CASE REPORT

Vitiligid hypopigmentation associated with pembrolizumab in metastatic head and neck cancer

Ajaz Bulbul1,2,*

1Division of Internal Medicine, Department of Hematology/Oncology, Texas Tech University Health Sciences Center School of Medicine, Lubbock, TX, USA, and 2Department of Internal Medicine, Department of Hematology/Oncology, University of New Mexico, NM, USA

*Correspondence address. Department of Internal Medicine, Department of Hematology/Oncology, University of New Mexico, 101 S Canal St, Carlsbad, NM 88220, USA. Tel: +1-505-504-8731; E-mail: ajazbulbul@gmail.com

Abstract

Cutaneous adverse events are common with the use of immunotherapy. Although only 5% of patients develop severe reactions, about half will develop mild to moderate cutaneous adverse events. Vitiligo has been seen in melanomas treated with checkpoint inhibitors (CPI). We describe the first known case of Vitiligoid irAE (immune-related adverse event) in a non-melanoma solid cancer treated with pembrolizumab.

CASE REPORT

A 32-year-old man with stage IVA T2N2M0 squamous cell cancer of the tonsil (p16 positive) was initially treated with induction Docetaxel Carboplatin and 5FU followed by carboplatin and XRT to 70 Gy achieved a complete response in August 2015. In January 2017, he had a metastatic recurrence with a 1.7 × 1.3 cm right upper lobe lesion and 2.3 × 1.4 cm right paratracheal lesion. PD-L1 IHC showed high (90%) expression. The patient received pembrolizumab between February 2017 and February 2018 achieving an early complete response within 2 months of his treatment with no eventful grade three toxicities except for immune-mediated hypothyroidism which was managed with levothyroxine. His medical history was negative for any skin disorders or skin cancers.

Five months after stopping his treatment he noticed two solitary hypopigmented vitiligious patches (Fig. 1) and a small cluster of hyperpigmented lesions (Fig. 2) one on his left preauricular area and the other on the right angle of his mouth. No preceding erythema was noted. The lesions were non-pruritic. His most recent imaging in July 2018 continues to show no evidence of disease. A skin punch biopsy of the hypopigmented lesions was sent for pathological analysis (Figs 3–5). Morphological description of (hematoxylin–eosin) HE findings showed mild epidermal acanthosis, parakeratosis, and some interface dermatitis with few dyskeratotic cells and underlying lymphocytic infiltrate with scattered dermal melanophages. Immunohistochemical (IHC) Fontana stain, negative SOX10 stain identifies no argentaffin granules and melanin or melanoma making this consistent with a vitiligo lesion morphologically appearing to be immunotherapy related.

DISCUSSION

Cutaneous adverse events are common with the use of immunotherapy. Although only 5% of patients develop severe reactions, about half will develop mild to moderate cutaneous adverse events [1]. Vitiligid irAE (immune-related adverse event) in a non-melanoma solid cancer has not been commonly described in literature when treated with pembrolizumab.

The development of vitiligo represents a well-recognized adverse event in patients with melanoma treated with anti-CTLA-4 and anti-programmed death (PD-1)/programmed death
ligand (PD-L1) antibodies. Depigmentation may result from induction of antimelanoma immunity through a cytotoxic T-cell-mediated response with a cross-reaction against different epitopes or antigens expressed by both melanoma cells and normal melanocytes (e.g. MART-1, GP100, TRP1-2, tyrosinase) [2, 3].

The overall incidence of newly developed vitiligo with PD-1 inhibitors varies between 8 and 25% [2]. The relative risk of all-grade vitiligo with anti-PD-1 and anti-CTLA-4 (meta-analysis) is 16.3% [4]. Vitiligoid lesions, however, occur more frequently with anti-PD-1 agents than with other immunotherapies (overall incidence of 3.4%) previously used in melanoma, including anti-CTLA-4 [5].

Vitiligo has not been described to date in other types of solid cancers treated with PD-1/PD-L1 antibodies [6], but a potential underestimation because of a lack of systematic examination of the entire skin surface cannot be ruled out.

