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Vemurafenib-induced DRESS/DIHS resulting in spontaneous melanoma regression: an immunological reaction shedding new light on melanoma treatment?

Dear Editor,

A 58-year-old female with stage IIIA melanoma on the back was treated with wide local excision and sentinel lymph node biopsy.

Three years later, a CT scan showed a nodule on the right lower lung lobe with the core needle biopsy revealing metastatic melanoma (bearing BRAF V600E mutation). The patient was treated with pembrolizumab and resection of the nodule.

Despite treatment with pembrolizumab, the disease progressed after 9 months with multiple lung and subcutaneous metastases. Hence, the patient was treated with vemurafenib and cobimetinib.

Seven days later, the patient developed influenza-like symptoms with facial edema and a widespread rash. Skin biopsy supported a cutaneous drug eruption, and the RegiSCAR DRESS/DIHS (Drug Reaction with Eosinophilia and Systemic Symptoms/Drug-Induced Hypersensitivity Syndrome) validation score was 5, a probable case based on a rash consistent in morphology with DRESS with up to 80% body surface area in involvement, elevation of liver enzymes, and eosinophilia. Renal function was within normal limits, and no other systemic involvement was found. Viral screening for HSV-1, HSV-2, VZV, CMV, EBV, influenza, parainfluenza, and adenovirus was negative. Also, serology for rubella and measles was negative. Vemurafenib and cobimetinib was discontinued, and the patient was hospitalized with a diagnosis of DRESS/DIHS. The patient was treated with corticosteroids (IV, po, and topically) with improvement; solumedrol 250 mg IV once, followed by prednisone 60 mg po qd for 5 days with a slow taper for 3 weeks.

On the 6 week follow-up, unexpectedly, PET CT scan showed major partial response, and her melanoma did not progress until 4 months following DRESS/DIHS (Fig. 1). Upon disease progression, dabrafenib and trametinib were initiated with prednisone, which was tapered off over 2 weeks. No flare-ups of DRESS/DIHS occurred during this time. Within 4 days, all subcutaneous metastases were gone, and a near complete response was maintained for 10 months. Unfortunately, later brain metastases appeared, leading to her death within 1 month.

Here we present a case of vemurafenib-induced DRESS/DIHS. Following DRESS/DIHS, unexpectedly, the patient's melanoma regressed significantly despite just 1 week of targeted therapy and was maintained for 4 months. There are two additional cases of vemurafenib-induced DRESS/DIHS with subsequent melanoma spontaneous regression.[1-3] In these three cases, the response of melanoma regression was unexpected. In reviewing the cases, the following similarities were observed: same dose of vemurafenib (960 mg BID), uniquely short lag period in two of three cases (4 and 8 days), and morphological characteristics of a morbilliform eruption progressing to erythroderma in a few days (Table 1).

This observation of cancer spontaneous regression following vemurafenib-induced DRESS/DIHS, not reported in other

