Regression of nevi, vitiligo-like depigmentation and halo phenomenon may indicate response to immunotherapy and targeted therapy in melanoma

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We present two patients with stage IV melanoma, the first with BRAF wild-type melanoma with multiple visceral metastases treated with immunotherapy (pembrolizumab) and the second with BRAFV600E melanoma with subcutaneous and lymph nodes metastasis treated with BRAF and MEK-inhibitors (dabrafenib/trametinib). Already after the second cycle of immunotherapy, the first patient developed a diffuse regression of nevi, perceptible only with the use of dermoscopy and 3 months later a clinically evident poliosis of the eyebrows. The second patient, treated with dabrafenib/trametinib, developed small areas of leukoderma on his chest and white halos around nevi with a dermoscopic globular or structureless pattern. Both observations are suggestive for an immune reaction against melanocytic cells, which is further supported by the complete response to systemic therapy in both patients. It has been demonstrated that the development of vitiligo-like depigmentation during immunotherapy is associated with a better prognosis; in our patient, the phenomenon of poliosis appeared much later than the dermoscopic presence of regression among his nevi, suggesting that the latter may be an early sign (along with vitiligo-like phenomena) of good response to immunotherapy. On the other hand, the development of halo nevi and leukoderma during treatment with BRAF/MEK-inhibitors, suggests that not only immunotherapy but also targeted therapy may induce an immunologic response against melanoma and nevi, again indicative of a favorable prognosis. More data are needed to confirm these findings; however, they indicate that dermatologists should be involved in the follow-up of patients with melanoma, both in studies and clinical practice. *Melanoma Res* **31: 582–585**

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Introduction

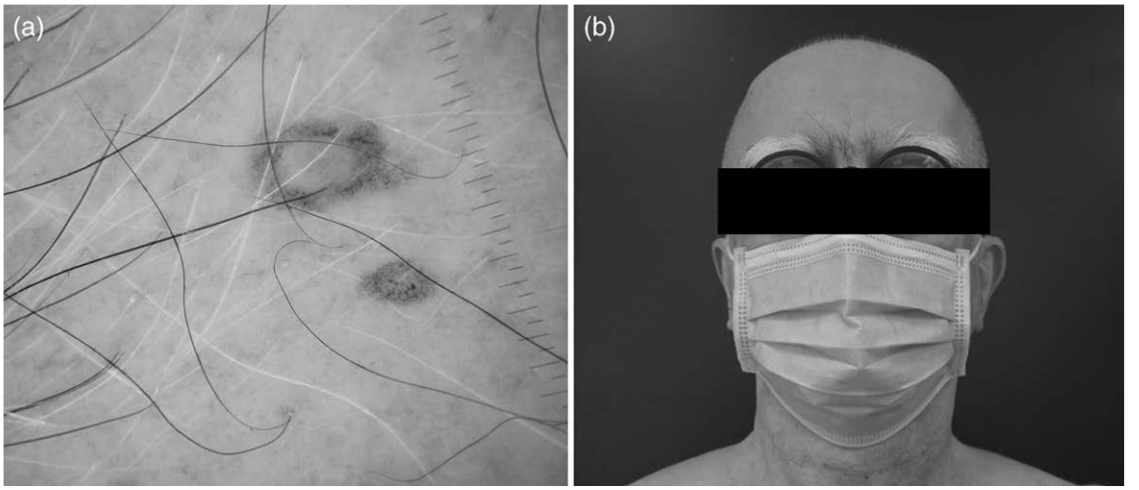
Actually, immune checkpoint inhibitors (pembrolizumab, nivolumab and ipilimumab) and targeted therapy (BRAF- and MEK-inhibitors) represent first-line treatments in metastatic melanoma.

Immunotherapy may be associated with a range of different cutaneous adverse effects, including vitiligo-like depigmentation. Interestingly, the latter has been associated with recession of the metastatic tumor and prolonged survival, configuring vitiligo as a positive response-predictive biomarker to the treatment [1,2]. Moreover, clinical fading of globular-structureless nevi is often reported in patients receiving BRAF-inhibitors alone or BRAF- and MEK-inhibitors, because these categories of nevi frequently exhibit BRAF mutations [3–5].

Herein we present two patients with stage IV melanoma who developed cutaneous manifestations suggestive of the immune response against melanocytes during both immunotherapy and targeted therapy and discuss the potential significance of our observations.

