Nivolumab-associated vitiligo-like depigmentation in a patient with acute myeloid leukemia: A novel finding

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INTRODUCTION

Programmed cell death−1 receptor (PD-1) inhibitors enhance the antitumoral immune response via immune checkpoint inhibition. In a healthy immune system, the binding of ligands to PD-1 induces T-cell inactivation and prevents overactive immune responses. However, PD-1 ligands are also expressed by a variety of tumors, including melanomas, renal cell carcinomas, and brain tumors, in an effort to evade the host immune response. Although immune checkpoint inhibitors have revolutionized care for cancer patients, new cutaneous and systemic toxicities are still being discovered.

Nivolumab is a humanized IgG4 anti−PD-1 monoclonal antibody that is currently approved by the US Food and Drug Administration for the treatment of melanoma, non−small cell lung cancer, renal cancer, and classical Hodgkin lymphoma.[1] Several adverse effects of immune-targeting therapies are described and are referred to as *immune-related adverse events* (irAEs). Systemic irAEs include enterocolitis, pneumonitis, hepatitis, nephritis, hypophysitis, and autoimmune thyroid disease. In addition, dermatologic toxicity is the most common irAE of checkpoint inhibitors and ranges from pruritus and mild dermatoses to severe reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis.[2] Vitiligo-like depigmentation is well described in melanoma patients receiving immunotherapy with PD-1 inhibitors and may be associated with favorable outcomes.[3]

Here we report a case of vitiligo-like depigmentation in a patient with acute myeloid leukemia (AML) receiving nivolumab as part of a phase II clinical trial. To our knowledge, this is the first reported case of vitiligo-like depigmentation associated with PD-1 inhibitor treatment in a patient with a nonmelanoma malignancy. Previous reports of PD-1 inhibitor−associated vitiligo-like depigmentation have been exclusively described in patients being treated for melanoma.

Abbreviations used:

AML:	acute myeloid leukemia
irAEs:	immune-related adverse events
PD-1:	programmed cell death−1

CASE REPORT

A 66-year-old man with AML in remission after chemotherapy and non−small cell lung carcinoma previously treated with chemotherapy and local radiation was referred to the dermatology department with an asymptomatic, hypopigmented eruption that began 4 months after starting nivolumab. The patient was started on nivolumab as part of a phase II clinical trial for prevention of AML recurrence, and a bone marrow biopsy performed 3 months before presentation found no evidence of disease. The patient had no personal or family history of melanoma and reported no history of changing skin lesions. A comprehensive review of systems was negative, and the patient reported no other adverse reactions from treatment.

The patient described the rash as light patches that began on the trunk and extremities without any preceding trauma or inflammation. Examination

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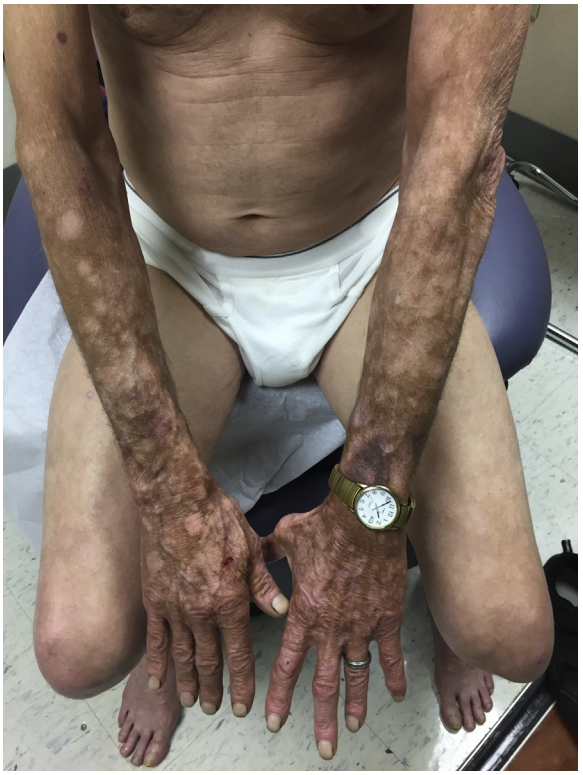

Fig 1. Depigmented macules and patches were distributed on the patient's forearms and hands.

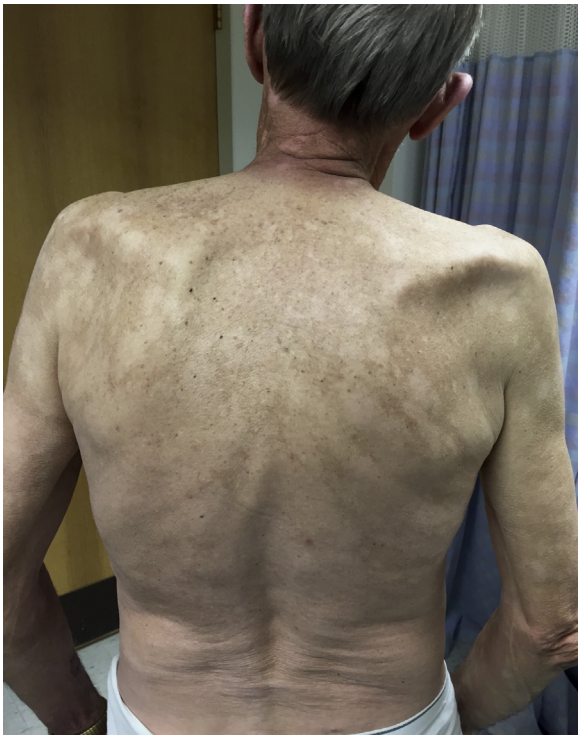

Fig 2. Depigmented macules and patches were scattered on the back.

