Title

Chemotherapy reaction induced by ixabepilone, a microtubule stabilizing agent, mimicking extramammary Paget's disease in a patient with breast carcinoma

Journal

Journal of Cutaneous Pathology, 43(12)

ISSN

0303-6987

Authors

Millsop, Jillian W
Sharon, Victoria R
Petukhova, Tatyana
et al.

Publication Date

2016-12-01

DOI

10.1111/cup.12833

Peer reviewed

HHS Public Access

Author manuscript

J Cutan Pathol. Author manuscript; available in PMC 2018 May 29.

Published in final edited form as:

J Cutan Pathol. 2016 December ; 43(12): 1215–1219. doi:10.1111/cup.12833.

Chemotherapy Reaction Induced by Ixabepilone, a Microtubule Stabilizing Agent, Mimicking Extramammary Paget's Disease in a Patient with Breast Carcinoma

Jillian W. Millsop, MD, MS[1], **Victoria R. Sharon, MD, DTMH**[1], **Tatyana Petukhova, MD, MS**[1], **Maxwell A. Fung, MD**[1,2], and **Maija Kiuru, MD, PhD**[1,2]

[1]Department of Dermatology, University of California, Davis, Sacramento, California, U.S.A.

[2]Department of Pathology, University of California, Davis, Sacramento, California, U.S.A.

Abstract

The histopathologic characteristics of reactions caused by the many novel anticancer agents are under-recognized. We report a case of a 67-year-old female with locally advanced metastatic breast cancer, who initially presented with an extensive reticulated erythematous patch on the trunk caused by intravascular metastases confirmed by a skin biopsy. Due to disease progression, she was started on ixabepilone, a mitotic inhibitor. While receiving ixabepilone, another skin biopsy was obtained and initially interpreted as extramammary Paget's disease. However, the biopsy showed metaphase arrest of numerous keratinocytes in the basilar and suprabasilar epidermis. Atypical epithelial cells were only present in the intravascular spaces similar to the initial biopsy. Given the temporal association between the initiation of ixabepilone therapy and the epidermal mitotic arrest, a diagnosis of chemotherapy reaction to ixabepilone was rendered. Ixabepilone is an analog of epothilone, a microtubule stabilizer causing mitotic arrest of the cell cycle approved for the treatment of metastatic and locally advanced treatment-resistant breast cancer. The demonstration of epidermal mitotic arrest caused by ixabepilone is without precedent. The case emphasizes the importance of considering a chemotherapy reaction in the histologic differential diagnosis of epidermal mitotic arrest in a cancer patient receiving chemotherapy.

Keywords

chemotherapy; ixabepilone; metaphase arrest; mitosis; extramammary Paget's disease; skin

Introduction

The rapid expansion of novel anticancer agents has resulted in significant advances in the treatment of cancer patients but has also broadened the spectrum of cutaneous adverse events. Conventional chemotherapeutic agents are well known to cause cutaneous reactions including hand-foot syndrome (palmoplantar erythrodysesthesia) (1–4), neutrophilic eccrine

Corresponding author: Maija Kiuru, MD, PhD, Assistant Professor of Clinical Dermatology and Pathology, Department of Dermatology, University of California, Davis, 3301 C Street, Suite 1400, Sacramento, CA 95816, mkiuru@ucdavis.edu, Phone: 916-734-6373, Fax: 916-442-5702.

hidradenitis (5), radiation recall dermatitis (6), alopecia (7–9), hyperpigmentation (10, 11), urticarial hypersensitivity reaction (12), and sclerotic reactions (13) among many others. Although the classic cutaneous reactions associated with chemotherapy agents are well known, the histopathologic characteristics of reactions caused by the many novel anticancer agents are under-recognized.

In this report, we present the histopathologic features of a chemotherapy reaction secondary to ixabepilone, a microtubule stabilizer, approved for the treatment of metastatic and locally advanced treatment-resistant breast cancer. (14, 15) We emphasize the importance of considering a chemotherapy reaction in the histologic differential when evaluating a skin biopsy from a cancer patient receiving chemotherapy.

