Inflammatory melanoma in transit metastases with complete response to talimogene laherparepvec

Jonathan T. Blackmon,[a] Michael S. Stratton, MD,[b] Young Kwak, MD,[b] Peter G. Pavlidakey, MD,[c] Andrzej T. Slominski, MD,[d] Svetlana B. McKee, RN, BSN,[e] Toni M. Viator, RN,[f] Ju Young Kim, PhD,[g] Conway C. Huang, MD,[h] and Robert M. Conry, MD[e]
Lookout Mountain, Georgia; Birmingham, Alabama; and Carlsbad, California

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INTRODUCTION

Inflammatory melanoma was first described in 1984 in 2 patients presenting with nodular cutaneous melanomas resected from the back followed 4 to 12 months later by recurrence in the form of diffuse, indurated, erythematous skin 20-25 cm in diameter with scattered nodularity.[1] Microscopic examination found melanoma cells in the dermis and dermal lymphatics. Both patients died of hematogenous metastases within 6 months of their inflammatory melanoma recurrences.[1] Although histopathologic examination of melanoma frequently finds an associated inflammatory cell infiltrate, gross clinical inflammation is extremely rare.[1] A search of PubMed and Google Scholar performed on August 5, 2016 found 3 additional case reports of inflammatory melanoma, 2 of which involved direct dermal lymphatic extension from grossly involved lymph nodes.[2-4] Here we report the first, to our knowledge, successfully treated case of surgically incurable inflammatory melanoma with emphasis on molecular and immunophenotypic characterization.

Abbreviation used:

TVEC: Talimogene laherparepvec

CASE REPORT

A 79-year-old white man presented with an ulcerated, epithelioid, melanotic melanoma of the left dorsal forearm, 1.6 mm deep, that was widely excised with negative margins and a negative sentinel lymph node biopsy from the left axilla (T2b, N0, M0). Beginning a year after his primary excision, and over a period of 23 months, 6 separate satellite melanoma nodules within 2 cm of the original scar were excised. Eight months later, a surgical oncologist aggressively excised additional satellite melanoma nodules, and repeat sentinel lymph node biopsy found melanoma in 1 of 3 left axillary nodes. The *BRAF* gene was wild-type. Positron emission tomography/computed tomography found no evidence of metastatic melanoma. Melanoma again recurred locally 2 months later with 6 pigmented dermal satellite nodules. Radiotherapy consisting of 36 Gy in 6 fractions over 2 weeks was delivered to the left forearm encompassing all previously affected sites with a 2-cm margin. Four months later, he had a clinical complete response to radiotherapy with all satellite nodules becoming macular, but 2 months thereafter he presented with 60 new punctate, black, dermal nodules affecting most of the left forearm with a confluent, erythematous plaque extending from the dorsum of the left hand and thumb to the mid upper arm (Fig 1, *A*). Skin

From Covenant College[a]; the Deparment of Dermatology[b] and Divisions of Dermatology and Pathology,[c] Dermatopathology,[d] Hematology Oncology,[e] and Dermatology[h]; and Comprehensive Cancer Center,[f] University of Alabama at Birmingham; and Navigate BioPharm Services, Inc, a Novartis company, Carlsbad.[g]

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Correspondence to: Robert M. Conry, MD, Melanoma Program Director, Associate Professor, Division of Hematology Oncology, University of Alabama at Birmingham, 2145 Bonner Way, Birmingham, AL 35243. E-mail: rconry@uabmc.edu.

