

UC Davis

Dermatology Online Journal

Title

Enfortumab vedotin-induced bullous dermatitis

Permalink

<https://escholarship.org/uc/item/0d16q2nd>

Journal

Dermatology Online Journal, 31(3)

Authors

Wang, Robin

Fernandez, Kristen

Zelman, Brandon

et al.

Publication Date

2025

DOI

10.5070/D331365370

Copyright Information

Copyright 2025 by the author(s). This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, available at <https://creativecommons.org/licenses/by-nc-nd/4.0/>

Peer reviewed

Case Presentation

Enfortumab vedotin-induced bullous dermatitis

Robin Wang, MD^{1a}, Kristen Fernandez, BA², Brandon Zelman, DO³, Jodi Speiser, MD³, Madhu Dahiya, MD⁴, David Eilers, MD⁵

¹ Department of Dermatology, Loyola University Medical Center, Maywood, Illinois, United States, ² Stritch School of Medicine, Loyola University, Maywood, Illinois, United States, ³ Department of Pathology and Laboratory Medicine, Loyola University Medical Center, Maywood, Illinois, United States, ⁴ Pathology & Laboratory Medical Service, Edward Hines, Jr Veterans Affairs Hospital, Hines, Illinois, United States, ⁵ Section of Dermatology, Edward Hines, Jr Veterans Affairs Hospital, Hines, Illinois, United States

Keywords: bullous dermatitis, cutaneous toxicity, enfortumab vedotin, nectin-4

Dermatology Online Journal

Vol. 31, Issue 3, 2025

Abstract

Enfortumab vedotin is a first-in-class antibody-drug conjugate used in the treatment of locally advanced or metastatic urothelial carcinoma. A range of cutaneous adverse events has been reported with enfortumab vedotin use. Nectin-4, a transmembrane protein overexpressed by urothelial carcinoma cells, is the intended target of enfortumab vedotin. However, as nectin-4 is also expressed by epidermal keratinocytes, sweat glands, and hair follicles, it is believed that cutaneous toxicity is mediated through off-target delivery of enfortumab vedotin. We present a patient with metastatic urothelial carcinoma who developed a grade 3 bullous dermatitis after his second treatment cycle of enfortumab vedotin and pembrolizumab therapy. Histopathologic findings showed intraepidermal blisters with prominent dyskeratotic and necrotic keratinocytes. Temporary withholding of enfortumab vedotin and pembrolizumab and treatment with potent topical corticosteroids led to significant improvement and enfortumab vedotin (with pembrolizumab) was resumed at a reduced dosage of enfortumab vedotin without recurrence. We present this case to highlight clinical manifestations, histopathologic findings, and management of enfortumab vedotin-induced cutaneous toxicity.

plantar erythrodysesthesia, widespread vesicular eruption,² and rarely, Stevens-Johnson syndrome/toxic epidermal necrolysis.^{3,4} Nectin-4, a transmembrane protein overexpressed by urothelial carcinoma cells, is the intended target of enfortumab vedotin. However, as nectin-4 is also expressed by epidermal keratinocytes, sweat glands, and hair follicles, it is believed that cutaneous toxicity is mediated through off-target delivery of enfortumab vedotin.^{4,5} We present a patient with metastatic urothelial cancer who developed a grade 3 bullous dermatitis while undergoing enfortumab vedotin and pembrolizumab therapy to highlight the clinical manifestations and management of enfortumab vedotin-induced cutaneous toxicity.

Case Synopsis

A 76-year-old man with a history of metastatic urothelial carcinoma presented to the emergency department with a seven-day history of a progressively painful, erythematous eruption. The patient had received his second treatment cycle of enfortumab vedotin and pembrolizumab therapy one week prior to presentation. On examination, there were ill-defined erythematous patches over his chest, abdomen, and extensor extremities with tense bullae over his dorsal feet (**Figure 1A-C**). No mucous membranes were involved.

