

Drug rash with eosinophilia and systemic symptoms related to brentuximab vedotin: A report of 2 cases



Laura Ragmanauskaite, MD, Meera Brahmhatt, MD, and Justin T. Cheeley, MD
Atlanta, Georgia

INTRODUCTION

Brentuximab vedotin is a monoclonal antibody targeting CD30⁺ cells, first approved by the Food and Drug Administration for the treatment of CD30⁺ cutaneous T-cell lymphoma in 2017.¹ Although a nonspecific maculopapular rash was noted in 11% of patients treated with brentuximab vedotin during clinical trials, drug reaction with eosinophilia and systemic symptoms (DRESS) has not been previously described, to our knowledge.¹ We report 2 cases of patients with CD30⁺ cutaneous T-cell lymphoma who developed DRESS after initiation of brentuximab vedotin.

CASE REPORTS

Case 1

A 48-year-old black woman with large-cell transformed CD30⁺ cutaneous T-cell lymphoma presented with influenzalike symptoms, fever (temperature 40.1°C/104.2°F), and a new rash on her face and trunk 3 days after her third cycle of brentuximab vedotin. The patient began receiving brentuximab vedotin 45 days earlier because her condition was unresponsive to phototherapy, interferon, and total-skin electron-beam radiotherapy. Her course was further complicated by multiple admissions for treatment of bacteremia, fungemia, or both in the months preceding the first cycle of brentuximab vedotin, including an admission for *Staphylococcus haemolyticus* bacteremia treated with levofloxacin and doxycycline 23 days before she started the first cycle of brentuximab vedotin.

Abbreviation used:

DRESS: drug reaction with eosinophilia and systemic symptoms

On examination, the patient had right-sided cervical lymphadenopathy and numerous small, flesh-colored, pink and hyperpigmented papules without ulceration or umbilication, scattered over the face and trunk. Unchanged eroded, poikilodermatous, scaly plaques consistent with her known cutaneous T-cell lymphoma were noted.

Her laboratory study results were notable for new-onset eosinophilia ($0.59 \times 10^3/\mu\text{L}$; reference range $<0.36 \times 10^3/\mu\text{L}$) and elevated aminotransferase and creatinine levels (aspartate aminotransferase 229 U/L, reference range 13-39 U/L; alanine aminotransferase 179 U/L, reference range 7-152 U/L; creatinine 1.31, reference range 0.60-1.20 mg/dL). Punch biopsy of the left side of the neck revealed vacuolar-interface dermatitis on histology.

The patient's presentation was concerning for DRESS, given the new exanthem morphology with vacuolar interface alteration, fever, new-onset eosinophilia, and hepatocellular injury. However, given her rapid recovery with topical corticosteroids, unclear causative agent, and lack of previous reports of brentuximab vedotin-induced DRESS, a joint decision was reached to cautiously proceed with the fourth cycle of brentuximab vedotin at 50% dose reduction and dexamethasone premedication.

One month later and 6 days after the fourth cycle of brentuximab vedotin, the patient was admitted

From the Department of Dermatology, Emory University School of Medicine, Atlanta.

Funding sources: None.

Conflicts of interest: None disclosed.

Correspondence to: Justin T. Cheeley, MD, Department of Dermatology, Emory University School of Medicine, 1525 Clifton Rd NE, Atlanta, GA 30322. E-mail: justin.cheeley@emory.edu.

JAAD Case Reports 2020;6:1119-22.