Report of a case

Clinical and histopathologic findings

Our patient was a 67-year-old female diagnosed with right locally advanced metastatic breast cancer in 2008. The breast cancer was human epidermal growth factor receptor 2 (HER-2) negative and hormone receptor negative. Initially, she received six cycles of cyclophosphamide and docetaxel and underwent a mastectomy. Two months after the mastectomy, she was found to have recurrence of the tumor and subsequently received six cycles of gemcitabine and carboplatin. Two years later, she was found to have tumor recurrence of the chest wall and metastasis to the left femur. At this time, she received radiation therapy to the left femur, and underwent therapy with denosumab and capecitabine. After the patient was found to have tumor progression in the dermal chest wall, her chemotherapy regimen was changed to paclitaxel and one year later to eribulin. No rash was observed while the patient received paclitaxel.

The patient initially presented to our dermatology clinic in January 2015 while receiving eribulin after a four-month history of a new pruritic rash on the lower back and left chest. On skin examination, she had extensive reticulated, erythematous to hyperpigmented patches and plaques involving most of the back extending to the left chest and left axilla (Figure 1). A biopsy was performed of the lower back.

The biopsy specimen of the lower back showed intravascular collections of malignant epithelial cells with duct formation, consistent with metastatic breast cancer (Figure 2A). The overlying epidermis was unremarkable (Figure 2B).

Due to disease progression, the patient’s chemotherapy regimen was changed from eribulin to ixabepilone. After two cycles of ixabepilone, another skin biopsy was obtained for mutation testing. Due to the pathologist’s concern for extramammary Paget’s disease, the hematoxylin and eosin (H&E) -stained sections were sent in consultation to our Dermatopathology Service. The skin biopsy specimen of the back showed significantly increased mitotic activity predominantly in the basilar and suprabasilar layers of the epidermis with numerous keratinocytes in metaphase arrest. (Figure 3A, 3B). A few dyskeratotic keratinocytes were also present. Atypical epithelial cells were only present in

the intravascular spaces similar to the initial biopsy, and this was consistent with persistent intravascular metastatic disease (Figure 3C).

Given the temporal association between the initiation of ixabepilone therapy, a microtubule stabilizing agent that blocks cell cycle in mitosis, and the histopathologic findings of the extensive epidermal mitotic arrest, a diagnosis of chemotherapy reaction to ixabepilone was rendered in addition to persistent intravascular metastatic carcinoma.

Ixabepilone was subsequently discontinued after her fourth cycle given the persistence of the skin involvement by the metastatic carcinoma and spread to the arms and chest. She was subsequently started on liposomal doxorubicin in July 2015, and the cutaneous involvement persisted.

Discussion

Significant advances have been made in the treatment of cancer patients with many novel anticancer agents. However, cutaneous adverse reactions are not rare. As these medications are used increasingly in the population, dermatologists and dermatopathologists should be aware of the clinical and histologic patterns, respectively, of the potential cutaneous adverse effects related to these medications. (1, 7, 16–18)

Interface dermatitis combined with dysmaturation of keratinocytes are pathognomonic features for a chemotherapy reaction. Dysmaturation is characterized by disorganized appearing epidermis with enlarged pleomorphic keratinocytes and dyskeratosis. (19) This reaction pattern is particularly associated with long-term, high-dose, or multiagent chemotherapy, such as with bleomycin, busulfan, or hydroxyurea. Furthermore, dysmaturation and vacuolar interface alteration involving the epidermis or adnexal epithelium typifies toxic erythema of chemotherapy (TEC), a clinically and histologically unifying term for a heterogenous group of disorders including epidermal dysmaturation, neutrophilic eccrine hidradenitis, eccrine squamous syringometaplasia, and acral erythema (erythrodysesthesia). (20) (21) Traditionally, neutrophilic eccrine hidradenitis is characterized by a dense neutrophilic infiltrate surrounding the eccrine coils. (7) This is most commonly implicated by cytarabine or bleomycin. Eccrine squamous syringometaplasia shows squamous metaplasia with epithelial apoptosis of the upper portion of the eccrine duct, typically secondary to doxorubicin and other anthracyclines, cyclophosphamide, chlorambucil, and antimetabolites such as methotrexate or fluorouracil. (19) Acral erythema is characterized by vacuolar interface alteration, keratinocyte necrosis, and mild spongiosis, occasionally with features of syringosquamous metaplasia and eccrine neutrophilic hidradenitis.

