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Severe cutaneous drug reaction associated with enfortumab vedotin

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To the Editor:

Oncological diseases are one of the main causes of mortality in our population. We have an increasingly broad therapeutic arsenal, which is sometimes associated with cutaneous adverse events. We present the first case of enfortumab vedotin-related rash in our hospital.

A 74-year-old man diagnosed with metastatic urothelial carcinoma, presented to clinic while undergoing third-line treatment with enfortumab vedotin. The patient exhibited general deterioration, fever, gastrointestinal symptoms, and skin lesions of two days' evolution. The last dose of enfortumab vedotin had been administered 6 days prior.

Skin examination revealed diffuse macular erythematous lesions in the inguinal and axillary folds, as well as more subtle lesions on the forearms and facial area. Laboratory testing revealed leukopenia, abnormal liver profile, and elevated levels of C-reactive protein and procalcitonin.

The patient required hospitalization and was diagnosed with drug-induced rash. Treatment was started with topical clobetasol propionate cream and systemic intravenous antibiotics. The following days the patient worsened with persistent fever and increased skin lesions. Examination showed extensive epidermal detachment in the folds (**Figure 1A**, **B**), erosions in the genital mucosa, and some bullous lesions on the forearms (**Figure 1C**). There was erythema and plantar pain but there were no lesions on the buccal mucosa.

A biopsy was performed on one of the forearm lesions, which showed interface dermatitis with necrotic keratinocytes and full-thickness epidermal necrosis and subepidermal blistering with reepithelialization. Apoptotic bodies were identified in both the reepithelialized areas and the roof of the blister. The underlying dermis exhibited vascular dilation and a sparse lymphocytic infiltrate in the

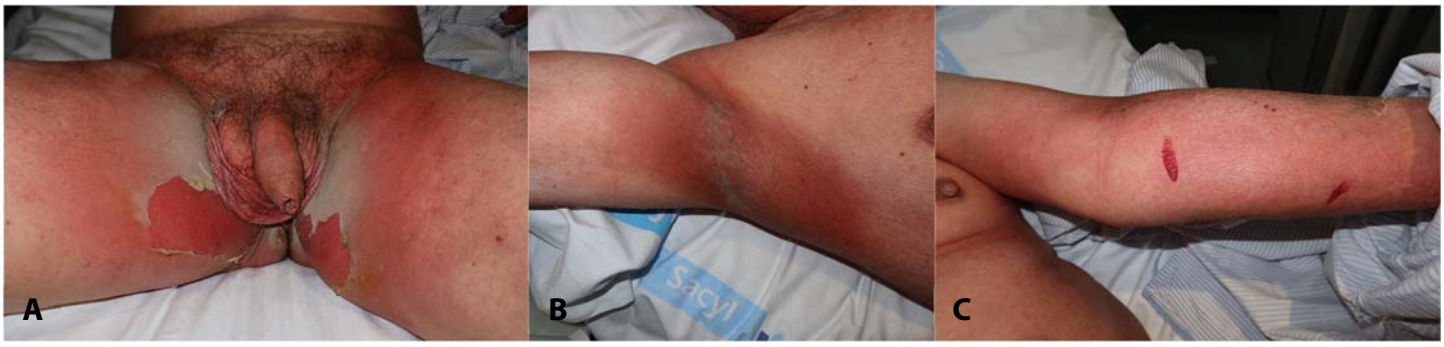

Figure 1. ***A, B)*** *Epidermal detachment in the inguinal and axillary folds.* ***C)*** *Bullous lesions on the left forearm.*

perivascular and interstitial areas. There were no significant numbers of eosinophils observed (**Figure 2**). In the histological analysis, no findings suggestive of eccrine squamous syringometaplasia were found. The clinical and histological findings allowed us to establish the diagnosis of severe cutaneous drug toxicity with partial epidermal necrosis related to enfortumab vedotin, likely secondary to collateral damage from expression of nectin4 in the skin. Systemic corticosteroid therapy was initiated and local application of betamethasone/gentamicin cream was applied in the denuded areas. Consequently, an improvement of the symptoms and signs was observed in the next 48 hours without progression of the detached areas. All the lesions were resolved one week later.

