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DERMATOLOGIC THERAPY WILEY

LETTER

Brentuximab extravasation injury in a patient with mycosis fungoides with large cell transformation

Dear Editor,

Primary cutaneous lymphomas are non-Hodgkin lymphomas without extracutaneous disease at the time of diagnosis and are typically indolent.[1,2] CD30 positivity may suggest the potential for large cell transformation and progression.[3] Brentuximab vedotin (BV) is an anti-CD30 antibody-drug conjugate newly approved to treat CD30+ cutaneous lymphomas.[1]

An 87-year-old man was diagnosed with patch-stage mycosis fungoides. Despite initial therapy with topical steroids and narrowband ultraviolet B phototherapy, he continued to have severe pruritus and progressed to develop plaques involving >70% of body surface area, with a tumoral ulcer forming on the scrotal skin. Biopsy of the ulcerated tumor demonstrated CD30+ T-cells with large cell transformation. Systemic therapy was initiated with BV. Five minutes after starting his 7th infusion through a peripheral intravenous line (PIV) along the left antecubital fossa, he experienced skin infiltration. The infusion was stopped, and a cold compress was applied in 15-min intervals. There was swelling at this site without pain, tenderness, or erythema. A new PIV was placed in the right arm and the BV infusion completed successfully without complication. When the patient was discharged home, all swelling had resolved, and he was instructed to continue applying cold compresses in 15-min intervals. The patient returned 3 days later for evaluation of swelling, blistering, pain (7 out of 10 in severity), warmth, and erythema over the volar aspect of his left forearm (Figure 1A,B). On exam, there was no crepitus or joint involvement, and he was discharged home with cephalexin for possible cellulitis. One week later, he returned for a regular visit with superficial epidermonecrosis, left forearm pruritus, and desquamation with blister collapse (Figure 1C). The diagnosis of BV extravasation injury was made and the patient was treated with local emollients. There were no other sequelae, and the extravasation injury completely resolved within 2 months of the initial insult. He completed 16 cycles of BV with improvement of pruritus, resolution of cutaneous tumors, and flattening of patches with post-inflammatory hyperpigmentation.

Although the reaction was not confirmed with histopathology or drug challenge test, the timeframe and course were indicative of extravasation injury. This case represents the second report of BV extravasation and the first in an African American patient.[4] This patient lacked the neuropathic symptoms described in the first report, but both involved a well-circumscribed blistering lesion, onset after a day, progression over a week, and full symptom resolution in 2 months without significant intervention (Table 1).

BV is an anti-CD30 antibody conjugated with monomethyl auristatin E (MMAE), an anti-microtubule agent.[5] MMAE redistributes from plasma quickly with prolonged and extensive distribution in tissues; its concentration in skin is relatively low compared to other tissues, trailing behind the lungs, spleen, kidneys, and heart by factors of 10 or more.[6]

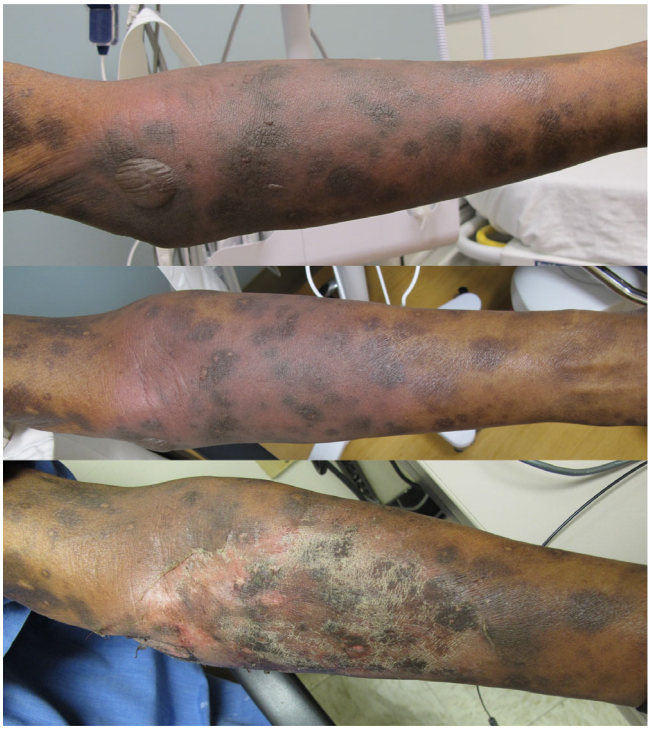

FIGURE 1 (A, top) Ill-defined dusky erythema and superficial bulla along the anterior forearm adjacent to site of intravenous line. (B, center) Patchy hyperpigmentation at sites of cutaneous T-cell lymphoma amid dusky erythema at site of extravasation. (C, bottom) One week after initial extravasation, with superficial epidermonecrosis, desquamation, and patchy erosions in various stages of healing.

