Tumoral melanosis after immunotherapy with pembrolizumab —a response sign mimicking melanoma

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Abstract

Tumoral melanosis is a rare histopathological finding characterized by aggregates of melanophages, in the absence of melanocytes, usually observed in sites of regressed melanocytic lesions, including melanoma. A 72-year-old woman with a history of a completely excised melanoma on her right arm (T3bN0M0, Stage IIb) presented with clinically-evident regional lymph node metastasis. This was treated with right axillary lymphadenectomy. Subsequently, a 2-centimeter blue-colored patch over the excision scar was identified, along with a blue nodule within the posterior aspect of the same arm, consistent with in-transit metastases. Additional metastases on the right hilar region of the lungs were detected by PET/CT. Hence, the patient began immunotherapy with pembrolizumab. After three months, a second PET/CT revealed a complete response, but the patient maintained the blue-colored patch previously observed. Given the discrepancy between the clinical and metabolic response she underwent a skin biopsy; histological examination showed findings compatible with tumoral melanosis resulting from complete regression of a metastatic lesion. In cases of metastatic melanoma under immunotherapy with anti-PD1 agents, especially pembrolizumab, tumoral melanosis has been anecdotally associated with tumor regression and favorable treatment response. The patient has been maintained on pembrolizumab, accomplishing 15 cycles, and has had a complete response to date.

Keywords: pembrolizumab, immunotherapy, melanoma, tumoral, melanosis

Introduction

Tumoral melanosis is a rare histopathological finding characterized by aggregates of heavily pigmented macrophages (melanophages) in the absence of melanocytes. It is usually observed in sites of regressed melanocytic lesions, including melanoma [1]. The significance of regression, particularly when complete, in the setting of melanoma is still debatable. Some authors postulate that this phenomenon is associated with an increased risk of metastatic disease, whereas others deny any worsening of prognosis [2]. The first is based on the theory that the presence of metastatic melanoma (MM) within a regional lymph node may stimulate an immune response, resulting in regression of the primary lesion [3]. The proposed mechanism comprises the recognition of abnormal antigens expressed by the tumor via blood and lymph node T cells [3].

Case Synopsis

A 72-year-old woman with a history of a completely excised melanoma on her right arm (3 millimeters Breslow thickness, ulcerated) classified as T3bN0M0 (stage IIB), presented with clinically evident regional lymph node metastasis after 8-month follow-up. She underwent a complete right axillary lymphadenectomy, and 11 out of 32 removed lymph nodes had metastatic disease. Mutational analysis for BRAF in the affected nodes was wild type.

Shortly after, a 2-centimeter blue-colored patch over the excision scar was identified, along with a blue nodule within the posterior aspect of the same arm. These lesions had strong uptake of 18-fluorodeoxyglucose on Positron Emission Tomography/Computed Tomography (PET/CT), consistent with in-transit metastases. Further metastatic lesions on the right hilar region of the lungs were detected, **Figure 1**.

