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PD-1 inhibitor induced alopecia areata

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Abstract

Immune checkpoint modulators are becoming more prevalent in clinical use for the treatment of metastatic melanoma and other malignancies. These drugs, including programmed death 1 (PD-1) inhibitors, have a high incidence of immune adverse events, including cutaneous manifestations. Alopecia is a known side effect with these drugs, but previous reports describe chemotherapy-induced alopecia. We report a case of alopecia areata in a patient on monotherapy with pembrolizumab (PD-1 inhibitor). It is important for the dermatologist to recognize and appropriately treat to decrease morbidity for these patients.

Keywords: pembrolizumab, nivolumab, PD-1 inhibitor, alopecia

Introduction

Immune checkpoint modulators, such as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) inhibitors, are potent anti-cancer therapies that direct the body's immune system to target malignant cells [1]. These therapies have demonstrated effective and long-lasting results against a variety of malignancies but are associated with a high incidence of immune adverse events (iAE), [1, 2]. Cutaneous iAEs have been frequently reported with checkpoint inhibitors; however, autoimmune-mediated alopecia after treatment with PD-1 inhibitors is still uncommon [3]. We present a case of localized alopecia areata (AA) occurring during pembrolizumab monotherapy for melanoma.

Case Synopsis

A 64-year-old woman presented to our institution in June 2016 with superficial spreading melanoma, Breslow depth of at least 3.2mm with >1 mitoses/millimeter $(mm)^2$ without ulceration, on the right upper back. The site had originally been biopsied in 2014 and was interpreted as an irritated, superficially ulcerated, benign atypical intradermal nevus. No further treatment was performed. She represented to an outside dermatologist in May 2016 with a concerning lesion along the biopsy scar, which was then found to have the aforementioned pathology results. Later review of the original biopsy from 2014 was consistent with superficial spreading melanoma, Breslow depth of 0.9mm. Computerized tomography (CT) of the chest, abdomen, and pelvis did not have clear evidence of metastatic disease, although it did show multifocal nodularity in the lungs and small hypodense lesions in the liver. Wide local excision had no residual melanoma and sentinel lymph node biopsy (SLNB) found 1 of 2 axillary nodes positive for metastatic melanoma. Complete axillary lymph node dissection was attempted, but no lymph nodes were recovered. Because of the delay in initial treatment, positive SLNB and concern for possible metastases on imaging, she was started on single agent pembrolizumab in November 2016. The patient has had no clinical evidence of tumor recurrence to date. Repeat CT demonstrated an increase in size of the right upper lobe pulmonary nodule; however, subsequent biopsy was negative for malignancy. Overall, the patient is tolerating pembrolizumab well with mild side effects (dermatitis with pruritus, fatigue, and reflux).

Nine months after starting pembrolizumab, the patient reported hair loss during routine follow up. Two 2cm annular patches of hair loss on the right vertex and left frontal scalp were seen on exam and were clinically consistent with AA. The patient declined treatment and pembrolizumab was continued at the same dose. At two months follow up, the vertex site had about 50% regrowth with poliosis (**Figure 1**). No new areas of hair loss were noted. When the patient returned for follow up after another 3 months, she had complete regrowth of the site with poliosis (**Figure 2**).

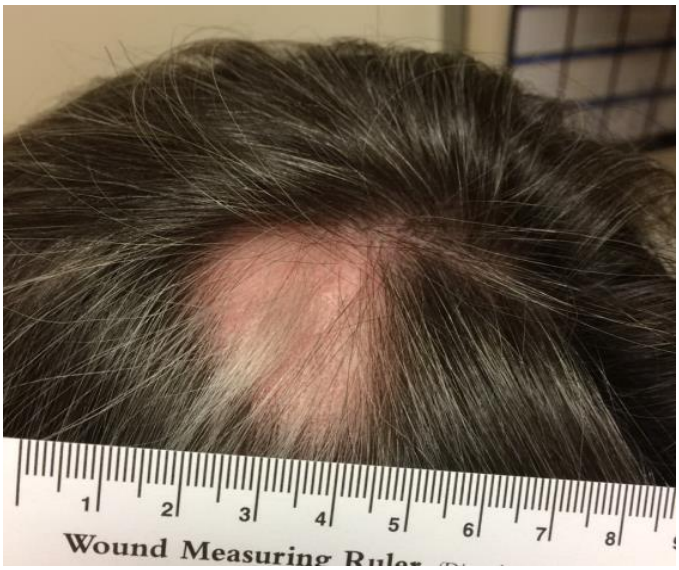

Figure 1. *Circular patch of alopecia on vertex scalp with central area of poliosis.*