Histopathologic evaluation of a punch biopsy from the edge of a bullae on the left dorsal foot showed interface dermatitis with prominent dyskeratotic and necrotic keratinocytes and relatively paucicellular intraepidermal blisters (**Figure 2A-B**). Direct immunofluorescence showed possible keratinocyte surface deposition of IgG in a background of nonspecific deposition (**Figure 2C**). Serologic testing for bullous pemphigoid and desmoglein antibodies was negative. Based on clinical and histopathologic findings with severe symptoms limiting activities of daily living, the patient was diagnosed with a grade 3 enfortumab vedotin-induced bullous dermatitis.

Introduction

Enfortumab vedotin is a first-in-class antibody-drug conjugate approved in 2019 for the treatment of locally advanced or metastatic urothelial carcinoma.¹ Notably, a range of cutaneous adverse events has been reported with enfortumab vedotin use, including maculopapular rash, bullous dermatitis, exfoliative dermatitis, palmar-



Figure 1. A-C) Clinical images of bullous dermatitis presenting one week after treatment cycle two of enfortumab vedotin and pembrolizumab therapy.

The patient was treated with fluocinonide 0.05% ointment with rapid improvement within one week and subsequent desquamation of the involved areas. Enfortumab vedotin and pembrolizumab therapy were held for one treatment cycle and both were resumed with enfortumab vedotin at a 20% dose reduction after improvement of his bullous dermatitis to grade 1. The patient continues to tolerate therapy with his bullous dermatitis remaining at grade 1 or lower.

Case Discussion

Enfortumab vedotin is an antibody-drug conjugate composed of an anti-nectin-4 antibody linked to cytotoxic agent monomethyl auristatin E used in the treatment of locally advanced or metastatic urothelial carcinoma.¹ Cutaneous adverse events are reported to occur in 58% of patients, with grade 3 or 4 cutaneous adverse events occurring in 14% of patients.⁶ The most frequent manifestations include maculopapular rash and pruritus, and less commonly, bullous dermatitis, exfoliative dermatitis,

stomatitis, palmar-plantar erythrodysesthesia, and symmetrical drug-related intertriginous and flexural exanthema.⁶ Rarely, cases of Stevens-Johnson syndrome/toxic epidermal necrolysis have been reported.⁴

Nectin-4, a transmembrane protein overexpressed by urothelial carcinoma cells, is the intended target of enfortumab vedotin. However, nectin-4 is also expressed by epidermal keratinocytes where it plays an essential role in supporting cell-cell adhesion at adherens junctions.^{4,5} Mechanistically, it is postulated that enfortumab vedotin induces cutaneous toxicity through off-target delivery of monomethyl auristatin E, which may manifest with a range of clinical presentations as described and findings of interface dermatitis, dyskeratosis, and necrotic keratinocytes on histopathology.^{4,5}

Our patient presented with a painful bullous dermatitis one week after administration of enfortumab vedotin and pembrolizumab therapy, with histopathologic findings showing intraepidermal blistering with prominent dyskeratotic and necrotic keratinocytes, suggestive of the proposed mechanism of off-target delivery of enfor-