Enfortumab vedotin is the first anti nectin4 antibody and monomethyl auristatin E conjugated drug, intended for the treatment of urothelial carcinoma [1]. Nectin4 is expressed in healthy skin and plays important roles in cell adhesion, which explains the association of this drug with the development of multiple cutaneous adverse events. In the literature, different forms of cutaneous reactions have been documented in 29-48% of patients receiving the treatment, typically occurring at a median of 15.9 days after initiation, with maculopapular rash being the most common form [2,3]. Other patterns include SDRIFE-like lesions, bullous forms, exfoliative dermatitis, or palmoplantar erythrodysesthesia [2-4]. Furthermore, significant associations with severe toxicoderma have been observed in 10% of cases, such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), [5]. Skin biopsies obtained from patients with reactions related to this drug typically show dyskeratosis primarily in the roof of subepidermal blisters and this finding can even be identified in biopsies obtained from healthy skin, like results seen in biopsies from patients with lesions related to other chemotherapies [6,7].

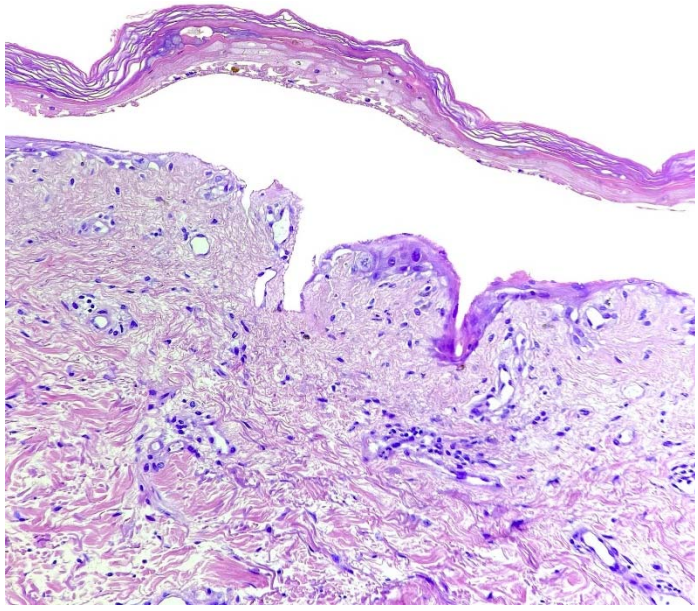

Figure 2. *Cutaneous biopsy performed on one of the forearm lesions, which showed subepidermal blistering with reepithelialization. H&E, 10×.*

Our patient developed a severe intertriginous form, similar to malignant intertrigo, although with some differential aspects. Our patient had not received any classic drug associated with toxic erythema of chemotherapy (classic antineoplastic drugs) that is associated with damage to the eccrine ducts, but he had received enfortumab vedotin, which acts as an inhibitor of microtubule conjugation. Other clinical and histological findings such as facial involvement, bullous lesions, erosions of the genital mucosa, the absence of eccrine squamous syringometaplasia, and chronic periadnexal inflammatory infiltrate are findings that occur more typically as side effects of enfortumab vedotin than those that occur in malignant intertrigo. [8].

The management of enfortumab vedotin reactions depends on the severity. Mild forms can be treated with topical corticosteroids without discontinuing the treatment. Severe cases (recurrent grade three exanthemas, grade 4, SJS/TEN) require immediate and definitive treatment discontinuation and initiation of systemic therapy, although there is no standardized treatment for these patients [9]. Our patient developed severe blistering and a life-threatening condition. Initially, it may be difficult to differentiate clinically and histologically from SJS/TEN. As in the case described by Christina et al. [5]. A clue that can help us distinguish this reaction from true SJS/TEN could be the lack of involvement of the oral mucosa. Despite this, the development of blistering in patients receiving treatment with enfortumab vedotin is advisable to discontinue treatment given the potential risk of mistaking the

enfortumab vedotin skin reaction (probably secondary to collateral damage of nectin4 expression in the skin) with SJS/TEN.

Toxic erythema of chemotherapy is a skin reaction that involves multiple drugs, typically classic antineoplastic drugs. Although the pathophysiology of the epithelial damage caused by enfortumab vedotin is different, this skin reaction that our patient presents could be compatible with malignant intertrigo, a severe manifestation of toxic erythema of chemotherapy. Collaboration between oncologists and dermatologists is essential in the characterization, detection, and management of adverse skin reactions associated with new cancer therapies.

Potential conflicts of interest

The authors declare no conflicts of interest.

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