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CASE REPORT

Onset of vitiligo following targeted therapy for BRAF^{V600E}-mutated melanoma: case report

Sonia Brugnara MD[1], Mariacristina Sicher MD[2], Elena Maria Bonandini MD[3], Mattia Barbareschi MD[3], Carlo Renè Girardelli MD[2], Orazio Caffo MD[1]

[1]Oncology Unit, S. Chiara Hospital, Trento, Italy; [2]Dermatology Unit, S. Chiara Hospital, Trento, Italy; [3]Pathology Unit, S. Chiara Hospital, Trento, Italy

Abstract

Systemic treatment for metastatic melanoma has advanced dramatically in recent years with an impressive increase in the rate of overall survival. The two main different strategies are targeted therapies (i.e. BRAF and MEK inhibitors) and immunotherapy with monoclonal antibodies against the immune checkpoint proteins programmed death-1 (PD-1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4). Vitiligo often accompanies immunotherapy in melanoma patients and even correlates with tumor regression after checkpoint blockade. At present, a correlation between vitiligo onset and outcome from immunotherapy is acknowledged; however, evidence of a correlation between vitiligo and efficacy of combination-targeted therapy is lacking. We describe our experience in a patient who received dabrafenib and trametinib and developed vitiligo-like depigmentation after treatment cessation.

Keywords: BRAF, immune system activation, MEK, melanoma, targeted therapy, vitiligo, V600E mutation.

Citation

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Introduction

Systemic treatment for metastatic melanoma has advanced dramatically in recent years with an impressive increase in the rate of overall survival (OS). There are two main new strategies. Firstly, targeted therapies (BRAF and MEK inhibitors) directed against MAP kinase (MAPK) pathway. This is constitutively activated in approximately 50% of the patients due to an activating mutation in position V600 of *BRAF*, which causes uncontrolled growth and survival of tumoral cells. Resistance to therapy with BRAF kinase inhibitors is associated with reactivation of the (MAPK) pathway. Inhibition of the MAPK pathway downstream of BRAF was hypothesized to suppress mechanisms of resistance.[1–3] MEK inhibition has been validated as a therapeutic approach in the same patient population.[3] The second strategy is immunotherapy with monoclonal antibodies against the immune checkpoint proteins programmed death-1 (PD-1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4). Immune checkpoint inhibitors (ICIs) have proven to be able to co-opt the adaptive immune system to attack tumor cells.[1–5]

Moreover, ICIs also induce long-lasting clinical responses, mainly due to an immune system activation during treatment.[6–8] Immune system activation may be indicated by vitiligo-like depigmentation, a sign of the immuno-related toxicity, which also represents a prognostic and predictive marker.[9] Notably, this type of toxicity is rarely observed during treatment with BRAF and MEK inhibitors; however, its frequency is unknown and it is unclear whether the depigmentation may have predictive or prognostic value.

In our opinion, it can be valuable to collect information concerning this toxicity in patients treated with targeted therapy for metastatic melanoma showing a V600E mutation. The present report is aimed to describe the case of one patient who received dabrafenib and trametinib and developed vitiligo-like depigmentation after treatment cessation. Patient consent was obtained before the drafting of the present manuscript. Due to the purely anecdotal nature of the reported case, formal approval by a Review Board was not required; however, the relevant Ethical Committee (S. Chiara Hospital,

Figure 1. Hypopigmented patches on the patient's back.