2352-5126

© 2020 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jidcr.2020.08.020>

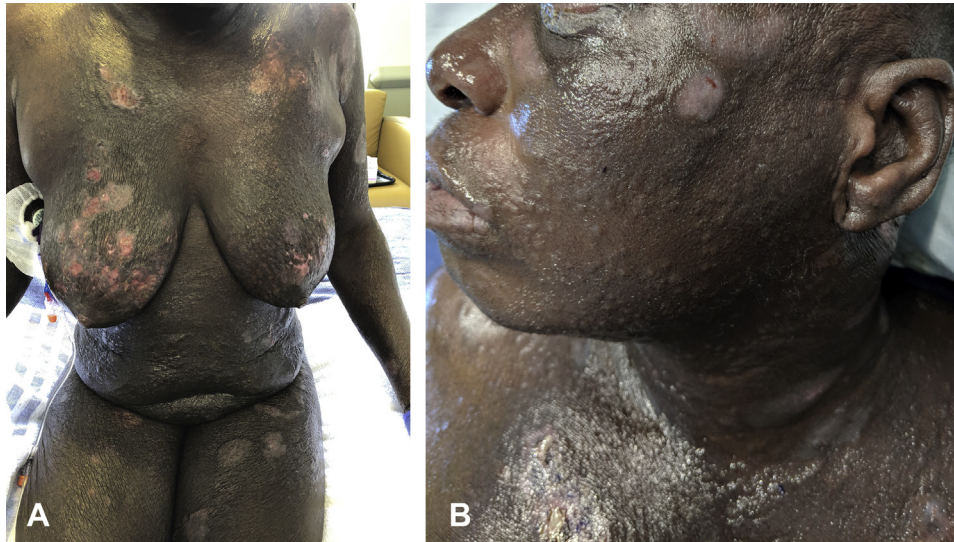


Fig 1. Brentuximab vedotin–induced drug reaction with eosinophilia and systemic symptoms. **A**, Examination findings during the patient's second presentation after the fourth cycle of brentuximab vedotin. Numerous flesh-colored, pink, and hyperpigmented papules scattered diffusely over the chest were noted. Erythematous circular erosions and hyperpigmented, scaly plaques consistent with the patient's previous examination findings of cutaneous T-cell lymphoma were also present. **B**, Examination findings during patient's second presentation after the fourth cycle of brentuximab vedotin. Numerous flesh-colored, pink, and hyperpigmented papules scattered diffusely over the face were noted. Erythematous circular erosions and hyperpigmented, scaly plaques consistent with patient's previous examination findings of cutaneous T-cell lymphoma were also present.

with recurrence of symptoms, including fever (temperature 38.6°C/101.5°F) and exanthem (Fig 1, A and B). During the first 2 days of hospitalization, the patient's laboratory findings were significant for increasing levels of eosinophilia (0.46 to $0.83 \times 10^3/\mu\text{L}$), creatinine (1.02 to 1.23 mg/dL), and aminotransferases (aspartate aminotransferase 46 to 75 U/L; alanine aminotransferase 38 to 75 U/L).

Brentuximab vedotin–induced DRESS was diagnosed based on European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples criteria. The patient received systemic steroids (solumedrol 1 mg/kg intravenously) followed by oral prednisone taper once her laboratory abnormalities resolved.

Case 2

A 39-year-old black woman with stage IIIa (International Society for Cutaneous Lymphomas and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer) CD30⁺ folliculotropic cutaneous T-cell lymphoma (T4N0B0) presented with fever and painful swelling of her legs and hands, which spread to include her trunk, face, and neck. Approximately 10 days before symptom onset, she began therapy

with brentuximab vedotin for cutaneous T-cell lymphoma after failure of treatment with total-skin electron-beam radiotherapy, phototherapy, and methotrexate.

Examination result was notable for fever (temperature 39.7°C/103.5°F), exfoliative erythroderma affecting nearly 80% total body surface area, and edema of the face, legs, and arms (Fig 2, A and B). Laboratory study results were significant for new-onset eosinophilia ($1.50 \times 10^3/\mu\text{L}$; reference range $<0.36 \times 10^3/\mu\text{L}$) and a mild elevation in aminotransferase levels (aspartate aminotransferase 66 U/L, reference range 13–39 U/L; alanine aminotransferase 84 U/L, reference range 7–152 U/L). A biopsy of the left arm was performed. On histology, acanthosis and mild spongiosis with scattered intraepidermal lymphocytes were noted in epidermis. A superficial, perivascular, and interstitial, predominantly lymphocytic inflammatory infiltrate with rare eosinophils was observed in the dermis. Flow cytometry of the peripheral blood was performed to evaluate for possible cutaneous T-cell lymphoma progression or Sézary syndrome. The results demonstrated a small population of CD4⁺ T cells that lacked CD7 and CD26, like those observed previously in this patient.