TEC is a term that encompasses the many clinical presentations and histologic findings of the skin, often with overlapping features, associated with the administration of chemotherapeutic agents.(20) More common chemotherapeutic agents that are associated with TEC include taxanes, cytarabine, anthracyclines, capecitabine, 5-fluorouracil, and methotrexate. However, many more chemotherapeutic agents also exhibit similar findings. (21) Clinically, patients with TEC often present with erythematous patches or edematous

plaques, typically on the acral surfaces and intertriginous areas, 2 days to 3 weeks after onset of the chemotherapeutic agent; pain, burning, pruritus, and/or paresthesias; petechiae, dusky hue, and/or bullae in erythematous areas; desquamation and resolution of rash without treatment; and possible recurrence of the rash if the chemotherapeutic agent is delivered again.(21) Histologically, common features of TEC include enlarged cells with nuclear pleomorphism, mitotic arrest, abnormal mitotic configurations, keratinocyte apoptosis, vacuolar degeneration of the basal layer, edema of the dermal layer, loss of polarity of epidermal cells, keratinocyte crowding, and/or eccrine squamous syringometaplasia.(21)

Other anticancer therapy reactions include hyperpigmentation, radiation recall (characterized by epidermal atrophy, vacuolar interface alteration, and superficial dermal vascular ectasia), urticaria, spongiotic dermatitis, interstitial granulomatous reaction, dermal sclerosis, and anagen effluvium.(19) The dramatic increase in the use of targeted anticancer agents has expanded the cutaneous reaction pattern significantly. Some of the best examples of such reactions include suppurative folliculitis caused by epidermal growth factor receptor (EGFR) inhibitors (16) and cystic atypical squamous proliferations caused by vemurafenib and other BRAF inhibitors (16).

Ixabepilone is a microtubule stabilizing agent, a semisynthetic analog of epothilone B approved in 2007 by the Food and Drug Administration for the treatment of metastatic and locally advanced breast cancer.(22) It is chemically modified to retain the features of natural epothilone B, effective at promoting cell arrest at the G2/M phase to cause apoptosis by binding tubulin and stabilizing microtubules. (23, 24) Additionally, it enhances the pharmacokinetic profile of the natural epothilone and overcomes tumor resistance *in vitro*. (25) Side effects from ixabepilone use include neutropenia and symptoms of fatigue, mucositis, anorexia, neuropathy, gastrointestinal upset, arthralgia, myalgia, and alopecia.(26) Clinical trials and few case reports have also identified a rash following use of ixabepilone, presenting as erythema and hyperpigmentation in a stocking glove distribution along the extremities and an acneiform eruption. (26–28) One case report described onycholysis and subungal hemorrhagic bullae in a patient treated with ixabepilone. (29) The histopathologic characteristics of these cutaneous adverse events are poorly documented.

In our case, ixabepilone therapy was associated with a striking metaphase arrest of keratinocytes in the epidermis. Metaphase arrest as a dominating histologic pattern in the skin has been rarely documented in the literature in association with other mitotic inhibitors, such as etoposide. (30) In addition to causing dysmaturation, etoposide can cause metaphase arrest with characteristic fragmented nuclear chromatin resulting in so-called ‘starburst cells’, one of the findings seen in TEC. (30) Our case of the ixabepilone reaction is also consistent with TEC and should be included among the chemotherapeutic agents that can cause TEC. As demonstrated by our case, the differential diagnosis for this histologic reaction pattern includes intraepidermal carcinoma, such as squamous cell carcinoma in situ or extramammary Paget’s disease, such as was initially suspected in this case. (31) As distinguishing features, squamous cell carcinoma in situ shows full thickness atypia with disorderly maturation and dyskeratotic keratinocytes in addition to mitoses at various levels in the epidermis. Extramammary Paget’s disease, characterized by singly disposed and clusters of large cells with abundant, pale cytoplasm and prominent vesicular nuclei, may

occasionally show scattered mitoses.(31) Additionally, the tumor cells in primary extramammary Paget's disease are typically CK7 positive, as well as positive for CEA, EMA, and CAM5.2. (32)

Conclusion

The many novel anticancer agents have resulted in tremendous advances in the treatment of cancer, but also expanded the variety of cutaneous adverse events. The demonstration of epidermal mitotic arrest associated with ixabepilone therapy emphasizes the importance of considering a chemotherapy reaction in the histologic differential diagnosis when evaluating skin biopsies from cancer patients receiving chemotherapy.

Acknowledgments

Dr. Kiuru's involvement in the case report described was in part supported by the National Cancer Institute, National Institutes of Health, through grant #K12CA138464. No other funding was provided to support this manuscript.

