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A case report of disappearing pigmented skin lesions associated with pembrolizumab treatment for metastatic melanoma

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Abstract

Pembrolizumab is an immune checkpoint inhibitor that targets the programmed cell death (PD)-1 receptor. Common cutaneous adverse side effects of PD-1 inhibitors include maculopapular rash, pruritus, vitiligo, and lichenoid skin and mucosal reactions. Here, we describe a man in his sixties with metastatic melanoma treated with pembrolizumab who subsequently developed fading or disappearance of pigmented skin lesions, lightening of the skin, and poliosis of the eyebrows, eyelashes, and scalp and body hair. Compared to baseline high-resolution three-dimensional total body photography, we observed fading or disappearing of solar lentigines, seborrheic keratoses, and melanocytic naevi, suggesting that PD-1 inhibitors may affect the evolution of these benign skin lesions. With dermatoscopic follow-up, altered lesions showed either blue-grey peppering/granularity or fading in colour without other identifiable features. No halo lesions or lesions with surrounding inflammation were identified. One changed pigmented lesion that showed blue-grey peppering/granularity on dermoscopy was biopsied and interpreted as a macular seborrheic keratosis with melanophages. Further studies are required to elucidate the effects of PD-1 inhibition on benign skin lesions.

Introduction

Pembrolizumab is an immune checkpoint inhibitor that targets the programmed cell death (PD)-1 receptor on T-cells and is approved by the U.S. Food and Drug Agency for treatment of metastatic melanoma, non-small cell lung cancer, and head and neck squamous cell

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Conflicts of Interest:

Dr. Marchetti reports that he has served as a consultant to IGNYTA.

Dr. Postow reports he has participated in advisory boards for Novartis and Bristol-Meyers Squib (BMS); receives honoraria from BMS and Merck; has a research grant with BMS

Mr. Wolner, Dr. Marghoob, and Dr. Pulitzer have no conflicts of interest to disclose.

cancer.(1) Cutaneous toxicities are the most common immune-related adverse event associated with checkpoint inhibitors, occurring in 30–40% of patients treated with pembrolizumab.(2) Maculopapular rash appears most frequently but vitiligo, pruritus, lichenoid skin and mucosal reactions, psoriasis, oral mucositis, and bullous pemphigoid have all been reported.(3–5) Here, we describe a patient whose pigmented lesions, including naevi, seborrheic keratoses, and lentigines, faded or disappeared after initiating pembrolizumab therapy.

Report of a case

A man in his sixties presented with at least stage IIIa melanoma (T2aN1aMx) of the right lower back status post wide local excision and sentinel lymph node biopsy. Four months later, he was diagnosed with *HRAS* mutant metastatic melanoma to the liver and initiated pembrolizumab therapy 2mg/kg/dose every 3 weeks. The patient experienced partial disease response after 3-months of treatment, which has remained durable for a total duration of 13-months with ongoing pembrolizumab 2mg/kg/dose every 3-weeks. He was not treated with any form of systemic therapy prior to pembrolizumab.

The patient reported whitening of the eyelashes and eyebrows 4-months after starting pembrolizumab, with subsequent development of whitening of the scalp and body hair. He later reported dilution of skin pigmentation and fading or disappearance of pigmented skin lesions. Compared to high-resolution three-dimensional whole-body stereophotogrammetry imaging and dermatoscopic images taken within 1-month prior to therapy, skin examination 1-year after pembrolizumab initiation was notable for poliosis of body and scalp hair, eyelashes, and eyebrows and fading and/or disappearance of naevi and other pigmented lesions on his body, including solar lentigines and seborrheic keratoses (Figures 1–2). Consistent with this observation, a skin biopsy performed on a changing pigmented lesion with dermatoscopic features of regression after 3-months of pembrolizumab was interpreted as a macular seborrheic keratosis with melanophages (Figure 3). A PD-L1 immunohistochemical stain showed positive staining of elongated dendritic cells in the superficial papillary dermis. Pigmented lesions were observed to fade both with and without dermoscopically identified regression structures (i.e., blue-grey peppering/granularity). No halo naevi or lesions with surrounding inflammation were observed and no changes were noted in dermatofibromas. The patient has experienced no other toxicities during pembrolizumab treatment.

