Toxic Erythema of Chemotherapy in Enfortumab Vedotin Presenting as Pseudocellulitis Limited to the Lower Extremities: A Case Series and Review of the Literature

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Abstract

Enfortumab vedotin (EV) is an antibody-drug conjugate used as a second- or third-line therapy for patients with urothelial carcinoma. Adverse cutaneous reactions have been reported for nearly half of patients on EV. These reactions include severe cutaneous adverse reactions (SCARs), and they range from idiosyncratic hypersensitivity reactions to toxic erythema. We report three cases of patients with invasive/metastatic urothelial carcinoma treated with EV who presented with toxic erythema of chemotherapy with large bulla formation limited to the distal lower extremities. These cases are notable for their unique distribution of lesions and clinical resemblance to cellulitis, resulting in antibiotic treatment prior to dermatology consult in two of the three cases. Additionally, all three cases resolved with high potency topical steroid treatment and the therapeutic drainage of intact bullae. Finally, patients in two out of the three cases were able to retrial EV at a reduced dose or altered dosing schedule. Thus, this case series highlights a unique morphologic cutaneous toxicity to EV.

Keywords: Toxic erythema of chemotherapy, enfortumab vedotin, antibody-drug conjugate, pseudocellulitis.

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INTRODUCTION

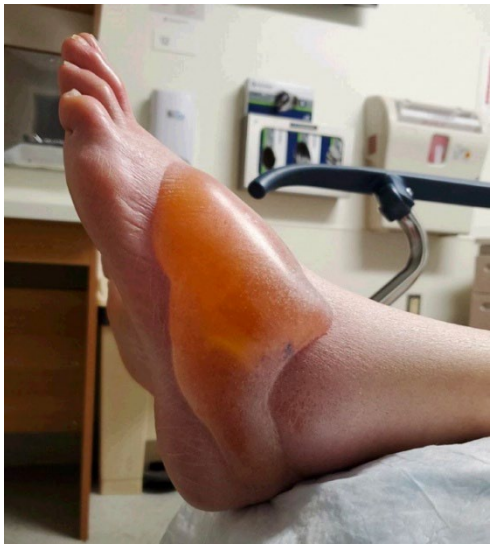
Enfortumab vedotin (EV) is an antibody drug conjugate targeting nectin-4, indiciated for patients with metastatic urothelial cancer who have undergone or are ineligible for other therapies, including platinum chemotherapy and PD-1/L1 inhibitors.[1] Adverse skin reactions occur in nearly half of patients, ranging from severe cutaneous adverse reactions (SCARs) to toxic erythema, likely due to nectin-4 expression in the skin.[2,3] This report details three cases of toxic erythema of chemotherapy (TEC) with bulla formation of the distal lower extremities in patients on EV for urothelial carcinoma.

CASE REPORTS

Case 1

A 75-year-old male presented with bullous lesions on the left foot 116 days post-EV initiation (Figure 1). Examination revealed a large bulla on the dorsal left foot and erythema with erosions on the right foot. Initially treated with antibiotics, he remained afebrile without mucosal involvement. Biopsy ruled out autoimmune etiologies, and dermatology provided supportive wound care, prescribed clobetasol, and discontinued antibiotics. An asymptomatic papular rash was also noted on the thighs, with biopsy findings consistent with a drug eruption. EV was resumed at a reduced dose and schedule. The patient's rash resolved before his 6-week follow up and did not recur during the 72-day follow-up before he passed away in hospice care.

Figure 1. *Large circumferential tense bulla with sediment and an erythematous base on the left dorsal foot.*



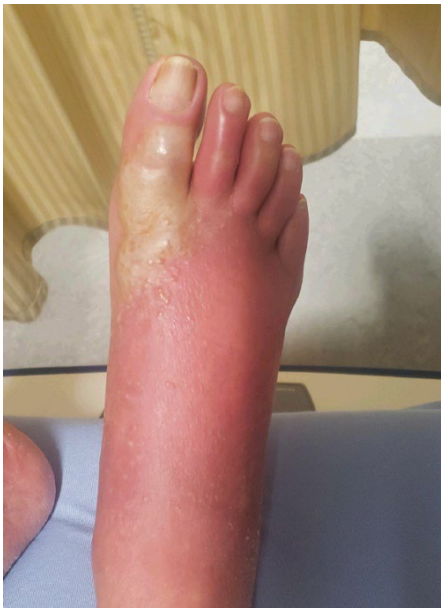
Case 2

A 70-year-old male presented with bilateral foot pain, erythema, and edema 55 days after starting EV. An examination showed erythematous patches with overlying thin skin on the dorsal feet. A blister had formed on his right ankle, and previous photos showed purple erythema with vesicles. The patient had been treated with a prednisone taper and clobetasol, which improved symptoms. EV was permanently discontinued, and the rash did not recur during the 121-day follow-up period.

