Successful transition to encorafenib following vemurafenib-induced drug rash with eosinophilia and systemic symptoms syndrome

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Key words: BRAF inhibitors; checkpoint inhibitors; cobimetinib; dabrafenib; drug reaction with eosinophilia and systemic symptoms; encorafenib; malignant melanoma; MEK inhibitors; metastatic melanoma; pembrolizumab; RESS syndrome; SCARs; severe cutaneous adverse reactions; vemurafenib.

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe drug-induced adverse reaction, which can be fatal in up to 10% of cases. The most frequently associated medications include anticonvulsants, allopurinol, sulfasalazine, and nevirapine.[1] Vemurafenib is an oral BRAF kinase inhibitor, approved by the U.S. Food and Drug Administration in 2011 for unresectable or metastatic melanoma with the BRAF V600E mutation. In 2013, the first case of DRESS syndrome due to vemurafenib was described.[2] Subsequent publications demonstrate that severe cutaneous reactions to the combination of vemurafenib with cobimetinib occurs not infrequently: in a series of 68 patients receiving this combination, 16% developed DRESS.[3]

Herein, we report a case of DRESS syndrome in a patient receiving vemurafenib and cobimetinib for metastatic melanoma. After recovery, she was successfully switched to encorafenib and binimetinib without recurrence after 6 months.

Abbreviation used:

DRESS: drug reaction with eosinophilia and systemic symptoms

CASE REPORT

A 50-year-old woman with diabetes and hypothyroidism presented to the dermatology clinic with an enlarging pigmented nodule on her right plantar foot in the summer of 2018. A punch biopsy revealed invasive melanoma with a BRAF V600E mutation and with a Breslow depth of 1.3 mm. She underwent wide local excision, including amputation of the second, third, and fourth toes, and sentinel lymph node biopsy revealed no in-transit disease. In the fall of 2019, she presented with 6 new tender pigmented macules on her right thigh, which were found to be metastatic melanoma. A positron emission tomography scan showed increased uptake in the right inguinal lymph node, which was confirmed as metastatic melanoma via core needle biopsy.

The patient was started on pembrolizumab (200 mg intravenously once every 3 weeks). After 5 cycles, due to disease progression, she was switched to oral vemurafenib (960 mg twice daily) and cobimetinib (60 mg daily). Beginning on day 6 of this new regimen, she complained of stomach pain, nausea, and diarrhea, with onset over the following 5 days of headaches and dry mouth. Her oncologist advised that she reduce vemurafenib and cobimetinib to 480 mg twice daily and 20 mg daily, respectively.

On day twelve, she presented to the emergency department for aches, chills, throat pain, and a mildly pruritic rash on her face and upper chest with a temperature of 102.5°F. She was admitted, and vemurafenib and cobimetinib were discontinued. Chem 7, complete blood count, serum lactate dehydrogenase, blood cultures, urinalysis, chest X-ray, glomerular filtration rate, and nasopharyngeal swab for COVID-19 were within normal limits or negative.

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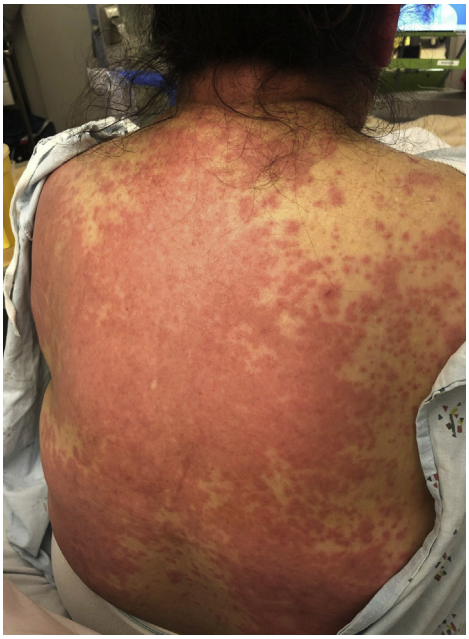

Fig 1. Erythematous edematous papules and plaques covering the entire back, 13 days after commencing vemurafenib and cobimetinib.

In 24 hours, she developed a widespread eruption of erythematous edematous papules and plaques, involving the extremities, palms, upper chest, face, and entire back (Figs 1 and 2). Prominent facial edema and mild erythema of her uvula and posterior pharynx were noted. Treatment was started with IV methylprednisolone (1.5 mg/kg/day) and topical steroids.

Repeat laboratory tests revealed eosinophilia (12%; normal range, 0-7%) and elevated alanine aminotransferase levels (98 U/L; normal range, 0-41 U/L). A biopsy was performed, which showed perivascular and interstitial mixed inflammatory dermatitis with eosinophils, without neutrophilic inflammation or leukocytoclasis. Given her clinical and pathologic findings, she was diagnosed with DRESS syndrome.

