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SEVERE CUTANEOUS TOXICITY IN A 67-YEAR-OLD PATIENT WITH METASTATIC UROTHELIAL CARCINOMA UNDERGOING THERAPY WITH ENFORTUMAB VEDOTIN AND PEMBROLIZUMAB

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ABSTRACT

Introduction: Enfortumab vedotin (EV) combined with pembrolizumab (EV+P) is a promising first-line therapy for metastatic urothelial carcinoma. While it has shown significant efficacy, severe cutaneous adverse events such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. We present this case as another example of severe skin off-target toxicity associated with this treatment, emphasising the importance of recognising this potential complication.

Case description: A 67-year-old male with metastatic urothelial carcinoma, chronic kidney failure and liver cirrhosis presented with fever, respiratory symptoms and a pruritic rash after two doses of EV+P. The rash rapidly worsened, leading to extensive skin desquamation affecting 20–30% of his body surface area. Skin biopsies confirmed SJS with early-stage TEN (SJS/TEN overlap). The patient was treated with high-dose intravenous steroids, empirical antibiotics for neutropenia and intensive topical care. Significant re-epithelialisation occurred by day 13, and the patient was discharged on day 15 with cessation of EV+P therapy.

Conclusion: This case demonstrates the potential for severe cutaneous toxicity in patients receiving EV+P, especially those with complex comorbidities. Early recognition and prompt, aggressive management with systemic corticosteroids are essential for improving outcomes. The case highlights the need for vigilance in monitoring for such adverse events and reporting them to improve patient safety.

KEYWORDS

Enfortumab vedotin, pembrolizumab, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), cutaneous toxicity

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LEARNING POINTS

- *High clinical suspicion:* recognition of early signs of dermolysis is essential in managing severe cutaneous toxicity associated with enfortumab vedotin.
- *A multidisciplinary approach:* the management of Stevens-Johnson syndrome/toxic epidermal necrolysis should involve a multidisciplinary team, especially in patients with complex comorbidities.
- *Pharmacovigilance:* continuous monitoring and prompt reporting of adverse events to health authorities are vital for improving patient safety and therapeutic outcomes.

INTRODUCTION

Enfortumab vedotin (EV) is a novel therapeutic option for untreated metastatic urothelial carcinoma. While it was initially introduced as a second-line therapy for this, recent approvals have expanded its use in combination with pembrolizumab (EV+P) as a first-line treatment for patients with locally advanced or metastatic urothelial carcinoma. This combination has been shown to be superior to platinum-based chemotherapy, demonstrating enhanced tumour suppression and sustained antitumor immunity[1]. However, post-approval cases of cutaneous adverse events, ranging from mild rashes to severe conditions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported[2]. Here, we present a case of severe cutaneous toxicity under EV+P therapy, leading to the development of an SJS/TEN overlap affecting 10–30% of body surface area, and its successful management with high-dose intravenous steroids.

CASE PRESENTATION

A 67-year-old male patient was admitted to the general internal medicine ward by his nephrologist due to a deterioration in his general condition over the previous three days. The patient reported fever peaking at 39.4°C, shivers and signs of an upper respiratory tract infection, including a dry cough. Concurrently, the patient developed a highly pruritic rash on his chest.

The patient's medical history was significant for metastatic urothelial carcinoma with pulmonary metastases. He had been undergoing palliative first-line treatment with EV+P. The treatment was administered at a reduced dose (EV: 87 mg for both the first and second doses) due to the patient's chronic kidney failure, requiring haemodialysis and liver cirrhosis (Child-Pugh class B). The first dose was administered for ten days and the second dose three days prior to hospitalisation. In addition to his oncological condition, the patient had a history of hypertensive heart failure with preserved ejection fraction, type 2 diabetes and a known type IV allergy to penicillin.

