CASE REPORT

Regression of pigmented lesions in a patient with metastatic melanoma treated with immunotherapy

Zachary Schwager, MD, Mary E. Laird, BA, and Jo-Ann Latkowski, MD
New York, New York

Key Words: immunotherapy; melanoma; nevi; programmed cell death protein 1 inhibitors.

INTRODUCTION

The programed cell death protein 1 (PD-1) inhibitors nivolumab and pembrolizumab are promising new therapies for the treatment of metastatic melanoma. PD-1 inhibitors function by blocking down regulatory pathways of T-cell activity, thereby increasing T-cell activation and antitumor activity. Hypopigmentation, including vitiligo, may occur in up to 15% to 25% of treated patients and is hypothesized to occur by immune destruction of benign melanocytes by antitumor T cells. We present the case of a patient with metastatic melanoma who experienced fading and disappearance of numerous melanocytic nevi after being treated with PD-1 inhibitors.

CASE REPORT

A 69-year-old man with history of V600E BRAF-mutated metastatic melanoma presented for total body skin examination. He reported that over the prior 6 months he experienced significant lightening of the skin on his trunk and disappearance of many longstanding moles.

A 0.7-mm melanoma with features of regression over his right back was originally diagnosed and was treated with wide local excision. Ten years later, right inguinal lymphadenopathy developed, and a lymph node dissection found metastatic melanoma. Metastatic lesions were subsequently identified in the right groin, bones, and lungs. He was initially treated with various regimens of ipilimumab, trametinib, and dabrafenib but had progression of disease. In October 2015, he was started on pembrolizumab but discontinued after 4 cycles secondary to thyroiditis. Subsequently, the patient was briefly enrolled in a phase II trial of glembatumumab vedotin; however, he unenrolled because of neuropathy and disease progression. At this time in June 2016, the patient was started on ipilimumab and nivolumab. After experiencing transaminitis, he was continued on nivolumab alone, which he tolerated well.

Over this treatment course, total body skin examinations were regularly performed with photographs taken to document new or changing lesions. At presentation in March 2017, review of body photography confirmed fading or disappearance of numerous melanocytic nevi and lentigines over the patient’s back (Fig 1, A-C), which appeared to coincide with initiation of anti–PD-1 therapy in 2015, about 2 years before his current visit. Additionally, recent imaging showed stable disease, and there was clinically appreciable shrinking of the tumor in his right groin.

DISCUSSION

Immune destruction of nonmalignant melanocytes is a recognized phenomenon in patients with melanoma. Halo nevi, vitiligo, and other forms of melanoma-associated leukoderma are rare but well described and are thought to represent immune

From New York Harbor Veterans Affairs Medical Center and The Ronald O. Perelman Department of Dermatology, New York University.

Funding sources: None.
Conflicts of interest: None declared.
Correspondence to: Jo-Ann Latkowski, MD, The Ronald O. Perelman Department of Dermatology, 240 E 38th Street, 11th floor, New York, NY 10016. E-mail: Jo-ann.Latkowski@nyumc.org.

JAAD Case Reports 2018;4:421-3.
2352-5126
Published by Elsevier on behalf of the American Academy of Dermatology, Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
https://doi.org/10.1016/j.jdcr.2017.10.019
sensitization to melanocyte-specific antigens in growing melanomas. Recent studies confirmed that circulating antibodies to melanocyte cytoplasmic proteins can be isolated in patients with halo nevi those with melanoma, and tumor-specific CD8+ T cells can be found in lesions of melanoma-associated vitiligo.

Melanoma associated hypopigmentation occurs at a significantly higher rate in patients treated with immunotherapies, and PD-1 blockade specifically is associated with a markedly increased incidence. Vitiligo-like lesions and other hypopigmentation are reported in up to 15% to 25% of patients receiving PD-1 inhibitors. Only 3.4% of patients treated with ipilimumab (a cytotoxic T-lymphocyte–associated antigen 4 [CTLA-4] inhibitor) go on to have vitiligo.

It is hypothesized that increased immune surveillance and antitumor cytotoxic T-cell activity may enhance immune destruction of nonmalignant melanocytes through recognition of shared antigens including MART-1, gp100, and tyrosinase. Interestingly, only patients with melanoma receiving immunotherapy have hypopigmentation. Patients receiving PD-1 inhibitors for other malignancies do not have significant increases in vitiligo. This finding supports the hypothesis that hypopigmentation in PD-1–treated melanoma patients occurs by immune cross-reaction to antigens shared by melanoma cells and benign melanocytes. Additionally, available data show a superior treatment response in melanoma patients who have hypopigmentation, especially vitiligo, after treatment with immunotherapies. Thus, hypopigmentation may be a marker of robust and effective cellular immune response to melanoma antigens.

