CASE REPORT

Concurrent erythema multiforme and psoriasiform eruption during enfortumab vedotin plus pembrolizumab therapy for advanced urothelial carcinoma

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ABSTRACT

Enfortumab vedotin (EV) plus pembrolizumab is an effective first-line treatment for advanced urothelial carcinoma, but clinically significant cutaneous adverse events may require treatment interruption or discontinuation. We report a 74-year-old man with metastatic upper-tract urothelial carcinoma who achieved a complete metabolic and radiologic response after three cycles of EV plus pembrolizumab. After six cycles and before cycle 7, he developed painful plantar lesions that progressed to Common Terminology Criteria for Adverse Events (CTCAE) grade 3 cutaneous toxicity involving the lower limbs, trunk, and oral cavity. Clinicopathological assessment supported erythema multiforme, while a morphologically distinct psoriasiform eruption was identified on the upper limbs. EV plus pembrolizumab was discontinued, and systemic and topical corticosteroid-based treatment produced marked improvement within approximately one month. In view of the grade 3 toxicity and ongoing complete response, treatment was not restarted. This case highlights the uncommon coexistence of two clinically distinct cutaneous patterns during combination therapy and underscores the value of early dermatologic assessment, clinicopathological correlation, and multidisciplinary management when an eruption evolves or displays atypical morphology.

KEYWORDS: urothelial carcinoma; enfortumab vedotin; pembrolizumab; erythema multiforme; psoriasiform eruption; antibody-drug conjugate

INTRODUCTION

The treatment landscape of locally advanced and metastatic urothelial carcinoma has changed substantially with the introduction of immune checkpoint inhibitors and antibody-drug conjugates. In the phase III EV-302/KEYNOTE-A39 trial, enfortumab vedotin, a Nectin-4-directed antibody-drug conjugate, combined with the programmed cell death protein 1 inhibitor pembrolizumab improved overall survival, progression-free survival, and objective response compared with platinum-based chemotherapy, establishing the combination as a first-line standard [1].

Cutaneous adverse events are a clinically important feature of EV-containing therapy. A systematic review and meta-analysis reported skin reactions in approximately half of EV-treated patients, with grade 3 events in approximately 10% [2]. EV-related toxicity is biologically plausible because Nectin-4 is expressed in epidermal keratinocytes and because the monomethyl auristatin E payload disrupts microtubules after intracellular release. Pembrolizumab can cause a broad spectrum of immune-mediated inflammatory dermatoses, including lichenoid, psoriasiform, and severe mucocutaneous reactions [3]. When the two drugs are administered together, clinical attribution may therefore be difficult.

Grade 3 erythema multiforme-like drug eruption during EV plus pembrolizumab has recently been described with detailed dermatopathological assessment [4]. Distinct sequential eruptions attributed to EV-associated interface dermatitis and pembrolizumab-associated psoriatic disease have also been reported in the same patient [5]. However, the concurrent presentation of erythema multiforme and a separate psoriasiform eruption during EV plus pembrolizumab appears to be uncommon. We describe this dual clinical phenotype after complete tumor response and discuss the decision not to rechallenge after resolution of the acute toxicity.

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CASE PRESENTATION

A 74-year-old man was referred for treatment of upper-tract urothelial carcinoma. His medical history included arterial hypertension treated with a beta-blocker and a diuretic, and he was receiving low-dose acetylsalicylic acid. He had stopped smoking 14 years earlier and reported no relevant family history of malignancy.

In July 2025, he underwent right laser cordectomy; the histological report was not available for review. He reported several years of intermittent hematuria and lower abdominal pain, which had worsened during the preceding two months. A right ureteral stent was subsequently placed. Cystoscopy and biopsy of the pelvic ureter in August 2025 showed grade 2 papillary urothelial carcinoma. Abdominal computed tomography demonstrated grade IV right hydronephrosis and an approximately 60-mm neoplastic stenosis of the distal ureter extending to the ureteral orifice, together with a suspicious 12-mm right external iliac lymph node. A 9-mm hepatic angioma was also reported.

In October 2025, the patient underwent right nephroureterectomy. Histopathological examination demonstrated high-grade (G3) invasive urothelial carcinoma extending into adipose tissue (pT3). Postoperative 18F-fluorodeoxyglucose positron emission tomography showed uptake in the right renal pelvis. Computed tomography in November 2025 demonstrated iliac lymphadenopathy measuring approximately 3.5 cm.

