SKIN

BRIEF ARTICLE

Linear Depigmented Macules and Patches in Elderly Man

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ABSTRACT

The development of immune checkpoint inhibitors such as programmed cell-death receptor 1 (PD-1) antagonists has rapidly advanced chemotherapy within the last several decades. PD-1 targeted immunotherapy drugs like pembrolizumab, ipilimumab, nivolumab, and durvalumab have known associations with several immune-mediated dermatological reactions. We report a case in which an elderly male experienced segmental vitiligo after use of durvalumab therapy for small cell lung cancer. Distinct from non-segmental vitiligo, segmental vitiligo presents in a unilateral blaschkoid distribution and typically does not cross the midline. To our knowledge, checkpoint inhibitor-induced segmental vitiligo has yet to be documented.

INTRODUCTION

PD-1 inhibitors have been associated with several dermatologic conditions including various dermatitides and vitiligo, as well as more serious conditions such as drug hypersensitivity syndrome, Stevens-Johnson Syndrome, and toxic epidermal necrolysis.[1,2]

Vitiligo is not an uncommon adverse dermatologic condition in the setting of immune checkpoint inhibitor use. One study showed that ipilimumab-induced vitiligo was seen in 11% of metastatic melanoma patients.[3] In fact, vitiligo has the highest level of evidence for association with all checkpoint inhibitor therapy. Segmental vitiligo, that is depigmentation in a blaschkoid distribution that detail embryonic cell migration, has yet to be reported with PD-1 checkpoint inhibitors.

CASE REPORT

An 82-year-old African American male with a history of small cell lung cancer presented with new onset spreading depigmented macules and patches. At the time of presentation, the patient had received six months of a chemotherapy regimen consisting of taxol, carboplatin, and durvalumab. The patient stated that he first noticed pink pruritic macules on the right dorsal forearm within weeks of starting chemotherapy. Within the next several months, these macules evolved into depigmented macules and patches. A similar small group of macules later appeared on the contralateral posterior neck. The patient was extremely bothered by the appearance of his condition and attempted to treat it with over-the-counter hydrocortisone cream without success. The patient denied use of other medications as well as personal or family history of any autoimmune conditions.

Physical examination revealed a linear distribution of depigmented macules coalescing into patches on the proximal posterior right upper arm with distal extension curving anteriorly towards the right dorsal forearm (**Figure 1**). An additional linear grouping of four small, depigmented macules was present on the left posterior neck immediately adjacent to midline (**Figure 2**). All depigmented macules demonstrated accentuation with Wood's lamp examination.

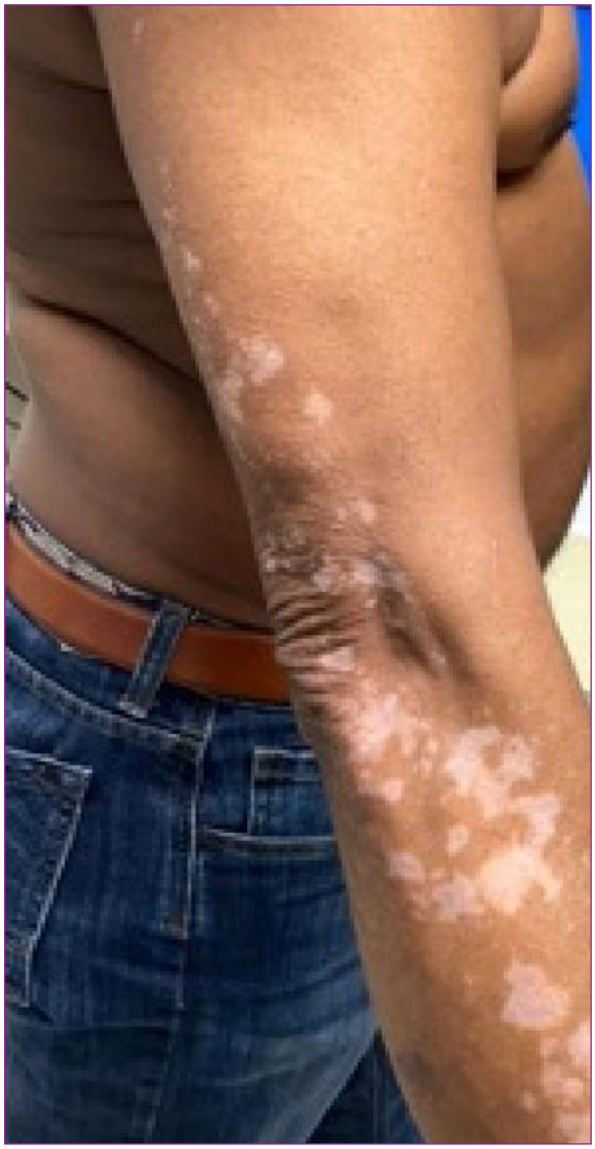

Figure 1. Blaschkoid distribution of depigmentation is observed on the proximal posterior right upper arm with distal extension curving anteriorly towards the right forearm.

