Enfortumab vedotin-induced widespread vesiculobullous eruption mimicking disseminated herpetic infection in a patient with metastatic urothelial carcinoma

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Abstract

Enfortumab vedotin (EV) is a monoclonal antibody drug conjugate composed of antibody against nectin-4 and linked to the microtubule inhibitor monomethyl auristatin E that is used to treat metastatic urothelial carcinoma. Enfortumab vedotin-associated cutaneous adverse events are common and are clinically diverse, ranging from papulosquamous eruption to vesiculobullous eruptions such as Stevens-Johnson syndrome/toxic epidermal necrolysis and erythema multiforme-like eruption with vesiculobullae. Despite clinically diverse appearance, histopathology of EV-associated cutaneous adverse reactions often demonstrates interface dermatitis. We present the clinical and histopathologic features in a unique case of EV-associated widespread vesiculobullous eruption initially concerning for disseminated herpetic infection in a patient undergoing treatment of metastatic urothelial carcinoma with EV and pembrolizumab.

Keywords: bullous, dermatitis, drug-eruption, enfortumab, toxicity, vesicular

Introduction

Enfortumab vedotin (EV) is a monoclonal antibody drug conjugate against the cell adhesion molecule, nectin-4, approved by the Food and Drug Administration to treat metastatic urothelial carcinoma in patients who have failed platinum-based chemotherapy and immunotherapy [1]. Enfortumab vedotin binds nectin-4-expressing cancer cells and triggers the release of the antibody-linked microtubule inhibitor monomethyl auristatin E (MMAE), [1]. Inhibition of microtubule function induces apoptosis of cancer cells. Enfortumab vedotin-associated cutaneous adverse events are common, occurring in 48% of patients in clinical trials, with most described as "low grade," "maculopapular" and "diffuse" [1]. However, more severe and higher-grade cutaneous adverse reactions have been reported and include Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), [2], erythema multiforme-like rash with interface dermatitis [3], symmetrical drug-related intertriginous and flexural exanthema, bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia [4].

We present the clinical and histopathologic features in a unique case of EV-associated widespread vesiculobullous eruption initially concerning for disseminated herpetic infection in a patient undergoing treatment of metastatic urothelial carcinoma with EV and pembrolizumab.

Case Synopsis

A 68-year-old man with history of metastatic urothelial carcinoma on EV and pembrolizumab every three weeks presented to the dermatology clinic for a worsening blistering rash. The rash started approximately two weeks after the third cycle of EV and pembrolizumab as few erythematous, pruritic

and burning papules scattered on trunk and extremities. The rash was treated by the oncology department with topical hydrocortisone 2.5% cream with resolution. However, after the sixth cycle of EV and pembrolizumab, the rash recurred with more numerous lesions and more widespread distribution; it was unresponsive to low potency topical corticosteroids. Enfortumab vedotin and pembrolizumab were both held by his oncologist and patient was referred for urgent dermatologic evaluation. On physical examination, the patient had multiple, non-grouped, discrete monomorphous papules and tense, non-crusted vesicles on an erythematous base symmetrically and widely distributed throughout the arms, legs, and trunk (**Figure 1**). No ulcerations, oral, or genital lesions were present. The patient denied cough, shortness of breath, or abdominal pain. He had no history of genital ulcers, oral herpetic lesions, or varicella infection, though he recalled a remote history of varicella infection in household members. He had not received the herpes zoster vaccination. In addition to EV and pembrolizumab, the patient's medications included lisinopril, ondansetron, hydrochlorothiazide, loratadine, tamsulosin, atorvastatin, and melatonin, none of which were new or recently adjusted.

