CRCP Case Reports in Clinical Practice

Case Report

Journal Homepage: http://crcp.tums.ac.ir

Severe Cutaneous Toxicity Associated with Enfortumab Vedotin in Advanced Urothelial Carcinoma: A Case Report

Sina Salari[1], Alireza Rezvani[2], Maryam Salimi[1*], Ehsan Beyramzadeh[1], Farid Javandoust Gharehbagh[3]

1. Hematology and Oncology Department, Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2. Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.
3. Imam Reza Hospital, Iranian Social Security Organization (ISSO), Urmia University of Medical Sciences, Urmia, Iran.

Use your device to scan and read the article online

Citation Salari S, Rezvani A, Salimi M, Beyramzadeh E, Javandoust Gharehbagh F. Severe Cutaneous Toxicity Associated with Enfortumab Vedotin in Advanced Urothelial Carcinoma: A Case Report. Case Reports in Clinical Practice. 2026; 11(3): 111-115. DOI:10.18502/crcp.v11i3.22793

Running Title Cutaneous Toxicity with Enfortumab Vedotin in Urothelial Carcinoma

ABSTRACT

Enfortumab vedotin (EV), an antibody–drug conjugate targeting Nectin-4, has become an important therapeutic option for patients with advanced urothelial carcinoma. Although cutaneous adverse events are frequently observed with EV, severe cutaneous toxicity is rare and may be associated with mortality.

We describe a 77-year-old woman with metastatic urothelial carcinoma who developed a severe cutaneous adverse reaction after initiation of EV in combination with pembrolizumab for platinum-refractory disease. Within the first treatment cycle, following the initial doses of EV, she developed progressive dermatologic symptoms beginning with pruritus and erythema and rapidly evolving into widespread painful erosive and desquamative skin lesions with epidermal detachment and oral mucosal involvement. The cutaneous involvement affected approximately 70% of the total body surface area (TBSA), predominantly involving the trunk and extremities. No evidence of ocular involvement or genital mucosal lesions was identified. EV was discontinued, and the patient received systemic corticosteroids. Her clinical course was complicated by secondary infection and sepsis, and she died due to sepsis-related complications.

This case highlights the diagnostic and therapeutic challenges of severe EV-associated cutaneous toxicity, particularly given its clinical overlap with other severe cutaneous adverse reactions and the frequent limitations encountered in critically ill oncology patients. Early recognition of evolving skin toxicity and prompt interruption of treatment are essential to reduce the risk of severe complications.

Article info:
Received: April 22, 2025
Revised: May 16, 2025
Accepted: June 12, 2025

Keywords:
Urothelial carcinoma; Enfortumab vedotin; Drug-related side effects; Adverse reactions

*** Corresponding Author:**
Maryam Salimi
Address: *Hematology and Oncology Department, Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*
E-mail: *drmaryamsalimi152245@gmail.com*

Introduction

Urothelial carcinoma is one of the most common malignancies of the urinary tract and is associated with a substantial disease burden in its advanced stages. Despite initial responsiveness to platinum-based chemotherapy, outcomes for patients with metastatic disease have remained poor, owing to the limited durability of response and cumulative treatment-related toxicity [1].

In recent years, antibody–drug conjugates (ADCs) have emerged as a transformative therapeutic strategy for advanced bladder cancer, combining tumor-specific targeting with potent cytotoxic payloads [2]. Enfortumab vedotin [3], an ADC targeting Nectin-4, exploits the high expression of this adhesion molecule on urothelial carcinoma cells to deliver monomethyl auristatin E directly to malignant tissue, thereby enhancing antitumor activity [4]. Studies have demonstrated meaningful improvements in response rates and survival outcomes with EV, establishing it as a key component of modern treatment algorithms for advanced urothelial carcinoma [5, 6]. While the efficacy of EV is well established, its safety profile is characterized by a variety of adverse events, among which cutaneous toxicity is prominent. Dermatologic reactions range from mild maculopapular eruptions to severe, treatment-limiting cutaneous toxicity [3]. Although severe cutaneous adverse reactions are uncommon, they may be potentially fatal [7, 8].

The rarity and heterogeneous presentation of severe EV-associated skin toxicity lead to diagnostic and therapeutic challenges, particularly given its potential to mimic severe cutaneous adverse reactions such as Stevens–Johnson syndrome or toxic epidermal necrolysis [9]. As treatment paradigms increasingly incorporate EV, whether alone or in combination with pembrolizumab, increasing clinical awareness and detailed reporting of uncommon but serious dermatologic events are essential to facilitate early recognition and appropriate management [10]. In this study, we present a case of severe cutaneous toxicity associated with EV in a patient with advanced urothelial carcinoma, highlighting its clinical course, management, and implications for multidisciplinary care.