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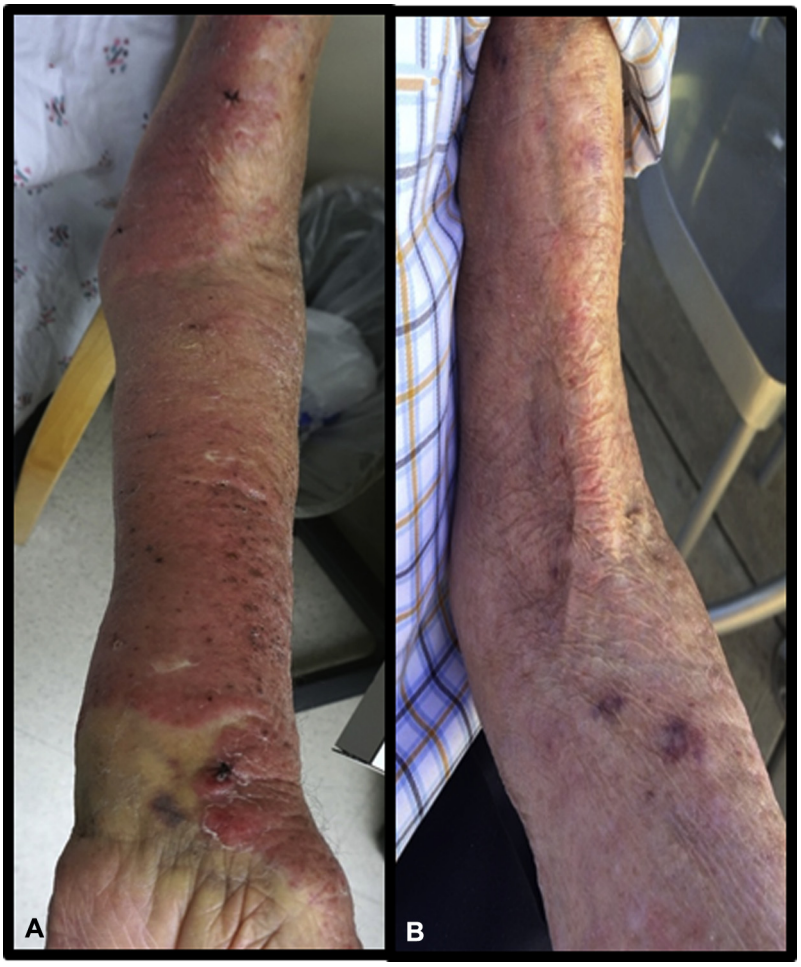

Fig 1. **A**, Sharply demarcated red plaque with intermixed dark brown to black papulonodules from the volar wrist proximal to the upper arm. **B**, Posttreatment improvement in inflammatory plaque.

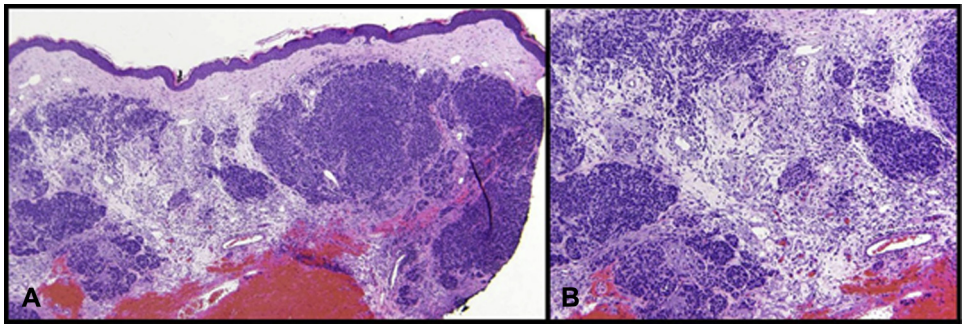

Fig 2. **A**, Large nodules of atypical melanocytes present within the dermis intercalating between solar elastosis. **B**, Nodules of atypical melanocytes intercalating between solar elastosis with both nests and single cells. (Original magnifications: **A**, ×4; **B**, ×10.)

punch biopsies from the left biceps; volar wrist; and the medial, lateral, and volar forearm all found a diffuse inflammatory plaque with widespread dermal intercalation by predominantly amelanotic melanoma cells (Fig 2, *A* and *B*). Quantitative multiplexed immunohistochemistry for expression and proximity of PD1 and PD-L1 from 4 tumor biopsy sections over the left forearm conducted by Navigate BioPharm Services Inc (Carlsbad, CA) using AQUA technology found that PD-L1 expression in melanoma cells varied from 1% to 70% depending on the biopsy location, and there was an average