Based on the clinical morphology of these lesions in an immunocompromised patient, the initial clinical differential diagnosis included disseminated herpetic infection. However, bedside Tzanck smear was negative for multinucleated cells or other features of herpetic viral cytopathic change. Polymerase chain reaction (PCR) for herpes simplex I/II and varicella zoster were negative. Punch biopsy of a representative vesicle demonstrated interface dermatitis with subepidermal vesicle formation, mild epidermal spongiosis, and mixed inflammation with eosinophils (**Figure 2**). No viral cytopathic change was seen on the biopsy specimen. Direct immunofluorescence of perilesional skin was negative for autoimmune blistering disease.

With clinicopathologic correlation, the diagnosis of a vesiculobullous drug eruption was made, with the most likely culprit medications being either EV or pembrolizumab. Enfortumab vedotin and pembrolizumab continued to be held and he was treated with clobetasol 0.05% cream twice daily with resolution of all lesions within a few days. Subsequently, his oncologist resumed pembrolizumab every three weeks but discontinued EV due to EV-induced neuropathy and concern for EV-associated rash. The patient successfully received another 23 cycles of pembrolizumab without rash recurrence and with sustained partial tumor response. Given that the patient continued multiple cycles of pembrolizumab without rash recurrence and with clinicopathologic correlation, EV was believed to be the most likely culprit medication of the vesiculobullous eruption.

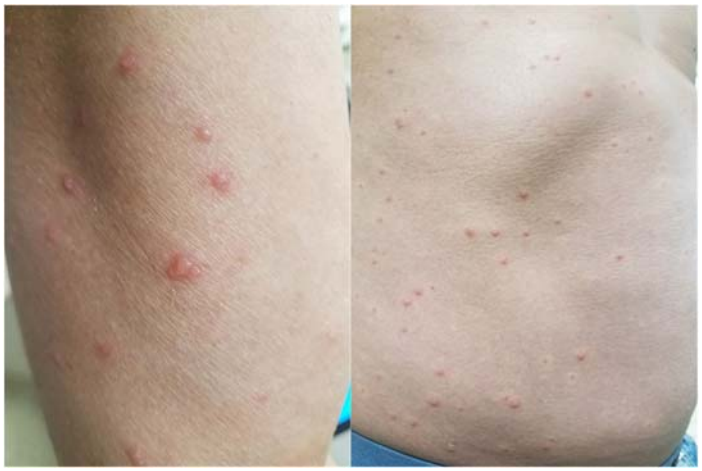

Figure 1. *Multiple discrete monomorphous papules and tense, non-crusted vesicles on an erythematous base.*

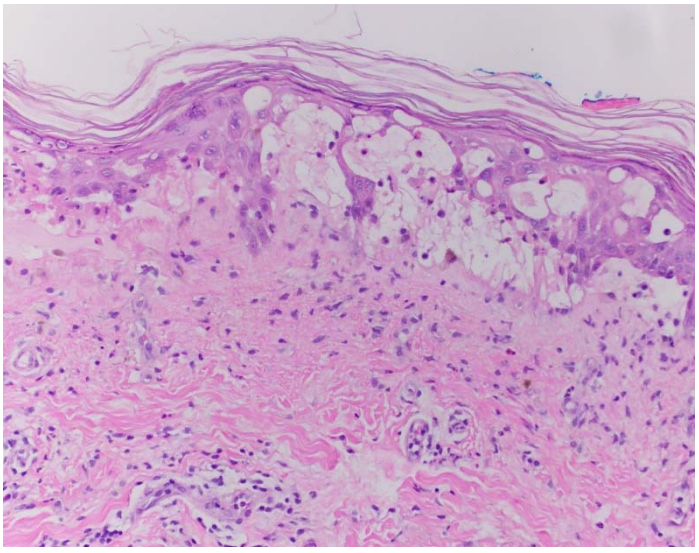

Figure 2. *Interface dermatitis with subepidermal vesicle formation, mild epidermal spongiosis and mixed inflammation with eosinophils. H&E, 200×.*