References

1. Sanborn RE, Sauer DA. Cutaneous reactions to chemotherapy: commonly seen, less described, little understood. Dermatologic clinics. 2008; 26(1):103–19. ix. [PubMed: 18023774]
2. von Gruenigen V, Frasure H, Fusco N, DeBernardo R, Eldermire E, Eaton S, et al. A double-blind, randomized trial of pyridoxine versus placebo for the prevention of pegylated liposomal doxorubicin-related hand-foot syndrome in gynecologic oncology patients. Cancer. 2010; 116(20): 4735–43. [PubMed: 20629022]
3. Marigny K, Aubin F, Burgot G, Le Gall E, Gandemer V. Particular cutaneous side effects with etoposide-containing courses: is VP16 or etoposide phosphate responsible? Cancer chemotherapy and pharmacology. 2005; 55(3):244–50. [PubMed: 15526203]
4. Akoglu G. Docetaxel-induced palmoplantar erythrodysesthesia syndrome and long-lasting multiple nail changes. Indian journal of pharmacology. 2014; 46(2):225–7. [PubMed: 24741199]
5. Lienesch DW, Mutasim DF, Singh RR. Neutrophilic eccrine hidradenitis mimicking cutaneous vasculitis in a lupus patient: a complication of cyclophosphamide. Lupus. 2003; 12(9):707–9. [PubMed: 14514135]
6. Borroni G, Vassallo C, Brazzelli V, Martinoli S, Ardigo M, Alessandrino PE, et al. Radiation recall dermatitis, panniculitis, and myositis following cyclophosphamide therapy: histopathologic findings of a patient affected by multiple myeloma. The American Journal of dermatopathology. 2004; 26(3): 213–6. [PubMed: 15166509]
7. Reyes-Habito CM, Roh EK. Cutaneous reactions to chemotherapeutic drugs and targeted therapies for cancer: part I. Conventional chemotherapeutic drugs. Journal of the American Academy of Dermatology. 2014; 71(2):203 e1–e12. quiz 15-6. [PubMed: 25037800]
8. de Jonge ME, Mathot RA, Dalesio O, Huitema AD, Rodenhuis S, Beijnen JH. Relationship between irreversible alopecia and exposure to cyclophosphamide, thiotepa and carboplatin (CTC) in high-dose chemotherapy. Bone marrow transplantation. 2002; 30(9):593–7. [PubMed: 12407434]
9. Chu CY, Yang CH, Chiu HC. Gemcitabine-induced acute lipodermatosclerosis-like reaction. Acta dermato-venereologica. 2001; 81(6):426–8. [PubMed: 11859947]
10. Romankiewicz JA. Cyclophosphamide and pigmentation. American journal of hospital pharmacy. 1974; 31(11):1074–5. [PubMed: 4432858]
11. Llistosella E, Codina A, Alvarez R, Pujol RM, de Moragas JM. Tegafur-induced acral hyperpigmentation. Cutis. 1991; 48(3):205–7. [PubMed: 1935249]
12. Makrilia N, Syrigou E, Kaklamanos I, Manolopoulos L, Saif MW. Hypersensitivity reactions associated with platinum antineoplastic agents: a systematic review. Metal-based drugs. 2010 2010.

