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Annals of Oncology Case Reports

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Associated Toxicity in Immunosuppressed Patients with Enfortumab Vedotin - An Essential Differential Diagnosis - Case Report

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Received: July 07, 2024

Accepted: July 23, 2024

Published Online: July 30, 2024

Journal: Annals of Oncology Case Reports

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Antibody-drug conjugates; Urothelial carcinoma; Enfortumab vedotin; Sacituzumab govitecan.

Abstract

Enfortumab vedotin is an Antibody-Drug Conjugate (ADC) used to treat urothelial cancer. It has recently been associated with reports of Stevens Johnson syndrome/Toxic Epidermal Necrolysis (TEN). I report the clinical case of a 74-year-old man who developed an extensive skin lesion, clinically mimicking TEN.

Considering differential diagnoses is essential as it can have implications for the prognosis and treatment of the disease. Further investigation is needed to ascertain real cases of toxic epidermal necrolysis versus opportunistic infections and/or other toxicities due to chemotherapy.

Introduction

Enfortumab Vedotin (EV) is an antibody drug-conjugated directed at Nectin-4, an adhesion protein on the urothelial cancer cells surface. Nectin-4 is expressed in the skin, where it plays a role in cell-cell binding [1]. Thus, disruption of Nectin-4 by EV can lead to dermatological toxicities, recently associated with several reports of Toxic Epidermal Necrolysis (TEN).

Previous cases of EV-associated skin toxicity have demonstrated a wide spectrum of severity of presentation, with some requiring EV discontinuation. There are 2 reports of fatal TEN despite EV discontinuation; in both cases, late discontinuation probably allowed the rash to progress despite treatment [2].

The variation in the presentation and severity of these reactions makes it particularly difficult to determine whether EV treatment can be safely continued despite the development of the rash [3]. Characterizing these presentations and learning the right time to discontinue medication is crucial. This case highlights the importance of raising awareness of skin toxicities associated with EV therapy and the need to closely monitor patients to detect adverse skin reactions.

We report a clinical case of a patient who developed an extensive skin lesion under EV, clinically TEN suspicious.

In this clinical case, we will discuss the therapy instituted after PD under Enfortumab vedontin, including consideration of the role of Sacituzumab-govitecan in this same case.

Case presentation

A 74-year-old man with metastatic bladder cancer, in lymph node and liver, PD-L1 negative, received 1st line treatment with

Cite this article: Gonçalves J, Ângelo I, Gramaça J, Pina I. Associated toxicity in immunosuppressed patients with Enfortumab Vedotin - an essential differential diagnosis – Case Report. Ann Oncol Case Rep. 2024; 4(2): 1019.

Carboplatin-Gemcitabine (6 cycles), due to ineligibility for cisplatin. Four months later, Progression Disease (PD) with multiple bone disease was documented on bone scintigraphy. The patient received 2nd line treatment with Pembrolizumab for 14 months. On January of 2022, the patient was hospitalized due to Grade 3 colitis, treated with vedolizumab, and remained without systemic treatment until March 2022. On August 2022, PD was documented (liver and osteo-medullary) and started 3rd line treatment with EV 1.25mg/Kg D1, D8 and D15 every 28 days in September.

During the first week of treatment, he presented with a large, painful, erythematous plaque, with burning and itching, ulceration and rounded margins in the left sacral region (15x10cm), plus 5-6 smaller lesions (0.5x0.5cm), with loss of skin continuity with devitalised tissue, in continuity with the perineum and genital mucosa (Figure 1).

Given the clinical suspicion of TEN vs. herpes zoster infection, EV was suspended and empirical antibiotic and valacyclovir were prescribed.

Blood tests had herpes zoster antibodies positive and skin biopsy was inconclusive.

After 14 days, lesions reduced with necrotic plaques (Figure 2). One month later due to clinical improvement, EV was restarted with dose reduction - 1.0mg/Kg D1, D8 and D15 every 28 days (Figure 3-4).

The patient maintained clinical and imaging stability (in CT-TAP and bone scintigraphy) until November 2023, when he progressed in terms of liver (with an increase of more than 20% in lesions) and bone (left clavicle and dorsal column lesions (D7-D11).

The patient starts Sacituzumab Govitecan in December 2023.

In cycle 2, the dose was reduced by 25% for anorexia G2 and diarrhea G2. In cycle 5, the dose was reduced to 50% for Fatigue G3. A thromboembolism was documented, which led to hospitalisation and the patient losing performance status to maintain treatment. He died in May 2024.

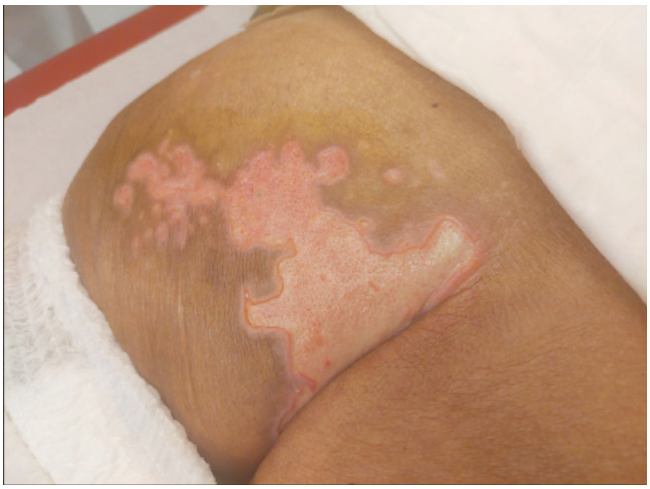

Figure 1: Day 10 of cycle1. Erythematous plaque with loss of continuity with the devitalised tissue, and in continuity with the perineum and genital mucosa.