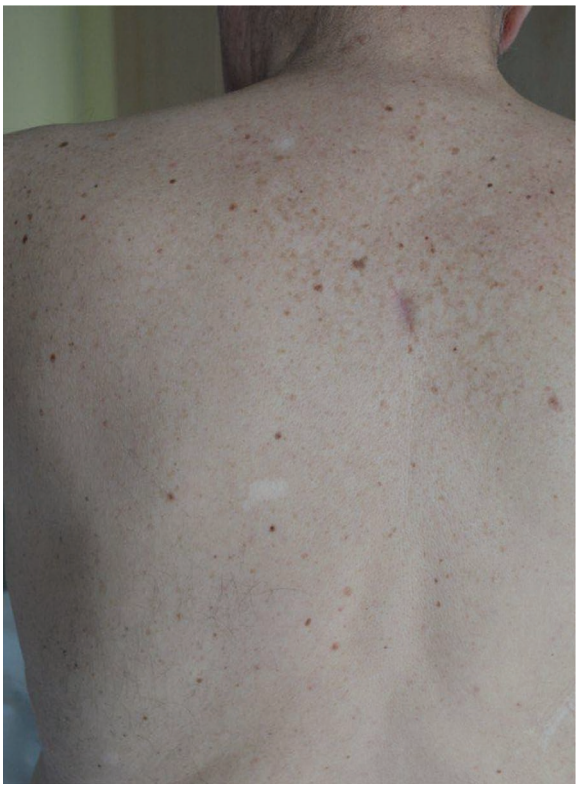
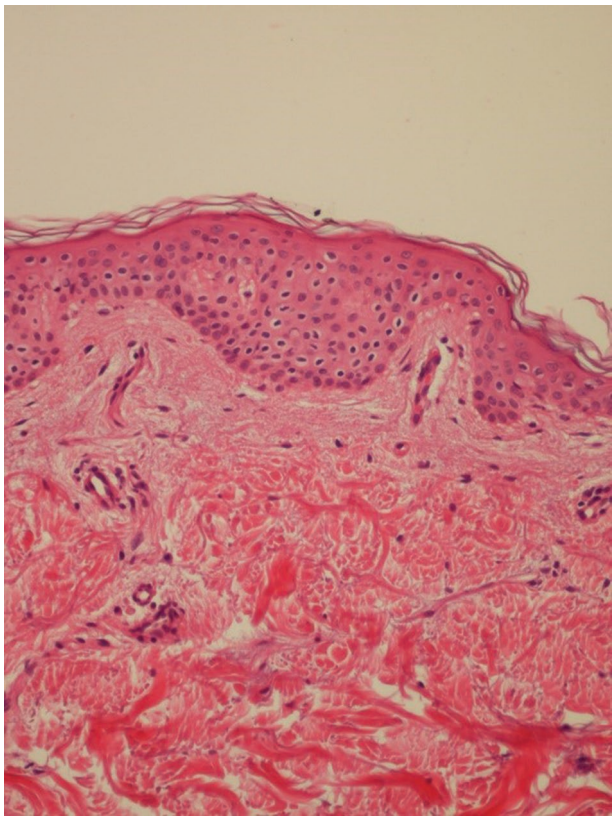


Figure 2. The absence of melanocytes and pigment in the epidermis was shown in hematoxylin and eosin stained slices.



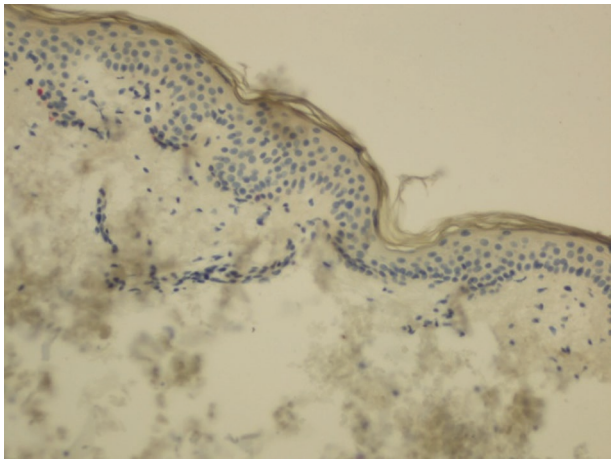
Trento, Italy) was informed. The present case was reported according to CARE guidelines.

Case presentation

In 2002, a 57-year-old man underwent excision of a cutaneous lesion on the left parasternal region, which was diagnosed as a melanoma showing a superficial spreading phenotype. The histologic examination showed a thickness of 0.3 mm, Clark level III, 1 mitosis/mm^2, with active chronic inflammation, capillary neogenesis and pigmented histiocytes in the dermis. The patient was staged as stage IB pT1b, N0, M0. Regular follow up was carried out at fixed intervals until November 2013 when left axillary lymphadenopathy was detected with ultrasound. A needle biopsy confirmed the presence of melanoma cells while an additional metastatic site was detected in the right para-tracheal nodes by a subsequent positron emission tomography (PET) scan. Brain computed tomography (CT) scan did not show metastatic cerebral involvement, and LDH levels were within the normal ranges. A *BRAF* mutation analysis was performed, showing the V600E mutation. Consequently, the patient started first-line treatment with vemurafenib in January 2014 (only monotherapy is available in Italy). Unfortunately, the treatment was interrupted after a few days due to the occurrence of a grade 2 allergic reaction (allergic reaction/immune system disorders G2 CTC AE 4.03). After this hypersensitivity episode was resolved, we tried to restart vemurafenib at the reduced dose but palatal edema and swelling with pain were observed (allergic reaction/immune system disorders G2 CTCAE 4.03). After hypersensitivity resolution, vemurafenib was restarted at a further reduced dose, but a new allergic reaction led to a definitive stop in treatment. In March 2014, a PET scan demonstrated a partial remission of the disease, and we tried to restart systemic therapy by using the other BRAF inhibitor, dabrafenib, administered in combination with the MEK inhibitor, trametinib. The combined treatment was well tolerated in the absence of allergic reactions and 3 months later, in August 2014, complete response was observed. Treatment was continued until April 2016, when the patient asked to interrupt the treatment following the persistent finding of an absence of disease documented by PET scans.

