Vitiligo-like Depigmentation in a Patient Undergoing Treatment with Nivolumab for Advanced Renal-cell Carcinoma

Dear Editor,

Nivolumab is a fully human monoclonal antibody that targets the programmed cell death 1 (PD-1) immune checkpoint. It has been approved for its use in several types of advanced solid tumors, including melanoma, lung cancer, and renal cell carcinoma (RCC). The inhibition of PD-1 leads to an enhanced adaptive immune response against tumor cells through the activation of T-cells.

Vitiligo-like depigmentation (VLD) is a well-known side-effect in patients with melanoma that are being treated with anti PD-1 therapies (1). However, its development in patients undergoing treatment with nivolumab for cancers other than melanomas has been described very rarely. To our knowledge, herein we report the second case of nivolumab-induced VLD in a patient with metastatic RCC (2).

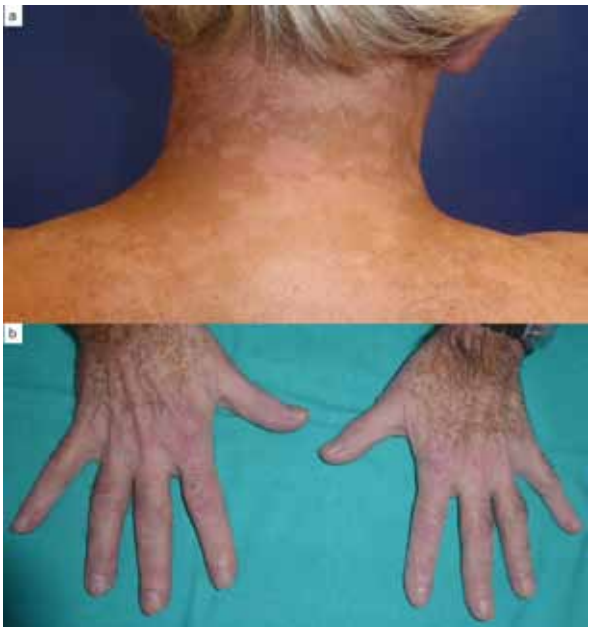

Figure 1. Flecked achromic macules on sun-exposed areas. Preservation of perifollicular pigment was observed on the dorsal aspect of both hands.

The patient was a 63-year-old man who had a medical history of advanced RCC. He had initially undergone nephrectomy, and three months later he presented with local relapse and lung metastases. He had then received different treatment regimes, presenting with progression each time, until he finally started treatment with nivolumab. Five months after its introduction, the patient developed a disseminated hypochromic eruption. No other drugs were started over that period. He had no personal or family history of vitiligo or other autoimmune disorders. Dermatological examination revealed multiple, symmetrical, well-demarcated, depigmented macules involving his face, neck, torso, hands, and forearms. (Figure 1, a). Preservation of pigment in hair follicles could be seen on the dorsal aspect of his hands (Figure 1, b).

Two 4-mm punch biopsies were taken, one from one from a depigmented patch and another from normally pigmented skin. In the first one, immunohistochemical analysis with Melan-A immunostaining demonstrated the absence of melanocytes, whereas melanocytes were present in the second one. A CD-8+ positive infiltrate was present in both biopsies, especially in the first one (Figure 2). The patient was diagnosed with VLD associated with nivolumab therapy. Since the patient was asymptomatic, no treatment was prescribed. He was advised to protect the achromic areas from sun exposure.

In our patient, a causal association between the onset of VLD and the treatment with nivolumab cannot be completely ruled out. However, the clinical presentation with flecked macules in sun-exposed areas was consistent with what has been described in other patients presenting with VLD after starting treatment with this chemotherapeutic agent. The time to onset in our case was also within the limits which have been previously reported for this side-effect (16-52 weeks) (3). Therefore, we believe that a causal association is very probable.

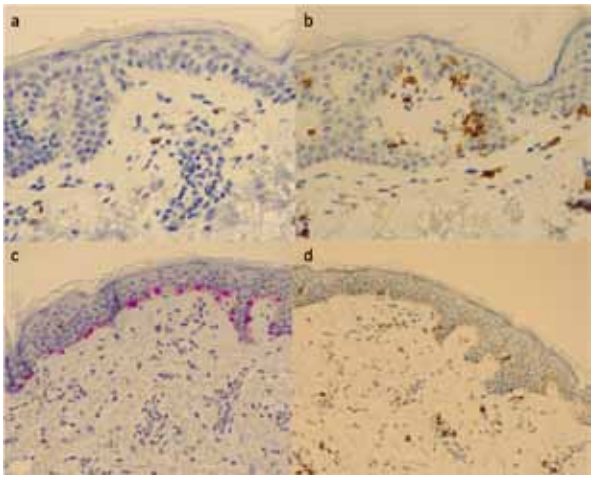

Figure 2. (a) An absence of melanocytes was demonstrated with Melan-A immunostaining in the biopsy from one of the lesions. (b) Melan-A immunostaining of healthy pigmented skin revealed the presence of melanocytes and melanin pigment in the basal layer. CD8+ immunostaining showed an inflammatory infiltrate dominated by CD8+ T lymphocytes both in the achromic areas (c) and in perilesional skin (d).

In patients with advanced melanoma who are treated with PD-1 inhibitors, the development of vitiligo-like lesions has been proved to be associated with improved progression-free and overall survival rates (4,5). This mechanism is not fully understood, but it has been suggested that inhibition of PD-1 could cause a loss of tolerance to melanocytic antigens, thus leading to a CD-8 T-cell dependent destruction of melanocytes present in the melanoma as well as in healthy skin (3,5). The presence of CD8 T-lymphocytes in our patient's biopsies supports this theory. However, the development of this condition in patients suffering from non-melanoma cancers suggests that different mechanisms, independent from melanoma, could also be involved. Larger studies are needed in order to determine if VLD also correlates with better survival rates in patients treated with nivolumab for non-melanoma malignancies.

In conclusion, new checkpoint inhibitors can cause VLD not only in patients suffering from melanoma but also in those affected by other tumors. We believe dermatologists should play a key role in the management of this side-effect. Therefore, we ought to be familiar with it in order to be able to identify and treat it appropriately without discontinuation of anticancer treatment.

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