found dozens of depigmented, oval macules and patches (0.5−3 cm), most prominent on the bilateral forearms (Fig 1), upper arms, and back (Fig 2). Scattered depigmented macules were noted on the bilateral temples, neck, medial canthi, and upper chest. The lesions had no associated scale or erythema. Examination under Wood's lamp confirmed depigmentation (Fig 3). Aside from solar purpura on the forearms, the remainder of the total body skin examination was unremarkable, without any atypical pigmented lesions or lymphadenopathy. The diagnosis of PD-1 inhibitor−associated vitiligo-like depigmentation was made.

Given the asymptomatic nature of the findings, the patient elected for close monitoring with routine skin surveillance and no additional treatment. The patient subsequently underwent a complete ophthalmic examination with no evidence of ocular melanoma, and a repeat bone marrow biopsy found no evidence of disease recurrence. The patient continued treatment with nivolumab without additional adverse effects, and the vitiligo-like depigmentation remained stable at a 2-month follow-up examination with his oncologist.

DISCUSSION

PD-1 inhibitors are associated with a variety of cutaneous irAEs, including pruritus, maculopapular eruptions, eczema, lichenoid dermatoses, psoriasiform eruptions, vitiligo, sarcoidosis, and severe reactions such as Stevens-Johnson syndrome/toxic epidermal necrolysis.[3,4] A recent review found that more than 40% of patients with melanoma treated with PD-1 inhibitors had cutaneous irAEs.[5] Of PD-1 inhibitor−associated cutaneous irAEs, vitiligo-like depigmentation is relatively common, reported in more than 25% of patients with advanced stage III or IV melanoma on nivolumab.[3] It has been hypothesized that PD-1 inhibitors induce vitiligo-like depigmentation in melanoma patients via the anti-melanoma immune response, which may also target healthy melanocytes owing to overlapping antigen expression.[6]

To the best of our knowledge, this case is the first reported instance of PD-1 inhibitor−associated vitiligo-like depigmentation in a patient with a nonmelanoma tumor. Although PD-1 inhibitor−associated vitiligo-like depigmentation has been associated with a favorable response to treatment in patients with metastatic melanoma, its prognostic value for nonmelanoma tumors is unknown.[7] Furthermore, the mechanism by which vitiligo-like depigmentation occurred in a patient without a known melanoma remains unclear. One possible explanation is that an autoimmune predisposition was uncovered by T-cell activation via immunotherapy. An alternative explanation is that the patient

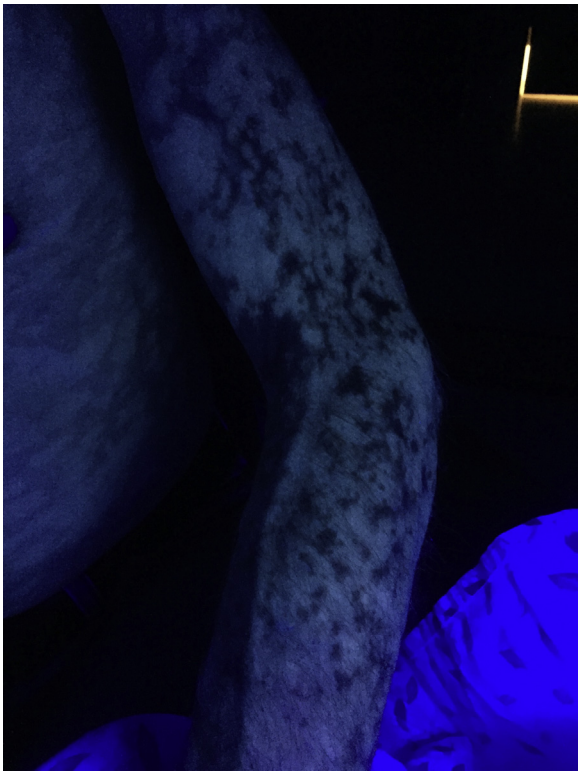

Fig 3. Examination under Wood's lamp highlights the widespread areas of depigmentation.

had an undiagnosed cutaneous or mucosal melanoma that regressed and was not detectable on examination or radiographic imaging.

As PD-1 immunotherapy gains increasing popularity in the treatment of nonmelanoma cancers, the identification of additional patients with vitiligo-like depigmentation may shed light on the mechanism and prognostic value of this cutaneous adverse event.

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