Incidental improvement of programmed cell death-1 receptor inhibitor-induced vitiligo after initiation of dupilumab therapy for refractory pruritus

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Key words: checkpoint inhibitor; dupilumab; Dupixent; PD-1 inhibitor; vitiligo.

INTRODUCTION

Dupilumab is a subcutaneously injected monoclonal antibody that targets the interleukin 4 (IL-4) receptor alfa subunit of the IL-4 and IL-13 receptors, leading to the blockade of IL-4 and IL-13 signaling of the T helper (TH) cell type 2 pathways. However, dupilumab's downregulation of the TH2 signaling pathway may result in cytokine disequilibrium, resulting in an imbalanced, unopposed amplification of TH1 and other inflammatory pathways. It is thought that many of dupilumab's side effects such as alopecia, psoriasis, and persistent facial dermatitis are attributable to this iatrogenic cytokine imbalance.[1]

Vitiligo is a common autoimmune condition resulting in skin depigmentation, which often causes psychological distress and reduced quality of life. Vitiligo is a TH1 immune disorder, and there have been prior reports of both new onset vitiligo[1] and exacerbation of existing vitiligo[2] following initiation of dupilumab. However, herein, we describe an incidental case of a patient experiencing improvement of their programmed cell death-1 receptor (PD-1) inhibitor-induced vitiligo following the off-label use of dupilumab for refractory pruritus.

CASE REPORT

A 68-year-old Hispanic man with a history of hepatocellular carcinoma presented to the dermatology clinic for evaluation and treatment of persistent pruritus. The patient had been receiving sorafenib and nivolumab, a PD-1 inhibitor, in combination with transarterial chemoembolization for hepatocellular carcinoma, but discontinued all treatments and medications 5 months prior due to the development of diffuse pruritus, hypothyroidism, and vitiligo on the fingers and dorsum of both hands (Fig 1). The patient's primary concern was pruritus that had not improved despite discontinuing nivolumab. At this time the patient was unbothered by the vitiligo, which had remained stable; therefore, no treatment was provided. The vitiligo was not in a distribution that suggested koebnerization, and the pruritus was believed to be multifactorial with possible contributions from past nivolumab therapy, his ongoing malignancy, xerosis, and hepatic dysfunction. Over the course of the next 2 months the patient used a variety of antipruritic medications including oral cetirizine, Sarna lotion, triamcinolone, and gabapentin without significant improvement.

The patient was lost to follow-up for 18 months and then returned to the clinic with a primary concern of vitiligo. Although the patient had noted

Abbreviations used:

IL-4: interleukin 4
PD-1: programmed cell death-1 receptor
TH: T helper

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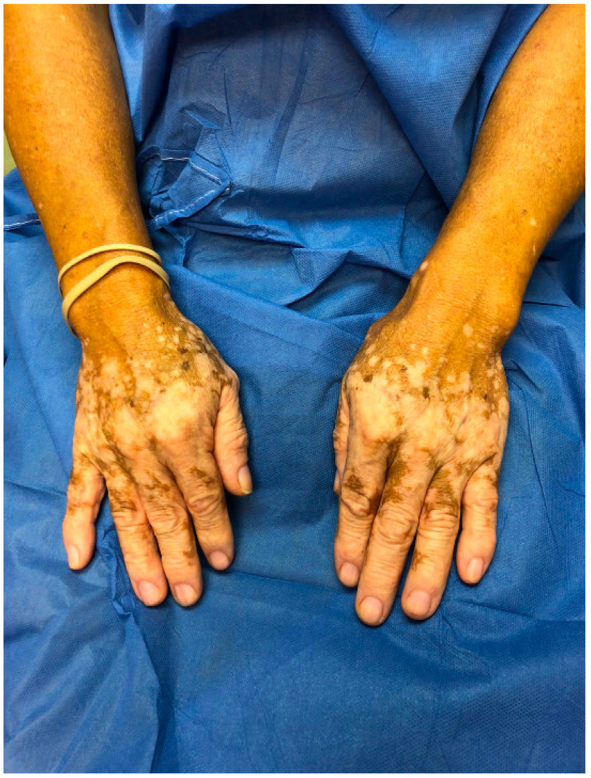

Fig 1. Baseline vitiligo on the dorsums and fingers prior to starting dupilumab.