TABLE 1 Summary of the current case and the previously published case of BV extravasation injury

	BV extravasation case 1 [4]	BV extravasation case 2 (this case)
Patient demographics	80-year-old Caucasian male	87-year-old African American male
Condition BV was treating	Mycosis fungoides	Mycosis fungoides
Vessel	Median cephalic vein of the right forearm	Not documented; right antecubital fossa
Onset of extravasation injury	Erythema in 24 h, blistering in 72 h	72 h
Presenting symptom	Well-circumscribed blistering lesion	Well-circumscribed blistering lesion
Additional symptoms	Motor > sensory, demyelinating > axonal polyneuropathy of the right median nerve	Localized pruritus, epidermonecrosis
Time to symptom resolution	8 weeks	8 weeks
Intervention	None	Topical emollients
Cycle of BV	9	7
Subsequent cycles of BV administered	0	9

Abbreviation: BV, Brentuximab vedotin.

There is little known regarding a mechanism of toxicity to skin unaffected by CD30+ lesions. BV's valine-citrulline linker and para-aminobenzyloxycarbonyl spacer are designed to be unstable in acidic environments like lysosomes; perhaps skin's relative acidity destabilizes the linker enough for BV to dissociate and MMAE to exert local toxicity.

Extravasation injury with chemotherapy has a prevalence of 0.1%–6% when administered through a PIV and 0.26%–4% when administered through central venous access. Prevention includes appropriate vascular access, education of staff and patients, and prompt evaluation. Reports have focused on anthracyclines, taxanes, mitomycin C, and vinca alkaloids. Extravasation with monoclonal antibodies such as rituximab and trastuzumab has been considered more benign and has attracted less attention.[7,8] As BV becomes increasingly used for lymphoid malignancies, we hope this information will guide others who need to manage this clinical scenario.

AUTHOR CONTRIBUTIONS

Amanda Walker wrote the majority of the case report section, and Eileen Kim wrote the majority of the remaining parts of the paper. Chinmoy Bhate and Victor T. Chang also wrote different parts of the paper, provided significant guidance, and Chinmoy Bhate obtained clinical images and consent as well. All authors contributed to the writing and editing of all parts of the paper.

CONFLICT OF INTEREST

Dr. Chang receives institutional funding from Amgen, Celgene, and Incyte. These are not relevant to the current submission. The other authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

INFORMED CONSENT

Informed consent was obtained from the patient represented in this de-identified case report.

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REFERENCES

1. Hristov AC, Tejasvi T, Wilcox A. Cutaneous T-cell lymphomas: 2021 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2021;96(10):1313-1328.
2. Peterson E, Weed J, Lo Sicco K, Latkowski JA. Cutaneous T cell lymphoma: a difficult diagnosis demystified. *Dermatol Clin*. 2019;37(4):455-469.

3. Willemze R, Cerroni L, Kempf W, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood*. 2019;133(16):1703-1714.
4. Hoffmann JC, Soliman M, Koch JC, Liman J, Schön MP, Mitteldorf C. Demyelinating neuropathy and local toxicity caused by extravasated Brentuximab vedotin. *J Eur Acad Dermatol Venereol*. 2020;34(10):e626-e628.
5. Moquist PN, Bovee TD, Waight AB, et al. Novel Auristatins with high bystander and cytotoxic activities in drug efflux-positive tumor models. *Mol Cancer Ther*. 2021;20(2):320-328.
6. Chang HP, Cheung YK, Shah DK. Whole-body pharmacokinetics and physiologically based pharmacokinetic model for monomethyl Auristatin E (MMAE). *J Clin Med*. 2021;10(6):1332.
7. Ferrari LA, Dinoi GL, Saibene G, et al. Cytotoxic extravasation: an issue disappearing or a problem without solution? *Tumori*. 2016;2016(3):290-293.
8. Pluschnig U, Haslik W, Bayer G, et al. Outcome of chemotherapy extravasation in a large patient series using a standardised management protocol. *Support Care Cancer*. 2015;23(6):1741-1748.