

Letter

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Severe cumulative skin toxicity during toripalimab combined with vemurafenib following toripalimab alone

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Dear Editor

Targeted therapy and PD-1/L1 inhibitors are the main treatments for BRAF V600-mutated melanomas [1,2]. Recently, PD-1 inhibitors for melanoma with toripalimab have been developed [3], and vemurafenib is a synthetic oral BRAF inhibitor. Previously, skin toxicity appeared to be more severe in patients receiving vemurafenib following anti-PD-1 therapy [4,5]. Here we describe a rare and severe cumulative dermatologic toxicity (grade 4) that developed in a patient with metastatic cutaneous melanoma during toripalimab combined with vemurafenib following toripalimab alone.

A 52-year-old Chinese woman with abdominal cutaneous melanoma presented with multiple metastases. The patient received 3 mg/kg of toripalimab intravenously every 2 weeks, for four cycles and initiated toripalimab combined with vemurafenib 960 mg twice orally after detecting the BRAF V600E mutation. After two months, the patient developed a disseminated cutaneous eruption with red pruritic macules throughout the body, which after 2 days, became confluent with pruritus, burning, tightness, and tenderness (Figure 1a). The patient had small vesicles on the palms and wrists, mild oral mucosal

erosions, and mild edema on the lower eyelids. The patient felt extreme pain. After urgent dermatology consultation, toripalimab and vemurafenib were withheld, and prednisone 2 mg/kg/day was initiated. After 1 week, the symptoms responded to corticosteroid therapy and the skin on the back and neck showed epidermal detachment, and prednisone was reduced gradually to 40 mg. However, the metastatic lesions relapsed, and the treatment was restarted. Since this was a rare and severe skin toxicity (grade 4), toripalimab was discontinued permanently. We restarted vemurafenib at the standard dose, along with prednisone 40 mg/day. Symptoms of skin toxicity partially appeared again, such as red macules, tightness (Figure 1b), and tenderness with fever of 38.8°C. Vemurafenib was discontinued again, and the rash quickly resolved with prednisolone 60 mg. After 2 weeks, we cautiously attempted to resume vemurafenib at a lower dose of 480 mg twice orally with prednisolone 10 mg/day. After 2 weeks, the dose of vemurafenib was increased to 960 mg twice orally, with no further recurrence of the rash, and prednisolone was tapered to 4 mg. On follow-up, the patient's skin symptoms did not worsen, and the dose was deemed tolerable.

Causality assessment between toripalimab/vemurafenib and the severe skin rash via Naranjo nomogram questionnaire yielded a score of 7/10 [6], which means side-effect is very probably caused by toripalimab and vemurafenib. Corticosteroids are the mainstay of treatment of most irAEs related to immunotherapy [2].

Similar cases have been reported in which a more severe rash occurred as the patient was previously treated with anti-PD-1 therapy [4,5]. The patient's skin toxicity was observed during toripalimab combined with vemurafenib following toripalimab alone, and reappeared partly as vemurafenib was readministered. Moreover, BRAF-targeted therapy with vemurafenib increases tumor CD8 + T-cell infiltration and upregulates PD-L1 [7]. Data indicated that adding vemurafenib may increase the immunotherapy effect of anti-PDL1 agent atezolizumab by increasing PD-L1 expression. Intricate interactions occurring during sequential and combined

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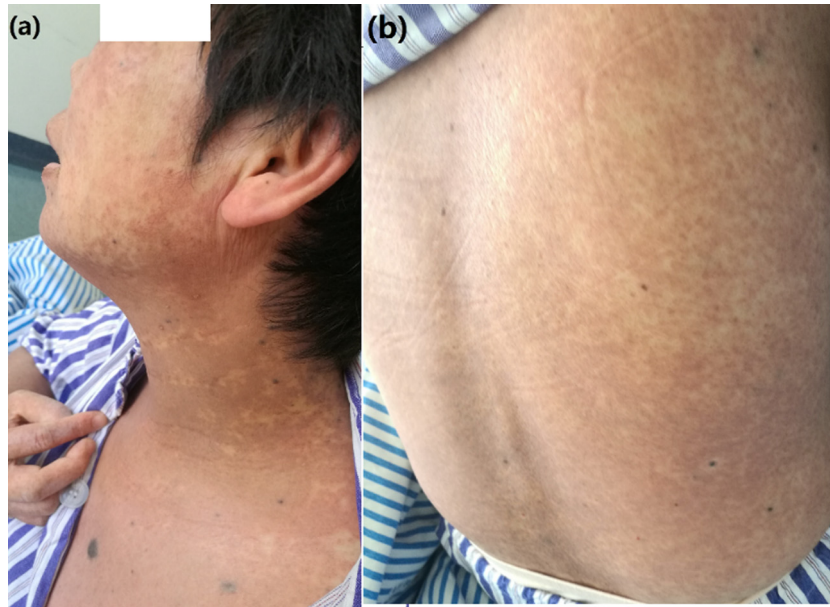


Figure 1: (a) Patient with disseminated cutaneous eruption of dark red pruritic macules throughout the body. (b) Non-diffuse red macules without pruritus almost entire body after vemurafenib rechallenge.

therapies with immune checkpoints and kinase inhibitors may lead to hypersensitivity. There have been several cases of successful vemurafenib rechallenge with dose reduction and corticosteroid administration [4,5]. We reattempted twice and successfully restarted vemurafenib by gradual dose escalation with prednisolone dose tapering.

According to the National Comprehensive Cancer Network guidelines for melanoma [2], anti-PD-1 monotherapy is the preferred regimen, and combination-targeted therapy is recommended as first-line therapy if BRAF V600-activating mutation is present. Particularly, cases combining vemurafenib with anti-PD-1 therapy after receiving anti-PD-1 therapy alone will increase, similar to the one in present study. Thus, our case highlights the importance of maintaining a high level of vigilance for severe additive skin toxicity if vemurafenib is combined with toripalimab.

Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies, and in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

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Data availability statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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