Discussion

A meta-analysis of 12 clinical trials that investigated the utility of pembrolizumab or nivolumab did not report on the incidence of changing skin lesions.(4) A single-institution study of 82 patients in Australia treated with anti-PD-1 therapy for metastatic melanoma from May 2012 to February 2015 identified 34 patients that had pre-therapy dermatology assessments, which included full body skin examination and photographs, and subsequent follow-up examinations.(5) One patient (1.2%) developed hypopigmented naevi and five patients (6.1%) developed new naevi, suggesting that checkpoint inhibitors may affect naevogenesis. The median duration of anti-PD-1 therapy was 5.7 months; the median

duration of follow-up was not specified. Of note, 51 patients had previously received ipilimumab.(5)

The co-inhibitory molecule PD-L1 is often upregulated on cancer cells, leading to impaired T-cell responses in the local tumour microenvironment. PD-L1 expression, however, is not limited to malignant tumours. Rodic et al and Taube et al identified PD-L1 expression by 5% of melanocytes in 7% (1/14) and 35% (14/40) of benign melanocytic naevi, respectively.(6, 7) Therefore it is biologically plausible that PD-1 inhibition may affect the natural history of benign melanocytic neoplasms. To the best of our knowledge, the expression of PD-L1 in seborrheic keratoses and solar lentigines remains unknown.

The co-occurrence of vitiligo and poliosis in our patient suggests a role for autoimmunity in the fading/disappearance of his pigmented lesions. Vitiligo results from the loss of functional melanocytes in the epidermis; it has been recognized to occur spontaneously or during treatment in melanoma patients. In fact, the occurrence of vitiligo in melanoma patients is estimated to be 3.7%, which is 7- to 10-fold higher than in the general population. (8) A meta-analysis found a 3.4% cumulative incidence of vitiligo in the setting of immunotherapy; the occurrence of vitiligo was associated with improved overall survival (HR: 0.25, $p<0.003$). (9) A 2016 prospective study of vitiligo in patients receiving pembrolizumab found that 25% (17/65) developed vitiligo; an objective response to treatment was similarly associated with a higher occurrence of vitiligo (71% v. 28%, $p=0.002$). (10) The cause of melanoma-associated vitiligo has not been elucidated, but the infiltration of the same clone of CD8+ T-cells in the tumour and in vitiligo lesions and the circulation of antibodies directed against melanoma-associated antigens shared by normal melanocytes and involved in melanin synthesis (i.e., MART -1, gp100, and tyrosinase-related proteins 1 and 2) suggests an autoimmune mechanism. (10) The release of melanocyte-associated antigens by therapy could therefore explain a breakdown of immune tolerance to self-antigens expressed in benign tumours. Supporting this hypothesis is the recognition that vitiligo has not yet been reported to occur during anti-PD-1 therapy outside of the treatment of melanoma. (10)

While we highlight the fading and disappearance of naevi in the context of pembrolizumab and melanoma, the natural history of naevi remains poorly characterized. Cross-sectional studies show that humans are born with few, if any, naevi. (11) Childhood is a dynamic period characterized by the appearance, fading, and disappearance of naevi; overall, however, total body naevus count increases and is estimated to peak in early adulthood. (12) Cross-sectional studies of adults and the elderly have shown relatively lower total body naevus counts, whether these findings are due to differences among birth cohorts or continued dynamism characterized by a net loss of naevi in later life remains unclear; the contribution of the immune system to naevogenesis is unknown. (12) Naevi have been observed to disappear via the halo phenomenon leaving behind a hypopigmented macule, replacement with regression structures, or fading without evidence of any of the two prior features. ¹² In our patient, we observed pigmented lesions to disappear only via the latter two pathways.