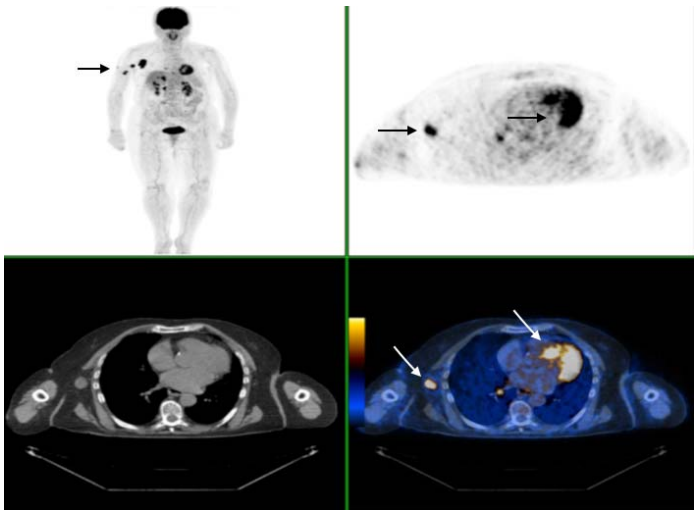

Figure 1. *In-transit metastasis and right hilar metastatic lesions on PET/CT.*

Considering the diagnosis of wild-type MM, the patient began immunotherapy with pembrolizumab, 2mg/kg intravenously every three weeks. After three months of therapy, a second PET/CT revealed a complete metabolic response, without any detectable lesion, **Figure 2**. Oddly, the patient maintained the blue-colored patch, unchanged from what was previously observed. Given the discrepancy between the clinical appearance and imaging results, a skin biopsy of the lesion was performed. Histopathological examination demonstrated multinodular aggregates of melanophages within the deep dermis and hypodermis, surrounded by lymphocytic infiltrate; no residual melanoma cells were identified, **Figure 3**. Immunohistochemistry revealed strong positivity for CD3 and a 5-10% PD1 positivity in the lymphocytic population, **Figure 4**. These findings were consistent with tumoral melanosis as the result of complete regression of a metastatic lesion. The patient has been maintained on pembrolizumab, accomplishing 15 cycles with a complete response to date.

Case Discussion

The advent of immune checkpoint inhibitors has changed the treatment paradigm for MM. These agents include anticytotoxic T-lymphocyte associated antigen four antibodies (ipilimumab) and programmed cell death-1 receptor inhibitors (nivolumab and pembrolizumab). Their anti-neoplastic activity is achieved by the blockade of immune suppressive checkpoint pathways, leading to the stimulation of host immunity against the tumor [4]. On the other hand, their increasing use has brought to attention numerous immune mediated side effects, little described until now, which can affect virtually any organ system. Some examples include enterocolitis, pneumonitis, hepatitis, hypophysitis, inflammatory arthritis, and a variety of skin manifestations [5]. With respect to the latter, they can further be categorized in four groups according to histological patterns: inflammatory, immunobullous, alteration of epidermal keratinocytes, and alteration of epidermal melanocytes, in which tumoral melanosis is included [5].

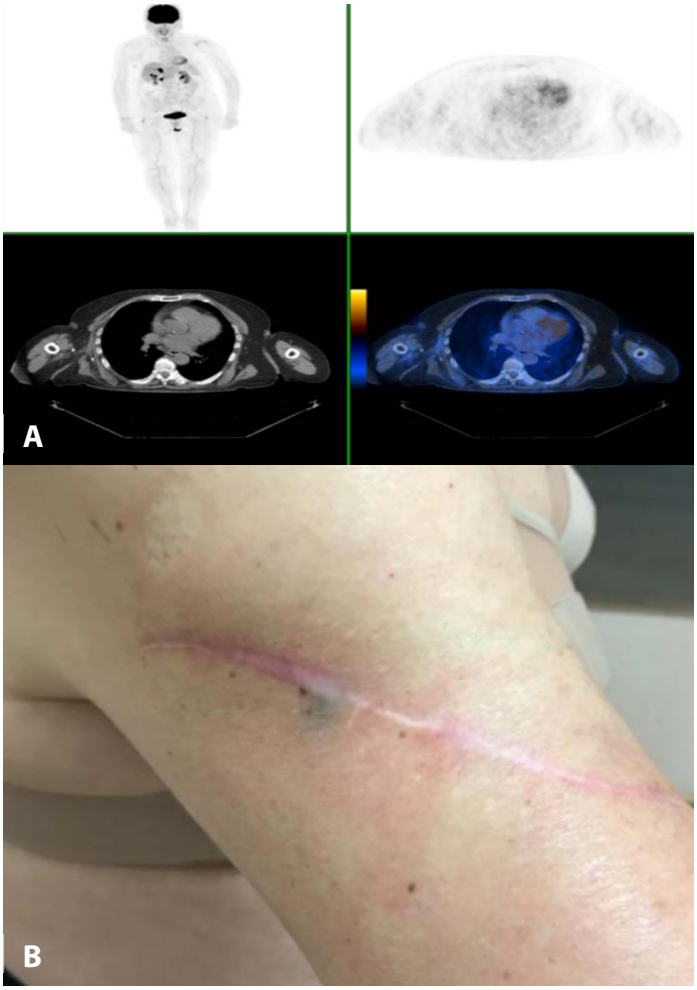

Figure 2. *Discrepancy between clinical and metabolic response.* ***A)*** *PET/CT revealing a complete metabolic response.* ***B)*** *Blue-colored patch measuring 2×1 centimeters over the excision scar on the right arm.*

