Vitiligo-like lesions located over In-transit metastases of malignant melanoma as a clinical marker of complete response to pembrolizumab.

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Abstract

Anti-programmed cell death (PD)-1 therapies in metastatic tumors have a high incidence of immune adverse events, including cutaneous manifestations such as vitiligo-like lesions. This side effect is associated with increased survival and it is a clinical marker of response to treatment. This case report is a graphic representation of the appearance of vitiligo-like lesions over in-transit metastases of malignant melanoma linked to a complete response to treatment with pembrolizumab.

Keywords: melanoma, pembrolizumab, vitiligo.

Introduction

Pembrolizumab is a humanized IgG4 monoclonal antibody directed against the programmed death cell receptor 1 (PD-1), a major checkpoint in the effector phase of cytotoxic T cells. It has demonstrated promising clinical results in melanoma immunotherapy [1].

Vitiligo, a clinically visible immune-related adverse event, has been associated with clinical benefit in the context of pembrolizumab treatment. This dermatosis, has been reported as a secondary effect in 11%-25% of the patients treated with pembrolizumab [2]. Most of the published cases are associated with generalized vitíligo. However, we present a case of depigmentation at the site of primary melanoma and in the areas of in-transit metastases, as a graphic representation of the appearance of vitiligo-like lesions linked to a complete response to treatment with pembrolizumab.

Case Synopsis

An 82-year-old woman diagnosed with BRAF negative nodular melanoma and Breslow thickness of 3.9mm on her left foot with wide excision and negative sentinel node presented with in-transit

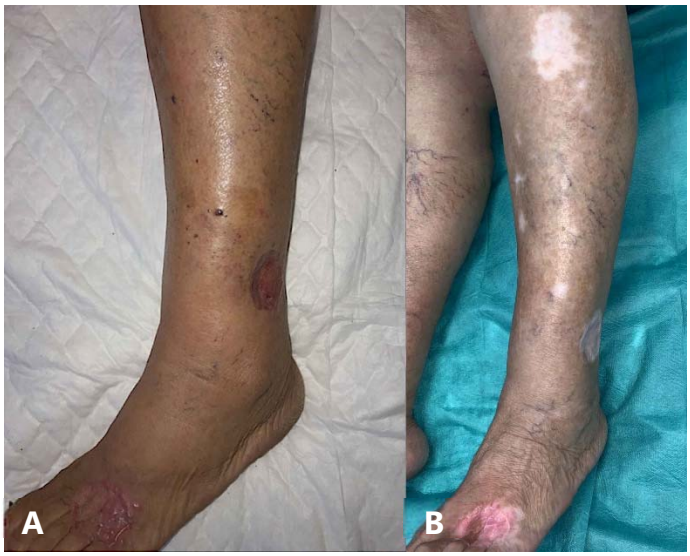

Figure 1. ***A)*** *Melanoma in situ with in-transit metastases, graft scar on foot and wide resection of cutaneous metastases of lateral malleolus, before pembrolizumab treatment.* ***B)*** *Vitiligo-like lesions developed over cutaneous metastases after pembrolizumab immunotherapy.*

metastases. After six months of follow-up new tumors of the external malleolus and the pretibial region of her left leg developed. These were treated with extensive surgery (**Figure 1A)**. Two years later, the patient presented with progression of her metastatic disease with an increase in the number of in-transit metastases. In addition, a PET CT scan showed involvement of left supraclavicular, mediastinal, left inguinal, and pulmonary hilum lymph nodes.

Treatment with pembrolizumab 2mg/kg was initiated, and after 12 cycles a complete clinical and PET-CT scan response was demonstrated. During the follow-up, vitiligo-like lesions developed in the area of the primary tumor and in the areas of in-transit metastases, the appearance of these lesions were associated with the complete response in the imaging tests (**Figure 1B)**.

Case Discussion

The treatments with anti-PD1 and anti-CTLA4 antibodies have revolutionized the management of metastatic melanoma and are increasingly used in advanced solid organ tumors. The most common adverse side effects of PD-1 inhibitors include maculopapular rash, pruritus, vitíligo, and lichenoid and mucosal skin reactions [3]. The appearance of autoimmune diseases, such as the development of vitiligo-like lesions associated with pembrolizumab immunotherapy, has already been correlated with improved survival rates [2, 4, 5]. It has recently been shown that this hypopigmentation is biologically different from classic vitiligo because they are often located in photoexposed areas and do not present the Koebner phenomenon. In addition, patients who have developed this vitíligo-like hypopigmentation while undergoing immunotherapy have had no increased personal or family medical history of autoimmune diseases [6]. The most accepted hypothesis is that it could result from an immune-mediated destruction through recognition of melanoma-associated antigens shared by normal melanocytes and melanoma cells. PD-1 antibodies activate the immune response by preventing an inhibitory signal and probably induce responses against antigens shared by melanomas and normal melanocytes [2, 7]. Recently it has been demonstrated by skin samples and blood analysis a strong infiltrate of CXCR3 expressing CD8 T cells and elevated levels of interferon-γ and tumor necrosis factor.

Generalized (acrofacial, classic, and universal) and localized vitiligo (focal and segmental) are the phenotypes of vitíligo-like lesions associated with pembrolizumab treatment. At present, two cases have been published, such as the one we have described around cutaneous metastases [2, 6].

Conclusion

This case shows vitíligo-like hypopigmentation that particularly involved the sites of in-transit metastases in association with complete clinical response.

Potential conflicts of interest

The authors declare no conflicts of interests

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