Our findings in this patient were not limited to melanocytic neoplasms and included fading of solar lentigines and regression of seborrheic keratoses. Benign lichenoid keratoses (BLKs) have been proposed to be a regressive form of pre-existent epidermal tumours, including solar lentigo or seborrheic keratosis. Supporting this hypothesis is that *FGFR3*, *PIK3CA*, and *RAS* mutations, which have been identified in solar lentigines and seborrheic keratoses, are present in up to 50% of BLKs.(13) Histopathologically, BLKs are characterized by circumscribed interface dermatitis with a lichenoid lymphocytic infiltrate of mainly CD8+ cells, among other features, suggesting an immunologically-driven pathogenesis that remains incompletely elucidated. Dermoscopically, the pigmented variants of these lesions are characterized by the appearance of blue-grey peppering/granularity, which histopathologically corresponds to melanin in the superficial dermis. Lichenoid reactions have been reported to occur in association with PD-1 and PD-L1 inhibitors, including inflammation surrounding pre-existing seborrheic keratoses.(5, 14)

Further studies are required to validate our observation and to determine the incidence of these skin lesion changes. Of note, a Google search performed on October 15, 2016 using the term “disappearing moles immunotherapy” identified patients who self-reported the fading or disappearance of “age spots” and “naevi” on the Melanoma Research Foundation’s Melanoma Patients Information Page community blog after ipilimumab and interferon therapy.(15) Ultimately, a better understanding of the local microenvironment of benign skin lesions may improve our understanding of the factors that influence tumour progression and oncogenesis. As this is a case report of a single patient, we are limited in our ability to draw definitive conclusions. An additional limitation is the lack of histological sampling and molecular characterization of fading/disappearing naevi. An alternative explanation for our observation includes fading/disappearance not related to PD-1 inhibition or due to chance alone.

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Additional Statements

- What's already known about this topic?
 - The most common cutaneous adverse side effects of PD-1 inhibitors include maculopapular rash, pruritus, vitiligo, and lichenoid skin and mucosal reactions.
- What does this study add?
 - We observed the fading and disappearance of pigmented skin lesions, including naevi, seborrheic keratoses, and solar lentigines, following initiation of pembrolizumab for metastatic melanoma, suggesting that PD-1 inhibitors may alter the natural lifecycle of these skin lesions.

Figure 1.

Clinical images of the anterior trunk, posterior trunk, and dorsal hand before (A, C, E) and 13-months after (B, D, F) initiating pembrolizumab therapy. Most pigmented lesions have faded or disappeared. Note: Panels A, C, and E were acquired with three-dimensional whole-body stereophotogrammetry imaging. Irregularities in anatomic outline are secondary to the computer rendering process.

Figure 2.

Dermatoscopic images of representative skin lesions taken prior to (left panels) and 13-months after (right panels) initiating pembrolizumab therapy. Naevi (A-F) faded with (D) and without (B,F) peppering. Seborrheic keratosis (G) undergoing regression with peppering (H). A dermatofibroma on the lower extremity exhibited no visible changes (I-J).

Figure 3.

Clinical (A) image of a pigmented macule on the chest that was noted to change in colour 3-months after initiating pembrolizumab. Dermatoscopic image (B) shows blue-grey peppering/granularity. (C) Haematoxylin and Eosin, 400x original magnification photomicrograph; a sparse lichenoid infiltrate extends to the dermo-epidermal junction where there is subtle interface alteration and numerous superficial dermal melanophages. Epidermis shows acanthosis and basketweave hyperkeratosis consistent with a macular seborrheic keratosis. (D) PD-L1 immunohistochemical stain, 400x original magnification photomicrograph; positive staining is seen in elongated dendritic cells amidst melanin-bearing melanophages of the superficial papillary dermis.