13. Yamamoto T. Bleomycin and the skin. The British journal of dermatology. 2006; 155(5):869–75. [PubMed: 17034512]
14. Lopus M, Smiyun G, Miller H, Oroudjev E, Wilson L, Jordan MA. Mechanism of action of ixabepilone and its interactions with the betaIII-tubulin isotype. Cancer chemotherapy and pharmacology. 2015; 76(5):1013–24. [PubMed: 26416565]
15. De Luca A, D'Alessio A, Maiello MR, Gallo M, Chicchinelli N, Pergameno M, et al. Evaluation of the pharmacokinetics of ixabepilone for the treatment of breast cancer. Expert opinion on drug metabolism & toxicology. 2015; 11(7):1177–85. [PubMed: 26073581]
16. Reyes-Habito CM, Roh EK. Cutaneous reactions to chemotherapeutic drugs and targeted therapy for cancer: Part II. Targeted therapy. Journal of the American Academy of Dermatology. 2014; 71(2):217 e1–e11. quiz 27-8. [PubMed: 25037801]
17. Macdonald JB, Macdonald B, Golitz LE, LoRusso P, Sekulic A. Cutaneous adverse effects of targeted therapies: Part II: Inhibitors of intracellular molecular signaling pathways. Journal of the American Academy of Dermatology. 2015; 72(2):221–36. quiz 37-8. [PubMed: 25592339]
18. Macdonald JB, Macdonald B, Golitz LE, LoRusso P, Sekulic A. Cutaneous adverse effects of targeted therapies: Part I: Inhibitors of the cellular membrane. Journal of the American Academy of Dermatology. 2015; 72(2):203–18. quiz 19–20. [PubMed: 25592338]
19. N, B. Cutaneous adverse reactions to drugs. In: Calonje, JEBT.Lazar, AJ., McKee, PH., editors. McKee's Pathology of the Skin. 4. Sanders Elsevier; 2012.
20. McCalmont TH. Tec. Journal of cutaneous pathology. 2013; 40(9):785–7. [PubMed: 23962116]
21. Bolognia JL, Cooper DL, Glusac EJ. Toxic erythema of chemotherapy: a useful clinical term. Journal of the American Academy of Dermatology. 2008; 59(3):524–9. [PubMed: 18694683]
22. Lee FY, Smykla R, Johnston K, Menard K, McGlinchey K, Peterson RW, et al. Preclinical efficacy spectrum and pharmacokinetics of ixabepilone. Cancer chemotherapy and pharmacology. 2009; 63(2):201–12. [PubMed: 18350296]
23. Bode CJ, Gupta ML Jr, Reiff EA, Suprenant KA, Georg GI, Himes RH. Epothilone and paclitaxel: unexpected differences in promoting the assembly and stabilization of yeast microtubules. Biochemistry. 2002; 41(12):3870–4. [PubMed: 11900528]
24. Bollag DM, McQueney PA, Zhu J, Hensens O, Koupal L, Liesch J, et al. Epothilones, a new class of microtubule-stabilizing agents with a taxol-like mechanism of action. Cancer research. 1995; 55(11):2325–33. [PubMed: 7757983]
25. Lee FY, Borzilleri R, Fairchild CR, Kim SH, Long BH, Reventos-Suarez C, et al. BMS-247550: a novel epothilone analog with a mode of action similar to paclitaxel but possessing superior antitumor efficacy. Clinical cancer research : an official journal of the American Association for Cancer Research. 2001; 7(5):1429–37. [PubMed: 11350914]
26. Conlin AK, Vahdat L. Dermatological toxicity of ixabepilone. Anticancer research. 2006; 26(3B): 2279–80. [PubMed: 16821602]
27. Gonzalez-Angulo AM, Lei X, Alvarez RH, Green MC, Murray JL, Valero V, et al. Phase II Randomized Study of Ixabepilone Versus Observation in Patients With Significant Residual Disease After Neoadjuvant Systemic Therapy for HER2-Negative Breast Cancer. Clinical breast cancer. 2015
28. Gadgeel SM, Wozniak A, Boinpally RR, Wiegand R, Heilbrun LK, Jain V, et al. Phase I clinical trial of BMS-247550, a derivative of epothilone B, using accelerated titration 2B design. Clinical cancer research : an official journal of the American Association for Cancer Research. 2005; 11(17):6233–9. [PubMed: 16144926]
29. Alimonti A, Nardoni C, Papaldo P, Ferretti G, Caleno MP, Carlini P, et al. Nail disorders in a woman treated with ixabepilone for metastatic breast cancer. Anticancer research. 2005; 25(5): 3531–2. [PubMed: 16101175]
30. Yokel BK, Friedman KJ, Farmer ER, Hood AF. Cutaneous pathology following etoposide therapy. Journal of cutaneous pathology. 1987; 14(6):326–30. [PubMed: 2832457]
31. Du X, Yin X, Zhou N, Zhang G, Shi H, Cao S. Extramammary Paget's disease mimicking acantholytic squamous cell carcinoma in situ: a case report. Journal of cutaneous pathology. 2010; 37(6):683–6. [PubMed: 19615013]

32. Sah SP, Kelly PJ, McManus DT, McCluggage WG. Diffuse CK7, CAM5.2 and BerEP4 positivity in pagetoid squamous cell carcinoma in situ (pagetoid Bowen's disease) of the perianal region: a mimic of extramammary Paget's disease. Histopathology. 2013; 62(3):511–4. [PubMed: 23020200]