Case presentation

A 77-year-old woman with no significant past medical history and no history of smoking presented with lower urinary tract symptoms and was subsequently diagnosed with urothelial carcinoma of the bladder. Initial staging investigations revealed metastatic disease with pulmonary involvement. The patient was treated with first-line platinum-based chemotherapy consisting of gemcitabine and cisplatin for four cycles, resulting in a favorable radiologic response, including regression of pulmonary metastases. Given persistent urinary symptoms related to the primary bladder tumor, the patient underwent palliative transurethral resection of the bladder tumor. Following surgical intervention, systemic chemotherapy with gemcitabine and cisplatin was resumed. Despite treatment, subsequent evaluations demonstrated disease recurrence and progression, indicating platinum-refractory disease. Due to the disease progression after platinum-based chemotherapy, systemic therapy with EV was initiated in combination with pembrolizumab. EV at a dose of 1.25 mg/kg was administered during the treatment cycle, and pembrolizumab was administered concurrently at a fixed dose of 200 mg every 3 weeks.

Following the initial doses of EV on days 1 and 8, the patient gradually developed cutaneous symptoms beginning with pruritus and erythema. These symptoms then progressed to painful erosive and ulcerative skin lesions accompanied by epidermal detachment (Figure 1). The cutaneous involvement affected approximately 70% of the total body surface area (TBSA), predominantly involving the trunk and extremities. In addition to widespread cutaneous involvement, oral mucosal lesions were also observed. However, no evidence of ocular involvement or genital mucosal lesions was identified during clinical evaluation. Based on the severity and progression of these manifestations, EV was discontinued.

Given the severity of the cutaneous manifestations and the need to differentiate this condition from other severe cutaneous adverse reactions (SCARs), particularly Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), diagnostic evaluation was pursued. However, the patient developed severe thrombocytopenia, with platelet counts declining to below 40,000/µL. The thrombocytopenia was considered multifactorial, likely related to the cumulative myelosuppressive effects of prior platinum-based chemotherapy, advanced malignancy, and the systemic inflammatory response associated with severe cutaneous toxicity and subsequent infection. After appropriate supportive measures and careful assessment of bleeding risk, a skin biopsy was performed without immediate hemorrhagic complications. No evidence of disseminated intravascular coagulation (DIC) was identified. A biopsy specimen was obtained from an area of active

