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.1-5 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.

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.2 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.

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 ×10⁹/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.
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, 2013;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, <1:10), 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.


COMMENT & RESPONSE

Efficacy of Topical Antifungal Agents in the Treatment of Dermatophytosis: An Incomplete Meta-Analysis

To the Editor The authors are to be congratulated for conducting this important but challenging systematic review. However, while accepting its degree of complexity, we are at variance with the confidence expressed by the authors in the strengths of their study, including a thorough search of the literature and exclusion of lower-quality reports assessed using the Jadad score.

A thorough literature search is a key requirement of a high-quality systematic review and, as the authors confirm, should show all the evidence available at the time of the study. Although their search appeared comprehensive, language of publication was clearly a restriction; ie, only studies in English, Spanish, and Portuguese were included. The exclusion of studies based on language of publication is a significant source of bias, which has been well documented, and in this review, the language restriction excludes studies published in the German language. Hand searching of pre-1987 issues of Mykosen would have identified additional eligible trials, most of which are written in German, and which, based on the flowchart included as the first figure in the article, would have represented a not insignificant percentage of the total number of included trials. The review excluded a number of German studies equivalent to the number of Spanish and Portuguese studies that were included, clearly illustrating the impact of language bias and the not inconsequential gap in the evidence included in this systematic review.

In addition, the limitations of numerical quality scores, eg, the Jadad Scale, are well documented and widely acknowledged. The Cochrane Handbook for Systematic Reviews of Interventions, referred to by the authors, explicitly discourages the use of numerical quality scores in view of their increased emphasis on the quality of the reporting rather than the conduct of trials.

The authors claim a degree of certainty about the methodologic quality of their included studies and state that the “absence of information about the allocation should not have affected the confidence of the results.” However, inadequate reporting of key quality items, ie, sequence generation and concealment, does somewhat limit our degree of confidence in judgments of low risk of bias for these domains. The Cochrane risk-of-bias tool was used by the authors to assess “evidence generated...not being considered as conforming to the eligibility criteria” but these key assessments and corresponding judgements are conspicuously absent in the report.

Although we are in broad agreement that the conclusions of this report reflect the findings, we express concern with the methods used to reach these conclusions, which are not reflective of a robust and comprehensive process used to synthesize all the available evidence for this clinical topic.

Zbys Fedorowicz, MSc, DPH
Esther J. van Zuuren, MD