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Complete response of Merkel cell carcinoma with talimogene laherparepvec (TVEC) monotherapy

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Abstract

Merkel cell carcinoma (MCC) is a rare neuroendocrine neoplasm, warranting surgical excision with sentinel lymph node biopsy. In later stages, adjuvant chemotherapy and radiation are required owing to its aggressive malignant behavior. We describe a 62-year-old woman who presented with multifocal recurrence of MCC and was not a candidate for immunotherapy or surgery. The patient underwent four treatments of intratumoral talimogene laherparepvec (TVEC) and demonstrated a complete response with no histologic evidence of remaining MCC on four scouting biopsies. Although TVEC therapy is currently approved for the treatment of advanced stage melanoma, it is still being investigated in MCC. This case supports the use of TVEC as monotherapy in select patients with locally advanced MCC who are not candidates for surgery or systemic immunotherapy.

Keywords: carcinoma, Merkel, talimogene laherparepvec, TVEC

Introduction

Merkel cell carcinoma (MCC) is a rare, aggressive cutaneous neuroendocrine neoplasm associated with high rates of mortality [1], which commonly presents in areas of cumulative high ultraviolet (UV) light exposure [2]. Males are nearly twice as likely to be affected compared to females [2], with a median age of onset of 75-80 years [3]. Recognized risk factors include UV exposure, immunosuppression, and infection with Merkel cell polyomavirus [1]. Cutaneous manifestations are commonly the only clinical presentation of MCC, occurring in 50%-76 % of cases as a solitary, painless, pink-red or blue, firm nodule or plaque. The tumor shows a predilection for the head and neck region, followed by lower limbs and upper extremities [4]. The goal of MCC treatment is to achieve locoregional control through surgical excision or immunotherapy (e.g., pembrolizumab), [1]. Herein, we describe a patient with MCC, who was not a candidate for surgery or immunotherapy and achieved complete response with intratumoral talimogene laherparepvec (TVEC) therapy.

Case Synopsis

A 62-year-old woman presented to dermatology clinic for numerous itchy pink papules on the left forearm that appeared over the past several months. She had a history of MCC and was concerned for recurrence. When she was originally diagnosed with MCC a year and half earlier, she was deemed a poor surgical candidate due to her medical comorbidities and was started on pembrolizumab. Following her second infusion, she was hospitalized for decompensated heart failure presumed secondary to an infusion reaction. Her hospitalization was complicated by septic shock, resulting in a prolonged intensive care unit admittance and several months of rehabilitation. She reported that the original presenting MCC lesions disappeared following the two infusions of pembrolizumab. Her past medical history was also significant for breast cancer, cervical cancer, hypertension, congestive heart failure, diabetes mellitus type 2, emphysema, anxiety, and hypothyroidism.

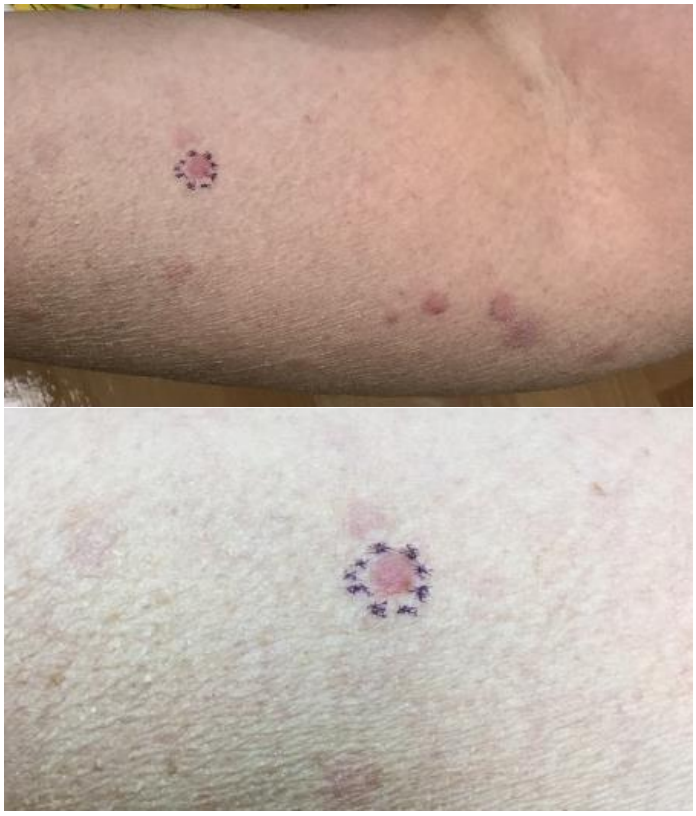

Figure 1. *Numerous homogenous pink structureless papules on the left anterolateral forearm.*