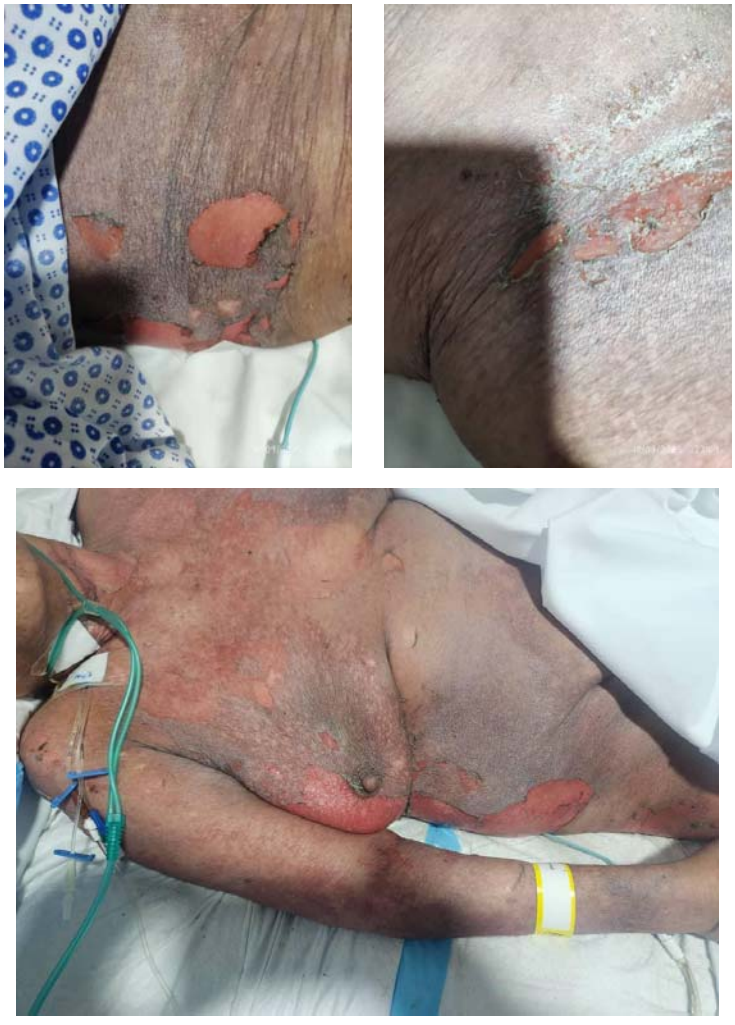

Fig. 1. Severe cutaneous toxicity following EV therapy

cutaneous involvement. Histopathologic examination revealed extensive epidermal keratinocyte necrosis, epidermal detachment from the underlying dermis, subepidermal blister formation, and a superficial lymphocytic inflammatory infiltrate. These histopathologic findings, together with the temporal relationship between symptom onset and EV administration, the rapid progression of skin lesions, mucosal involvement, and the erosive/desquamative clinical pattern, were consistent with severe enfortumab vedotin-associated cutaneous toxicity with SJS/TEN-like features. Additional clinical and laboratory evaluations did not reveal findings suggestive of alternative severe cutaneous reactions, including drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) or other severe hypersensitivity reactions. Therefore, the final diagnosis was established as severe enfortumab vedotin-associated cutaneous toxicity with SJS/TEN-like features.

The patient was treated with intravenous methylprednisolone at a dose of 1 mg/kg/day for 5 consecutive days. Following initial clinical stabilization, corticosteroid therapy was gradually transitioned to oral prednisolone with a tapering regimen over a 3-week period. Comprehensive supportive management was provided, including daily wound care, fluid and electrolyte management, pain control, nutritional support, and close monitoring for secondary infections.

Despite supportive care, her hospital course was complicated by secondary infection. Blood cultures obtained at the time of clinical deterioration were positive for *Pseudomonas aeruginosa*, consistent with secondary bacterial sepsis related to extensive disruption of the skin barrier. The infection was considered to originate from the compromised cutaneous lesions with subsequent bloodstream dissemination. Broad-spectrum intravenous

antibiotics were initiated and adjusted according to antimicrobial susceptibility results. She developed sepsis requiring transfer to the intensive care unit. After approximately ten days of hospitalization, the patient experienced progressive clinical deterioration and ultimately died due to sepsis-related complications, despite appropriate antimicrobial therapy and supportive care.

Discussion

This case showed a rare but severe cutaneous adverse reaction occurring in a patient with advanced urothelial carcinoma treated with EV in combination with pembrolizumab. Although EV has become an important therapeutic option for patients with platinum-refractory disease, the present case illustrates the potential for rapid progression of dermatologic toxicity to a life-threatening clinical course, despite prompt drug discontinuation and supportive management.

Cutaneous adverse events are among the most frequently reported toxicities associated with EV. They are thought to be related, at least in part, to the expression of Nectin-4 in normal epidermal tissues [4]. Previous studies have described a broad clinical spectrum of EV-related skin reactions, ranging from mild maculopapular eruptions to severe erosive and desquamative presentations that may necessitate treatment interruption [3]. Although the overall incidence of severe cutaneous adverse reactions is low, these events are associated with substantial morbidity and, in rare cases, mortality [7, 8].

The diagnosis and management of severe EV skin toxicity can be particularly challenging due to its heterogeneous presentation and clinical overlap with other severe cutaneous adverse reactions. Recent reports emphasize that EV-related eruptions may mimic these conditions without fulfilling classic histopathologic or clinical criteria, potentially complicating early recognition and risk stratification [9] . In the present case, histopathologic examination of a skin biopsy specimen confirmed extensive epidermal necrosis, subepidermal blister formation, and superficial lymphocytic infiltration, which were consistent with severe EV-associated cutaneous toxicity with SJS/TEN-like features. The final diagnosis was established as severe enfortumab vedotin-associated cutaneous toxicity with SJS/TEN-like features, based on the histopathologic findings, temporal association with therapy, and exclusion of alternative etiologies. The causal relationship between enfortumab vedotin and the severe cutaneous toxicity was further supported by the close temporal association between drug exposure and symptom onset, the characteristic clinical presentation, and the absence of alternative identifiable causes. The rapid progression of cutaneous manifestations following the initial doses of EV and the clinical course after treatment discontinuation supported a probable drug-related adverse reaction.

Severe cutaneous toxicity in patients receiving combination therapy with EV and pembrolizumab needs careful consideration. Immune-related dermatologic adverse events associated with pembrolizumab are well described. However, EV-associated skin reactions typically occur early in treatment and may exhibit a more erosive or desquamative phenotype [3, 9]. Although a synergistic effect between antibody–drug conjugates and immune checkpoint inhibitors cannot be excluded, current evidence suggests that severe cutaneous toxicity in this context is more frequently attributed to EV [10]. Nevertheless, the potential contribution of combination therapy requires further investigation.