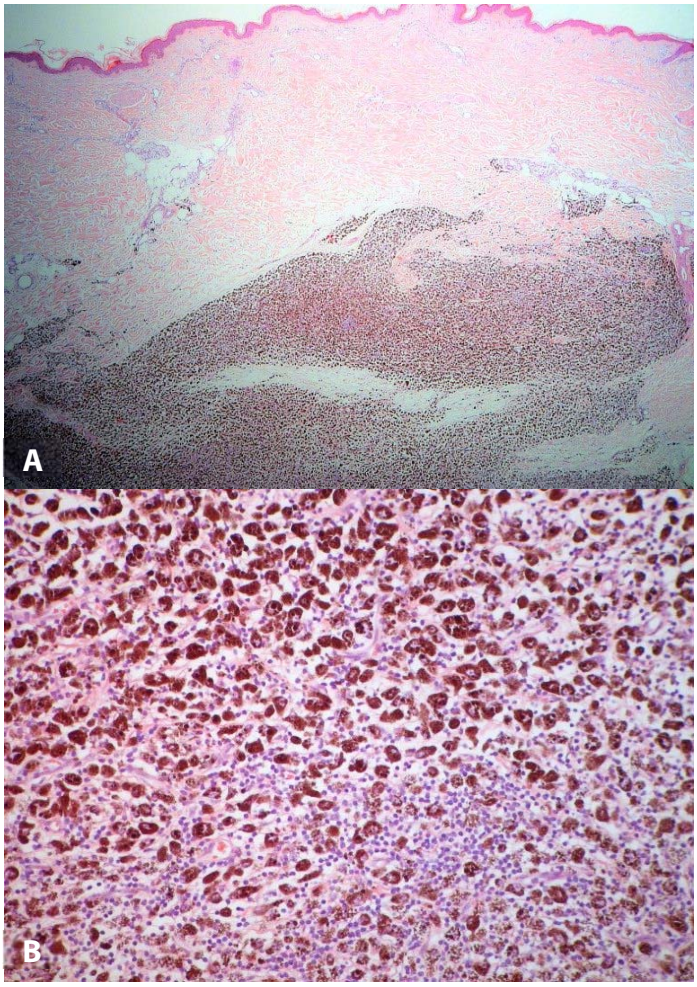

Figure 3. *Histopathological examination of the blue-colored lesion.* ***A)*** *Multinodular aggregates of melanophages, within the deep dermis and hypodermis.* ***B)*** *Lymphocytic infiltrate surrounding the melanophages. H&E, 200×.*