On examination, the patient displayed numerous homogenous pink structureless papules on the left anterolateral forearm (**Figure 1**). A punch biopsy of the left forearm revealed a basaloid tumor with neuroendocrine features, positive for CK20 in a perinuclear dot-like pattern (**Figure 2A**, **B)** and negative for TTF1 and Napsin A, consistent with MCC. Laboratory analysis was significant for negative anti-merkel cell antibody titers and positive VP1 capsid antibody titers. A positron emission tomography computed tomography scan was performed for staging, which revealed multifocal locoregional disease in the left arm without distant metastases. Given the multifocal and cutaneous nature of her disease and serious adverse reaction to prior immunotherapy, the patient was started on intratumoral TVEC therapy after discussion at a multi-disciplinary tumor board. Following the first injection, the patient experienced a mild fever, chills, and aches for two days. The patient exhibited clinical resolution following four treatments of TVEC and underwent four scouting biopsies at the sites of previous lesions, all of which showed robust inflammation and no remaining MCC (**Figure 3**).

Case Discussion

Classically, MCC tumors present as solitary flesh-colored, pink-red to violaceous dome-shaped firm nodules that are rapidly growing and present equally in areas of sun exposure and non-sun exposure [4]. Less commonly, in 20% of cases, MCC presents as papules with overlying scale; nearby skin shows signs of UV damage (e.g., actinic keratosis, solar lentigines, telangiectasias) and the tumor can often be confused for basal cell or squamous cell

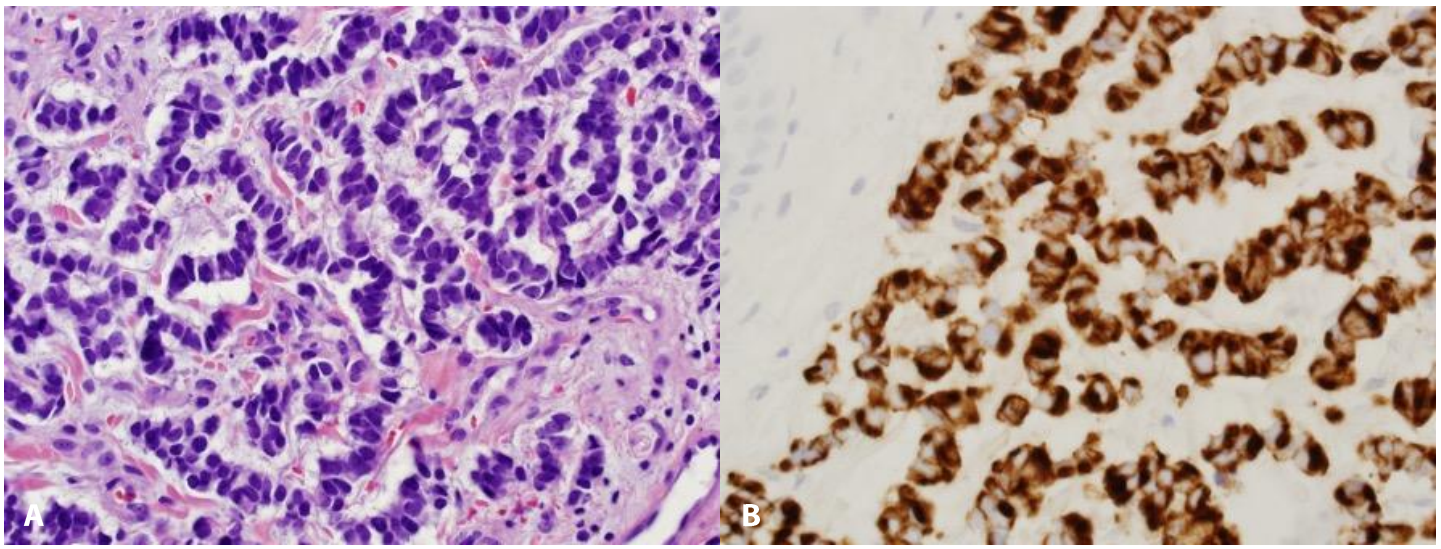

Figure 2. ***A)*** *H&E stain of punch biopsy revealing a basaloid tumor with neuroendocrine features, 400×.* ***B)*** *Immunohistochemistry positive for CK20 with perinuclear dot-like attenuation, 400×.*

