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Durable complete response in a patient with BRAF-mutated advanced melanoma with ocular and skin toxicities from BRAF/MEK targeted therapy after immune checkpoint inhibitor treatment: a case report

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Consent for publication: the patient in this manuscript has given written informed consent for the publication of their case details.

Availability of data and materials: data sharing does not apply to this article, as no new data were created or analyzed in this study.

Abstract

Here we report the case of a woman suffering from advanced melanoma who developed severe toxicities with BRAF and MEK inhibitors (BRAFis, MEKis), given as second-line therapy after failure of immunotherapy, who achieved a complete and durable response lasting for over 5 years. Significant progress has been achieved in the treatment of advanced melanoma with immune checkpoint inhibitors (ICIs) and targeted therapies using BRAFis and MEKis. While these treatments improve survival, they also pose risks of severe toxicities. Notably, when targeted therapy follows immunotherapy, immune-mediated toxicities may emerge months later due to tumor microenvironment modulation. Despite these risks, both approaches offer a durable response in eligible patients. Further understanding is needed to determine how prior immunotherapy may influence subsequent toxicity risks of target therapy. Understanding these factors could optimize treatment strategies and improve patient outcomes.

Introduction

Melanoma represents one of the most common and lethal skin cancers, with an increasing incidence globally.[1] Over the past decade, significant progress has been made in improving survival rates, particularly among advanced melanoma patients.

Immunotherapy involving immune checkpoint inhibitors (ICIs) has been approved as a single agent for the treatment of metastatic or unresectable melanoma. Among ICIs, pembrolizumab and nivolumab (PD-1) are commonly used in the treatment of metastatic melanoma. These agents can also be combined with ipilimumab, a distinct immune checkpoint inhibitor targeting CTLA-4.[2]

In addition to immunotherapy, targeted therapy using BRAF and MEK inhibitors (BRAFis, MEKis) has recently shown promise in enhancing survival in patients with advanced cutaneous melanoma.

In patients with BRAF mutations, inhibitors such as vemurafenib and dabrafenib have been approved for both single-agent and combination administration with MEK inhibitors, including cobimetinib and trametinib, respectively.[3]

Of more recent approval, the association of new BRAFi and MEKi agents, encorafenib and binimetinib, has been shown to provide an improvement in progression-free survival in patients with metastatic melanoma and a BRAF mutation.[4]

Despite promising results in several studies, these treatments are associated with various toxicities and side effects, which can sometimes be severe.[5]

Here, we report a case of a patient who developed both skin and ocular toxicities after switching from immunotherapy to targeted therapy.

Case Report

A 37-year-old woman was diagnosed with melanoma in the lymph node region after excision of a massive congenital nevus on the left upper arm. The patient underwent surgical removal of left axillary lymphadenopathy, which revealed melanoma positivity in 49/52 lymph nodes. Adjuvant targeted therapy with vemurafenib, a BRAFi, was initiated and continued from 2011 to 2014. During this period, she also underwent a left mastectomy due to locoregional recurrence. Given her desire for fertility preservation, it was agreed to discontinue the treatment.

In 2015, a PET scan detected pleural recurrence at the costovertebral region, requiring removal of chest wall nodules. First-line ICI therapy with nivolumab was started, for which the patient completed 55 cycles by 2018. While a total body CT scan performed in 2017 showed lesion reduction, subsequent disease progression to left retroperitoneal and supraclavicular lymph nodes was clearly evidenced by July 2018 (Figure 1).

This led us to initiate treatment with a second-line target therapy using dabrafenib, another BRAFi, in combination with the MEKi trametinib. However, 10 days into the therapy, the patient was urgently admitted to the hospital with hyperthermia and abdominal pain, requiring temporary discontinuation of treatment until resolution. Upon treatment resumption one month later, the patient developed a diffuse, nonpruritic maculopapular rash on her lower and upper extremities, along with fever, requiring oral steroid and antihistamine medication, which led to symptom resolution. Upon resumption of full therapy, a total body CT scan performed in November 2018 showed a complete response in left retroperitoneal and supraclavicular lymph nodes.

In January 2019, further therapy discontinuation became necessary due to diffuse arthralgias, lower extremity cramps, and fever, all of which improved after administration of prednisone (25 mg). On hematochemical examination, G2 leuko-neutropenia (WBC: 2450/μL, neutrophils 1850/μL) was also observed.

In May 2019, targeted therapy was restarted, followed by total body CT findings indicating stability of retroperitoneal lymphadenopathy and left costovertebral lesions (Figure 2).

Three months later, the patient developed a cutaneous leg rash and fever, prompting discontinuation of the therapy and steroid administration, which resulted in a good response (Figure 3). Despite reducing the dosage, recurrent fever and further complications led us to decide to switch therapy to encorafenib and binimetinib, BRAFi and MEKi, respectively. A subsequent CT scan showed partial/complete response in the left costovertebral region lesion, resolution of left axillary and left parasternal lesions, and stable retroperitoneal lymphadenopathy of upper limit size.

