Enfortumab vedotin toxic epidermal necrolysis–like blistering dermatosis: A case series and review of the literature

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Key words: drug rash; enfortumab vedotin; medical dermatology; medical oncology; urothelial cancer.

INTRODUCTION

Enfortumab vedotin (EV) is an antibody-drug conjugate used as a third-line agent for the treatment of locally advanced or metastatic urothelial carcinoma.

Dermatologic adverse events are frequent and occurred in 48% of patients in the pivotal trial.[1]

Multiple cases of blistering skin reactions resembling Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) have been reported in patients treated with EV.[2]

In this case series, we present 2 cases of patients treated with EV who developed severe blistering eruptions similar to SJS-TEN but with distinct histological features.

Abbreviations used:

EV:	enfortumab vedotin
IVIG:	intravenous immunoglobulin
MMAE:	monomethyl auristatin E
SJS:	Steven-Johnson syndrome
TEN:	toxic epidermal necrolysis

CASE 1

An 87-year-old woman with invasive urothelial carcinoma presented to our hospital with a 10-day history of a painful, erythematous rash that developed on the trunk a few days after her first cycle of EV. The rash worsened after the second infusion with progressive erythema, worsening pain, and blister formation. On admission, flaccid bullae were observed on the intertriginous skin folds, bilateral thighs, upper arms, and posterior neck with a positive Nikolsky sign in many areas (Fig 1). Skin biopsy revealed epidermal-dermal separation with a neutrophilic infiltrate within the blister (Fig 2). Histopathological findings were inconsistent with classic SJS/TEN due to minimal apoptosis of the epidermis. Direct immunofluorescence and indirect immunofluorescence were negative. She denied any other new medications or changes in dosage and was diagnosed with an EV-induced SJS/TEN-like blistering reaction. She was transferred to the medical intensive care unit for continued care and was seen by ophthalmology, otolaryngology, and gynecology but did not develop mucosal involvement. Treatment included intravenous methylprednisolone 1 mg/kg daily, 1 dose of subcutaneous etanercept 50 mg, and 2 g/kg/d intravenous immunoglobulin (IVIG) for 3 days along with supportive wound care. Her condition improved with resolution of the erythema and reepithelization on day 12 of hospitalization. Steroids were tapered, and the patient was discharged home.