Case Discussion

Enfortumab vedotin is a monoclonal antibody drug conjugate composed of antibody directed against nectin-4 and linked to the microtubule inhibitor MMAE. Nectin-4 belongs to the family of calcium-dependent, immunoglobulin-like adhesion molecules found in adherens junctions and expressed in various epithelial carcinomas including bladder, breast, lung, ovarian, head/neck and esophageal cancers [5]. However, nectin-4 is also expressed in normal skin keratinocytes. Therefore, it has been hypothesized that targeting of nectin-4 in keratinocytes by EV with subsequent delivery of MMAE may result in skin toxicity [6]. Another proposed mechanism of EV-induced skin toxicity includes the bystander effect, in which intracellular MMAE diffuses across cell membranes causing apoptosis in adjacent cells. Based on observations of common rashes in clinical trials evaluating other antibody-drug conjugates utilizing MMAE, some have proposed that EV-induced cutaneous toxicity may be related solely to the MMAE payload, independent of anti-nectin-4 activity [7]. For example, cutaneous toxicity was seen in 27-31% of patients treated with brentuximab vedotin, 45% of patients treated with glembatumumab vedotin, and 13-31% patients treated with polatuzumab vedotin [7].

Vesiculobullous dermatitis secondary to EV has been reported in post-marketing safety data. However, the specific clinical and histopathologic findings have not been fully described in the literature [8]. Bullous lesions as part of the clinical presentation of SJS/TEN induced by EV have been reported [9,3]. However, it is important to differentiate bullous lesions as part of SJS/TEN and less severe vesiculobullous dermatitis secondary to EV, such as in our case, as there have been multiple reports of SJS/TEN including fatal cases induced by EV [2]. In reported cases of EV-induced SJS/TEN, patients had oral lesions and widespread skin sloughing in addition to bullous lesions (tense or flaccid), findings that were not seen in our patient (**Table 1**). On histopathology of EV-induced rashes, interface dermatitis has been previously described numerous times, though the associated clinical presentation has been diverse including: papulosquamous eruption without clinically apparent blisters [4,7], Stevens-Johnson syndrome/toxic epidermal necrolysis with clinical bullae [9], and an erythema multiforme-like rash with papules, vesicles, and bullae [3]. There have also been reports of other histopathologic findings in EV-induced rashes, such as suprabasal dyskeratosis, which was not seen in our case [10]. Our case highlights an additional unique presentation of EV-induced widespread vesiculobullous eruption with interface dermatitis. However, in contrast to more severe EV-induced cutaneous toxicity such as SJS/TEN and erythema multiforme-like eruption, the vesiculobullous eruption in our patient was milder and readily treated with high potency topical corticosteroids.

Our clinical differential diagnosis also included bullous pemphigoid secondary to pembrolizumab, which the patient received in conjunction with EV. Immune checkpoint inhibitors such as pembrolizumab, a monoclonal antibody directed against programmed death-1 receptor, are well documented to cause bullous pemphigoid [11]. However, the histopathology and immunofluorescence studies were not consistent with BP in our case. In addition, after rash resolution, the patient was able to resume pembrolizumab for multiple cycles as monotherapy without rash recurrence, thereby making it less likely that the vesiculobullous eruption was induced by pembrolizumab. Finally, because our patient was immunocompromised owing to his cancer, it was also important to consider disseminated herpetic infection in our clinical differential diagnosis. Herpetic lesions clinically present as small erythematous papulovesicles on an erythematous base ("dew drops on a rose petal") which may crust, similar to lesions seen in our patient [12]. However, in our patient, Tzanck, PCR, and histopathology were all negative for herpetic infection.

Conclusion

We describe a unique case of EV-induced widespread vesiculobullous eruption that initially raised concern for disseminated herpetic infection in

a patient with metastatic urothelial carcinoma. Our case contributes a novel clinicopathologic correlation of EV-induced cutaneous toxicity with interface dermatitis on histopathology to the literature. It is important for dermatologists and dermatopathologists to recognize the expanding clinical and histopathologic spectrum of EV-associated cutaneous adverse events.

Potential conflicts of interest

The authors declare no conflicts of interest.

