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Hypopigmented skin lesions on immunotherapy

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Case

A 33-year-old African American woman with metastatic alveolar soft-part sarcoma of the right lower extremity, with a history of above knee right leg amputation, received treatment with Nivolumab (an anti-PD1 antibody) with an initial good tolerance. Her past medical history was negative for any skin cancers.

After 2 months of treatment, the patient presented with diffuse hyperpigmented macules. This was considered related to her chronic atopic dermatitis and she was prescribed topical steroids and moisturizing. Four months later the patient presented with diffuse macular rash and pruritus. A skin punch biopsy of the back revealed mild epidermal acanthosis, focal parakeratosis and interface dermatitis with numerous dyskeratotic cells and underlying lichenoid lymphocytic infiltrate with scattered dermal melanophages. Oral steroids were started and three weeks later the rash had resolved, however the patient developed numerous hypopigmented macules and patches, covering more than 30% of her body surface area (Figure 1A) compared to the prior skin exam (Figure 1B). A new biopsy showed epithelial basal vacuolar changes, underlying lichenoid lymphoplasmacytic infiltrate with scattered eosinophils and interface dermatitis with marked pigment incontinence and a reduced number of junctional melanocytes (Figure 2). A periodic acid-Schiff stain for fungus and an immunohistochemical study for spirochetes were negative.

Although the patient presented a partial response with –60% decrease per response evaluation criteria for solid tumors (RECIST1.1), the treatment was discontinued after 7 months and she continued to receive systemic and local steroids. Nine months after end of immunotherapy, the restaging scans showed a persistent response to treatment.

What is the most likely diagnosis?

A. Pityriasis rosea

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- B.** Vitiligo
- C.** Secondary syphilis associated rash
- D.** Tinea versicolor

The correct answer is **B. Vitiligo**

Discussion

Immune checkpoint inhibitors such as anti-CTLA4, anti-PD-1 and anti-PD-L1 monoclonal antibodies are emerging as standard treatments in various malignancies.

The list of current indications is likely to expand as these immunotherapies are tested with promising results in many cancer types. Immunotherapies have a unique pattern of toxicities similar to autoimmune symptoms¹ called immune-related adverse events (irAEs) and may have a different pattern of response than chemotherapy with possible initial tumor growth (pseudoprogression) due to lymphocytic infiltrates and delayed treatment response². Another unique aspect of treatment with immune checkpoint point inhibitors is the lack of current known predictive biomarkers of response².

Vitiligo is an acquired pigmentary disorder characterized by hypopigmented macules caused by autoimmune destruction of melanocytes³. In patients with melanoma, vitiligo-like symptoms can occur as an irAE in between 3.4% and 25% of patients during treatment with an immune checkpoint inhibitor^{4,5}. However, in other tumor types, vitiligo during immunotherapy is a rare event and to our best knowledge this is the first report of vitiligo during immunotherapy in other solid tumors beyond melanoma⁶.

One of the pathophysiologic mechanisms of vitiligo appearance during treatment with immunotherapy suggest a T cell mediated melanoma specific autoimmune mechanism with lymphocyte infiltration in the tumor and in the hypopigmented lesions and presence of antibodies against melanoma-associated antigens (such as MART-1, gp100) which are present on melanoma cells and normal melanocytes^{5,7}. Another possible mechanism is through autoantibodies against melanocytes, recognizing tyrosinase, TRP-1, and TRP-2⁸. However, there is limited knowledge on the pathology of vitiligo in patients with other tumor types than melanoma.

Before the appearance of hypopigmented lesions, our patient presented with hyperpigmented lesions, followed by rash with the initial biopsy showing lymphocytic infiltrates suggesting an underlying cytotoxic mediated autoimmune mechanism. The continued tumor shrinkage after the discontinuation of immunotherapy in our patient might favor the T cell activation hypothesis.

In patients with melanoma receiving treatment with anti-PD-1 antibodies the case of vitiligo reported were often more generalized and bilaterally distributed over the body than vitiligo occurring in normal population⁵. This is consistent with our case, which had a systemic distribution of the hypopigmented lesions.

Patients who presented with vitiligo during immunotherapy were found to have a higher frequency and severity of irAEs than those without vitiligo^{4,5,9}. However, our patient has not presented with any other irAEs. Vitiligo occurrence during immunotherapy was reported to be associated with higher objective tumor response rate and significantly improved progression-free and overall survival in patients with melanoma^{4,5,10}.

Although vitiligo was observed to precede the radiologic objective responses, the occurrence of vitiligo cannot be considered an early sign of response to immunotherapy.

The onset of vitiligo was reported 4–5 months after start of treatment⁵, similar to our case in which the hypopigmented lesions appeared 6 months after start of treatment and was persistent at the 9 months follow-up after discontinuation of treatment.

In conclusion, vitiligo can be observed in other tumors beyond melanoma while receiving immunotherapy and could be a sign of potent immune activation.

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Declaration of interests

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Figure 1:
Clinical photograph of the left lower extremity with hypopigmented lesions (1A) compared with prior skin examination (1B).

Figure 2:
The skin biopsy (high power, magnification X20) reveals significant pigment incontinence in addition to interface and lichenoid dermatitis and a reduced number of junctional melanocytes