Discussion

Nectin-4 is found in different epithelial cancers, as well as in epidermal keratinocytes located in the lower epidermis, eccrine and apocrine sweat glands, and hair follicles, potentially playing a role in skin toxicity induced by EV [4]. EV is a novel ADC approved in patients with advanced bladder cancer following platinum-based and immune checkpoint inhibitor therapy.

EV-related skin toxicities are common, occurring in 48% of patient during the pivotal trial but are also vary in severity, leading to discontinuation in some cases [5].

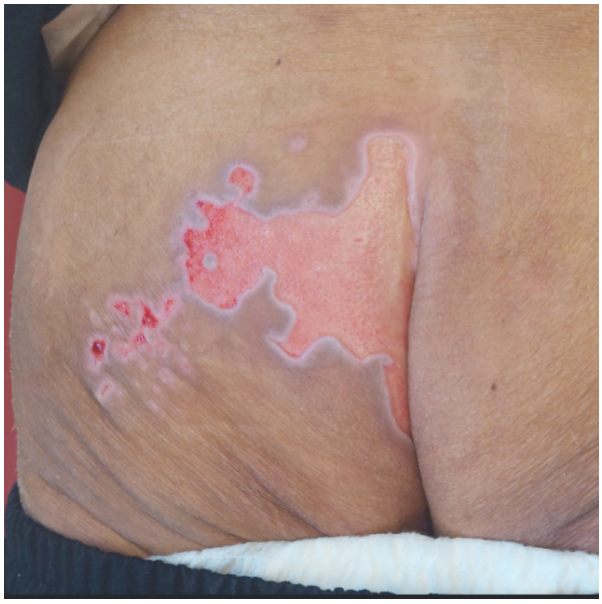

Figure 2: Day 24 of cycle 1.

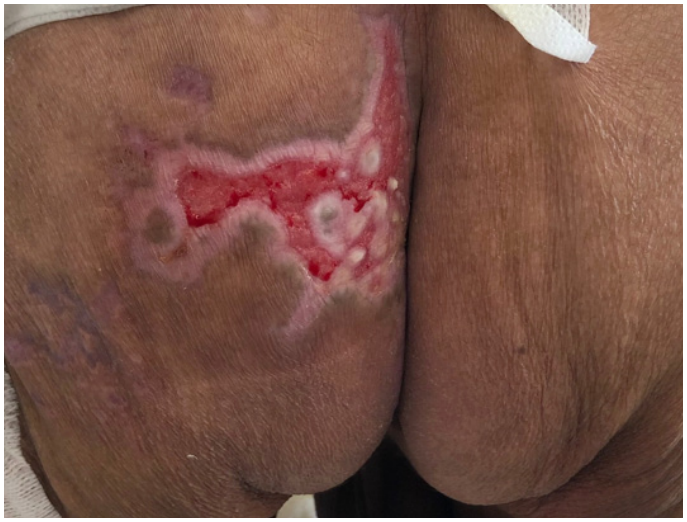

Figure 3: Day 44 of cycle 1. Reduced lesions with necrotic plaques.

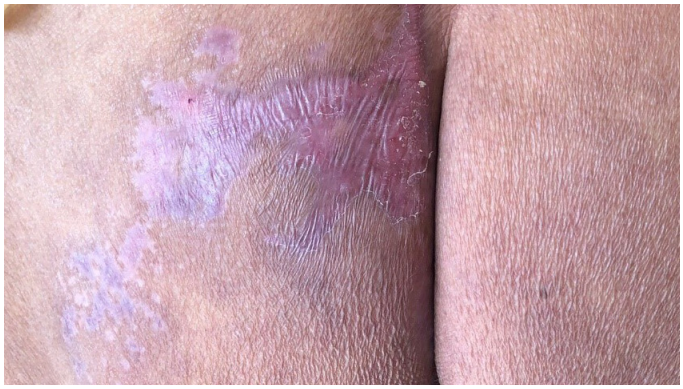

Figure 4: Day 65 of cycle 1. Re-epithelialised skin tissue.

Two reports show fatal TEN despite stopping EV, suggesting late discontinuation may allow rash progression [2]. Patient presentation was inconsistent with TEN but had potential severity, prompting EV discontinuation. Heterogenous presentation make it challenging to determine EV safety post-rash and understanding the optimal discontinuation timing is vital. This case emphasizes the need for awareness of EV-associated skin toxicities and close patient monitoring for adverse reactions.

Sacituzumab govitecan is also an ADC approved in 3rd and subsequent lines, targeting Trop-2, and is associated with a response rate of 27% [6].

However, with these new approaches to disease management, it remains essential to understand safety, efficacy, and operational considerations, including the adverse event profile of each antibody-drug conjugate, in order to optimize results for patients with bladder cancer.

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