Cases reports

The first case refers to a 60-year-old man with brain, lung, liver and renal BRAF wild-type metastases from an unknown primary melanoma. After stereotactic radiation of the brain metastases, he received the monoclonal anti-PD-1 antibody pembrolizumab at a dosage of 2 mg/kg of body weight every 3 weeks. A dermatologic visit was carried out after the second cycle of pembrolizumab. Clinical examination did not indicate pathologic findings, despite some clinically unremarkable appearing brown nevi on the trunk; however, upon dermoscopy, most nevi showed small gray dots suggestive of a regression process (Fig. 1a). Radiologic staging, performed after the fourth cycle of pembrolizumab, revealed stable disease and treatment was continued. At the next dermatologic visit, 5 months after starting immunotherapy, an evident whitening of the eyebrows (poliosis) was noted (Fig. 1b), in addition to the persisting regression of nevi. At this point, computed tomography staging revealed the partial response of the lung metastases and stable disease of the remaining metastases.



(a) Dermoscopy of two nevi revealing multiple small gray dots, indicative of an immune process of regression. (b) Poliosis of the eyebrows.

The second patient is a 70-year-old man with stage IV BRAF V600E mutated melanoma, with multiple subcutaneous and lymph node metastases from a 2.9 mm primary melanoma located on his back 5 years before. He initiated treatment with dabrafenib/trametinib (BRAF/MEK-inhibitors) with complete response after 6 months. He continued the treatment unmodified for overall 2 years, with confirmed complete response. A dermatologic visit, carried out 2 years after treatment start, revealed small areas of depigmentation on his chest. Moreover, some nevi on his trunk displayed a hypopigmented halo. All halo nevi exhibited a globular or structureless pattern (Fig. 2a,b), whereas the halo phenomenon was not observed among nevi with a reticular pattern. Based on the ongoing complete response after 2 years of treatment and in light of the development of halo nevi suggestive for immune-response, the question whether to continue treatment was discussed at our tumor board. Because the patient tolerated well the treatment, a final decision to continue was made.

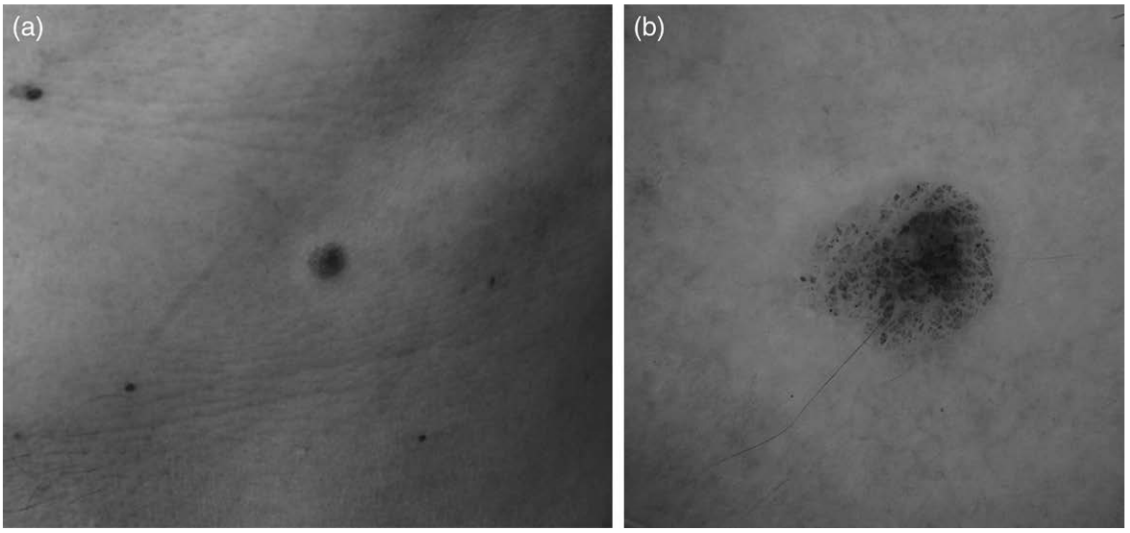
Discussion

The development of vitiligo-like depigmentation or regressing nevi is increasingly described among patients with melanoma receiving immunotherapy [1,6,7]. These phenomena have been explained as the result of an active immune response against antigens shared by melanoma and normal melanocytes, such as MART-1, gp100 and tyrosinase [6]. Vitiligo and other forms of depigmentation have been observed only in patients affected by melanoma treated with immunotherapy, but not in other forms of cancers [6]. There are evidence suggesting that vitiligo-like depigmentation is associated with improved efficacy of immunotherapy, representing a favorable prognostic factor. The most important substantiation comes from a recent meta-analysis showing a two-fold decreased risk of disease progression and a four-fold decreased risk of death in patients with stage IV melanoma developing vitiligo during immunotherapy, compared with patients without vitiligo development [1].