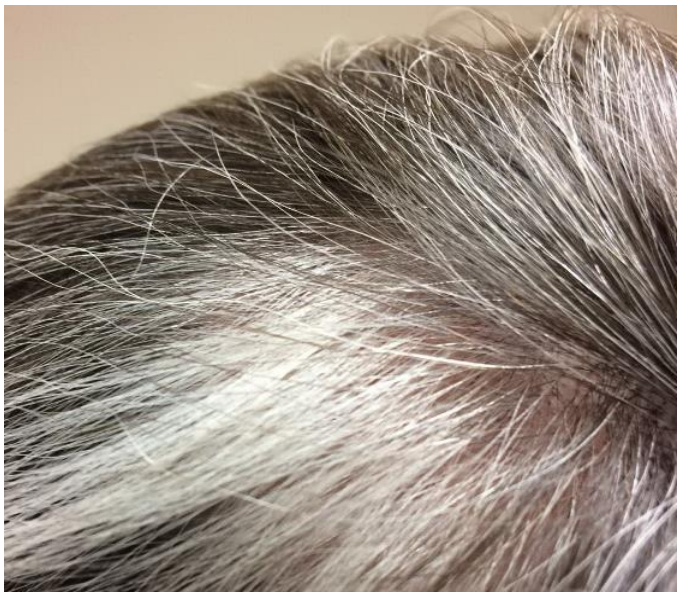

Figure 2. *Area on vertex scalp with regrowth with poliosis without treatment.*

Case Discussion

PD-1 inhibitors (nivolumab, pembrolizumab) belong to the family of immune checkpoint modulators and function by inhibiting negative regulators of immune activation, which leads to non-specific activation and thus potentiates anti-tumor immunity [1, 2]. Nivolumab and pembrolizumab were FDA approved for the treatment of unresectable or metastatic melanoma in 2014. Additional indications for PD-1 inhibitors, such as renal cell carcinoma and non-small cell lung carcinoma, are currently being explored [1, 2]. As a result, the use of PD-1 inhibitors is likely to increase in coming years and dermatologists need to be aware of the cutaneous side effects associated with these medications. Dermatologic iAEs from PD-1 inhibitors include dermatitis, pruritus, blistering disorders, mucocutaneous lichenoid eruptions, rosacea, and psoriasis exacerbations [2].

Hair disorders represent one type of cutaneous side effect reported with immune checkpoint modulators; all-cause alopecia occurs in 1-2% of patients who receive immune modulating anticancer therapy (either CTLA-4 or PD-1 inhibitors), [2]. Alopecia areata was noted by Zarbo et al. in four patients during treatment with dual immune modulator treatment [2]. Alopecia areata with pembrolizumab monotherapy has not previously been reported, although the association might be anticipated given its mechanism of action. PD-1 inhibitors block the immune system's typical regulatory measures, including T-cell inactivation and likely facilitates the T-cell mediated attack on the hair bulb that leads to AA. This same rationale may underlie many of the iAEs seen with immune checkpoint modulators.

Cutaneous adverse events from CTLA-4 inhibitors are most commonly reversible and may resolve even without discontinuing the drug [1, 2]. Our patient had stabilization of disease with incomplete regrowth without treatment while continuing pembrolizumab. Regrowth of hair after immune checkpoint modulator therapy-induced AA frequently demonstrates poliosis, as seen in our patient and three of the cases reported by Zarbo et al.

Conclusion

Patients receiving therapy with immune checkpoint modulating therapy, including PD-1 inhibitors, are at increased risk for cutaneous iAEs, including AA. Prompt recognition of AA pattern hair loss, as opposed to more classic chemotherapy-induced alopecia, and initiation of treatment may lead to decreased morbidity for patients.

References

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