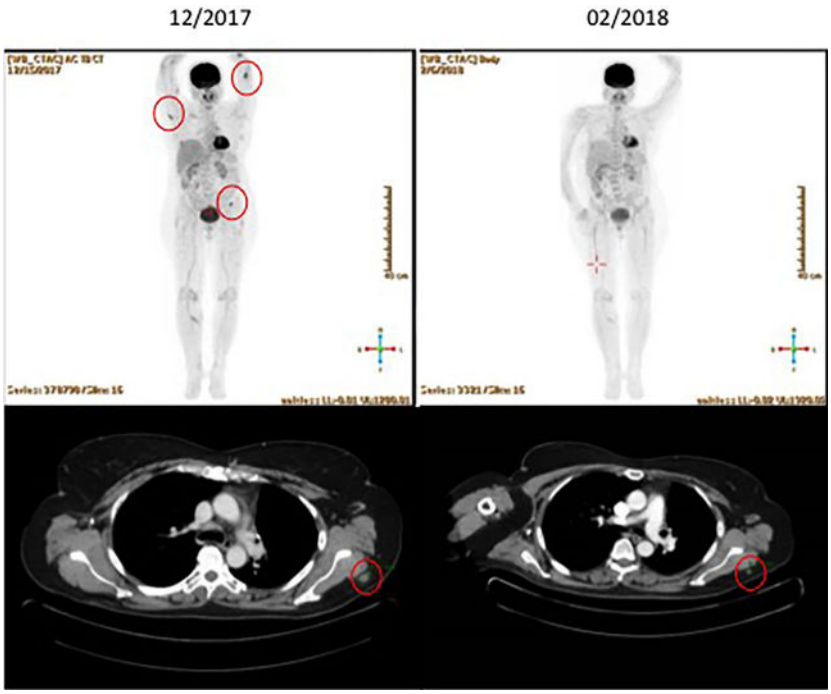

Figure 1 Durable melanoma regression after DRESS/DIHS. Selected PET CT images obtained before initiation of vemurafenib and cobimetinib (left) and 3 months after DRESS/DIHS (right). Exemplar metastases are indicated by a red circle

Table 1 Summary of reported cases of vemurafenib-inducing DRESS with subsequent melanoma regression

Report	Wenk *et al.* (2013)[2]	Munch *et al.* (2016)[1]	Present report (2019)
Sex	Female	Male	Female
Age (years)	80	65	61
Ethnic group	Unknown	Unknown	Caucasian
Dose of vemurafenib	960 mg BID	960 mg BID	960 mg BID
Lag period (days)	21	8	7
Skin and mucous membrane manifestations	Scattered pustules and generalized pink, pruritic papules coalescing into plaques on the face, trunk, and extremities with prominent facial edema. There was no mucosal involvement.	Maculopapular rash predominantly on photo-exposed areas progressing to erythroderma with pustules at the axillary and inguinal skin fold level, cheilitis, and facial edema.	Widespread rash on the anterior and posterior torso composed of confluent erythematous patches and purpuric plaques, progressing up to 80% body surface area and facial edema.
Systemic manifestations	Fever Lymphadenopathy Elevated liver enzymes, eosinophilia, and acute renal failure	Fever Lymphadenopathy Elevated liver enzymes, eosinophilia, and acute renal failure	Fever Elevation of liver enzymes, eosinophilia, and thrombocytopenia
Melanoma stage	Stage IIIC melanoma (T4aN2bM0)	Stage IIIC melanoma (T3bN2bM0)	Stage IV melanoma (M1b)
Status of melanoma after DRESS	At 6 weeks following vemurafenib-induced DRESS, the melanoma and the lymphadenopathy on the respective side of the melanoma were continually decreasing in size without any treatment.	In the 10 months following vemurafenib discontinuation, the patient remained in remission of their melanoma without any other treatment.	Major partial response at 6 weeks follow-up after DRESS and her melanoma did not progress until 4 months following DRESS with no treatment.

DRESS/DIHS cases or severe drug reactions, may be explained by the following hypotheses.

During acute stage and long resolution stages of a few weeks following DRESS/DIHS, an intense immune response was found by Shiohara *et al.*,[4] including changes of regulatory T cells and monocytes such as the release of various cytokines. This immunological imbalance that may induce melanoma regression is also considered the cause for the variety of autoimmune diseases occurring following DRESS/DIHS. Reactivation of HHV-6 has also been reported in DRESS/DIHS. This virus reactivation was found to activate extreme immunological reactions including large amounts of CD8+ T cells, tumor necrosis factor-alpha, interleukin-2 and interferon gamma, all of which have anti-cancerous properties.[4] Moreover novel treatments for cancer using oncolytic viruses were discovered. These immunological changes may explain the response causing spontaneous melanoma regression.

Another underlying cause could be the role of granulysin, a cytotoxic and proinflammatory protein excreted from T lymphocytes and natural killer cells involved in the pathogenesis of DRESS/DIHS. Multiple studies have reported anti-cancerous effects of granulysin.[5]

Surely, there could be another yet to be discovered immunological process involved in melanoma regression.

The fact that spontaneous regression of melanoma occurred after DRESS/DIHS in three reports of vemurafenib-induced DRESS/DIHS calls for further investigation of the immunological process and causality assessment of these cases that may shed new light on effective melanoma treatment.