A 4 mm punch biopsy of the right upper arm revealed basal vacuolization, apoptotic keratinocytes, and numerous pigment-laden macrophages. Areas of epidermis lacked pigmentation. A Fontana-Masson stain confirmed dermal melanophages as well as the absence of basal melanin. Furthermore, SOX-10 and Melan-A showed absence of melanocytes while colloidal iron stains with and without hyaluronidase demonstrated no increase in dermal mucin. These findings, in conjunction with clinical presentation and Wood lamp testing, were consistent with a diagnosis of vitiligo. In the context of the specific blaschkoid distribution of the depigmented macules and patches primarily on the right upper extremity, the timeline of the patient's exposure to durvalumab, and absence of personal or family history of autoimmunity, we concluded that the patient was experiencing durvalumab-induced segmental vitiligo. The patient was started on narrow band UVB phototherapy twice weekly and triamcinolone 0.1% ointment twice daily, which immediately halted further progression of the depigmentation and has resulted in repigmentation of many areas over the past 4 months of treatment.

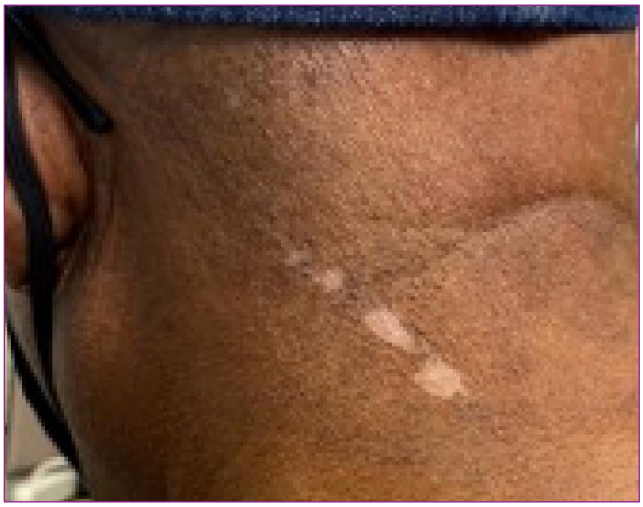

Figure 2. An additional linear arrangement of depigmented macules is seen on the left posterior neck immediately adjacent to midline.

DISCUSSION

Understanding the proposed mechanism of checkpoint inhibitor-induced vitiligo requires an appreciation for the physiologic function of the programmed cell-death receptor pathway. PD-1 is a receptor expressed on the surface of T cells while its ligand, PDL-1, is found on dendritic cells and macrophages. The interaction ultimately leads to attenuation of the T-cell response. This pathway, in which T-cell response can be weakened, has an important role in cancer progression. Some malignancies evolve to overexpress PDL-1, which weakens cytotoxic T cell response and allows malignant cells to evade immune response. Thus, the PD-1/PDL-1 pathway is an excellent chemotherapy target as it restores the immune system's ability to combat malignant cells.[3] Utilization of this pathway, however, may come at a cost in regard to autoimmunity. Segmental vitiligo is defined as depigmented macules affecting isolated body parts in a blaschkoid distribution (or embryonic epidermal cell migration patterns) that typically does not cross the midline[4]; however, in our patient, a small linear grouping does appear on the contralateral posterior neck. The significance of dermatological conditions that follow a blaschkoid distribution, while well documented, remains unclear. Furthermore, the reason depigmentation in our patient follows this unique pattern is uncertain currently, and further investigation into this phenomenon is required.

CONCLUSION

Depigmented macules develop in vitiligo due to autoimmune T cell-mediated destruction of melanocytes. The proposed mechanism for PD-1 inhibitor-induced vitiligo suggests that immune effector cells target a shared antigen among malignant cells and healthy melanocytes. PD-1 inhibitors furthermore create an environment in which such autoimmune destruction remains unchecked. We hypothesize that a similar mechanism is at play in our patient with the affected melanocytes expressing a shared or similar-appearing antigen with the patient's small cell lung cancer due to genetic mosaicism. Another possible explanation is that the affected cells are somehow less robust and are more prone to cellular death also due to genetic mosaicism. Although checkpoint inhibitor-induced vitiligo is well established, our case report remains unique, as to our knowledge, durvalumab-induced segmental vitiligo has yet to be documented.

Durvalumab use has been associated with several dermatological conditions. FDA clinical trial data showed that of 1,889 patients on durvalumab, 26% experienced rash or dermatitis with discontinuation of the drug occurring in 0.1%. Only 0.3% of patients reported affliction with non-segmental vitiligo.[5] It is important to accurately catalogue these dermatological reactions in order to optimize care for patients. Vitiligo, both segmental and non-segmental, should be recognized as potential dermatological conditions associated with durvalumab use. Further study regarding the significance of the segmental distribution is needed, though it does not appear to infer any deleterious consequences for our patient, as he is responding well to treatment.

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