The patient then sought an ophthalmologic consultation due to discomfort in the left eye and a decrease in visual acuity. Cystoid macular edema with a modest vascular tortuosity was found, for which fluoroangiography with indocyanine green and discontinuation of binimetinib were

recommended. We also decided to discontinue encorafenib due to concerns that the ocular pathology may be related to BRAF inhibition. About three months later, the patient was diagnosed with posterior uveitis in the left eye, for which an Ozurdex® injection was administered.

Considering the negative findings for recurrence of oncologic disease and worsening uveitis, we decided to proceed with treatments for left eye issues while continuing a rigorous oncologic follow-up. A total body CT scan performed in November 2020 revealed no signs of supra- or sub-diaphragmatic secondary lesions, whereas a subsequent eye consultation indicated complete reabsorption of the macular edema in her left eye. On fluoroangiography, peripheral inflammatory foci in the left eye were stable, with vasculitis and papillary hyperfluorescence regression.

Currently, the patient remains disease-free, with ongoing oncologic follow-up.

Discussion

Here we report the case of a woman suffering from metastatic melanoma who experienced significant ocular and skin toxicities during BRAFi and MEKi therapy, administered as a second-line treatment after the failure of immunotherapy, resulting in a complete response lasting over five years.

To better understand the hypothesis behind such a significant response despite the observed toxicities, it is essential to first review the mechanisms underlying these therapies.

It is well established that the combination of MEKis and BRAFis improves progression-free survival and overall survival in patients with BRAF-mutated melanoma. This benefit is largely attributed to MEKis' ability to overcome molecular resistance mechanisms that limit the efficacy of BRAFis alone.[6]

BRAFis have been shown to modulate the tumor microenvironment, enhancing immunotherapy by increasing antigen-presenting activity, as well as by reducing tumor secretion of immunosuppressive cytokines and increasing T-cell recognition of tumor antigens, thereby enhancing effector immune cell migration to the tumor.[7]

On the other hand, MEKi may enhance the anti-tumor effects in melanoma cells and decrease the toxicity associated with BRAFi treatment due to their ability to suppress the MAPK signaling pathway regardless of BRAF mutation.[8]

Similar to the action of BRAFis, MEKis also increase $CD8^+$ cell response in the tumor, protecting tumor-infiltrating cells from death caused by chronic T-cell receptor stimulation, preserving their cytotoxic activity, and upregulating tumor antigen expression and maintenance.[9]

When administered in conjunction, MEKis could balance the potential overreaction of effector cells and enhance the tumor microenvironment by targeting cytokine production and immunosuppressive cell populations within it.[10] This has been demonstrated in preclinical and clinical studies, where the

alteration of the microenvironment was found to modulate the activity of immune cell activation involved in immune-related adverse reaction development.[11]

It is well known that although there are significant results from treatment with BRAF/MEKis, there are a number of toxicities that can occur during treatment, some of which can be severe. Among these, the most frequently observed include adverse events of a cutaneous, cardiovascular, and ocular nature, as well as asthenia, pyrexia, and arthralgia.[12-14]

BRAFis and MEKis, when administered prior to or simultaneously with immunotherapy, may transiently modify the tumor microenvironment to enhance immunotherapy sensitivity.[15]

Observations reported in this medical case confirm those of other previously published case reports, according to which patients who have received ICI therapy may develop significant toxicities when switching to targeted therapy, with skin manifestations being the most common.[16]

However, immunotherapy also seems to have an impact on the severity of some toxicities, notably on rash severity.

In current treatment regimens, immunotherapy failure is often succeeded by targeted therapy as a second-line administration. In relation to this use, it has been suggested that there is a relationship between skin toxicity severity and prior immunotherapy administration as a single treatment regimen.[17]

When target therapy treatment with BRAF and MEK inhibitors follows immunotherapy, because of their effect on modulating the tumor microenvironment, an immune-mediated response or toxicity may occur several months after immunotherapy administration.[18]

This occurs because it is suspected that immunotherapy may have permanently inhibited the regulatory pathways of the immune system by promoting T-cell effector activation and thus leading to a hypersensitivity reaction when the target therapy is introduced.[19]

However, while there is a risk of toxicity, there are proven benefits to administering immunotherapy and target therapy regimens, as it appears that immune response activation combined with oncological signaling blocking may result in a more durable response in patients who are eligible for this treatment option.[20]

In our clinical case, significant cutaneous and ocular toxicities occurred, necessitating treatment interruption. However, as previously discussed, combining these treatments can provide a longer-lasting response, as demonstrated in our case, where a complete response was maintained for 5 years. The hypothesis for this significant response may stem from a dual mechanism of immune system reactivation; specifically, it is plausible that following the conclusion of immunotherapy and the initiation of targeted therapy, a synergistic response occurred due to the combined effects of targeted therapy and the residual effects of immunotherapy. This would therefore explain both the increase in toxicity and the long-term complete response.