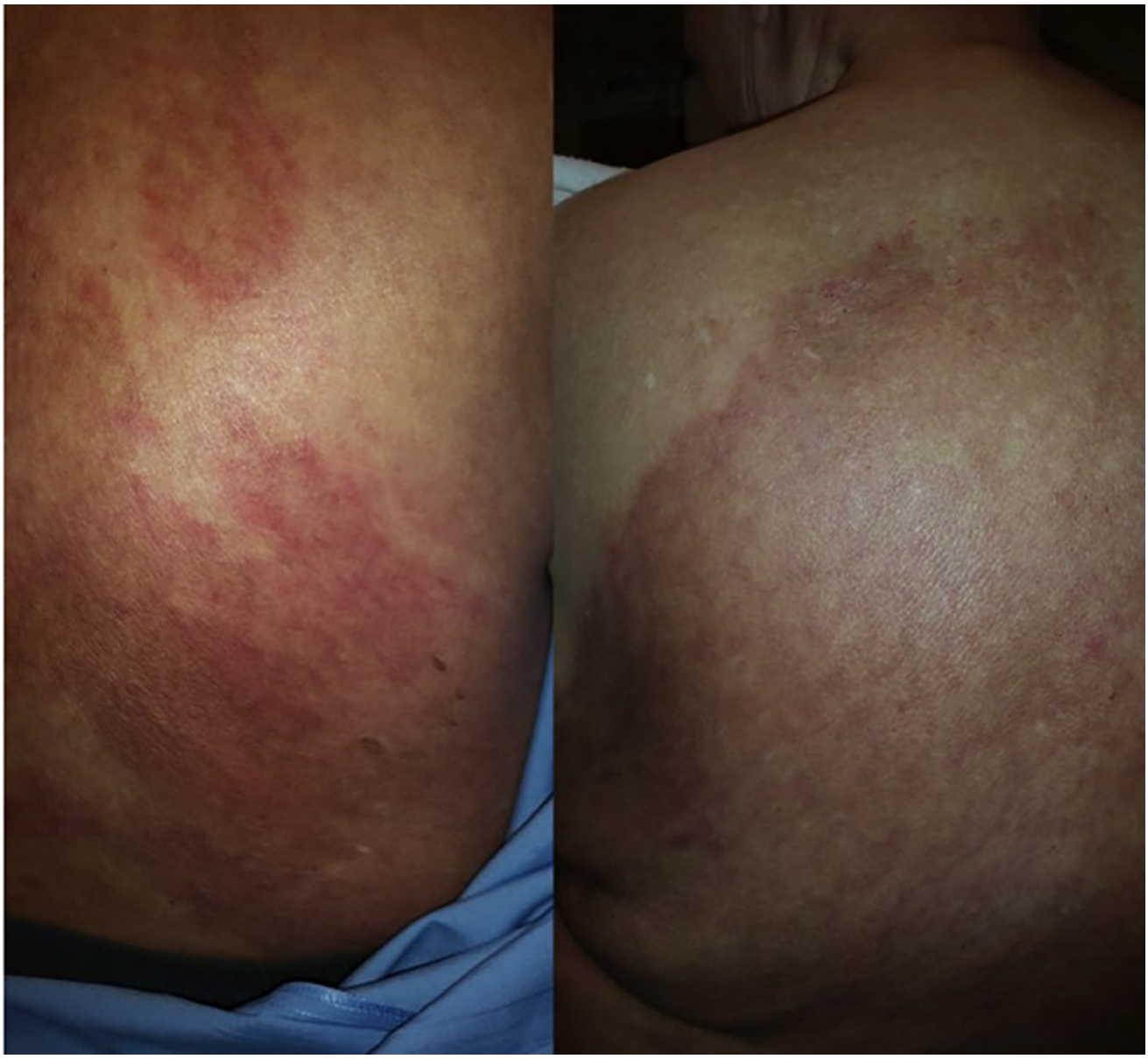

Figure 1.
Initial clinical presentation showing erythematous patches and plaques on the back.