The extensive cutaneous involvement (approximately 70% TBSA) in our patient, predominantly affecting the trunk and extremities, highlights the severity of this adverse reaction. The absence of ocular and genital involvement, while notable, does not exclude the diagnosis of severe EV-associated cutaneous toxicity, as the clinical presentation may vary. The development of severe thrombocytopenia in this patient warrants attention. While thrombocytopenia is not a classic feature of EV-associated toxicity, it may result from multifactorial causes, including cumulative myelosuppression from prior chemotherapy, bone marrow involvement by malignancy, and systemic inflammation secondary to severe cutaneous toxicity and infection. This complexity underscores the importance of comprehensive hematologic monitoring in patients receiving EV therapy.

Conclusion

This case emphasizes several important clinical implications. Early recognition of evolving skin toxicity and prompt discontinuation of EV are essential to reduce the risk of severe complications. Moreover, the subsequent development of secondary infection and sepsis in this patient highlights the vulnerability of oncology patients with skin disruption. As EV is increasingly incorporated into earlier lines of therapy, detailed reporting of severe and fatal cutaneous adverse events is crucial to enhance clinical awareness, inform management strategies, and guide future risk-reduction efforts.

Acknowledgments

None.

Ethical Considerations

Informed Consent

Written informed consent was obtained from the patient's next of kin for publication of this case report and accompanying images.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interests

The authors have no conflict of interest to declare.

References

[1] Hepp Z, Shah SN, Smoyer K, Vadagam P. Epidemiology and treatment patterns for locally advanced or metastatic urothelial carcinoma: a systematic literature review and gap analysis. J Manag Care Spec Pharm. 2021;27(2):240-55. https://doi.org/10.18553/jmcp.2020.20285

[2] Alameddine R, Mallea P, Shahab F, Zakharia Y. Antibody drug conjugates in bladder cancer: current milestones and future perspectives. Curr Treat Options Oncol. 2023;24(9):1167-82. https://doi.org/10.1007/s11864-023-01114-y

[3] Vlachou E, Matoso A, McConkey D, Jing Y, Johnson BA 3rd, Hahn NM, et al. Enfortumab vedotin-related cutaneous toxicity and radiographic response in patients with urothelial cancer: a single-center experience and review of the literature. Eur Urol Open Sci. 2023;49:100-3. https://doi.org/10.1016/j.euros.2023.01.002

[4] Zhang F, Li S. Antibody-drug conjugates as game changers in bladder cancer: current progress and future directions. Front Immunol. 2025;16:1591191. https://doi.org/10.3389/fimmu.2025.1591191

[5] Koshkin VS, Henderson N, James M, Natesan D, Freeman D, Nizam A, et al. Efficacy of enfortumab vedotin in advanced urothelial cancer: analysis from the Urothelial Cancer Network to Investigate Therapeutic Experiences (UNITE) study. Cancer. 2022;128(6):1194-205. https://doi.org/10.1002/cncr.34057

[6] Powles T, Valderrama BP, Gupta S, Bedke J, Kikuchi E, Hoffman-Censits J, et al. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. N Engl J Med. 2024;390(10):875-88. https://doi.org/10.1056/NEJMoa2312117

[7] Malik R, Xiang DH, Riew GJ, Sanchez-Melendez S, Afvari S, LeBoeuf NR, et al. Characterization of adverse cutaneous effects in the setting of enfortumab vedotin for metastatic urothelial carcinoma: a retrospective review. J Am Acad Dermatol. 2024;91(4):753-5. https://doi.org/10.1016/j.jaad.2024.06.037

[8] Reike MJ, Bahlburg H, Brehmer M, Berg S, Noldus J, Roghmann F, et al. Side effects of drug-antibody conjugates enfortumab-vedotin and sacituzumab-govitecan in targeted therapy in cancer. Cancer Epidemiol. 2024;90:102574. https://doi.org/10.1016/j.canep.2024.102574

[9] Ingen-Housz-Oro S, Elshot YS, Segura S, Marchand A, Pouessel D, Kluger N, et al. Skin toxicity of enfortumab vedotin: proposal of a specific management algorithm. J Eur Acad Dermatol Venereol. 2024;38(1). https://doi.org/10.1111/jdv.19454

[10] Brower B, McCoy A, Ahmad H, Eitman C, Bowman IA, Rembisz J, et al. Managing potential adverse events during treatment with enfortumab vedotin plus pembrolizumab in patients with advanced urothelial cancer. Front Oncol. 2024;14:1326715. https://doi.org/10.3389/fonc.2024.1326715