Clinical Letter

A distinctive bullous skin reaction associated with enfortumab vedotin-ejfv treatment for metastatic urothelial cancer: A case report

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Dear Editors,

enfortumab vedotin-ejvf (EV) is an antibody-drug conjugate combining a human anti-nectin-4 antibody with the cytotoxic microtubule disruptor monomethyl auristatin E (MMAE) [1]. EV received accelerated approval from the FDA in December 2019 for the treatment of patients with locally advanced or metastatic urothelial carcinoma [2]. Nectin-4 is a transmembrane protein found on the surface of most urothelial carcinoma cells, but it is also expressed in several other cancers. All four known nectins support cell-cell adhesion and, together with cadherins, are essential for the formation of the adherens junction. In normal human skin, nectin-4 is expressed in the suprabasal layers of the epidermis, and nectin-4 mutations in patients have been associated with ectodermal dysplasia syndromes [3].

Here, we report on a 68-year-old male patient who presented to us with progressive skin lesions under therapy with EV. Due to a progressive, hepatic, pulmonary, lienal, and lymphogenic metastatic urothelial carcinoma of the urinary bladder initially diagnosed in 2017, the patient first received inductive chemotherapy with gemcitabine/cisplatin followed by palliative radical cystectomy. In 2019, therapy with pembrolizumab was initiated, subsequently followed by a rechallenge chemotherapy with gemcitabine/cisplatin, vinflunine and pemigatinib (an inhibitor of fibroblast growth factor receptor). As the disease showed further progression under all treatment regimes, therapy with EV was initiated in October 2020 as per the recommended dosage regimen.

Several days after the second administration of EV, the patient developed generalized pruritus, a papular rash of the upper extremity and palmar-plantar erythrodysesthesia with consecutive exfoliation of the soles. These skin changes regressed well under topical glucocorticoids. After three administrations of EV, the patient presented for the first time in our dermatology outpatient clinic with symmetric, mostly flexural and axillary erythema that was diagnosed as SDRIFE (symmetrical drug related intertriginous and flexural exanthema) and which completely resolved after treatment with topical glucocorticoids. About twelve weeks after initial administration of EV with six administrations performed in total (the last occurring 4 weeks before), vesicles started to appear on the forearms (volar sides accentuated). Upon renewed presentation to our department in January 2021, disseminated, skin colored, firm vesicles and blisters primarily on the arms and trunk were seen (Figure 1). The mucous membranes were not affected, there was no pruritus, and the patient was otherwise in good general condition. Serologic testing for BP180, BP230, and desmoglein-1 and -3 antibodies was negative. Histological evaluation showed irregular acanthosis of the epidermis with intraepidermal, unusually sharply demarcated bullae. The directly surrounding spongiotic epidermis featured sporadic pleomorphic keratinocytes. The upper dermis showed a predominantly perivascular lymphocytic infiltrate with scattered eosinophils and melanophages (Figure 2). The observed histological pattern is not typical of common bullous drug reactions. Also, these findings are not characteristically seen in bullous autoimmune dermatoses where the loss of adherence among individual keratinocytes is more diffuse [4–6]. Direct immunofluorescence showed no positive staining for C3 or fibrinogen and no deposition of immunoglobulins.