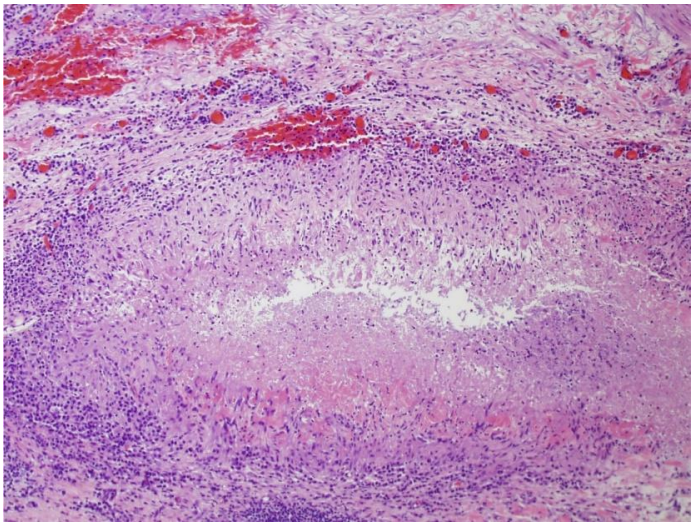

Figure 3. *H&E stain of scouting punch biopsy revealing granulomas with central caseating necrosis and immunohistochemistry negative for CK20, 100×.*

carcinoma. A third small sub-group presents with lymphadenopathy and without a known primary site [4]. Histologically, MCC is characterized by small round blue tumors cells with "salt-and-pepper" chromatin. Most express cytokeratins, such as CK20 (present in up to 95% of cases), which are identified through immunohistochemistry staining and demonstrate paranuclear dot-like and/or cytoplasmic patterns [4]. Typically, immunohistochemistry stains for TTF1 and CDX2 are negative and help distinguish MCC from small cell lung cancer, another neuroendocrine neoplastic process [4].

Merkel cell carcinoma treatment aims to achieve locoregional control while minimizing treatment related toxicity. Stages I-II MCC can often be treated with surgical excision with or without adjuvant radiotherapy [1]. The most successful treatments to date for nonresectable MCC (stage III or greater) are drugs targeting programmed cell death protein 1 (PD1; e.g., pembrolizumab), [5]. PD1 is present on activated CD4+ and CD8+ T lymphocytes, B-cells, natural killer cells, macrophages, and dendritic cells [6]. When PD1 binds programmed cell death protein ligand 1 or 2 (PDL1 or PDL2), negative signals inhibit T-lymphocyte anti-tumor activity, which is common in many neoplastic processes [6]. Thus, targeting the PD1/PDL1 axis with pembrolizumab (a humanized anti-PD1 monoclonal antibody) frees T-lymphocytes to perform anti-tumor immunity [7].

Talimogene laherparepvec (TVEC), a genetically modified herpes simplex 1 virus which encodes human granulocyte-macrophage colony-stimulating factor, was approved in 2015 for the treatment of advanced stage melanoma and was the first FDA-approved oncolytic viral immunotherapy [7]. Mechanistically, intratumoral injection of TVEC leads to direct lysis of malignant cells, thereby enhancing dendritic cell antigen presentation and systemic antitumor immunity [7]. Although not a novel treatment, few reports document successful treatment of MCC with TVEC. A prior case series of four similar patients with multifocal regionally advanced MCC demonstrated complete regional responses to TVEC, with median progression-free survival of 16 months [7]. Similarly, another report documents two patients who achieved durable complete regional responses at 5 months and 7 months following their final TVEC injection, respectively [8]. Interestingly, one report describes complete remission of non-injected lesions, which lends credence to the theory that TVEC therapy is capable of stimulating a systemic immune response [3]. Ongoing clinical trials are evaluating the utility of TVEC therapy for the treatment of metastatic MCC [9]. When used as monotherapy for metastatic melanoma, TVEC therapy has inferior survival benefit compared to monotherapy with checkpoint inhibitors such as pembrolizumab [3]. However, it is believed that TVEC therapy may produce synergistic effects when used in combination with PD1/PDL1 axis inhibitors, as seen in two patients who experienced complete response with combination therapy [10]. This case highlights TVEC monotherapy as having clinical value in the treatment of MCC in the proper clinical context and suggests that further prospective investigation is warranted.

Conclusion

Talimogene laherparepvec is the first approved oncolytic viral immunotherapy which induces both local and systemic immune responses. Several reports have emerged advocating TVEC to promote a complete response in the treatment of advanced MCC and this case advocates TVEC monotherapy as remaining a valid clinical option, especially in

patients who are unfit to undergo systemic immunotherapy.

Potential conflicts of interest

The authors declare no conflicts of interest.

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