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Table 1. *Existing literature on lesion morphology and pathology of enfortumab vedotin-induced cutaneous toxicities.*

EV-induced cutaneous toxicity	Age	Sex	Tumor	# of cycles of EV	Dose of EV	Lesion morphology	Pathology	Treatment	Outcome	Source
SJS/TEN	71	M	Metastatic urothelial carcinoma	2	1.25 mg/kg	Ulceration of right lateral upper lip, well-demarcated erythema of inferior tongue tip, and tender erythema of axillae, flanks, inguinal region, and soles of feet. Flaccid ruptured bullae covering ~11% body surface area	Subepidermal bullae with detached epidermis with scattered dyskeratotic cells and mixed dermal inflammatory infiltrate composed of lymphocytes, neutrophils, eosinophils, and macrophages	IV metylpredni-solone, cefepime, acyclovir, mupirocin	Patient expired	Viscuse et al.
TEN	72	M	Metastatic urothelial carcinoma	2	Not stated	Erythematous rash with associated skin sloughing developed on <20% of body, later progressed to >30%. Tense bullae on a background of erythema on his bilateral axillae, back, genitalia, posterior aspect of bilateral thighs, and bilateral heels. Single blister on posterior aspect of his oral cavity	Interface dermatitis with central areas of full-thickness epidermal necrosis	Supportive therapy, empiric vancomycin and meropenem	Patient expired	Francis et al.
EM-like reaction	77	M	Metastatic urothelial carcinoma	3	Not stated	Tender erythema in the axillae, scrotum, and inguinal folds. Pruritic papules and vesicles of the chest and back, and bullae on the dorsal 2nd and 3rd digits of the left foot	Bullous formation and interface dermatitis with dyskeratosis. Associated eosinophils and some neutrophils present.	Silver sulfadiazine cream, triamcinolone 0.1% ointment TID, and prednisone 60mg daily	Lesion improved, patient continued on EV without further complication	Viscuse et al.
Papulosqua-mous eruption without blisters	75	M	Metastatic urothelial carcinoma	1	Not stated	Ill-defined scaly erythematous papules on the chest, arms, and thighs	Subtle interface dermatitis accompanied by a perivascular lymphocytic infiltrate with eosinophils and neutrophils, marked dyskeratosis, and epidermal dysmaturation	Clobetasol ointment initially, prednisone subsequently	Initially improved, but later developed vasodilatory shock and expired	Dobry et al.
Papulosqua-mous eruption	65	M	Metastatic urothelial carcinoma	1	Not stated	Diffusely erythematous, indurated plaques on the arms, chest, and thighs	Spongiosis with epidermal atypia, necrosis, and superficial	Triamcinolone 0.1% ointment	Rash improved, later restarted on dose-	Dobry et al.

without blisters							perivascular infiltrate with eosinophils		reduced EV without rash recurrence	
Papulosqua-mous eruption without blisters	77	M	Metastatic urothelial carcinoma	1	Not stated	Erythematous patches on the trunk, arms, and thighs	Keratinocyte atypia, apoptosis, and superficial perivascular dermatitis with eosinophils and focal interface change	Prednisone and fluocinonide 0.05% ointment	Rash improved and did not recur with re-treatement at standard dosing	Dobry et al.
Vesiculo-bullous dermatosis	68	M	Metastatic urothelial carcinoma	3 initially, recurred after 6	Not stated	Multiple, non-grouped, discrete monomorphous papules and tense, non-crusted vesicles on an erythematous base symmetrically and widely distributed throughtout the arms, legs, and trunk	Interface dermatitis with subepidermal vesicle formation, mild epidermal spongiosis and mixed inflammation with eosinophils	Clobetasol 0.05% BID	Resolution. EV discontinued	This case report

BID, twice daily, EM, , EV, *enfortumab vedotin,* IV, intravenous, SJS, Stevens-Johnson syndrome, TEN, toxic epidermal necrolysis, TID, three times daily