Vemurafenib-Induced DRESS

The BRAF inhibitor vemurafenib was approved by the US Food and Drug Administration in 2011 for the treatment of metastatic melanoma in individuals harboring the somatic BRAF V600E mutation. Cutaneous adverse events from vemurafenib are frequent and include skin eruption, pruritus, photosensitivity, hyperkeratosis, squamous cell carcinoma, and keratoacanthomas. We report herein a case of vemurafenib-induced drug reaction with eosinophilia and systemic symptoms (DRESS).

Report of a Case | A woman in her 80s with hypertension and chronic kidney disease presented with a 1-year history of an enlarging violaceous growth on her calf. A biopsy revealed nodular melanoma with a Breslow depth of at least 5.6 mm. Positron emission tomography/computed tomography identified 2 suspect lymph nodes in the groin, and fine-needle aspiration confirmed metastatic melanoma harboring the V600E BRAF mutation. The patient began treatment with vemurafenib, 960 mg, twice daily. Three weeks later, she developed scattered pustules and generalized pink, pruritic papules coalescing into plaques on the face, trunk, and extremities (Figure) with prominent facial edema. There was no mucosal involvement, and lymph node examination revealed stableinguinal lymphadenopathy.

The patient complained of fevers, chills, and bone pain but was afebrile on admission and throughout her hospitalization. However, 3 days earlier, a low-grade fever of 37.3°C was documented in her outpatient record, and she was advised to start treatment with antipyretic drugs. Laboratory workup showed a white blood cell count of 12 400/μL, with 26% eosinophils and 1% atypical lymphocytes; transaminitis (aspartate transaminase level, 107 U/L; alanine transaminase level, 132 U/L); and a creatinine concentration of 3.3 mg/dL (baseline, 1.8 mg/dL). (To convert white blood cells to \( \times 10^9/L \), multiply by 0.001; creatinine to micromoles per liter, multiply by 88.4.) A drug eruption was suspected, and after review of the patient’s medications (metoprolol and hydrochlorothiazide, which she had been taking for at least 9 months), vemurafenib treatment was discontinued.

Skin biopsy findings supported a diagnosis of DRESS, with specimens displaying a mild to moderate dermal lymphocytic infiltrate, erythrocyte extravasation, occasional eosinophils, and scattered necrotic keratinocytes. The patient was treated with intravenous methylprednisolone followed by oral prednisone. Over the subsequent 6 weeks she experienced desquamation and resolution of her skin eruption and laboratory abnormalities. During this time, the melanoma of the skin and the ipsilateral lymphadenopathy continued to decrease in size.

Discussion | DRESS, a hypersensitivity drug reaction with systemic symptoms, is most commonly associated with the use of aromatic anticonvulsants, but it has also been reported with a number of other medications. Although the pathogenesis of this condition is incompletely understood, a defect in the detoxification of certain drugs is thought to play a role in its development, producing toxic metabolites that cause cellular injury or trigger an immune response.
More recently, viruses such as human herpesvirus (HHV)-6, HHV-7, Epstein-Barr virus (EBV), and cytomegalovirus have also been implicated in the development of this reaction. In a study by Picard et al, 76% of patients with DRESS (29 of 38) were found to have reactivation of either EBV, HHV-6, or HHV-7. In addition, high numbers of activated virus-specific cytotoxic CD8+ cells infiltrated the skin and other organs of these patients, potentially contributing to their dermatologic and visceral findings. Interestingly, our patient was found to have an elevated HHV-6 IgG titer (1:160; normal, <1:110), indicating possible viral reactivation. Epstein-Barr virus DNA was also detected at 3762 copies/mL (normal, <200 copies/mL), while CMV and HHV-7 test results were negative. It is unclear if these observations are a consequence or cause of disease.

The RegiSCAR international consensus group has proposed a scoring system for classifying DRESS cases. Based on these criteria, our patient's presentation is consistent with a diagnosis of DRESS. She likewise meets similar DRESS diagnostic criteria developed by a Japanese consensus group in 2006, which includes HHV-6 reactivation as a diagnostic feature. The occurrence of DRESS, a potentially life-threatening syndrome, in association with vemurafenib treatment has to our knowledge not been previously reported. Clinicians should be aware of this possible complication in patients treated with this important new drug.

Kurt S. Wenk, MD
Dominique C. Pichard, MD
Teresa Nasabzadeh, MD
Sekwon Jang, MD
Suraj S. Venna, MD

Author Affiliations: Department of Dermatology, Georgetown University Hospital/Washington Hospital Center, Washington, DC (Wenk, Pichard, Nasabzadeh); Medstar Melanoma Center at the Washington Cancer Institute, Washington, DC (Jang, Venna).

Corresponding Author: Kurt S. Wenk, MD, Department of Dermatology, Washington Hospital Center, 110 Irving St NW, Washington, DC 20010 (kswenk@gmail.com).


Conflict of Interest Disclosures: None reported.