EV plus pembrolizumab was initiated in November 2025: enfortumab vedotin 1.25 mg/kg intravenously on days 1 and 8 plus pembrolizumab 200 mg intravenously on day 1 of each 21-day cycle.

Baseline laboratory results included hemoglobin 15.2 g/dL, platelet count 262 x 109/L, and white blood cell count 5,530/microL.

The first three cycles were completed without clinically relevant hematologic or nonhematologic toxicity. An 18F-FDG PET/CT scan in March 2026 showed complete metabolic and radiologic response, with disappearance of the previously documented abdominal lymphadenopathy. Treatment was continued for three additional cycles.

In mid-June 2026, after six cycles and before cycle 7, the patient developed CTCAE grade 2 cutaneous toxicity characterized by paresthesia and pain involving both plantar surfaces. A dermatologic evaluation initially raised the possibility of a lichenoid drug eruption. The eruption subsequently progressed to Common Terminology Criteria for Adverse Events (CTCAE) grade 3, as assessed according to CTCAE version 5.0 [6] extending to the lower limbs, trunk, and oral cavity (Figure 1), and the pain interfered with sleep.

Laboratory evaluation showed white blood cell count 11000/microL with lymphocytosis, elevated C-reactive protein 40 mg/L and fibrinogen levels 700 mg/dL.

EV plus pembrolizumab was discontinued. Repeat dermatologic assessment and biopsy of a representative lesion supported a diagnosis of diffuse erythema multiforme involving the lower limbs, trunk, and oral cavity. The histopathological findings were reviewed at the time of the patient's diagnostic assessment by an external dermatopathologist. The epidermis showed scattered apoptotic keratinocytes, vacuolar alteration of the basal layer, intercellular edema, and focal epithelial necrosis without confluent full-thickness epidermal necrosis. The superficial dermis showed edema and a moderate perivascular

Fig. 1. Cutaneous manifestations before systemic corticosteroid treatment. (A) Erosive and hemorrhagic crusted lesions involving the upper and lower lips during treatment with enfortumab vedotin plus pembrolizumab (B) Multiple erythematous, scaly, and crusted papules and plaques involving both lower limbs. (C) Extensive psoriasiform eruption involving the dorsal surfaces of both hands and the upper limbs, characterized by well-demarcated erythematous plaques with prominent scaling and multiple scattered papular lesions.

inflammatory infiltrate composed predominantly of lymphocytes with eosinophils. The clinicopathological pattern, absence of extensive epidermal detachment, and lack of confluent full-thickness necrosis favored erythema multiforme over Stevens-Johnson syndrome/toxic epidermal necrolysis. The evolving clinical morphology and biopsy findings were not considered typical of a purely lichenoid drug eruption.

A morphologically distinct psoriasiform eruption was observed on the upper limbs. This second diagnosis was made clinically on the basis of well-demarcated erythematous plaques with overlying scale and a distribution distinct from the targetoid/interface eruption. No biopsy was performed on these lesions.

The patient received oral dexamethasone 8 mg once daily for 2 weeks, followed by 4 mg once daily for a further 2 weeks, together with an oral vitamin B12 complex and pregabalin 50 mg three times daily. Topical corticosteroids and salicylic acid were also prescribed. After approximately one month, the cutaneous manifestations had markedly improved and the pain had resolved (Figure 2). In view of the grade 3 toxicity and persistent complete radiologic response, EV plus pembrolizumab was not restarted.

Table 1 shows timeline of the patient's clinical course, treatment, cutaneous adverse events, management, and outcomes according CARE guidelines [7].

DISCUSSION

This report describes grade 3 cutaneous toxicity with two morphologically distinct manifestations during EV plus pembrolizumab: biopsy-supported erythema multiforme involving the lower limbs, trunk, and oral cavity, and a separate psoriasiform eruption affecting the upper limbs. The coexistence of these patterns, together with the decision not to rechallenge after complete radiologic response, is the principal contribution of the case. It also illustrates the difficulty of assigning causality when an antibody-drug conjugate and an immune checkpoint inhibitor, each capable of causing cutaneous toxicity through different mechanisms, are administered concurrently.

In EV-302/KEYNOTE-A39, EV plus pembrolizumab produced substantial survival and response benefits compared with platinum-based chemotherapy [1]. Dermatologic toxicity was common, and grade 3 or higher maculopapular rash occurred in approximately 8% of patients. In the meta-analysis by Gazzoni et al., the pooled incidence of all-grade skin reactions with EV was 49%, while grade 3 reactions occurred in 10% [2]. These findings place the present event within a recognized toxicity spectrum, although the combined clinical phenotype remains unusual.