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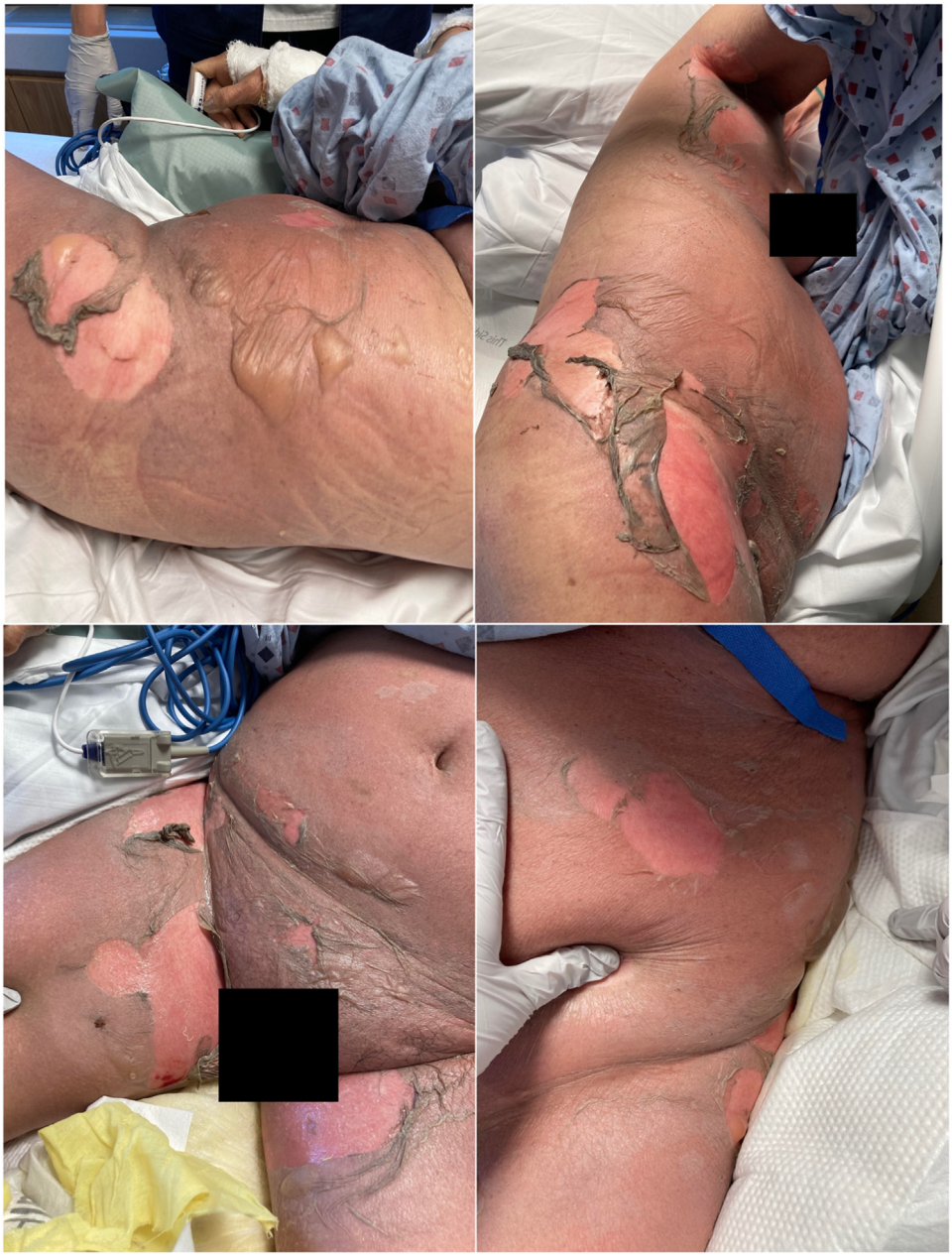

Fig 1. Case 1, Toxic epidermal necrolysis–like bullous drug rash. The patient had flaccid bullae on a background of erythema on the trunk, pelvis, and bilateral midthighs with notable skin sloughing on her lateral left thigh. There was significant separation of overlying epithelium in the intertriginous areas of the pelvis and axilla.

CASE 2

An 81-year-old woman with metastatic urothelial carcinoma presented to our hospital with an 8-day history of a painful, erythematous rash. She had started EV 5 weeks prior and received her most recent dose 3 days before the development of her rash. She had no other new medications or dosage changes. Upon admission she was noted to have diffuse, erythematous, tender patches along with extensive denudation on the trunk and bilateral extremities, involving over 40% of body surface area (Fig 3). Skin biopsies showed similar findings to case 1 with an epidermal-dermal separation with a neutrophilic infiltrate. Direct immunofluorescence and IIF were negative. Although there was focal dyskeratosis, much of the epidermis was viable and intact (Fig 4). Ophthalmology and otolaryngology evaluated the patient but did not see evidence of

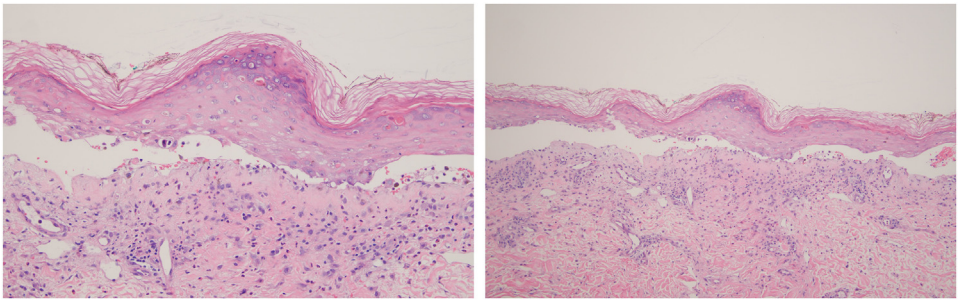

Fig 2. Case 1, Biopsy of the right thigh. The patient's biopsy showed detachment of viable epidermis from the dermis, with a blister cavity containing many neutrophils but no histomorphologic features of toxic epidermal necrolysis.