Fig 2. Improvement in dorsums and fingers vitiligo 3 months after starting dupilumab.

some repigmentation of his vitiligo on the dorsum of both hands since discontinuing nivolumab for 25 months, he reported progression of his vitiligo after contracting COVID-19 earlier that year. The patient's vitiligo was subsequently treated with triamcinolone 0.1% ointment without repigmentation.

The patient's subsequent visits to the clinic focused on treating his pruritus and the following therapies were attempted without any relief: antihistamines, gabapentin, naltrexone, diphenhydramine, topical corticosteroids, and 11 sessions of phototherapy with narrowband UV-B. Of note, his vitiligo remained unchanged during this time including during phototherapy. Due to the refractory nature of his pruritus, the patient began dupilumab therapy, off-label.

The patient reported significant improvement of his pruritus after the initial dose of dupilumab. Over the course of only 5 months on dupilumab 300 mg every other week the patient reported not only control of his pruritus, but an incidental improvement of the vitiligo of the dorsum and fingers of both hands (Figs 2 to 4). The patient was subsequently lost to follow-up.

DISCUSSION

Vitiligo is frequently induced by specific autoimmunity against melanocytes during immune checkpoint inhibitor therapy, especially in patients with advanced melanoma. By contrast, cases occurring in patients with cancers other than melanoma are less commonly reported. Vitiligo has been reported to occur in up to 25% of the patients on PD-1 inhibitors. The occurrence of depigmentation during immune checkpoint inhibitor therapy is significantly associated with a favorable prognosis such as higher survival rates. Vitiligo is more frequently induced during anti—PD-1 therapy than during anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) therapy. During immune checkpoint inhibitor therapy, CD8+ cytotoxic T cells are activated against melanoma-associated antigens, such as MART-1 and GP100, shared by melanocytes and melanoma cells, resulting in depigmentation. This patient presented with nivolumab-induced vitiligo and had discontinued nivolumab for 4 years prior to initiating dupilumab for refractory pruritus.[3]

Previous case reports have detailed patients developing novel vitiligo after initiating dupilumab therapy[1] or patients developing worsening vitiligo after initiating dupilumab therapy.[2] Although the exact molecular drivers of dupilumab-induced vitiligo are unclear, it has been hypothesized that dupilumab-induced IL-4 inhibition causes TH1/TH17 polarization that recruit self-reactive cytotoxic

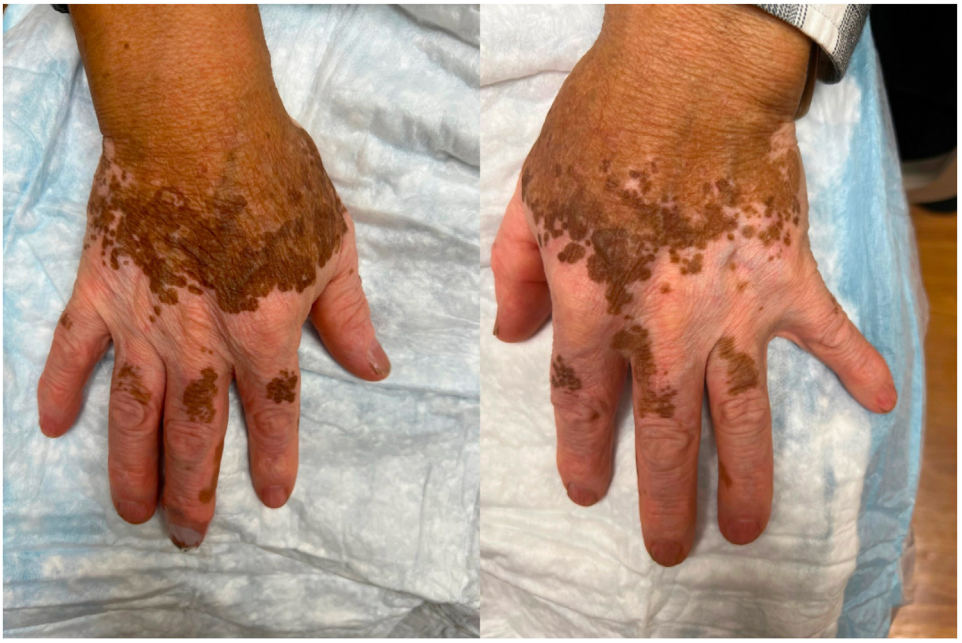

Fig 3. Improvement in dorsums and fingers vitiligo 4 months after starting dupilumab.

