

A rare presentation of enfortumab vedotin–induced toxic epidermal necrolysis



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Key words: enfortumab vedotin; general dermatology; medical dermatology; medical oncology; toxic epidermal necrolysis.

INTRODUCTION

Enfortumab vedotin is a novel treatment for metastatic urothelial carcinoma. In 2019, the United States Food and Drug Administration approved the drug as a third-line treatment for patients who had failed in previous trials of programmed cell death protein 1 and platinum-based chemotherapeutic agents.¹ The drug has demonstrated to have a significant response rate in early phase trials and is known for its tolerable side-effect profile.² The adverse effects of enfortumab vedotin include fatigue, peripheral neuropathy, alopecia, and rash.³ The most frequently reported rashes were characterized as diffuse “maculopapular.” All side effects were managed on an outpatient basis.

Toxic epidermal necrolysis (TEN) is a life-threatening mucocutaneous reaction that involves more than 30% of the skin. TEN is not a recognized side effect of enfortumab vedotin. However, we present a rare case of enfortumab vedotin–induced TEN in a 72-year-old man with metastatic urothelial carcinoma.

CASE PRESENTATION

A 72-year-old man with a past medical history of hypertension, atrial fibrillation, alcoholic liver cirrhosis (model for end-stage liver disease score of 28), and metastatic urothelial carcinoma presented to the hospital for the evaluation of a rash that developed shortly after his day 8 infusion. The patient was scheduled to receive enfortumab vedotin on days 1, 8, and 15 of a 28-day cycle at the M.D. Anderson Cancer Center. He tolerated day 1 of his medication well; however, after his day 8 infusion, an erythematous rash with associated skin sloughing

Abbreviations used:

MMAE:	monomethyl auristatin E
SCORTEN:	score of toxic epidermal necrolysis
SJS:	Stevens-Johnson syndrome
TEN:	toxic epidermal necrolysis

developed on <20% of his body (Fig 1). He was admitted to the M.D. Anderson Cancer Center for initial management, but as the rash progressed, he was transferred to the University of Texas Medical Branch’s burn intensive care unit on day 12. He was hemodynamically stable on admission. Physical examination demonstrated tense bullae on a background of erythema on his bilateral axillae, back, genitalia, posterior aspect of the bilateral thighs (Fig 2), and bilateral heels and a single blister on the posterior aspect of his oral cavity, raising concern for Stevens-Johnson syndrome (SJS)/TEN. At the initial presentation to our hospital, his score of toxic epidermal necrolysis (SCORTEN) was 7, and ABCD-10 score was 5.

His medication list was reviewed for the identification of a potential cause of SJS/TEN, and he was noted to take acetaminophen, acyclovir, metoprolol, and gabapentin consistently, with no recent dose changes. He had not recently taken antiepileptics or antibiotics. Based on his recent initiation of enfortumab vedotin and his rapid-onset development of the rash, the drug was deemed to be the cause and was discontinued, and he was started on a topical steroid. A biopsy was performed, and the pathology revealed interface dermatitis with central areas of full-thickness epidermal necrosis, consistent with an SJS/TEN overlap (Fig 3).

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Funding sources: None.

Conflicts of interest: None disclosed.

IRB approval status: Not applicable.

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JAAD Case Reports 2021;7:57-9.
2352-5126

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<https://doi.org/10.1016/j.jidcr.2020.10.020>



Fig 1. Toxic epidermal necrolysis. The patient had demonstrable skin sloughing and erythema on his back.



Fig 2. Toxic epidermal necrolysis. The patient had evident skin sloughing and erythema on the posterior aspect of his bilateral thighs and buttocks.