Since then, there has been regular follow-up every 3 months with clinical evaluations (dermatologic and oncologic evaluation), blood tests (LDH, biochemistry and blood count), and PET scans. In this timeframe, all laboratory tests (LDH levels in particular) and PET scans were normal. In February 2017, a dermatologic clinical examination found several hypopigmented patches on the patient's forehead and back, suggesting vitiligo (Figure 1). A skin biopsy confirmed the presence of vitiligo and excluded other types of hypopigmentation, such as hypomelanosis guttata or postinflammatory lesions. Lymphocyte subpopulations in the lesions were analyzed. The CD3+CD4+/CD3+CD8+ ratio was 3.3

Figure 3. Immunohistochemical staining with Melan A showed the absence of melanocytes in the epidermis, confirming the diagnosis of vitiligo.



(normal value 1–2.5), with prevalent Th lymphocytes (Figures 2 and 3). No examinations for the autoimmune disease were performed. Currently, 38 months after the combined treatment was stopped, the patient is in good clinical condition without any sign of active disease, although the patient still has vitiligo patches. Patches on the back have not changed, while the lesion on the forehead has disappeared.

Discussion

We described a patient with metastatic melanoma who presented vitiligo 10 months after discontinuation of therapy with the BRAF inhibitor, dabrafenib, in combination with the MEK inhibitor, trametinib, which had induced a complete response. The patient was still in remission at the time this report was written.

As vitiligo could be the result of an immunologic activity from the drugs used, this case is reported to discuss whether immune-related adverse events could be interpreted as an index of favorable outcomes.

Such considerations could be relevant to understand whether the occurrence of an immune-mediated event can be considered a prognostic marker and whether combined targeted therapy can be interrupted in metastatic melanoma responsive patients. Nevertheless, it must be mentioned that vitiligo could be correlated to melanoma, and not to targeted therapy itself. The 10-month interval between targeted therapy and vitiligo occurrence could suggest that either immunologic events were activated by therapy and continued for a long period, or that melanoma was still present, although not clinically detectable.

Survival of patients with metastatic melanoma was recently improved by new targeted therapies, with the median OS increasing from approximately 9 months before 2011 to at least 2 years in 2016, and probably longer for those with *BRAF*^{V600}-mutant disease. The standard of care has rapidly changed first to single-agent BRAF inhibition and then to combination therapy with a BRAF and a MEK inhibitor. Patients with normal LDH, low disease burden, and without brain metastases, who previously were indicated for first-line treatment with immunotherapy, have a greater benefit from targeted therapy. Long-term outcomes seem to be due to an immunomodulating activity of BRAF/MEK inhibitors.[10]

It was demonstrated that the intratumor T CD8+ lymphocyte infiltrate was increased during treatment with a BRAF inhibitor, and that this increase was correlated with tumor mass reduction and decrease of tumor metabolic activity.[11] These findings suggest that the immunologic response has a role in the tumor response to BRAF inhibitors.

In addition, the combination of a BRAF inhibitor and an ICI synergistically improved immunity and reduced tumor volume in an immunocompetent mouse model of cancer.[12]

Recent evidence supports the hypothesis that immune-related events during targeted therapy may correlate with better outcomes, based on immunosuppression decrease. Such adverse events may represent markers of long-lasting clinical response.[13,14] Finally, vitiligo has been described as associated with BRAF inhibitor administration.[15–18]

One of the main explanations about the relationship between melanoma and vitiligo-like disorders is the immune activation against melanoma-associated antigens expressed by normal melanocytes as a result of a cross-reaction from melanoma cells that share the same antigens. Antigen release by anticancer therapies could explain a breakdown of immune tolerance to self-antigens expressed in normal cells or in benign lesions, such as nevi causing vitiligo-like disorders.[19–21] This mechanism could be at the basis of the correlation between the onset of vitiligo-like disorders and the outcome of those patients.[22]

In conclusion, we present a clinical case that may support current evidence suggesting that BRAF/MEK inhibitor therapy in metastatic melanoma has immunologic activity and that immune-related adverse events during therapy may be regarded as prognostic indexes.

Contributions: Brugnara and Caffo were in charge of the patient; Sicher and Girardelli diagnosed vitiligo; Bonandini and Barbareschi performed histological examination. All authors contributed equally to the preparation of this article. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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Correspondence: Sonia Brugnara, Oncology Unit, S. Chiara Hospital, Trento, Italy. sonia.brugnara@apss.tn.it

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