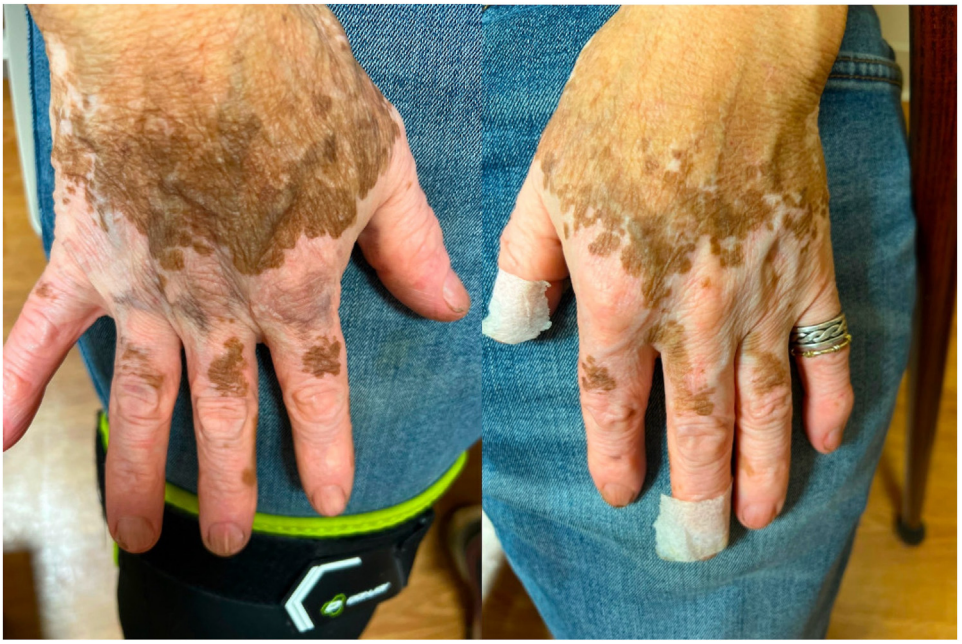

Fig 4. Improvement in dorsums and fingers vitiligo 5 months after starting dupilumab.

CD81 T cells that target melanocytes and promote disease progression through local interferon gamma production.[4]

This patient demonstrated an incidental improvement of his vitiligo following a 5-month course of dupilumab therapy. There have been previous anecdotal reports of patients having improvement in their vitiligo following the initiation of dupilumab therapy,[5] suggesting that vitiligo improvement in the setting of dupilumab therapy may be more than just an incidental finding.

Like vitiligo, alopecia areata has a pathogenesis that has been classically described as being TH1/TH17 mediated and there have been paradoxical

case reports of both dupilumab-induced and dupilumab-treated alopecia areata.[6]

The leading hypothesis that dupilumab's blockade of the TH2 response results in subsequent TH1/TH17 dysregulation and cytokine shift may be an oversimplification of a more complex pathogenesis. Paradoxical reports of both dupilumab-induced and dupilumab-improved vitiligo suggest that the pathogenesis of vitiligo may also involve a TH2 component with a complex crosstalk between the TH1, TH2, and TH17 pathways.

It is possible that the improvement in pigmentation seen in this patient was not due to dupilumab. However, given the improvement seen in his vitiligo during the short time span he was on dupilumab, the stability of his vitiligo prior to dupilumab, and a similar dual phenomenon existing in alopecia areata, which has overlapping mechanistic features with vitiligo, the possibility of dupilumab-improved vitiligo warrants further investigation.

Although we cannot recommend dupilumab for the treatment of vitiligo at this point, we hope to alert practitioners to the possibility of this association.

Conflicts of interest

None disclosed.

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