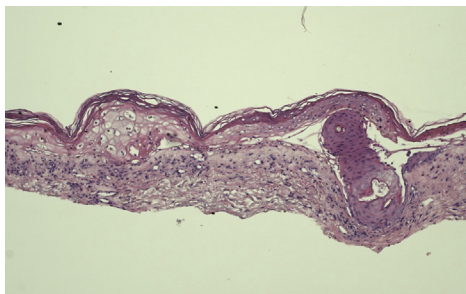


Fig 3. Biopsy of the right forearm. The patient's biopsy demonstrated an evidence of interface dermatitis with central areas of full-thickness epidermal necrosis/apoptosis, consistent with SJS/TEN spectrum. *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

Overnight, oliguria developed in the patient. Urine microscopy was performed, which revealed muddy brown casts, consistent with acute kidney injury secondary to acute tubular necrosis; the patient was thus started on a continuous renal replacement therapy. His rash progressed to involve >30% of his skin, and he was diagnosed with TEN;

thus, systemic steroids were contraindicated. As his condition deteriorated, we discussed different treatment options with his primary team. We considered intravenous immunoglobulin, noting that his continuous renal replacement therapy could offset potential fluid overload that can be caused by intravenous immunoglobulin. Cyclosporine was also discussed; continuous renal replacement therapy could offset further deterioration, however, his kidneys would suffer due to the cyclosporine. Etanercept was also contemplated as some studies have noted that a 50-mg subcutaneous injection could be beneficial for TEN, though there was an increased risk of infection. Based on his SCORTEN on admission, the primary team believed that the addition of a systemic medication would not affect his overall prognosis. The patient was continued on supportive therapy and empiric vancomycin/meropenem. On day 3 of hospitalization, his SCORTEN remained at 7/7. His hypotension did not resolve as a result he was started on norepinephrine and, eventually, vasopressin. The patient's condition continued to deteriorate as seen in laboratory evidence of hyperbilirubinemia and an increased international normalized ratio developed in the patient, which altered his model for end-stage liver disease score to 40. The patient experienced multiorgan failure and septic shock, and end-of-life measures were discussed with his family. The patient died 20 days after admission on February 27, 2020.

DISCUSSION

Enfortumab vedotin is an antibody–drug conjugate that has demonstrated success in treating metastatic urothelial carcinoma. Enfortumab vedotin comprises antinectin-4 antibody and a microtubule-disrupting agent monomethyl auristatin E (MMAE). The drug binds to nectin-4, expressed on tumor cells, with high affinity, which induces the internalization of MMAE and leads to subsequent cell apoptosis through impaired cell division.⁴

One of the most well-recognized adverse effects of enfortumab vedotin is rash. A “maculopapular” rash was noted in 48% of patients in a clinical trial conducted by Rosenberg et al.³ The rashes were managed with topical corticosteroids, and the majority of the patients experienced complete resolution at their follow-up appointment. SJS developed in 1 out of 125 patients within 4 days of the medication initiation.³ The drug was discontinued, and the patients experienced remission on systemic corticosteroids.

TEN is an immune-mediated mucocutaneous condition characterized by epidermal erythema,

detachment, and necrosis involving more than 30% of the skin. TEN is often caused by medications, with allopurinol, oxicam nonsteroidal anti-inflammatory drugs, antibiotics, and antiepileptic drugs being the most frequently implicated.⁵ Our patient presented with biopsy-proven TEN with <50% skin involvement. One potential link between enfortumab vedotin and TEN is nectin-4. Nectin-4 is present in the skin. It has a role in cell–cell adhesion, and a functional disturbance could lead to impaired cell–cell attachment, which could explain the epidermal detachment observed in TEN.⁶ In addition, similar antibody–conjugate drugs that incorporate MMAE have also caused rashes.⁷ Therefore, MMAE might have a role in the development of our patient's condition.

In conclusion, enfortumab vedotin–induced TEN is rare. As a drug that is touted for its tolerable side effects, more research on enfortumab vedotin's dermatologic safety profile is warranted. Physicians who prescribe enfortumab vedotin for metastatic urothelial carcinoma should be aware of the variety

of the benign and life-threatening cutaneous manifestations of this medication.

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