The mechanisms may overlap. EV binds Nectin-4, which is present in epidermal keratinocytes, and delivers the microtubule-disrupting payload monomethyl auristatin E. Histopathological abnormalities involving basal keratinocytes may therefore reflect on-target and payload-related injury. Pembrolizumab promotes T-cell activity and can trigger lichenoid, psoriasiform, and other immune-mediated eruptions [3]. Because both agents were administered simultaneously and neither was reintroduced separately, the contribution of each drug to the two patterns cannot be established with confidence.

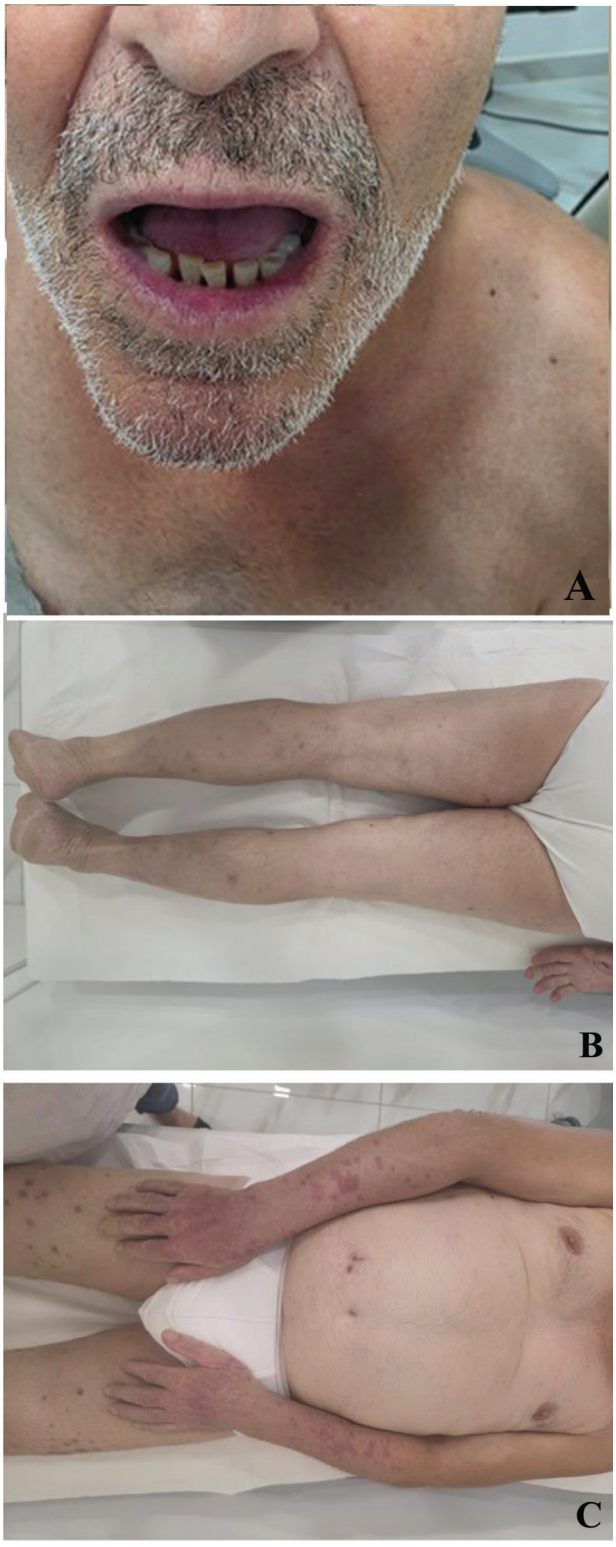

Fig. 2. Clinical response following systemic corticosteroid therapy: (A) near-complete resolution of the erythema multiforme–associated oral and labial lesions; (B) marked resolution of the erythematous, scaly, and crusted lesions of both lower limbs, with mild residual post-inflammatory hyperpigmentation; and (C) marked improvement of the psoriasiform eruption involving the hands and upper limbs, with residual erythema and post-inflammatory hyperpigmentation.

Table 1. Timeline of the patient's clinical course, treatment, cutaneous adverse events, management, and outcomes.