On examination, the patient was febrile with slightly elevated blood pressure but otherwise stable vital signs. Cardiopulmonary examination revealed mild, ubiquitous pulmonary crackles. Dermatological assessment showed extensive blanchable erythroderma and maculopapular exanthema over the torso, upper and lower extremities, with diffuse skin excoriation. The mucous membranes (oral, ocular and genital), face, scalp, hands and feet were initially free of pathologies *(Fig. 1 and Table 1)*. A CT scan of the thorax and abdomen was performed, revealing no infectious foci. The scan confirmed stable to lightly regressive pulmonary metastases from the urothelial carcinoma. Other relevant findings included known pre-existing ascites, hepatosplenomegaly, cirrhotic liver remodelling and a portal vein thrombosis with a transjugular intrahepatic portosystemic shunt.

Given the suspicion of an adverse event related to the oncological treatment, intravenous therapy with high-dose methylprednisolone (1 mg/kg, equivalent to 80 mg/day) was initiated. Due to the unclear condition with possible bacterial infection, empiric antibiotic therapy with ceftriaxone (2 g/day IV) was started. On the second day of hospitalisation, the patient's rash rapidly worsened, presenting with large areas of dermolysis (20-30% of body surface area), bullae formation and significant skin desquamation, particularly on the torso and upper extremities; he also developed painful oral mucosal erosions. He experienced intractable generalised pain and pruritus accompanied by prolonged states of agitation and anguish, necessitating therapy with opioids and benzodiazepines. Neutropenia (absolute neutrophil count 0.7 $\times 10^9$/l) was observed, prompting escalation to cefepime (1 g/day IV) and initiation of antifungal prophylaxis with intravenous fluconazole (150 mg three times weekly on dialysis days). Intensive topical therapy included dexpanthenol ointment and clobetasol propionate

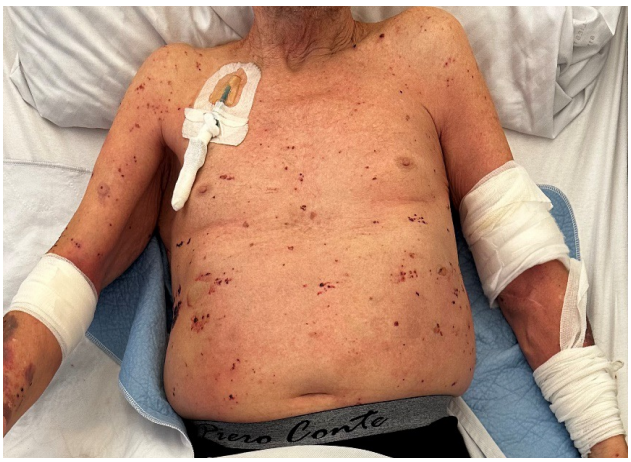

Figure 1. Day one of hospitalisation: erythroderma with maculopapular exanthema.

Parameter	Result	Normal range
C-reactive protein, CRP (mg/l)	↑ 45	< 5
Procalcitonin (µg/l)	↑ 1.59	< 0.5
Aspartate aminotransferase, AST (U/l)	↑ 93	10-40
Alkaline phosphatase (U/l)	↑ 153	40-130
Lactate dehydrogenase, LDH (U/l)	↑ 372	140-280
Gamma-Glutamyl transferase, GGT (U/l)	↑ 323	10-71 (men)
Leukocytes ($\times 10^9$/l)	↓ 2.2	4-11
Haemoglobin (g/l)	↓ 86	135-175 (men)
Platelets ($\times 10^9$/l)	↓ 148	150-400
Lymphocytes ($\times 10^9$/l)	19.5% (absolute: ↓ 0.4)	20-40% (absolute: 1-3)
Monocytes ($\times 10^9$/l)	↑ 14% (absolute: 0.3)	2-8% (absolute: 0.2-1)
Neutrophile absolute ($\times 10^9$/l)	↓ 1.4	1.5-7.7

Table 1. Blood results on the day of hospitalisation.

cream *(Fig. 2)*. Two skin biopsies revealed extensive epidermal necrosis with a well-structured stratum corneum, lymphocytic exocytosis, apoptotic keratinocytes and a mixed cellular infiltrate. The findings confirmed the diagnosis of SJS with potential early-stage TEN (SJS/TEN overlap) *(Fig. 3)*.

