpes simplex virus (HSV)-1, modified to selectively replicate within tumor cells and induce host antitumor immunity. Mechanistically, the virus causes direct tumoral cell lysis at the injection site and generates an immune response via release of tumor-associated antigens occurring in the context of virally mediated granulocyte-macrophage colony-stimulating factor production.¹ In prior studies, histopathologic analysis of responsive lesions confirmed the presence of HSV antigen-associated tumor necrosis and induction of host immune response including increased MART-1–specific CD8⁺ effector and reduction in CD4⁺ FoxP3⁺ regulatory T cells.^{3,4}

T-VEC has an excellent safety profile with no treatment-related fatalities and rare serious adverse events; most common are mild constitutional symptoms and local injection site reactions. Baseline HSV serostatus has no influence on patient tolerance or response to therapy.⁴ Subgroup analysis of phase 3 data suggests T-VEC is most efficacious in stage IIIB to IV M1a melanoma, with greater improvements in durable response rate and overall survival seen compared with those in the intention-to-treat population.⁵ Despite variable efficacy, responses have been documented for all lesion types.⁶

Similar to other immunotherapies, response to T-VEC may be delayed or include progression prior to response (PPR) (ie, pseudoprogression). In phase 3 data, the median time to response was approximately 4 months, and nearly half of responders experienced PPR.^{2,6} Distinguishing true progression from PPR is challenging and justifies continued treatment, assuming the patient is tolerating treatment. When administering T-VEC, clinicians should monitor response by assessing qualitative (thickness and morphology) and quantitative (size) changes in lesions on physical examination and imaging, as appropriate.

T-VEC has several limitations including logistical challenges surrounding storage, preparation, and administration of a live virus. Currently, T-VEC is classified as a biosafety level 1 agent; however, many centers follow level 2 procedures for added precaution.¹ No molecular biomarkers exist to improve patient selection; however, distribution of metastases is most informative given superior efficacy in non-visceral disease and the need for accessible lesions to inject.⁵ Furthermore, pace of disease and eligibility for other systemic therapies should be considered.

Histologic melanosis in both injected and uninjected lesions despite a minimally changed clinical examination in our patient classifies as stable disease

response per RECIST (Response Evaluation Criteria In Solid Tumors).⁷ Overall, this finding highlights the limitations of clinically assessing response to T-VEC and need for histologic evaluation. This finding also highlights the potential value of T-VEC for patients with progressive disease after systemic immunotherapy. It is possible that prior immunotherapy affected response to T-VEC in this case. Combination therapy with T-VEC or other intratumoral injections and immune checkpoint blockade agents is an active area of clinical investigation.^{1,8,9} The ability of intratumoral injections to generate an antitumor immune response may work synergistically with systemic checkpoint inhibitors and become more uniformly applicable in melanoma and other tumors. Thus, with possible expanded indications on the horizon, physicians should be aware of the advantages, limitations, and aforementioned clinical considerations for administering T-VEC and other intratumoral therapies.

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