The patient's cutaneous symptoms improved, she was transitioned to oral prednisone with a taper, and her eosinophilia resolved in 3 weeks. One month after her hospitalization, she was switched to oral encorafenib and binimetinib (BRAF and MEK inhibitors, respectively). At follow-up exams one and 4 months later, she had no clinical evidence of recurrent DRESS. Five months after starting encorafenib and binimetinib, repeat positron emission tomography and computed tomography scan revealed no evidence of any suspicious hypermetabolic uptake, sign of active malignancy, or metastatic disease.

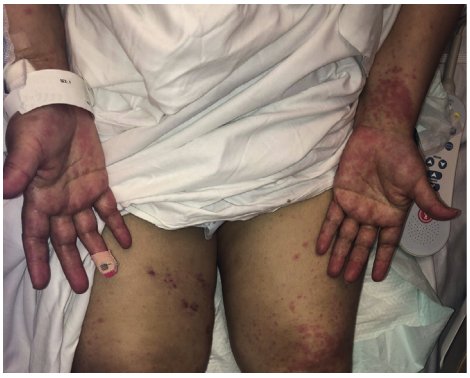

Fig 2. Involvement of the palms, ventral wrists, and thighs.

DISCUSSION

DRESS syndrome is a severe, potentially life-threatening drug-induced adverse reaction. The present case highlights the importance of vemurafenib-induced DRESS syndrome, which is often characterized by early onset compared with DRESS syndrome induced by other medications (7-12 days compared with typically 2-6 weeks). Previous PD-1 inhibitor use is associated with more severe cutaneous toxicity from vemurafenib,[3] as our patient experienced (receiving pembrolizumab 4 days prior to vemurafenib).

BRAF mutations are present in 50%-60% of melanomas overall,[4] and vemurafenib as a first-line option for these patients confers significantly improved morbidity and mortality compared with the prior standard of care.[5,6] Clinicians can expect to encounter this regimen in practice and should be privy to this potentially life-threatening adverse event.

When DRESS due to vemurafenib occurs, these patients are often successfully switched to dabrafenib without recurrence. A recent systematic review showed, of 31 severe cutaneous adverse reactions to BRAF/MEK inhibitors, all were caused by vemurafenib except one (which was dabrafenib-caused).[3] It remains to be identified why vemurafenib is so disproportionately causative of DRESS syndrome compared with other BRAF/MEK inhibitors.

The pathogenesis of DRESS syndrome is poorly understood. Proposed mechanisms include detoxification defects leading to reactive metabolite formation, immunologic reactions, slow acetylation, and reactivation of herpes viruses. The pattern of cutaneous eruptions and organs involved are various, and no link has been established between type of visceral involvement and type of causative drug. Adding to this challenge, half of the causative drugs are associated with only a single case of DRESS

syndrome, and in most cases, the underlying mechanism is not investigated.[1]

One team suggested that vemurafenib's propensity to cause DRESS syndrome is related to it being both substrate (poor) and an inhibitor of P-glycoprotein, whereas dabrafenib is only substrate of the P-glycoprotein, a finding that may be related to inhibition of vemurafenib's excretion, resulting in increased plasma concentration.[7] Vemurafenib's half-life is 57 hours, which is much longer than those of dabrafenib (8 hours) and encorafenib (3.5 hours). Carbamazepine, the most common drug associated with DRESS syndrome,[1] has a similarly long half-life of 35-40 hours. However, other drugs commonly implicated in DRESS syndrome, such as allopurinol and sulfasalazine, do not have excessively long half-lives (1-2 and 7.6 hours, respectively). Prolonged or elevated presence in serum does not completely explain vemurafenib's propensity to induce DRESS syndrome, but it may be a piece of the puzzle.

Vemurafenib contains a sulfonamide moiety, and like other drugs with this trait, it has been linked to toxic epidermal necrolysis. Although dabrafenib shares this sulfonamide moiety, it possesses unique anti-inflammatory effects through inhibition of receptor-interacting protein kinase 3 (RIP3), tumor necrosis factor-alpha, and nitric oxide-induced necroptosis of keratinocytes. While some have suggested that dabrafenib's direct inhibition of these inflammatory pathways may confer protection against toxic epidermal necrolysis,[8] the possible relationship of these mechanisms with DRESS syndrome has yet to be studied. Encorafenib shares the same sulfonamide moiety as the 2 aforementioned drugs, and whether it possesses similar anti-inflammatory traits to dabrafenib is not known. Since the majority of patients with vemurafenib-induced DRESS syndrome are switched to dabrafenib,[3] we cannot conclude whether the lack of recurrence in our case depended on mere luck.

To conclude, the dearth of literature linking other BRAF inhibitors to DRESS syndrome and the absence of recurrent symptoms in our patient indicate that these reactions may be drug-specific rather than class-specific. The present literature indicates that following vemurafenib-associated DRESS syndrome, it appears safe to switch to an alternative BRAF inhibitor, including dabrafenib or encorafenib, though further research is needed to clarify the mechanisms of vemurafenib-associated DRESS and theoretical risk posed by other BRAF inhibitors.

Conflicts of interest

None disclosed.

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