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Letter to the Editor

Regarding "Management of Dermatologic Events Associated with the Nectin-4–directed Antibody-Drug Conjugate Enfortumab Vedotin"

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We read with interest the article published by Lacouture et al about dermatologic events induced by enfortumab vedotin (EV), a new anti-cancer therapy approved for advanced or metastatic urothelial cancer.[1,2] EV is an antibody-drug conjugate consisting of a nectin-4 (expressed at the surface of cancer cells)-directed IgG1 monoclonal antibody conjugated to monomethyl auristatin E (MMAE), a microtubule-disrupting agent. As reminded by Lacouture et al, nectin-4 is normally expressed at the surface of keratinocytes and epithelium of sweat glands and hair follicles.[1] This explains the frequency of dermatologic side effects of EV. Indeed, 43.9% of patients in the phase III trial had cutaneous side effects ("rash") of all grades (1-2: 29.4%; 3-4: 14.5%).[2]

Among severe cutaneous adverse effects, flexural exanthemas, bullous eruptions, including extensive exfoliative dermatitis and so-called Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), but without major mucosal involvement, were described.[3-5] In 2020, a post-marketing survey reported 8 cases of SJS/TEN in the US. Mean time to onset was 13 days after the first EV cycle. The authors calculated an overall significant risk of SJS/TEN with EV (200 cases/10^6).[6] However, no photographs were available in this study, and the diagnosis was based on a dermatologist assessment in only half of cases.

Other cases of severe blistering eruptions showed features that we consider as different from "classical" SJS/TEN.[7] Indeed, patients showed a predominance of the epidermal detachment in large folds, no diffuse purpuric macules, and no or very limited mucosal involvement. Of note, despite a limited skin detachment, the prognosis was poor, with some patients demonstrating multiorgan failure.[8] We recently reported six similar cases of this particular presentation, with fatal outcome in three patients.[9] All were men, of median age 67 years (range, 63-75 years), admitted between September and December 2021 in three French dermatology departments. The median time to onset was 12 days (range, 6-44

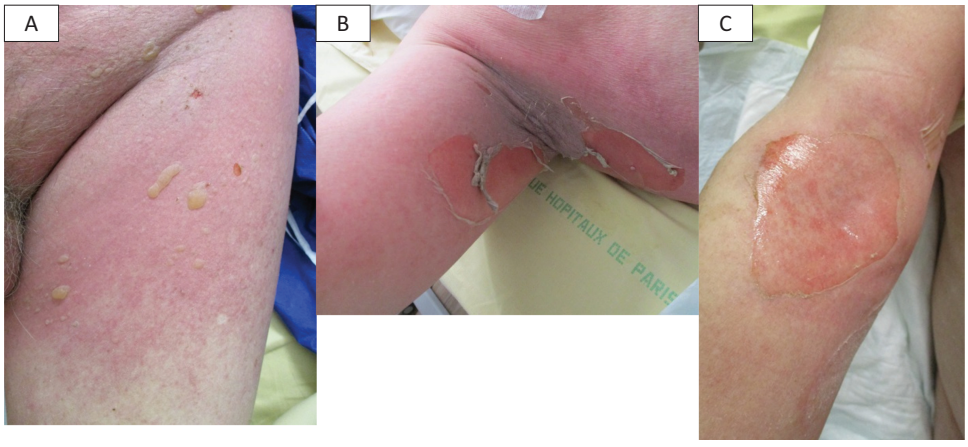

Figure 1. Clinical aspect in a 75-year-old man: erythematous plaques with blisters on the inguinal folds **(A)**, central epidermal sheet detachment on the axillary folds **(B)**, and the elbows **(C)**.

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days). Skin eruption was characterized in all cases by well-demarcated erythematous plaques with blisters and central skin detachment predominating in the large folds (Fig. 1). The maximal detachment was 20%. Three patients had limited mucosal lesions. Five patients had fever, 4 a cytopenia, 5 an acute kidney failure, and 2 a liver cytolysis. Five patients received topical steroids, and one patient received systemic steroids. Three patients died within 4 to 6 days due to multi-organ failure. The three other patients healed, and EV was definitely stopped. Skin biopsies demonstrated apoptotic keratinocytes and epidermal dysmaturation, with abnormal mitotic figures, involving the epidermis, eccrine ducts, and hair follicles.

We believe that EV may induce a very particular life-threatening cutaneous adverse effect characterized by blisters and detachment predominating in large folds, misdiagnosed as SJS/TEN in some cases. This clinicohistopathological presentation of "EV-related flexural necrolysis" corresponds rather to a direct skin toxicity of EV than to an immune-mediated mechanism as in classic SJS/TEN. Due to the risk of fatal outcome, physicians should recognize this adverse effect early and immediately stop EV. Future evaluation of both pharmacological and genetic parameters may be helpful to assess whether drug dosage adjustment could avoid definitive discontinuation of the drug.

Conflict of Interest

Constance Thibault: Astellas, BMS, Merck, Pfizer, MSD (C/A), Sanofi, AstraZeneca (RF), Ipsen, Janssen, Astellas, Sanofi, AstraZeneca (H), Janssen, BMS, Merck Pfizer, MSD, AstraZeneca (SAB). The other authors indicated no financial relationships.

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