Vitiligo usually develops after several months of treatment and does not appear to be dose related [7]. It can be preceded by erythematous inflammatory lesions and may appear to look like Pityriasis rosea [2]. Lesions are mainly generalized and
bilateral, but focal or segmental presentations can also be seen as vitililoid lesions localized around skin metastases [7]. Associated hair repigmentation or depigmentation can be also observed [8].

In pooled analysis, patients who presented with vitiligo during immunotherapy were found to have a higher frequency and severity of irAEs than those without vitiligo [2, 9]. Although vitiligo can precede the radiologic objective responses, the occurrence of vitiligo cannot be considered an early sign of response to immunotherapy. This perhaps could be an important indicator of antimelanoma immunity and associated improved survival. Whether this relates to solid cancers as well we are not sure [3]. It has been hypothesized that PD-1 inhibitors induce vitiligo-like depigmentation in melanoma patients via the antimelanoma immune response, which may also target healthy melanocytes owing to overlapping antigen expression [10].

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 [9].

The pathogenesis perhaps involves an aberrant targeting of antigens into the dermis/epidermis by reactivated CD4+CD8+ T cells, generate an inflammatory process after cross-reaction with normal skin. However, the specific self-antigens driving T-cell infiltration into the skin have not been identified [7]. Vitiligo can be observed in other tumor types beyond melanoma when receiving immunotherapy and may be a sign of potent immune activation.

ACKNOWLEDGEMENTS
Cloyce Stetson (Slides), Brent Paulger (diagnostic biopsy).

CONSENT
Consent was obtained.

CONFLICT OF INTEREST STATEMENT
Dr Bulbul has served advisory boards for AstraZeneca and Pfizer.

REFERENCES
1. Hwang SJE, Carlos G, Wakade D, Byth K, Kong BY, Chou S, et al. Cutaneous adverse events (AEs) of anti-programmed cell death (PD)-1 therapy in patients with metastatic melanoma: a single-institution cohort. J Am Acad Dermatol 2016; 74:455–461.e1.
2. Hua C, Boussemart L, Mateus C, Routier E, Boutros C, Cazenave H, et al. Association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab. JAMA Dermatol 2016;152:45–51.
3. Lo JA, Fisher DE, Flaherty KT. Prognostic significance of cutaneous adverse events associated with pembrolizumab therapy. JAMA Oncol 2015;1:1340–1.
4. Abdel-Rahman O, ElHalawani H, Fouad M. Risk of cutaneous toxicities in patients with solid tumors treated with immune checkpoint inhibitors: a meta-analysis. Future Oncol 2015;11:2471–84.
5. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372:320–30.
6. McDermott DF, Sosman JA, Sznol M, Massard C, Gordon MS, Hamid O, et al. Atezolizumab, an anti-programmed death-ligand 1 antibody, in metastatic renal cell carcinoma: long-term safety, clinical activity, and immune correlates from a phase Ia study. J Clin Oncol 2016;34:833–42.
7. Sibaud V, Meyer N, Lamant L, Vigarios E, Mazieres J, Delord JP. Dermatologic complications of anti-PD-1/PD-L1 immune checkpoint antibodies. Curr Opin Oncol 2016;28:254–63.
8. Hofmann L, Forschner A, Loquai C, Goldinger SM, Zimmer L, Ugurel S, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. Eur J Cancer 2016;60:190–209.
9. Nakamura Y, Tanaka R, Asami Y, Teramoto Y, Imamura T, Sato S, et al. Correlation between vitiligo occurrence and clinical benefit in advanced melanoma patients treated with nivolumab: a multi-institutional retrospective study. J Dermatol 2017;44:117–22.
10. Houghton AN, Eisinger M, Albino AP, Cairncross JG, Old LJ. Surface antigens of melanocytes and melanomas. Markers of melanocyte differentiation and melanoma subsets. J Exp Med 1982;156:1755–66.