PD1/PD-L1 interaction score of 1080, predictive of significant activity of this immune checkpoint pathway.[5] Analysis of myeloid-derived suppressor cells found that 14% to 85% of cells were $CD11b^{+}HLA\text{-}DR^{-}IDO\text{-}1^{+}$ cells. Tumor-associated macrophages analyzed by $CD11b^{+}HLA\text{-}DR^{+}IDO\text{-}1^{+}$ ranged from 1% to 15%. T-cell infiltration ranged from 1% to 10% of total cells and 2% to 4 % of the CD3 cells were found to be $CD25^{+}FOXP3^{+}$, indicative of a low burden of regulatory T cells. Mutational analysis by Foundation Medicine, Cambridge, MA found 9 significant genomic alterations affecting *HRAS*, *CDKN2A p16INK4a*, *TERT* promoter, *TP53*, *NF2*, *ERRFl1*, *FLT1*, *GRM3*, and *RAC1* among 315 genes interrogated. Positron emission tomography/computed tomography found mild hypermetabolism diffusely over the left forearm but no distant metastases. Talimogene laherparepvec (TVEC), an oncolytic viral vaccine, injected intratumorally into 20 sites within the dermal plaque, was initiated according to the labeled dose and schedule for surgically incurable stage IIIC melanoma in this 84-year-old man with serious cardiac comorbidity, making immune checkpoint blockade less attractive. After 8 doses of TVEC over 20 weeks, a clinical partial response was achieved by Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria (Fig 1, *B*), and positron emission tomography/computed tomography found a reduction in diffuse, superficial hypermetabolism over the left forearm and no new disease. Two months after the last TVEC dose, skin punch biopsies of residual raised, erythematous lesions from 4 sites across the left wrist, forearm, and upper arm found only granulomatous dermatitis thought secondary to TVEC injections with no detectable melanoma consistent with a pathologic complete response 7 months after initiation of oncolytic viral therapy.

DISCUSSION

Melanoma cell migration through dermal lymphatics draining the primary cutaneous site is fairly common and may produce satellite or in-transit metastases. However, inflammatory melanoma is very rare, with the case described herein representing, to our knowledge, only the sixth reported since 1984. These cases have all involved marked melanoma invasion of dermal lymphatics producing plugging which contributed to cutaneous edema. Our case also showed extensive intercalation of melanoma cells freely through the dermis outside lymphatic vessels producing a well-demarcated, erythematous plaque.

A murine model of inducible inflammatory melanoma has been described based on conditional deletion in melanocytes of *INK4a/ARF* tumor suppressor genes with concomitant expression of oncogene *HRAS G12V*.[6] Our patient's inflammatory melanoma contained an uncommon activating, oncogenic mutation in *H-Ras* (Q61R) and a loss of function mutation in the tumor suppression p16INK4a P114L mimicking the murine model. A molecular mechanism linking an inflammatory tumor microenvironment with melanoma de-differentiation, invasiveness, and recruitment of myeloid-derived suppressor cells observed in the model involves engagement of c-Jun by tumor necrosis factor-α, with reciprocal antagonism of microphthalmia-associated master transcription factor favoring ineffectual Th2-oriented chronic inflammation.[6-9] This phenotype is also associated with epithelial-mesenchymal transition in which melanoma cells lose contact with neighboring cells and develop migrating characteristics.[7]

Our patient initially presented with a pigmented, nodular melanoma of low-to-intermediate aggressiveness and lacking inflammation grossly. This phenotype persisted through multiple satellite recurrences resected on 5 occasions over almost 3 years. Although radiotherapy initially led to tumor regression, within 6 months, phenotypic switching occurred to a much more aggressive, relatively hypopigmented, and strikingly inflammatory form of melanoma containing functional *HRAS* and *INK4a* mutations as in the murine model of inflammatory melanoma. Gross inflammation and rapidly advancing dermal migration of melanoma cells may be mechanistically linked, and recruitment of myeloid-derived suppressor cells may impair adaptive immunity freeing the melanoma for more rapid dissemination.[10] The inflammatory melanoma reported herein had significant expression of the PD1/PD-L1 immune checkpoint, and our patient did achieved a pathologic complete response ongoing at 7+ months to immunotherapy with TVEC.

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