Case 3

A 71-year-old male developed bilateral foot bullae 120 days after starting EV. An examination revealed small scabbed vesicles on multiple toes without surrounding erythema, and he was treated with antibiotic ointment and supportive wound care. Six days later, he returned with worsening erythema, tenderness, and a blister on his right heel. Antibiotics were prescribed with minimal improvement. 148 days after starting EV, the patient presented with increased pain, pedal edema, erythema, and large bullae on the right big toe (Figure 2). EV was held, and dermatology drained the bullae, provided supportive wound care, and prescribed clobetasol. EV was resumed at a reduced dosing schedule. Rash did not reoccur for 197 days before the patient passed away in hospice care.

Figure 2. *Large bulla on the right great toe with surrounding erythema and edema.*



DISCUSSION

Each of our patients presented with bilateral lower extremity edema, erythema, and superficial bullae impairing their ability to ambulate within 120 days after starting EV (Table 1). The histopathology findings in Case 1 demonstrated lichenoid interface dermatitis on the thighs occurring concurrently with bullae formation on the dorsal feet after EV administration, suggesting a drug-related eruption.

Table 1. *Cutaneous reactions of the feet associated with enfortumab vedotin.*

Diagnosis	Gross Description of Reaction	Histopathologic Findings	Study
Toxic erythema of chemotherapy	Dusky erythema with vesicles and bullae	Biopsy of left thigh: Suprabasal blisters with dyskeratosis	Hasui 2023[5]
TEN	Macular, reticulate erythematous rash	N/A	Bansal 2022[6]
SJS/TEN	Tender erythema with flaccid bullae	Biopsy of left axillae: Subepidermal bulla with detached epidermis with scattered dyskeratotic cells and mixed dermal inflammatory infiltrate composed of lymphocytes, neutrophils, eosinophils, and macrophages	Viscuse 2021[7]
Erythema multiforme-like rash with interface dermatitis	Bullae	Biopsy of chest: Bullous formation Biopsy of inguinal fold: Interface dermatitis with dyskeratosis	Viscuse 2021[7]
Flexural exanthema	Swollen erythematous patches	N/A	Keerty 2020[9]

Diagnosis	Gross Description of Reaction	Histopathologic Findings	Study
Palmar-plantar erythrodysesthesia syndrome	N/A	N/A	Rosenberg 2020[8]
Toxic erythema of chemotherapy	Tense erythematous vesicles	Biopsy of abdomen: Intraepidermal blisters, spongiosis and keratinocyte apoptosis with mild-to-moderate immune cell infiltration	Oya 2022[10]
Toxic erythema of chemotherapy	Papulosquamous eruption	Biopsy of unnamed location: Subtle interface dermatitis accompanied by a perivascular lymphocytic infiltrate with eosinophils and neutrophils, marked dyskeratosis, and epidermal dysmaturation	Dobry 2021[11]
Toxic erythema of chemotherapy	Erythematous indurated plaques	Biopsy of unnamed location: Spongiosis with epidermal necrosis and infiltrate with eosinophils.	Dobry 2021[11]
Toxic erythema of chemotherapy	Erythematous patches	Biopsy of unnamed location: Epidermal atypia, apoptosis, and superficial perivascular dermatitis with eosinophils and focal interface change	Dobry 2021[11]
Toxic erythema of chemotherapy	Erythema and flaccid bullae; papular rash	Biopsy of left thigh: Lichenoid interface dermatitis most consistent with drug eruption Collagen type VII Igg, BP 180 S, and BP 230 S antibodies negative	Current report (Kaufman 2026)
Toxic erythema of chemotherapy	Erythema and scattered vesicles	N/A	Current report (Kaufman 2026)
Toxic erythema of chemotherapy	Erythema and bullae	N/A	Current report (Kaufman 2026)
Toxic erythema of chemotherapy	Dusky erythema with vesicles and bullae	Biopsy of left thigh: Suprabasal blisters with dyskeratosis	Hasui 2023[5]
TEN	Macular, reticulate erythematous rash	N/A	Bansal 2022[6]