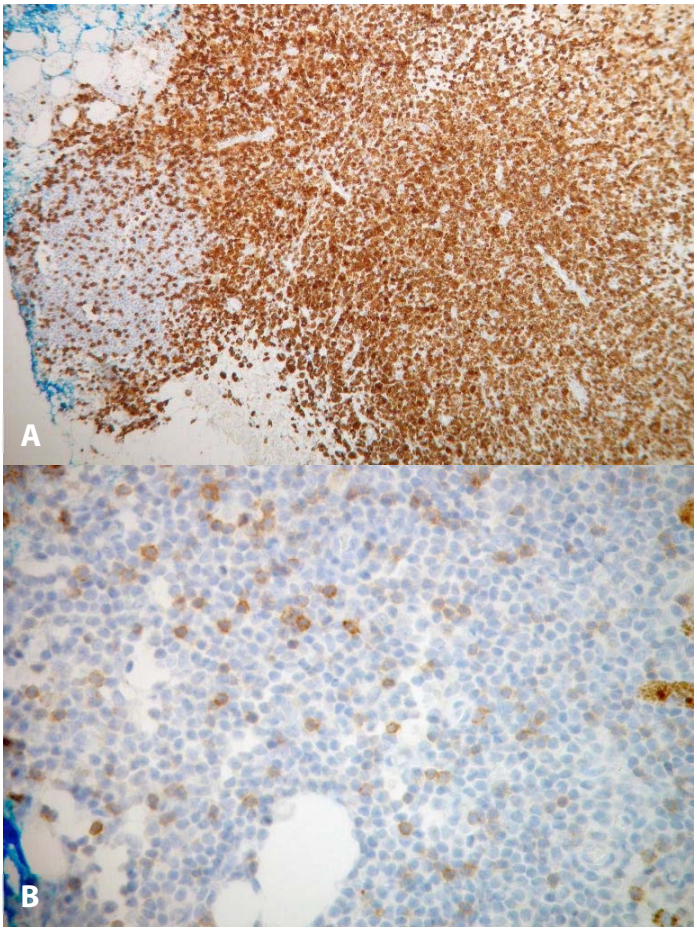

Figure 4. *Immunohistochemistry of the lymphocytic population of the lesion* ***A)*** *Strong positivity for CD3 stain, 100×.* ***B)*** *Five-10% positivity for PD1, 400×.*

The identification of tumoral melanosis in a site of completely regressed cutaneous melanoma can be a harbinger of metastatic disease. Paradoxically, in cases of MM under therapy with immune checkpoint inhibitors, tumoral melanosis has been anecdotally associated with tumor regression and favorable treatment response, with 8 cases reported to date [6-11], **Table 1**. Six of these are specifically related to pembrolizumab.

Guo et al. (2016) was the first describing a series of three cases, speculating that tumoral melanosis could be the pathologic treatment effect to anti-PD1 agents in MM patients. All the patients revealed complete response to therapy [8]. After that, three separate cases were reported, although one of them ended up demonstrating possible progression [9-11]. Our case, in particular, shows the absence of active lesions on PET/CT in the setting of a clinical lesion resembling melanoma, which turned out to be tumoral melanosis.

According to a study by Kong et al. (2016) regarding response evaluation in patients with MM on anti-PD1 therapy, those without active lesions on PET, even if they were noticeable clinically or by CT scan, did not show progressive disease. Instead, the ones with identifiable lesions on PET progressed, concluding that this imaging method may be a good negative predictor for progression in patients under immunotherapy with anti-PD1 [12].

Nevertheless, it is known that the immune activation caused by anti-PD1 agents may be the reason for false positives on PET scan and the term "pseudo-progression" has been applied to this scenario. If this is suspected, a biopsy and histological examination of the lesion should be done [12].

Table 1. *Reported cases of tumoral melanosis associated with pembrolizumab.*

	Age and gender	Clinical presentation	Histopathologic examination	PET/CT	Follow-up
Guo, R. et al. [8]	---	In-transit metastasis	Tumoral melanosis	Complete response	Disease free at 19-month follow-up
Guo, R et al. [8]	---	Axillary lymphatic nodes	Tumoral melanosis	Complete response	Disease free at 12-month follow-up
Guo, R et al. [8]	---	New lesion adjacent to the primary tumor excision scar	Tumoral melanosis	Complete response	Disease free at 3-month follow-up
Bari, O & Cohen, P R [9]	81-year-old male	3 blue macules over satellite metastasis excision scars	Tumoral melanosis	Complete response	Disease-free at 13-month follow-up
Helm, M F et al. [10]	70-year-old male	Blue-grey macule adjacent to the primary tumor excision scar	Tumoral melanosis	Stable disease	Stable disease at 5-month follow-up
Woodbeck R et al. [11]	64-year-old male	2-mm pigmented nodule adjacent to the primary tumor excision scar	Tumoral melanosis	Progressive disease	Possible progression but maintaining therapy

Conclusion

With the reported case, the authors would like to point out that clinically evident lesions may not correspond to subsequent histological findings, especially when metabolically inactive in the setting of immunotherapy. This suggests that in cases of MM, we should consider not only the clinical findings, but also the metabolic response criteria through PET/CT. In case of discrepancy, and whenever possible, histopathological confirmation must be sought.

Potential conflicts of interest

The authors declare no conflicts of interests

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