The patient received high-dose intravenous steroids for ten days, followed by a tapering course of oral prednisolone. Despite a further temporary decline in neutrophil counts (nadir: 0.5 $\times 10^9$/l), haematopoietic stimulation was not pursued as monocyte levels remained stable. By day 13, significant re-epithelialisation of the skin was observed and the patient's condition improved steadily. The antibiotic and antifungal therapies were stopped by day 14, and the patient was discharged on day 15 to continue follow-up care in the outpatient oncology clinic. Although EV+P therapy was discontinued, alternative immunotherapy options are currently under evaluation *(Fig. 4)*.

DISCUSSION

The patient received EV in combination with pembrolizumab as first-line treatment. Approximately 10 days after the first dose and following the second dose, the patient's condition declined with fever, upper respiratory symptoms and a widespread skin rash. This quickly progressed to extensive cutaneous lesions and absolute neutropenia. These developments were interpreted as the onset of SJS or an SJS-TEN overlap, affecting 20-30% of the total body surface area, which was later confirmed by histopathological findings.

The clinical presentation and histopathological findings of extensive epidermal necrosis and dermolysis are consistent with other cases of SJS and TEN reported in association with EV[2,3]. While the novel combination of EV+P has significantly

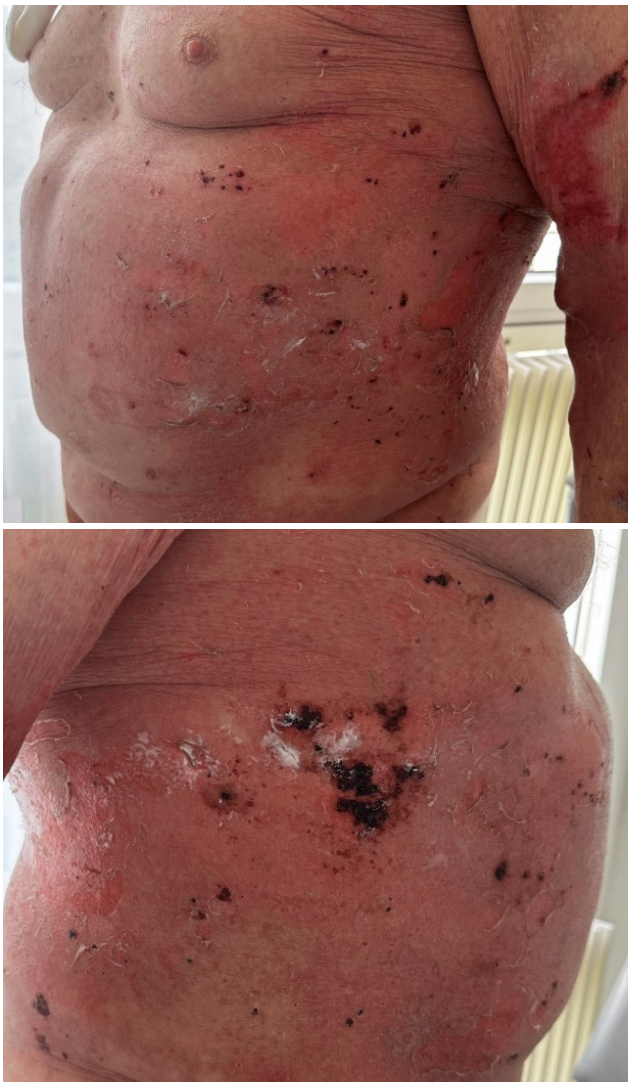

Figure 2. Day eight of hospitalisation: worsening exanthema with extensive dermolysis, microhaemorrhages, and bullae.