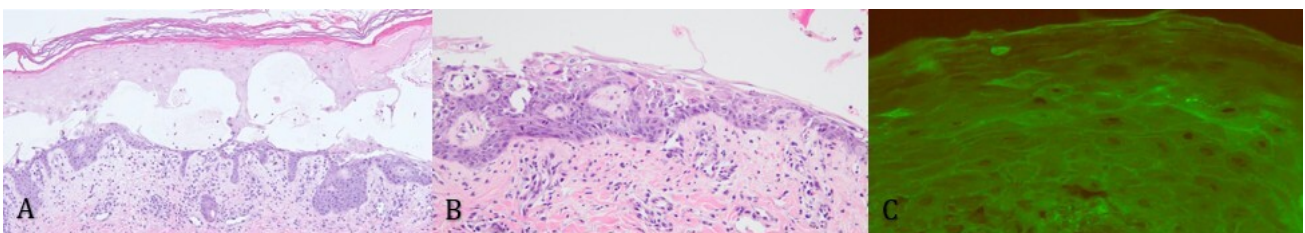


Figure 2. Hematoxylin and eosin stain of specimen from left dorsal foot showing interface dermatitis with prominent dyskeratotic and necrotic keratinocytes and intraepidermal blisters. **A)** 100X. **B)** 200X. **C)** Direct immunofluorescence of specimen from left dorsal foot, 400X, with possible keratinocyte surface deposition of IgG in a background of nonspecific deposition.

tumab vedotin to nectin-4 expressing keratinocytes. DIF revealed possible keratinocyte surface deposition of IgG in a background of nonspecific deposition which may represent enfortumab vedotin localization.⁷ Owing to severe symptoms limiting activities of daily living, enfortumab vedotin therapy was held for one treatment cycle until improvement to a grade 1 reaction. Treatment with a potent topical corticosteroid resulted in significant improvement, although a course of oral corticosteroid therapy would also be a reasonable option.

Cutaneous adverse events due to enfortumab vedotin are most likely to occur within the first few treatment cycles.^{3,4} Grade 1 and grade 2 reactions are most common and supportive care along with topical corticosteroid therapy is recommended.⁴ For grade 3 reactions, oral corticosteroid therapy and withholding of enfortumab vedotin until improvement to a grade 1 reaction, with subsequent resumption at a reduced dose should be considered.⁴ In most reported cases, enfortumab vedotin was able to be continued with the grade of reaction remaining unchanged or improved with therapy, likely because enfortumab vedotin mediates cutaneous toxicity through direct cytotoxicity instead of inducing an enduring state of immune activation.^{3,4} In cases of suspected Stevens-Johnson syndrome/toxic epidermal necrolysis, enfortumab vedotin should immediately be withheld and confirmatory investigations undertaken. Finally, prophylactic use of barrier creams and photoprotection may reduce the need for rescue therapies and improve quality of life.⁴

The authors considered the possibility that pembrolizumab induced our patient's bullous dermatitis, as both enfortumab vedotin and pembrolizumab may lead to cutaneous adverse events such as bullous dermatitis. However, we favor enfortumab vedotin-induced bullous dermatitis for the following reasons. Pembrolizumab is associated with bullous pemphigoid-like eruptions with pathogenic autoantibody production and a delayed onset of months after therapy initiation, features suggestive of nonspecific activation of the immune system as induced by immunotherapy.^{8,9} Histopathology demonstrates subepidermal blistering with an eosinophilic infiltrate and direct immunofluorescence demonstrates autoantibody deposition along the basement membrane zone.^{7,8} Our patient presented four weeks after therapy initiation, with a predominantly acral distribution of severe involvement and histopathologic findings of promi-

nent dyskeratosis and interface dermatitis, features suggestive of a toxic drug effect. Another case with similar histology and widespread vesicular eruption completely cleared with cessation of enfortumab vedotin in spite of continued multiple courses of pembrolizumab.² Moreover, bullous pemphigoid serologies were negative and direct immunofluorescence was negative for basement membrane antibody deposition. Finally, owing to the enduring state of immune activation induced by immunotherapy, bullous dermatitis caused by pembrolizumab typically requires a prolonged course of oral corticosteroid therapy (or other systemic therapy), discontinuation of immunotherapy; it may persist for several months or longer after discontinuation of immunotherapy.^{8,9} Thus, it would be unusual for pembrolizumab-induced bullous dermatitis to show the rapid and sustained response to topical corticosteroid treatment our patient experienced, especially after resumption of enfortumab vedotin and pembrolizumab therapy. In March 2024, results of a phase III trial demonstrated that the combination of enfortumab vedotin and pembrolizumab therapy led to a clinically relevant benefit over platinum-based chemotherapy, setting a new standard for treatment of advanced urothelial carcinoma.¹⁰