Although vitiligo is well recognized in immunotherapy-treated melanoma patients, we are aware of only one other case report of fading or disappearance of nevi or lentigines in this setting. In a case by Wolner et al., a patient with metastatic melanoma treated with pembrolizumab experienced fading or disappearance of nevi and numerous seborrheic keratoses and lentigines; this patient also had poliosis. In our case, clinically documented fading of lesions occurred in the approximately 2 years after initiation of treatment with PD-1 inhibitors (Fig 1, A–C). During this period, the patient initially received pembrolizumab, was then briefly enrolled in a clinical trial of non–PD-1 inhibitor therapy, and then started on nivolumab about 10 months before his current presentation. The patient believes that he noted significant lightening of skin and nevi in the months after initiation of nivolumab. Additionally, during treatment with nivolumab, there was evidence of disease regression on positron emission tomography/computed tomography and shrinkage of groin tumor mass clinically, raising the possibility that immune destruction of nevi correlated with antitumor activity in this patient.

These cases provide evidence that immune checkpoint inhibitors can affect dynamic changes in benign pigmented lesions when used to treat melanoma. In addition to tumor-nevus antigen cross-reaction, microenvironmental PD-1 ligand expression may play a role in this phenomenon. PD-1 ligand is highly expressed in local tumor environments, including melanoma, and exerts a protective, anti–T-cell effect. However, at least 5% of benign melanocytes and 35% of benign nevus cells also express PD-1 ligand. Thus, blockade of PD-1 may render benign pigmented lesions such as nevi and lentigines more susceptible to immune attack.

Our case is complicated by the fact that the patient underwent extensive treatment with nonimmunomodulatory therapies including BRAF and MEK inhibitors, and ipilimumab immunotherapy, before
anti-PD1 therapy. However, there was no appreciable hypopigmentation after these treatments (Fig 1, A and B). Hypopigmentation is rarely associated with anti-CTLA-4 therapy and unreported with BRAF and MEK inhibitors or glembatumumab vedotin. Nonetheless, it is unclear what impact these prior and concomitant treatments may have on the clinical course. Our hypothesis of causality in this case is based on the timing of therapy and clinical changes as well as an empirically supported mechanism by which increased immune surveillance may lead to targeted, T-cell-mediated destruction of melanocytes in the setting of PD-1 blockade.

We believe this is only the second published report of immunotherapy-induced fading of pigmented lesions in melanoma. It further describes and validates a rare, but possibly underrecognized phenomenon. Additional research is needed to better characterize the cellular immunology involved and to determine the incidence and any associated prognostic significance.

REFERENCES
1. Ott PA, Hodi FS, Robert C. CTLA-4 and PD-1/PD-L1 blockade: new immunotherapeutic modalities with durable clinical benefit in melanoma patients. Clin Cancer Res. 2013;19(19):5300-5309.
2. Hwang SJ, Carlos G, Wakade D, et al. Cutaneous adverse events (AEs) of anti-programmed cell death (PD)-1 therapy in patients with metastatic melanoma: a single-institution cohort. J Am Acad Dermatol. 2016;74(3):455-461.e1.
3. Hua C, Boussemaire L, Mateu C, et al. Association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab. JAMA Dermatol. 2016;152(1):45-51.
4. Bystryn J, Rigol D, Friedman RJ, Kopf A. Prognostic significance of hypopigmentation in malignant melanoma. Arch Dermatol. 1987;123(8):1053-1055.
5. Lynch SA, Bouchard BN, Vijayasardhini S, Yuasa H, Houghton AN. Antigens of melanocytes and melanoma. Cancer Metastasis Rev. 1991;10(2):141-150.
6. Le Gal F, Lefebvre P, Deschemin J, et al. Direct evidence to support the role of antigen-specific CD8 T cells in melanoma-associated vitiligo. J Invest Dermatol. 2001;117(6):1464-1470.
7. Teulings H, Limpens J, Jansen SN, et al. Vitiligo-like depigmentation in patients with stage III-IV melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis. J Clin Oncol. 2015;33(7):773-781.
8. Sanlorenzo M, Vujic I, Daud A, et al. Pembrolizumab cutaneous adverse events and their association with disease progression. JAMA Dermatol. 2015;151(11):1206-1212.
9. Wolner Z, Marghoob A, Pulitzer M, Postow M, Marchetti M. A case report of disappearing pigmented skin lesions associated with pembrolizumab treatment for metastatic melanoma. Br J Dermatol. 2017 [Epub ahead of print].
10. Rodic N, Anders RA, Eshleman JR, et al. PD-L1 expression in melanocytic lesions does not correlate with the BRAF V600E mutation. Cancer Immunol Res. 2015;3(2):110-115.