Fig 2. Brentuximab vedotin–induced drug reaction with eosinophilia and systemic symptoms. **A**, Examination showing significant facial edema and erythema with scaling. **B**, Examination showing significant bilateral lower extremity edema and erythema with scaling.

The patient's presentation, including new exanthem, eosinophilia, and hepatocellular injury, met European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples criteria for DRESS. During her hospitalization, her aminotransferases returned to normal levels and there was no further evidence of end-organ damage. Nevertheless, given that the rash involved 80% of total body surface area and her persistent eosinophilia, she was treated with topical and systemic steroids, as well as discontinuation of brentuximab vedotin.

DISCUSSION

DRESS is a rare and potentially life-threatening adverse drug reaction.² It is a challenging diagnosis because it may mimic infectious, vascular, or lymphoproliferative processes and may vary in both cutaneous symptoms and internal organ involvement.³ Several diagnostic criteria exist to aid clinicians including the European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples criteria and Bocquet criteria using comparable clinical features, with the latter being easier to use.²

Patients with DRESS typically present with pyrexia, pruritus, and mononucleosis-like symptoms followed

by an erythematous exanthem. Morbilliform macules and papules with associated facial edema descending to include the trunk and extremities are observed in most patients. Rarer cutaneous manifestations of DRESS include acute generalized erythematous pustulosislike eruption, erythroderma, erythema multiforme, and exfoliative dermatitis.⁴ Although DRESS can involve renal, cardiac, endocrine, and pulmonary systems, hepatic involvement is the most common.^{5,6} Hematologic abnormalities vary greatly as well, but commonly include eosinophilia and leukocytosis.³

When potential inciting agents are being identified, attention should be directed to the timeline of exposure and symptom development. DRESS most commonly manifests 2 to 6 weeks after exposure to the culprit drug, although reported latency periods range from 5.5 to 91 days.^{4,7} Drugs received for more than 3 months, discontinued more than 14 days before the onset of symptoms, or started less than 3 days before the onset of symptoms are not likely to be the causative agents.³

Recently, DRESS has been described in patients receiving targeted anticancer and certain biologic agents, including monoclonal antibodies.^{7,8} Although to our knowledge there are no current published reports of brentuximab vedotin causing DRESS, the Food and Drug Administration's Adverse Events Reporting System has 11 reported cases.⁹ Here we describe 2 cases in a single academic center within 1 year. Given that newer therapies, including brentuximab vedotin, do not have long-term data on adverse events, clinicians should suspect DRESS if appropriate clinical criteria are met even if the suspected inciting medication has no known published association.

REFERENCES

1. Prince HM, Kim YH, Horwitz SM, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. *Lancet*. 2017;390(10094):555-566.
2. Kim DH, Koh YI. Comparison of diagnostic criteria and determination of prognostic factors for drug reaction with eosinophilia and systemic symptoms syndrome. *Allergy Asthma Immunol Res*. 2014;6(3):216-221.
3. Kardaun SH, Sekula P, Valeyrie-Allanore L, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *Br J Dermatol*. 2013;169(5):1071-1080.
4. Watanabe H. Recent advances in drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms. *J Immunol Res*. 2018;2018:5163129.
5. Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. *Arch Dermatol*. 2010;146(12):1373-1379.
6. Cookson H, Creamer D, Walsh S. Thyroid dysfunction in drug reaction with eosinophilia and systemic symptoms (DRESS): an

- unusual manifestation of systemic drug hypersensitivity. *Br J Dermatol*. 2013;168(5):1130-1132.
7. Chen CB, Wu MY, Ng CY, et al. Severe cutaneous adverse reactions induced by targeted anticancer therapies and immunotherapies. *Cancer Manag Res*. 2018;10:1259-1273.
 8. Di Palma-Grisi JC, Vijayagopal K, Muslimani MA. Case reports of DRESS syndrome and symptoms consistent with DRESS syndrome following treatment with recently marketed monoclonal antibodies. *Autoimmune Dis*. 2019;2019:7595706.
 9. U.S. Food and Drug Administration. Brentuximab Vedotin. *FDA Adverse Events Reporting System (FAERS) Public Dashboard*. Available at: <https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4-0135608ddc13/sheet/33a0f68e-845c-48e2-bc81-8141c6aaf772/state/analysis>. Accessed April 2, 2020.