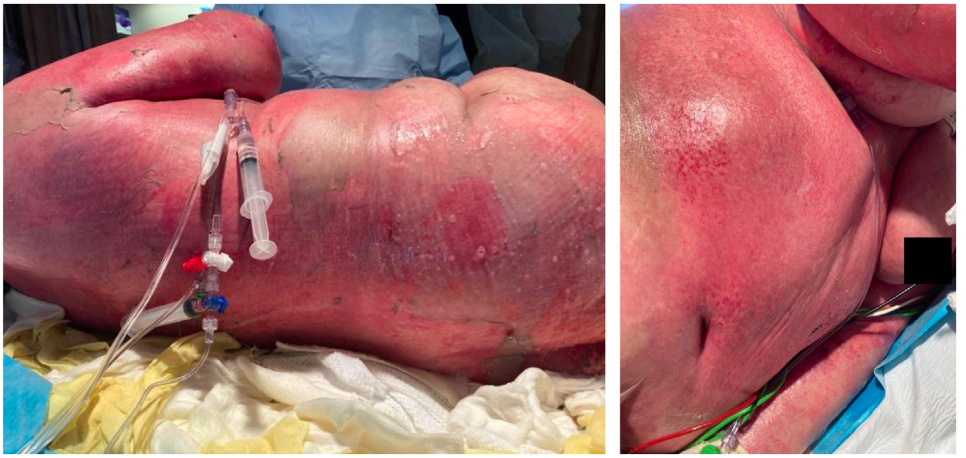

Fig 3. Case 2, Toxic epidermal necrolysis–like bullous drug rash. The patient had diffuse, erythematous, painful patches throughout the face, trunk, and bilateral extremities, with notable denudation. There was significant separation of overlying epithelium in the intertriginous areas of the axilla.

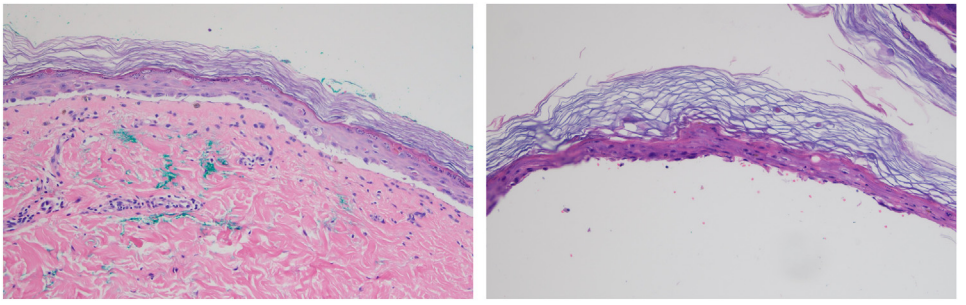

Fig 4. Case 2, Biopsy of the abdomen. The patient's biopsy showed epidermal-dermal separation in association with a neutrophilic component juxtaposed to the detached epidermis. Much of the epidermis was viable, although there is focal dyskeratosis.

mucosal involvement. This patient was also diagnosed with an EV-induced SJS/TEN-like blistering reaction. Antibiotics, IVIG (1 g/kg/d for 3 days), systemic steroids, and a single dose of etanercept (50 mg) were initiated. Given extensive involvement, she was transferred to our hospital's burn unit. Over the course of her hospitalization, some areas of skin reepithelialized quickly, while other areas remained

erythematous with denudation and serous exudate. Despite treatment with improvement in skin erythema and stabilization of blister formation, her overall condition worsened, and she passed away.

DISCUSSION

EV, an antibody-drug conjugate, targets Nectin-4 expressing cells, disrupting cell cycle progression.[3] Nectin-4 is expressed in various epithelial malignancies but also in epidermal keratinocytes in the lower part of the epidermis, eccrine and apocrine sweat glands, hair follicles possibly contributing to EV-induced skin toxicity.[3,4] Monomethyl auristatin E (MMAE), the potent antimitotic agent in EV, may also directly lead to skin toxicity, as seen with other antibody-drug conjugates incorporating MMAE such as brentuximab vedotin.[5] Cutaneous toxicity occurs in 48% of patients treated with EV, suggesting a combined effect of Nectin-4 induced keratinocyte disruption and MMAE induced toxicity.[1]

Although resembling SJS/TEN clinically given dusky erythema and blistering, our cases lacked hallmark features of SJS/TEN including full thickness epidermal necrosis on histopathology and facial or mucosal involvement, leading to a diagnosis of EV induced SJS/TEN-like blistering dermatosis. This is a critical distinction as the pathogenesis and management of these 2 conditions may differ.