Conclusion

Thus, it is likely that dermatologists, oncologists, and pathologists will encounter increasing cases of enfortumab vedotin-induced cutaneous adverse events. Furthermore, risk of cutaneous adverse events is increased with concurrent immune checkpoint inhibitor therapy which are well-described to induce toxicity through nonspecific activation of the immune system. We present this case of enfortumab vedotin-induced bullous dermatitis to highlight the pathophysiologic mechanisms and management of enfortumab vedotin-induced cutaneous toxicity. Further research is encouraged to determine optimal management based on individual patient factors and further elucidate pathophysiology.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. *N Engl J Med*. 2021;384:1125-1135. doi:[10.1056/NEJMoa2035807](https://doi.org/10.1056/NEJMoa2035807). PMID:33577729
2. Nihal A, Bacon P, Pei S. Enfortumab vedotin-induced widespread vesicobullous eruption mimicking disseminated herpetic infection in a patient with metastatic urothelial carcinoma. *Dermatol Online J*. 2024;30(6). doi:[10.5070/D330664684](https://doi.org/10.5070/D330664684)
3. Shahin A, Janeczek M, Butterfield R, et al. Characterization of cutaneous adverse events to enfortumab vedotin: a retrospective case-control study. *JAAD Int*. 2023;10:46-47. doi:[10.1016/j.jdin.2022.10.004](https://doi.org/10.1016/j.jdin.2022.10.004). PMID:36457993
4. Lacouture ME, Patel AB, Rosenberg JE, O'Donnell PH. Management of dermatologic events associated with the nectin-4-directed antibody-drug conjugate enfortumab vedotin. *Oncologist*. 2022;27:e223-32. doi:[10.1093/oncolo/oyac001](https://doi.org/10.1093/oncolo/oyac001). PMID:35274723
5. Challita-Eid PM, Satpayev D, Yang P, et al. Enfortumab vedotin antibody-drug conjugate targeting nectin-4 is a highly potent therapeutic agent in multiple preclinical cancer models. *Cancer Res*. 2016;76:3003-3013. doi:[10.1158/0008-5472.CAN-15-1313](https://doi.org/10.1158/0008-5472.CAN-15-1313). PMID:27013195
6. Astellas Pharma Inc. Package insert of PADCEV (enfortumab vedotin-ejfv). 2023. Accessed October 1, 2024. https://astellas.us/docs/PADCEV_label.pdf
7. Penny CL, Quow K, Rundle CW, et al. Clinical and direct immunofluorescence characteristics of cutaneous toxicity associated with enfortumab vedotin. *Br J Dermatol*. 2022;187:126-127. doi:[10.1111/bjd.21022](https://doi.org/10.1111/bjd.21022). PMID:35048357
8. Geisler AN, Phillips GS, Barrios DM, et al. Immune checkpoint inhibitor-related dermatologic adverse events. *J Am Acad Dermatol*. 2020;83:1255-1268. doi:[10.1016/j.jaad.2020.03.132](https://doi.org/10.1016/j.jaad.2020.03.132). PMID:32454097
9. Asdourian MS, Shah N, Jacoby TV, Reynolds KL, Chen ST. Association of bullous pemphigoid with immune checkpoint inhibitor therapy in patients with cancer: a systemic review. *JAMA Dermatol*. 2022;158:933-941. doi:[10.1001/jamadermatol.2022.1624](https://doi.org/10.1001/jamadermatol.2022.1624). PMID:35612829
10. Niegisch G. Enfortumab vedotin and pembrolizumab - a new perspective on urothelial cancer. *N Engl J Med*. 2024;390:944-946. doi:[10.1056/NEJMe2400311](https://doi.org/10.1056/NEJMe2400311). PMID:38446680