Cristina Olteanu [1], MD
Alon Scope [2], MD
Yael Steinberg-Silman [3,4], RN, MPH
Michael Ziv [5], MD
Neil H. Shear [6,7], MD, FRCPC
Roni P. Dodiuk-Gad [5,6,*,†], MD
Gal Markel [3,4,†], MD, PhD

[1]Division of Dermatology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada
[2]Medical Screening Institute, Sheba Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[3]Ella Lemelbaum Institute for Immuno-Oncology, Sheba Medical Center, Ramat-Gan, Israel
[4]Department of Clinical Microbiology and Immunology, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[5]Dermatology Department, Emek Medical Center, Bruce Rappaport Faculty of Medicine, Technion-Institute of Technology, Haifa, Israel
[6]Division of Dermatology, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada
[7]Division of Clinical Pharmacology and Toxicology, Department of Medicine, Sunnybrook Health Sciences Centre, Toronto, ON, Canada
*E-mail: rdodiukgad@gmail.com

†Equal contribution.

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Eruptive porokeratosis during pembrolizumab treatment of invasive cutaneous squamous cell carcinoma

Dear Editor,

Immune checkpoint inhibitors have emerged as breakthrough therapies for advanced solid tumors but have been associated with various adverse cutaneous events.[1,2] We report the first case, to our knowledge, of porokeratosis occurring during treatment with pembrolizumab, a programmed cell death protein 1 (PD1) inhibitor.

A 73-year-old man with history of invasive cutaneous squamous cell carcinoma (SCC) presented to dermatology with pruritic lesions on his right lower back and right buttock that erupted 5 months after starting pembrolizumab for advanced SCC. A left supraorbital invasive SCC was diagnosed in 6/2016. Over the ensuing 2 years, the disease proved refractory to three excisions, two cycles of radiation, orbital exenteration, and a brief course of cetuximab. The patient was started on pembrolizumab in 6/2018 for new cavernous sinus involvement.

He received 250 mg of intravenous pembrolizumab every 3 weeks, and at 5 months of treatment, he noticed the onset of the pruritic lesions over the course of a few weeks. After 7 months of treatment, pembrolizumab was discontinued due to severe myalgia and arthralgia. He was evaluated by dermatology for the pruritic eruption and reported no bleeding, ulceration, or ongoing changes. Physical examination showed well-circumscribed, thin pink-brown papules and plaques that had keratotic collarettes with a fine overlying scale on the right lower back and buttocks. There were a few similar papules on the right lateral abdomen and superolateral thigh (Fig. 1). A working diagnosis of lichenoid dermatitis was made, and he was started on topical halobetasol.

At 3-month follow-up, in the absence of lesional or symptomatic improvement, a shave biopsy was performed. Histologic sections showed a cornoid lamella consisting of a column of parakeratosis overlying a small focus of epidermis with loss of the granular layer and dyskeratotic keratinocytes, consistent with porokeratosis (Fig. 2). The patient was started on 5-

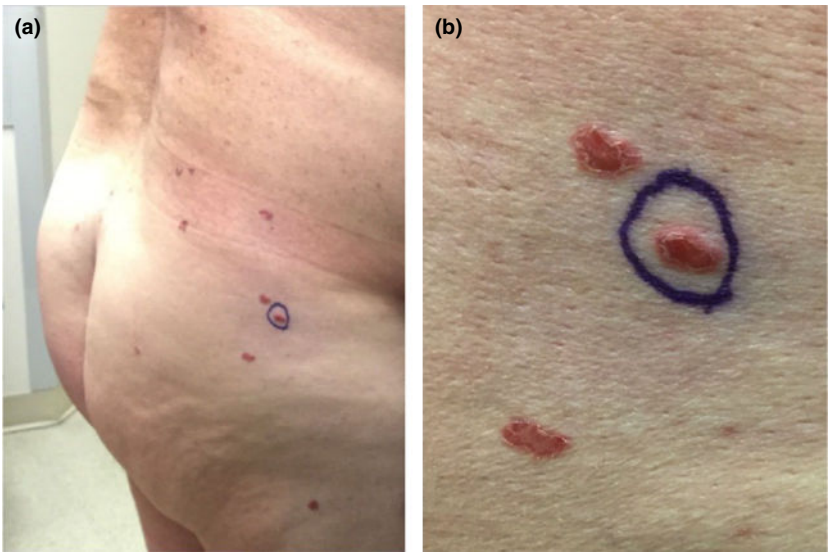

Figure 1 Right lower back and buttocks showing multiple erythematous papules. (a) Porokeratosis presented in zosteriform distribution over the right lateral abdomen, buttocks, and upper thigh. (b) Slightly raised, indurated, erythematous-brown papules with collarettes of scale [Colour figure can be viewed at wileyonlinelibrary.com]