Our histopathology results suggest that EV itself may act as an autoantibody, causing a subepidermal split at the level of the basement membrane zone along with irritant toxic erythema of chemotherapy-like changes consisting of focal dyskeratosis possibly related to the MMAE component of the drug. Importantly, and in contradistinction from SJS/TEN, in our cases the epidermis was largely viable. Direct immunofluorescence was negative in both of our cases, distinguishing true autoantibody formation in our patients versus the drug itself potentially acting as an autoantibody.

Similar cases in the literature highlight the association between EV and skin toxicity (Table I). In the pivotal trial, 1 of 125 patients developed a grade 3 rash 4 days after the first infusion, diagnosed as SJS, which resolved with drug discontinuation and systemic steroids.[1] Histopathology of most subsequent reported cases has varied from "interface dermatitis" to "focal dyskeratosis."

Several cases describe extensive blistering eruptions requiring drug discontinuation and hospitalization but lacked extensive mucositis or facial involvement which is a nearly universal feature in SJS/TEN.[6,9,13] Histopathology of these cases reported "areas of full thickness epidermal necrosis;" however, the degree of epidermal necrosis can be reflective of the choice of biopsy site. A biopsy taken of a fully formed blister from a variety of blistering conditions beyond SJS/TEN can show areas of keratinocyte necrosis due to lack of blood supply to the separated epidermis (rather than a true primary apoptotic process like is seen in SJS/TEN).[6,9,13]

Two additional cases reported clinical features consistent with SJS/TEN; however, the histopathology for these cases was either not performed or no epidermal necrosis was reported.[15,17] One other case reported a SJS/TEN-like clinical presentation with histopathology that was more consistent with toxic erythema of chemotherapy due to involvement of the acrosyringium.[18]

Optimal treatment in these cases is not yet known. Awareness of different pathological mechanisms in severe cutaneous toxicities related to EV may have important management implications. Our patients received a combination of IVIG, etanercept, and systemic steroids. Systemic steroids and etanercept may be helpful in reducing inflammation in these cases. IVIG, and even plasmapheresis, could potentially help eliminate the causative agent from the circulation, halting progression.

Determining safe administration of EV can be challenging, as it is a third-line option and may be the last therapeutic option for patients. Extensive body surface area involvement in cutaneous adverse events is related to higher mortality due to increased risk of sepsis, and these patients tend to have multiple comorbidities which leads to slower reepithelialization and further increases their risk of complications.

With these 2 reported cases and our review of the available literature, we hope to better define this newly described severe drug reaction that is SJS/TEN "like" but not SJS/TEN. Current cases suggest this unique antibody-drug conjugate targets Nectin-4 which is present at the level of the basement membrane zone of the skin and in the acrosyringium. This targeting leads to a variety of cutaneous presentations including a potentially severe blistering reaction with evidence of a toxic effect similar to toxic erythema of chemotherapy and a subepidermal split similar to SJS/TEN. Interestingly, both of our patients received immunotherapy in the form of checkpoint inhibitors prior to receiving EV. Further research is needed to determine whether this EV-induced blistering process could potentially be more severe in patients who were previously "primed" immunologically by the administration of immunotherapy prior to receiving EV. Further study is also needed to identify optimal treatments and explore population differences in Nectin-4 skin expression and/or specific human leukocyte antigen types that may predispose patients to severe drug reactions.