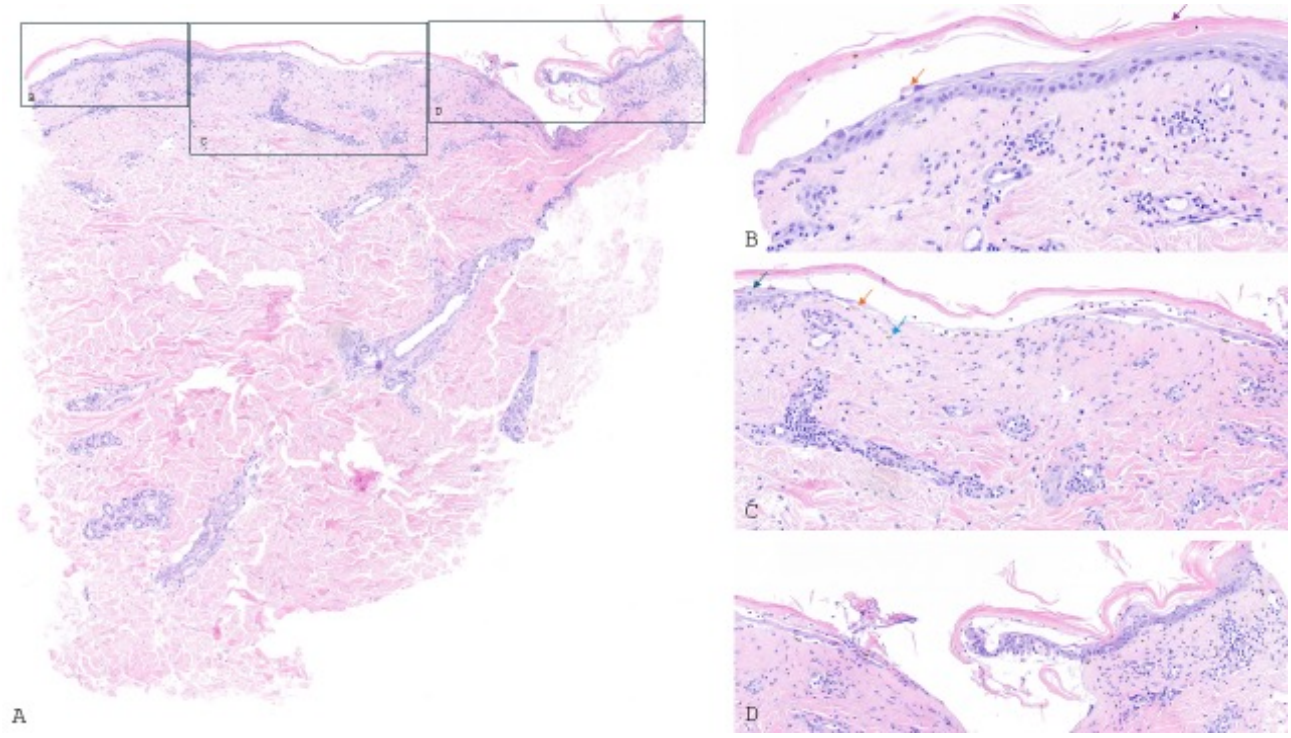

Figure 3. Histopathology: A) Overview of skin biopsy showing split formation and superficial/deep perivascular inflammatory infiltrate; B) Subcutaneous split formation with intraepidermal apoptotic keratinocytes (orange arrow); C) Complete epidermal necrosis with lymphocytic exocytosis (turquoise arrow) indicating satellite necrosis (orange arrow) with pigment incontinence (blue arrow); D) Subcorneal split formation with superficial perivascular lymphohistiocytic inflammation.

improved the prognosis for patients with metastatic urothelial carcinoma, severe dermal off-target toxicity remains a potential limitation of this treatment[2].

EV is an antibody-drug conjugate that specifically targets the transmembrane protein nectin-4, which is overexpressed in many tumours, including urothelial carcinoma. The specific binding of enfortumab to nectin-4 leads to the internalisation of the cytotoxic component monomethyl auristatin E into the target cell, followed by apoptosis. Nectin-4 is expressed not only in various solid tumour tissues but also, to a lesser extent, in normal human epidermis. This off-target expression in the skin likely contributes to the observed cutaneous toxicity[3,4].