Moreover, clinical fading of nevi, with or without an evident white halo, has been associated with treatment response of lymph node and visceral metastases [7,8].

Interestingly, our first patient developed a recognizable depigmentation (i.e. poliosis) much later compared to dermoscopic findings of regression in clinically normal appearing nevi. This observation points towards a subclinical very early immune-related reaction after only two cycles of pembrolizumab. To the best of our knowledge, subclinical regression detected only by dermoscopy has not been described during immunotherapy in nevi without halo. Libon *et al.*, [8] reported a fading of darker pigment during digital follow-up of nevi in a patient treated with ipilimumab, but they did not report about regression. Given the response to treatment in our patient, dermoscopic regression of nevi may be considered an early predictive feature for favorable response to immunotherapy.

On the other hand, fading of nevi, characterized upon dermoscopy by a globular-structureless pattern but not a reticular pattern, is a well-documented phenomenon in patients with melanoma receiving targeted therapy. This phenomenon is the result of involution/apoptosis and oncogene-induced sentence, and it is not due to immune-mediated regression [4,5]. This can be explained by the fact that globular and structureless pattern nevi commonly exhibit BRAF mutations [3] and, accordingly, they undergo senescence during inhibition of the MAP



(a) Nevus with a subtle hypopigmented halo visible to the naked eye. (b) Dermoscopy of the nevus revealing a globular pattern.

kinase pathway. In contrast, vitiligo-like depigmentation, regression or halo nevi, are considered immune-mediated reactions that are seldom reported in patients receiving targeted therapy [9]. However, it appears that targeted therapy may induce an immune-related response [10,11]. The development of leukoderma and halo around the nevi in our patient 2, points toward such immune-related reaction against melanocytes. Whether the development of halo nevi or leukoderma after complete response to targeted therapy may help in the future to decide treatment cessation, remains a matter of further study.

Irrespective of increasing reports about cutaneous depigmentation (vitiligo-like and halo phenomenons) as response-predictive biomarkers to immunotherapy and targeted therapy, these manifestations may be underreported in clinical trials [1]. In fact, most trials are carried out by oncologists, who are not familiar with the use of dermoscopy or Wood's lamp to detect subtle cutaneous signs. Moreover, cutaneous manifestations such as vitiligo are classified as nonsevere (grade 1) toxicities and therefore may be underreported [1].

Irrespective of an increasing number of reports suggesting the development of cutaneous depigmentation (leukoderma, vitiligo, regression or halo nevi) as a potential biomarker for favorable treatment response, cutaneous adverse events to immunotherapy or targeted therapy may be underreported in clinical trials for the following reasons [1]. First, many trials are carried out by medical oncologists, who are not familiar in the screening for skin manifestations which may be clinically imperceptible to an unexperienced eye. Second, oncologists have no formal training in the use of diagnostic tools such as dermoscopy or Wood's lamp, thus the use of these techniques is usually not required or performed in clinical trials. Third, subtle cutaneous manifestations such as leukoderma or vitiligo-like depigmentation commonly fall into the category of nonsevere (grade 1) autoimmune toxicity and maybe therefore underreported.

Conclusion

Our findings demonstrate that dermoscopic observation can detect a possible early marker of response to immunotherapy, that is, the gray dots that characterize immunologically based regression of nevi. In our case, this finding preceded the development of clinically evident poliosis, which can be likened to a vitiligo-like depigmentation. Our patient with these findings achieved a prolonged overall survival. On the other hand, we observed that the development of halo nevi can occur not only in patients treated with immunotherapy but also in ones on targeted therapy, implying an immune phenomenon against melanocytes different from the known fading of nevi carrying BRAF mutation.

Our both cases, along with current literature, support the notion that cutaneous side effects, such as vitiligo, can represent easily accessible response-predictive biomarkers to systemic therapies for metastatic melanoma. To gain more insights, regular dermatologic visits should be implemented in standard treatment protocols and clinical trials.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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