Table I. Review of enfortumab vedotin–related cutaneous adverse effects published in literature

Publication	Age & sex	Rash onset relative to EV	Rash distribution & morphology	Mucositis	Pathology	Treatment course	Outcome
Khanjar et al 2023 Case report USA	87 F	A few d after cycle 1, d 1 infusion (1st dose) Worsened after cycle 1, d 8 infusion (2nd dose)	≥30% of her body surface area (BSA), Erythematous patches on neck, trunk, bilateral thighs with flaccid bullae in intertriginous areas No facial involvement Positive Nikolsky sign over many erythematous areas	None	Subepidermal split with detachment of viable epidermis from the subjacent dermis with a blister cavity containing neutrophils	2 g/kg/d IVIG over 3 d Systemic steroids (IV methylprednisolone 1 mg/kg daily) for 4 d 1x etanercept 50 mg	Rash resolved within 12 d of admission Discharged home
	81 F	3 d after cycle 2 EV dose (dose NR)	≥ 40% of her BSA Diffuse, erythematous, painful patches on face, trunk, back, and bilateral extremities Denudation of back and thighs	None	Epidermal-dermal separation with focal dyskeratosis but viable and intact epidermis, in association with a neutrophilic infiltrate	1 g/kg/d IVIG for 3 d Etanercept 50 mg Systemic steroids (IV solumedrol 30 mg twice a day daily)	Rash improved but patient passed away during admission
Wu et al 2019 USA Case report[7]	70s M	A few d after cycle 1 d 1 infusion (1st dose)	Erythematous, scaly, variably excoriated pink papules on the neck, chest, abdomen, and back No facial involvement	None	Vacuolar interface dermatitis with maturation disarray of keratinocytes and a sparse perivascular lympho-eosinophilic infiltrate	0.05% clobetasol cream Oral antihistamine	Rash improved within 2 wk
Keerty et al 2020 USA Case report[8]	64 M	3 d after cycle 2 d 8 infusion (5th dose)	Estimated < 10% of his BSA Edematous, erythematous patches in intertriginous areas and dorsal aspects of feet No facial involvement	None	NR	0.1% triamcinolone cream Oral antihistamine	Rash resolved within 1 wk
Francis et al 2020 USA Case report[9]	72 M	A few d after cycle 1 d 8 infusion (2nd dose)	<20% of his BSA at onset, progressed to involve ≥30% of his BSA	A single blister on the posterior aspect of his oral cavity	Interface dermatitis with central areas of full-thickness	Supportive therapy Empiric vancomycin/ meropenem	Patient passed away on d 20 of hospitalization

			Tense bullae with background erythema on the axillae, back, genitalia, posterior aspect of the bilateral thighs, and bilateral heels		epidermal necrosis		
Hirotsu et al 2020 USA Research letter[10]	65 M	63 d after last EV dose (dose NR)	Pruritic, smooth, and scaly erythematous papules and thin plaques in flexural and acral areas	NR	Vacuolar interface dermatitis with keratinocyte dysmaturation	Topical steroids	Rash prognosis NR
	60 M	11 d after last EV dose (dose NR)	In 4/8 patients: vesicles, bullae		NR	Topical steroids	
	81 F	38 d after last EV dose (dose NR)	In 3/8 patients: hyperpigmentation and superficial desquamation		NR	Topical steroids Systemic steroids (oral prednisone 0.5-1 mg/kg daily)	
	70 M	4 d after last EV dose (dose NR)			Vacuolar interface dermatitis with eosinophils, keratinocyte dysmaturation	Topical steroids	
	80 M	13 d after last EV dose (dose NR)			Spongiotic dermatitis with focal vacuolar interface dermatitis and necrosis, eosinophils, scattered ring mitoses; second biopsy showing subepidermal split	Topical steroids Systemic steroids (oral prednisone 0.5-1 mg/kg daily)	
	70 F	4 d after last EV dose (dose NR)			NR	Topical steroids Systemic steroids (oral prednisone 0.5-1 mg/kg daily)	
	80 M	10 d after last EV dose (dose NR)			Vacuolar interface dermatitis with eosinophils and focal keratinocyte dysmaturation	Topical steroids	
	90 M	12 d after last EV dose (dose NR)			NR	Topical steroids Systemic steroids (oral prednisone 0.5-1 mg/kg daily)	