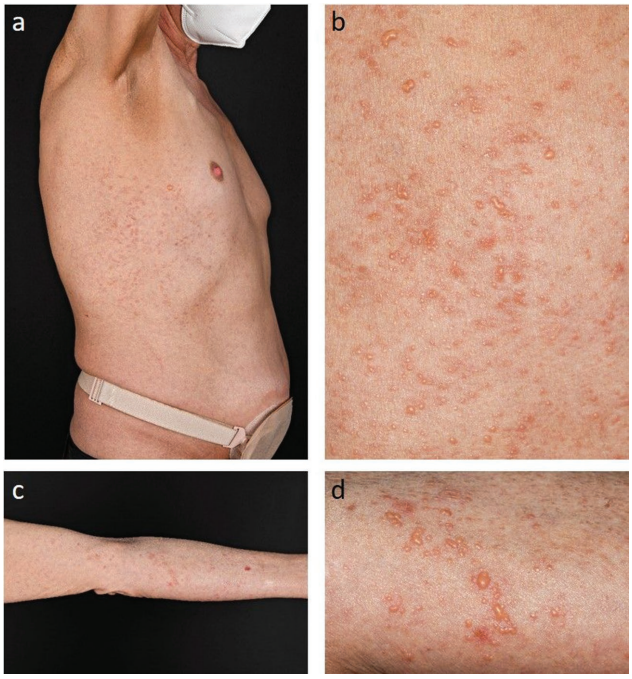

Figure 1 Skin findings at presentation. Non-pruritic, firm vesicles, especially on the trunk (a, b) and upper limb (c, d).

After one week under topical glucocorticoids, vesicles and blisters had completely resolved. However, the previously observed papular rash reappeared on the upper extremity and trunk with intermittent pruritus. Since staging investigations showed a regressive metastatic disease, therapy with EV was continued. To date, the patient has received two further administrations (8 in total) without any signs of recurrence of bullous eruptions.

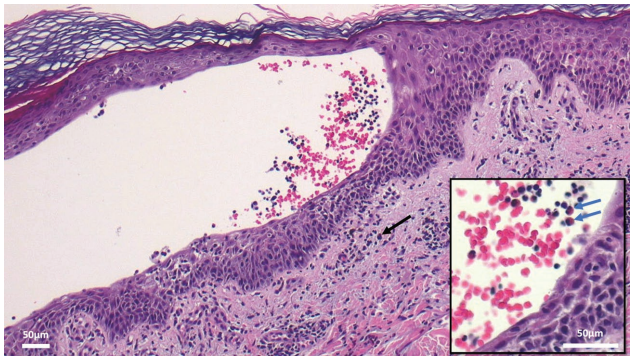

Figure 2 Histology. A punch biopsy from the upper arm demonstrated sharply demarcated intraepidermal bullae and a predominantly perivascular lymphocytic infiltrate in the upper dermis (hematoxylin-eosin stain, original magnification x 100). Blue arrows: eosinophilic granulocytes (inset detail), black arrow: melanophage.

In Phase I and II studies conducted to date (additional phase II and phase III trials are currently ongoing), EV has demonstrated a moderate toxicity profile with mostly non-specific side effects such as fatigue, alopecia, and decreased appetite. The most common adverse events leading to permanent discontinuation of EV treatment were peripheral neuropathy, rash, fatigue, and dyspnea [2]. The skin lesions most commonly reported under the term "rash" have been characterized as maculopapular, and 10 % of the study participants developed SDRIFE. Moreover, bullous dermatitis, exfoliative dermatitis, palmar-plantar erythrodysesthesia and pruritus are also mentioned in the summary of product characteristics of EV [7], and recently, two cases of EV-induced toxic epidermal necrolysis have been reported [8, 9]. While most of the adverse events are likely related to the microtubule-disrupting agent, MMAE, some of the observed skin reactions are possibly related to the blockade of cutaneously expressed nectin-4. However, other antibody-drug conjugates with MMAE have also been shown to have high rates of adverse skin reactions (for instance brentuximab vedotin, glemutumumab vedotin, and polatuzumab vedotin) [2].

Interestingly, our patient developed all of the EV-associated skin reactions listed by the manufacturer. Of these, possibly the most characteristic for EV is the clinical presentation with numerous firm vesicles and blisters without clinical signs of inflammation and the unusually sharply demarcated, intraepidermal bullae seen on histological examination.

In our patient, as in other described cases, the cutaneous side effects were controllable with continued EV therapy [9, 10]. A possible reason for this is that the toxic effect of EV may be only intermittently associated with the application and that there is no intrinsic disease activity, such as in the bullous autoimmune dermatoses.

Since Nectin-4 is expressed in the basal layers of the epidermis [3] and has a role in cell-cell adhesion, a specific cutaneous side effect of the anti-nectin-4 antibody is likely. Since EV is considered a breakthrough treatment option in metastatic urothelial carcinoma and bladder carcinoma is one of the most common cancers in men [11], it is very likely that we, as dermatologists, will see these distinct, skin-specific adverse reactions to EV more frequently in the future.

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Conflict of interest

None.

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