Other antibody-drug conjugates containing monomethyl auristatin E have also shown skin toxicity as a potential side effect, suggesting the possibility of nectin-4-independent mechanisms of toxicity[3]. In the context of drug approval, the efficacy and safety of EV were evaluated in the Phase 2 EV-201 study, where a variety of side effects were observed, including mild fatigue (54%), rash (53%), alopecia (48%), peripheral neuropathy (44%), decreased appetite (30%), diarrhoea (28%) and nausea (24%). Grade 3 or higher

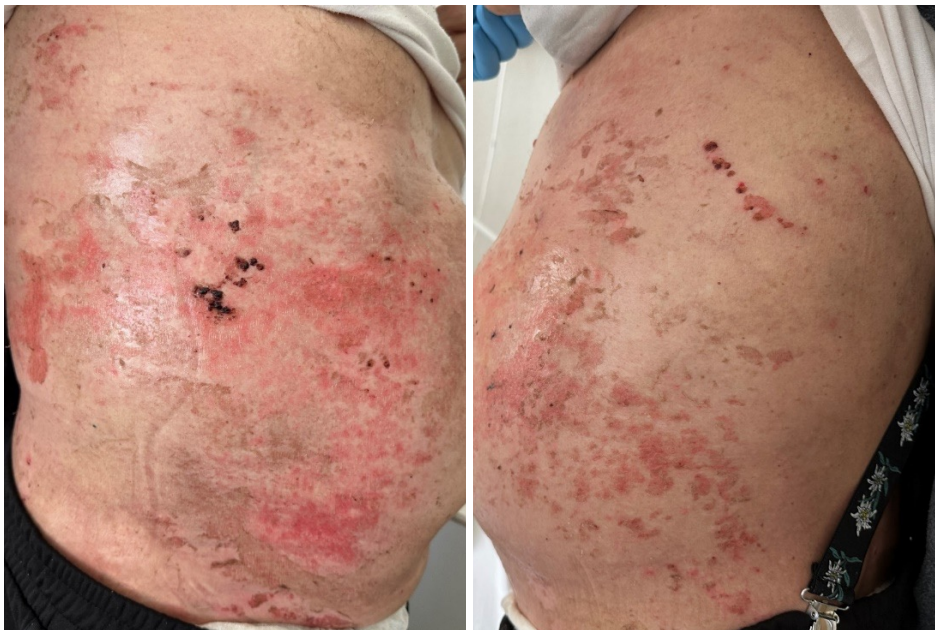

Figure 4. Day 13 of hospitalisation: extensive re-epithelialisation of the skin.

adverse events included neutropenia (9%), maculopapular rash (8%) and anaemia (6%). In two patients, skin toxicity led to the discontinuation of therapy, with one case progressing to Stevens-Johnson syndrome[5,6].

In this case, the rapid onset of severe skin toxicity within a few days of EV administration aligns with findings in the EV-201 study. This distinguishes it from immune-related adverse events associated with immune-checkpoint inhibitors, which typically have a time to occurrence of 3-12 weeks for psoriatic rash and 13-80 weeks for bullous pemphigoid[7,8].

A recent pharmacovigilance study by Yang et al.[9] analysed 212 cutaneous adverse events associated with EV reported to the US Food and Drug Administration's Adverse Event Reporting System. Of these cases, 13 were categorised as SJS and 9 as TEN[9]. SJS is considered to be primarily HLA-linked, involving cytotoxic CD8+ T-cell-mediated keratinocytic necroptosis. The standard treatment for SJS and TEN includes systemic corticosteroids, intravenous immunoglobulins (IVIg), cyclosporine and TNF-alpha antagonists[10,11]. However, in cases of EV-induced dermolysis, cessation of the causative agent is critical. While there is limited data on whether treatment with EV can be resumed following recovery from SJS/TEN, our patient responded well to high-dose glucocorticoids, and additional treatments such as intravenous immunoglobulin or other immunomodulatory therapies were not required.