Continued

Table I. Cont'd

Publication	Age & sex	Rash onset relative to EV	Rash distribution & morphology	Mucositis	Pathology	Treatment course	Outcome
Sasaki et al 2020 Japan Concise communication/ case report[11]	59 M	3 d after cycle 1 d 1 infusion (1st dose)—resolved Reoccurred NR days after cycle 2 d 1 infusion (4th dose)	Estimated <20% of his BSA Erythema concomitant with fine desquamation and wide erosions over trunk and extremities No facial involvement	No evidence of mucosal involvement	Full-thickness epidermal necrosis with band-like infiltration of inflammatory cells in the papillary dermis	Systemic steroids (oral prednisolone 60 mg/d for 3 d, 40 mg/d for 4 d, 20 mg/d for 14 d, with 5 mg/d tapering every wk)	Rash improved within 7 d
Viscuse et al 2021 USA Case report[6]	71 M	4 d after cycle 1 d 8 infusion (2nd dose)	11% of his BSA at onset, progressed to involve 18% of his BSA Tender erythema over the axillae, flanks, inguinal region, and soles of feet Flaccid ruptured bullae on the right posterior upper arm, left forearm, and right heel No facial involvement Positive Nikolsky sign	Small ulceration on right lateral upper lip Well-demarcated erythema of inferior tongue tip	Subepidermal bulla with detached epidermis with scattered dyskeratotic cells and mixed dermal inflammatory infiltrate composed of lymphocytes, neutrophils, eosinophils, and macrophages	Systemic steroids (IV methylprednisolone dose NR) Cefepime, acyclovir, and mupirocin	Patient passed away during hospitalization
	77 M	2 d after cycle 1 d 15 infusion (3rd dose)	Estimated ≥ 20% of his BSA Tender erythema over the axillae, scrotum, and inguinal folds Pruritic papules and vesicles on the chest and back Bullae on dorsal 2nd and 3rd digits of the left foot No facial involvement	None	Bullous formation and interface dermatitis with dyskeratosis, associated with eosinophils and some neutrophils	Silver sulfadiazine cream 0.1% triamcinolone ointment three times a day Systemic steroids (oral prednisone 60 mg daily) for 1-2 d	Significant improvement within 2 d
Dobry et al 2021 USA Case series[12]	75 M	7 d after cycle 1 d 1 infusion (1st dose)	Estimated <20% of his BSA Scattered, ill-defined, scaly, erythematous papuleson the chest, arms, and thighs No facial involvement	None	Subtle interface dermatitis with lymphocytes, eosinophils, and neutrophils, marked dyskeratosis, and epidermal dysmaturation	Clobetasol ointment	Rash improved but patient passed away during admission

	65 M	13 d after latest EV dose (dose NR)	Estimated <20% of his BSA, sparing face Scattered, ill-defined, scaly, erythematous papules on the chest, arms, and thighs	None	Spongiosis with epidermal atypia, necrosis, and superficial perivascular infiltrate with eosinophils	0.1% triamcinolone ointment	Rash resolved
	77 M	5 d after cycle 1 d 1 infusion (1st dose)	Estimated <20% of his BSA, sparing face Erythematous patches on trunk, arms, and thighs	None	Keratinocyte atypia, apoptosis, and superficial perivascular dermatitis with eosinophils and focal interface change	0.05% fluocinonide ointment Prednisone dose NR	Rash resolved
Enescu et al 2022 USA Case report[13]	73 F	1 d after cycle 2 d NR infusion (dose NR) Worsened 13 d later during cycle 3 (dose NR)	Estimated ≥ 20% of her BSA, sparing face Generalized erythema over the chest, arms, back, and abdomen with large erythematous patches on bilateral thighs Painful erythema with edematous plaques and multiple tense bullae on the bilateral shins	None	Focal interface dermatitis with necrotic keratinocytes and areas of full-thickness epidermal necrosis with secondary blister formation	Systemic steroids (oral prednisone 70 mg daily) for 3 d Topical steroids	Discharged within 48 h of admission Resolution of the rash 4 wk after discharge
Penny et al 2022 USA Research letter[14]	73 F	Onset during cycle 4 d NR (dose NR)	10% of her BSA, sparing face Pruritic erythematous rash on abdomen, chest, and extremities Tense intact bullae on the bilateral lower legs	None	Interface dermatitis with prominent spongiosis and eosinophils. DIF of perilesional skin showed cell surface deposits of IgG and C3 concentrated in the upper half of the epidermis	0.1% triamcinolone ointment Systemic steroids (oral prednisone dose NR daily) for 5 d Tapered to prednisone 10 mg daily for 8 wk while on EV	Rash resolved
	66 M	Onset 6 wk after EV initiation (last dose NR)	Estimated ≥10% of his BSA, sparing face Diffuse pruritus followed by fluid-filled 1−2-mm vesicles on the trunk and extremities	None	Epidermal spongiosis with dyskeratosis, and a paucicellular intraepidermal vesicle. DIF of perilesional skin showed cell surface deposition of IgG and C3, and linear deposition of IgM at the	0.1% triamcinolone ointment Next EV infusion was held	Rash resolved Reoccurrence of a mild intermittent rash once EV was resumed, treated with triamcinolone