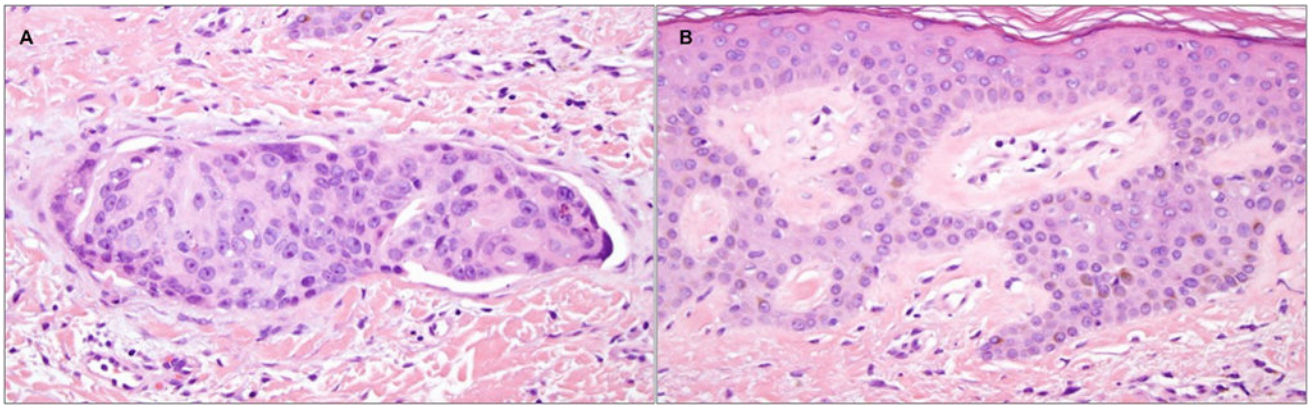

Figure 2.
Skin biopsy during eribulin therapy. A) Intravascular carcinoma. B) Normal epidermis.

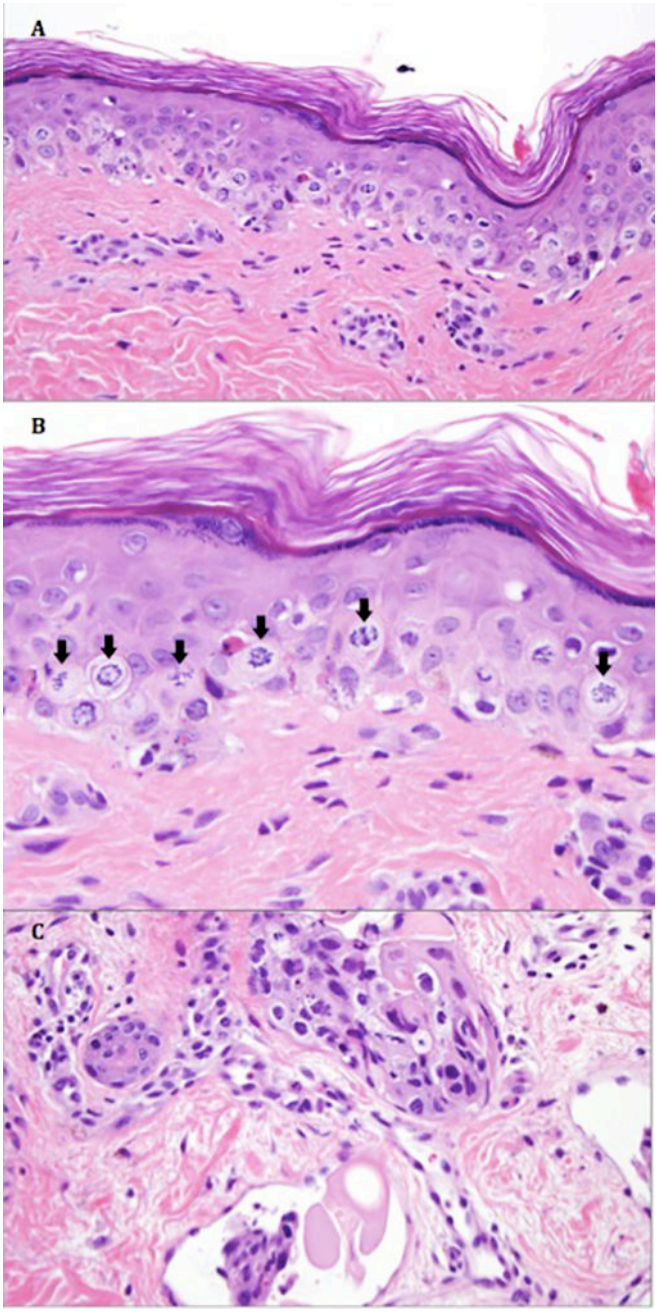

Figure 3.

Skin biopsy during ixabepilone therapy. A, B) Epidermis containing numerous keratinocytes in metaphase arrest with a few apoptotic cells. Arrows point to arrested mitotic figures. C) Intravascular carcinoma.