The complicating neutropenia observed in our patient has been reported as a side effect of EV in approximately 9% of patients[6]. The clinical picture of systemic inflammation combined with neutropenia necessitated empirical antibacterial and antifungal therapy, as described in similar cases. Broad-spectrum antibiotics, although not standard in SJS and TEN management, may be justified in the presence of neutropenia and the heightened risk of systemic infection due to extensive skin barrier disruption. The risk factors for developing cutaneous toxicity with EV may include the patient's pre-existing comorbidities, such as chronic kidney failure and liver cirrhosis, as well as the concurrent use of pembrolizumab[3,6]. These factors likely contributed to the severity of the cutaneous reaction observed in this case.

REFERENCES

1. ClinicalTrials.gov Identifier: NCT04223856. Enfortumab vedotin and pembrolizumab vs. chemotherapy alone in untreated locally advanced or metastatic urothelial cancer (EV-302). Sponsored by Astellas Pharma Global Development, Inc. Last updated July 26, 2024. Available from: https://clinicaltrials.gov/ct2/show/NCT04223856
2. Nguyen MN, Reyes M, Jones SC. Postmarketing Cases of Enfortumab Vedotin-Associated Skin Reactions Reported as Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis. *JAMA Dermatol* 2021;**157**:1237-1239.
3. Viscuse PV, Marques-Piubelli ML, Heberton MM, Parra ER, Shah AY, Siefker-Radtke A, et al. Case Report: Enfortumab Vedotin for Metastatic Urothelial Carcinoma: A Case Series on the Clinical and Histopathologic Spectrum of Adverse Cutaneous Reactions From Fatal Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis to Dermal Hypersensitivity Reaction. *Front Oncol* 2021;**11**:621591.
4. Rosenberg J, Sridhar SS, Zhang J, Smith D, Ruether D, Flaig TW, et al. EV-101: A Phase I Study of Single-Agent Enfortumab Vedotin in Patients With Nectin-4-Positive Solid Tumors, Including Metastatic Urothelial Carcinoma. *J Clin Oncol* 2020;**38**:1041-1049.
5. Rosenberg JE, O'Donnell PH, Balar AV, McGregor BA, Heath EI, Yu EY, et al. Pivotal Trial of Enfortumab Vedotin in Urothelial Carcinoma After Platinum and Anti-Programmed Death 1/Programmed Death Ligand 1 Therapy. *J Clin Oncol* 2019;**37**:2592-2600.
6. Yu EY, Petrylak DP, O'Donnell PH, Lee JL, van der Heijden MS, Loriot Y, et al. Enfortumab vedotin after PD-1 or PD-L1 inhibitors in cisplatin-ineligible patients with advanced urothelial carcinoma (EV-201): a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2021;**22**:872-882.
7. Gallo Marin B, Oliva R, Kahn B, Borgovan T, Brooks BE, Massoud CM. Pembrolizumab-induced Toxic Epidermal Necrolysis in a Patient with Metastatic Esophageal Adenocarcinoma. *R I Med J* (2013) 2022;**105**:34-36.
8. Watanabe T, Yamaguchi Y. Cutaneous manifestations associated with immune checkpoint inhibitors. *Front Immunol* 2023;**14**:1071983.
9. Yang H, Yu X, An Z. Cutaneous Toxicity Associated With Enfortumab Vedotin: A Real-Word Study Leveraging U.S. Food and Drug Administration Adverse Event Reporting System. *Front Oncol* 2022;**11**:801199.
10. Paradisi A, Abeni D, Didona D, Ricci F, Canzona F, Didona B. A new case series on etanercept treatment for toxic epidermal necrolysis. *Eur J Dermatol* 2020;**30**:561-568.
11. Hasegawa A, Abe R. Recent advances in managing and understanding Stevens-Johnson syndrome and toxic epidermal necrolysis. *F1000Res* 2020;**9**:F1000.