Continued

Table I. Cont'd

Publication	Age & sex	Rash onset relative to EV	Rash distribution & morphology	Mucositis	Pathology	Treatment course	Outcome
					dermoepidermal junction		
Bansal et al 2022 India Concise communication/ case report[15]	62 M	3 d after cycle 1 day 1 infusion (1st dose) Worsened after cycle 1 day 8 infusion (2nd dose)	Estimated ≥ 30% of his BSA Tender, macular, reticulate erythematous rash on the forearms, flanks, proximal thighs, lower trunk, intertriginous areas, and feet with denudation over the back and axillae Multiple scattered follicular pustules on the scalp with crusting over nasolabial folds Erythema without target lesions or blisters over palms and soles	Erosions over lips and palate Conjunctival redness and discharge from eyes	Not done	Antibiotics Topical steroids Systemic steroids	His overall clinical status deteriorated with concerns for septic shock He passed away 6 d postadmission
Guerrois et al 2022 France Letter to the editor[16]	*N* (6 cases) Median age (IQR) 67 (63-75) M	After the first EV administration with a median delay of 12 d (6-44 d)	*N*[6] Well-demarcated erythematous plaques with central skin detachment predominating in the large folds (axillary and inguinal folds) *N*[5] Pustules or blisters	*N*[3] Limited mucosal lesions (conjunctivitis-like lesion, oral erosion, and genital erosion)	5 patient biopsies 4 cases showed interface dermatitis with apoptotic keratinocytes, abnormal mitotic figures, and sparse inflammatory infiltrate 1 case showed a detachment of the epidermis with confluent necrosis, resembling TEN		*N*[3] Died within a median of 4 d due to multiorgan failure *N*[3] Rash resolution but EV treatment never retrialed
Singh et al 2022 USA Case report[17]	47 F	4 d after cycle 1 d 8 infusion (2nd dose)	25% of her BSA Diffuse erythema Exfoliating rash and bullae over the trunk, arms, legs chest, axilla, inframammary folds, and intertriginous areas Positive Nikolsky sign	Pruritus in the upper throat Grittiness in the eyes Oral erosions	Vacuolar interface dermatitis with no significant inflammatory infiltrate and dyskeratotic cells at all levels of the epidermis. Focal subepidermal separation is seen	Antibiotics 2x etanercept 50 mg 200 mg of IVIG over 3 d Systemic steroids (IV methylprednisolone dose NR)	Rash improved in 1 wk Discharged in 10 d, continued resolution outpatient

Birmingham et al 2022 USA Brief report[18]	63 M	A few d after cycle 1, d 8 infusion (2nd dose) Worsened 7 d after cycle 1, d 15 infusion (3rd dose)	45% of his BSA Widespread cutaneous erythema Bullae formation in intertriginous areas Near full-thickness desquamation affecting intertriginous and gravity-dependent areas	None	Full thickness epidermal and eccrine ductal atypia with dyskeratosis and suprabasilar acantholysis intraepidermally DIF studies were negative	Topical steroids 2 g/kg/d IVIG for 3 d	He passed away 14 d after admission due to multisystem organ failure

DIF, Direct immunofluorescence; *EV*, enfortumab vedotin; *F*, female; *IV*, intravenous; *IVIG*, intravenous immunoglobulin; *M*, male; *NR*, not reported; *TEN*, toxic epidermal necrolysis.

Conflicts of interest

None disclosed.

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