Time point	Clinical event
Baseline	Diagnosis of metastatic upper-tract urothelial carcinoma with lymph-node metastases.
Treatment initiation	Enfortumab vedotin plus pembrolizumab initiated as first-line systemic therapy.
After three cycles	Complete radiologic response of the metastatic lymph-node disease.
During treatment	Development of progressive erythema, extensive erosive and hemorrhagic crusted oral and lip lesions, diffuse psoriasiform eruption involving the upper limbs, and bilateral plantar pain.
Dermatologic assessment	Dermatologic assessment favored erythema multiforme with oral involvement; skin biopsy performed at an external pathology facility supported the diagnosis.
Toxicity management	Enfortumab vedotin plus pembrolizumab discontinued and systemic corticosteroid therapy initiated.
Follow-up	Marked clinical improvement, with near-complete resolution of the oral lesions and substantial regression of the cutaneous manifestations, leaving mild residual erythema and post-inflammatory hyperpigmentation.

The case reported by Murofushi et al. provides the closest comparison [4]. Their patient developed a grade 3 erythema multiforme-like eruption during cycle 3 of EV plus pembrolizumab, improved after systemic corticosteroids, and experienced recurrent rash after rechallenge. In contrast, our patient developed toxicity after six cycles, displayed both an erythema multiforme pattern and a distinct psoriasiform eruption, had already achieved complete metabolic and radiologic response, and was not rechallenged. Thus, our case does not claim the first occurrence of EV plus pembrolizumab-associated erythema multiforme; rather, it adds evidence that more than one cutaneous phenotype may coexist during the combination and may influence the risk-benefit assessment of treatment resumption.

The report by Mueller et al. is also relevant because it described two different eruptions in one patient: EV-associated interface dermatitis and pembrolizumab-associated psoriatic disease treated with ixekizumab [5]. That observation supports the biological plausibility of drug-specific or overlapping patterns during combination therapy. In our case, however, attribution remains presumptive because both agents were stopped together, no agent-specific rechallenge was undertaken, and the psoriasiform component was diagnosed clinically without histopathological confirmation.

The distinction among erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis, and a lichenoid drug eruption is clinically important. In this patient, oral involvement prompted careful reassessment; however, the absence of widespread epidermal detachment and confluent full-thickness epidermal necrosis, together with the reported interface changes and scattered apoptotic keratinocytes, supported erythema multiforme rather than SJS/TEN. The initial suspicion of a lichenoid eruption was revised when the distribution and morphology evolved and the biopsy findings became available. This course highlights the need for repeat dermatologic evaluation and biopsy when a treatment-associated eruption changes phenotype or fails to improve.

Hashimoto et al. reported an association between late-onset skin toxicity during EV plus pembrolizumab and longer progression-free and overall survival in a retrospective cohort [8]. Our patient likewise developed a delayed eruption after an excellent response. Nevertheless, this temporal concurrence cannot establish a biological or prognostic link in an individual patient, and the complete response should not be interpreted as a consequence of the cutaneous event. Similarly, an early complete response alone does not define an evidence-based treatment-de-escalation strategy. In this case, discontinuation was a safety-driven decision made in the context of grade 3 toxicity and an ongoing complete response.

A limitation of this report is the unavailability of the original histopathological images for erythema multiforme, as the biopsy was evaluated at an external private pathology facility that did not authorize their release. Nevertheless, the histopathological report, together with the clinical presentation, dermatologic assessment, temporal relationship with treatment, and response to corticosteroid therapy, supported the final diagnosis.

A causality cannot be assigned to EV or pembrolizumab individually; no drug-specific rechallenge was performed; and the psoriasiform component was diagnosed clinically without histological confirmation.

As EV plus pembrolizumab is used across an expanding range of urothelial carcinoma settings, clinicians may increasingly encounter complex or evolving skin reactions [9]. Early dermatologic assessment and multidisciplinary management are valuable, particularly when lesions are severe, atypical, mucosal, or morphologically heterogeneous.

CONCLUSION

EV plus pembrolizumab may be associated with more than one clinically distinct cutaneous toxicity in the same patient. The concurrent appearance of erythema multiforme and psoriasiform eruption in this case emphasizes the importance of careful morphologic assessment, clinicopathological correlation, and reassessment or repeat biopsy when an eruption evolves. Management and any decision to rechallenge should be individualized through multidisciplinary evaluation, considering toxicity severity, recovery, oncologic response, and the uncertainty regarding the causative agent.

Ethics and informed consent

Written informed consent was obtained from the patient for publication of the clinical information and accompanying anonymized images. A copy of the signed consent is available for review by the Editor-in-Chief on request.

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Conflict of interest

The authors declare no conflicts of interest.

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