Diagnosis	Gross Description of Reaction	Histopathologic Findings	Study
SJS/TEN	Tender erythema with flaccid bullae	Biopsy of left axillae: Subepidermal bulla with detached epidermis with scattered dyskeratotic cells and mixed dermal inflammatory infiltrate composed of lymphocytes, neutrophils, eosinophils, and macrophages	Viscuse 2021[7]
Erythema multiforme-like rash with interface dermatitis	Bullae	Biopsy of chest: Bullous formation Biopsy of inguinal fold: Interface dermatitis with dyskeratosis	Viscuse 2021[7]
Flexural exanthema	Swollen erythematous patches	N/A	Keerty 2020[9]
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Toxic erythema of chemotherapy	Papulosquamous eruption	Biopsy of unnamed location: Subtle interface dermatitis accompanied by a perivascular lymphocytic infiltrate with eosinophils and neutrophils, marked dyskeratosis, and epidermal dysmaturation	Dobry 2021[11]
Toxic erythema of chemotherapy	Erythematous indurated plaques	Biopsy of unnamed location: Spongiosis with epidermal necrosis and infiltrate with eosinophils	Dobry 2021[11]
Toxic erythema of chemotherapy	Erythematous patches	Biopsy of unnamed location: Epidermal atypia, apoptosis, and superficial perivascular dermatitis with eosinophils and focal interface change	Dobry 2021[11]
Toxic erythema of chemotherapy	Erythema and flaccid bullae	Epidermal dysmaturation with mitoses, dyskeratosis, and subepidermal clefting	Current report (Kaufman 2026)
Toxic erythema of chemotherapy	Erythema and flaccid bullae; papular rash	Lichenoid interface dermatitis most consistent with drug eruption Collagen type VII Igg, BP 180 S, and BP 230 S antibodies negative	Current report (Kaufman 2026)

Diagnosis	Gross Description of Reaction	Histopathologic Findings	Study
Toxic erythema of chemotherapy	Erythema and scattered vesicles	N/A	Current report (Kaufman 2026)
Toxic erythema of chemotherapy	Erythema and bullae	N/A	Current report (Kaufman 2026)

These cases are notable for their clinical resemblance to cellulitis and treatment as such prior to dermatology consult for two out of three cases. For Cases 1 and 3, the patients were initially treated with antibiotics due to the clinical presentation of bullae formation with surrounding erythema resembling cellulitis. All three patients' rashes resolved following treatment with high potency topical steroids, as well as additional oral steroids in Case 3.

The reactions seen in our patient cases are also notable because of the appearance of rash specifically on the distal lower extremities including the shins, heels, and ankles as well as dorsal and plantar feet rather than a diffuse skin reaction described in the literature.[4] There are few reports in the current literature of EV-related toxicity specifically favoring the distal lower extremities as in our patients, but existing reports have described rashes involving multiple areas of the body including the feet in the form of suprabasal blisters and dyskeratosis,[5] a macular, reticulate erythematous rash,[6] an erythema multiforme-like rash with interface dermatitis,[7] and erythrodysesthesia[8] among patients treated with EV (Table 1). There is only one case of cutaneous toxicity due to EV reported in the literature that describes appearance of a rash confined to the feet in the form of flexural exanthema.[9]

Two out of the three patients in this case series were able to re-trial EV at a reduced dose and/or at a reduced dosing frequency without recurrence of cutaneous toxicity. We hypothesize that this may be due to the mechanism of toxicity involving disruption of the cell adhesion molecule nectin-4,[3] which is expressed in epidermal keratinocytes, sweat glands, and hair follicles, with immunohistochemical studies demonstrating weak to moderate staining throughout the epidermis and skin appendages.[12] While nectin-4-mediated weakening of the dermoepidermal junction may not be sufficient alone to cause bullae formation, additional factors such as local edema, pressure, or friction may act synergistically to trigger blistering. When these co-factors are reduced or absent, we hypothesize that re-exposure to EV may be tolerated without recurrence of bullae. Further research is needed to better characterize the threshold at which skin-directed toxicity becomes clinically significant and to identify which patients may be suitable for rechallenge.

Due to the high incidence of adverse dermatologic effects with EV, it is important to consider EV as a cause for any rash noted in a patient taking the medication. Additionally, the excellent response to high potency topical steroids in these three patients suggests that patients who present with similar localized eruptions can be safely continued on EV while skin-directed therapies are employed.

CONCLUSIONS

We present three patients who developed toxic erythema of chemotherapy with large bulla formation limited to the distal lower extremities following the initiation of EV. Cutaneous toxicity from EV is common, although confinement of cutaneous reaction to the distal lower extremities has not been commonly reported in the current literature. Thus, this case series highlights a unique morphologic cutaneous toxicity to EV.

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