In this regard, our medical case adds new insights by documenting both skin and ocular toxicities, suggesting that prior exposure to ICIs may predispose patients to a broader spectrum or heightened severity of adverse effects when transitioning to targeted therapy. On the one hand, this highlights the importance of careful monitoring and personalized treatment approaches, as combining these treatments may yield significant results in terms of long-term disease response.

Conclusions

In current treatment regimens beyond clinical trials, targeted therapy is often used as post-first-line treatment for patients who have already received immunotherapy.

It may be useful to investigate the potential impact of prior immunotherapy duration, as well as whether there is a relationship between the timing of immunotherapy discontinuation and the onset of targeted therapy, and how this timing may influence not only the severity of observed toxicities but also the immune response that may be achieved against the tumor.

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Figure 1. Disease progression on CT scan and PET scan after 55 cycles with immunotherapy (nivolumab). Evidence on CT scan (July 2018) of clear disease progression (PD) localized to the left retroperitoneal and supraclavicular lymph node (upper figures); confirmed lymph node PD on CT-PET scan (lower figures).

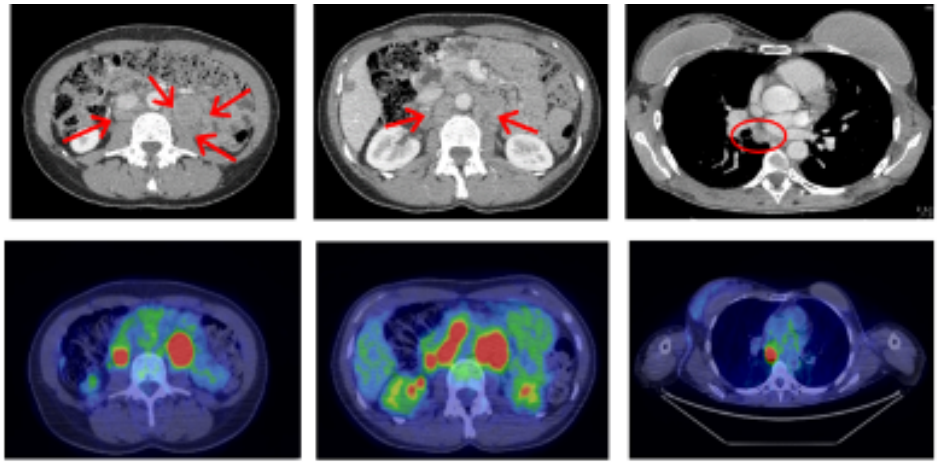

Figure 2. Complete response after dabrafenib (BRAFi) and trametinib (MEKi) treatment.
CT and PET scans (July 2018) before starting targeted therapy showed PD at the left retroperitoneal and supraclavicular lymph node (left figure); CT and PET scans (March 2019) during target therapy (dabrafenib and trametinib) showed a complete response, minimal accumulation of tracer at the left upper paratracheal lymph node, and a significant reduction in size. Non-fixation of tracer at pleuroparenchymal thickening reported in the left paravertebral region on the 2018 CT scan (right figure).

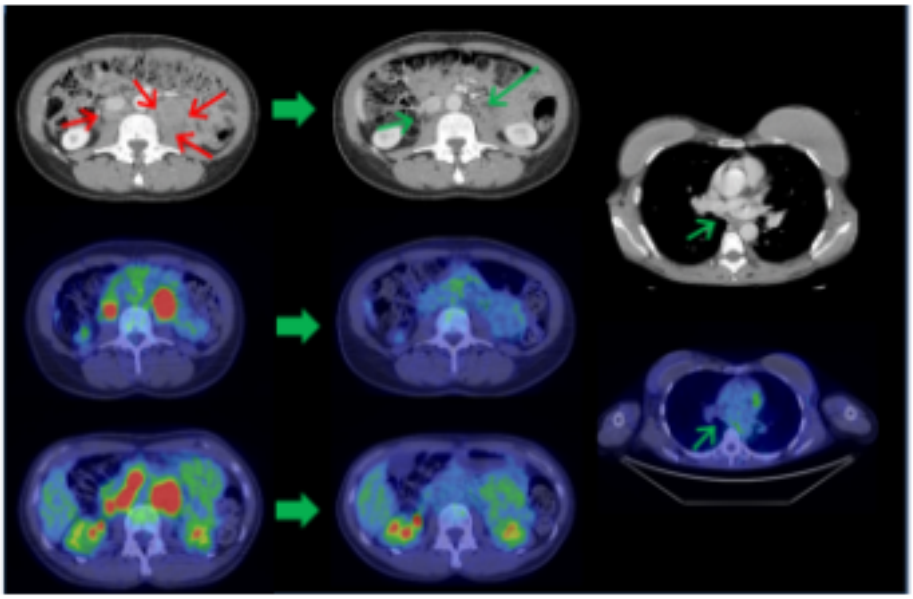

Figure 3. Diffuse maculopapular rash occurrence in lower and upper limbs post-dabrafenib and trametinib therapy.