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Title
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Permalink
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Journal
Dermatology Online Journal, 31(2)

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Publication Date
2025

DOI
10.5070/D331265294

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Case Presentation

A case of trastuzumab-deruxtecan-induced subacute cutaneous lupus erythematous

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Keywords: adverse, breast, cancer, cutaneous, cyclophosphamide, dermatitis, deruxtecan, doxorubicin, drug-induced, effect

Dermatology Online Journal

Vol. 31, Issue 2, 2025

Abstract

Drug-induced subacute cutaneous lupus erythematosus (DI-SCLE) is an erythematous, photodistributed, scaly, and annular cutaneous eruption that is clinically similar to subacute cutaneous lupus erythematosus. However, DI-SCLE is associated with medication use and generally resolves or greatly improves following discontinuation. Chemotherapeutic agents are common triggers of DI-SCLE. We report a patient with breast cancer who experienced multiple episodes of DI-SCLE associated with the use of different chemotherapeutic agents for treatment-resistant cancer. Notably, to the best of our knowledge, this case highlights the first reported association of DI-SCLE with trastuzumab deruxtecan. Additionally, this case is unique owing to a component of radiation recall dermatitis, as the rash was prominent in areas that had prior ionizing radiation. A prior history of DI-SCLE in oncology patients who continue to undergo treatment should prompt clinicians to consider DI-SCLE when faced with a new photodistributed, erythematous, annular, and scaly eruption. Early initiation of immunomodulating agents like hydroxychloroquine in patients with a history of moderate to severe DI-SCLE to chemotherapy who continue to undergo anti-cancer treatment may provide benefit and warrants further investigation.

Introduction

Drug-induced subacute cutaneous lupus erythematosus (DI-SCLE) presents with photodistributed, erythematous, annular or papulosquamous plaques and is temporally related to medication exposure.[1,2] DI-SCLE is clinically, histopathologically, and immunologically similar to idiopathic SCLE. However, DI-SCLE generally resolves or improves significantly following drug discontinuation.[1] Anti-SS-A antibodies are present in 80% of cases.[1]

Herein, we present a patient who experienced multiple episodes of DI-SCLE on different chemotherapy regimens for breast cancer, including the first reported association of DI-SCLE with trastuzumab deruxtecan. The rash was prominent in areas previously exposed to ultraviolet (UV) and ionizing radiation, suggesting a component of radiation recall dermatitis besides the typical involvement of sun exposed sites. A prior history of DI-SCLE to chemotherapy in patients with treatment-resistant cancer who continue to seek treatment should prompt dermatologists to consider DI-SCLE when presented with a new photodistributed, erythematous, and scaly eruption.

Case Synopsis

A 51-year-old woman with past medical history of multiple sclerosis, hyperthyroidism, and metastatic breast cancer presented to dermatology clinic with a painful rash of one month duration that began one week after starting weekly gemcitabine. The rash began on the left chest overlying a previously irradiated area. With each gemcitabine dose, the rash flared and progressed to involve the upper extremities and face. She was diagnosed with breast cancer four years prior and was treated with bilateral mastectomy, combination doxorubicin and cyclophosphamide followed by paclitaxel, radiation, and anastrozole. The patient's breast cancer recurred and was treated with capecitabine, then a combination of exemestane and palbociclib. Most recently, prior to gemcitabine, she had received three cycles of eribulin (on days one and 8 of 21-day cycle). A visual timeline of her clinical presentation is shown (**Figure 1**).

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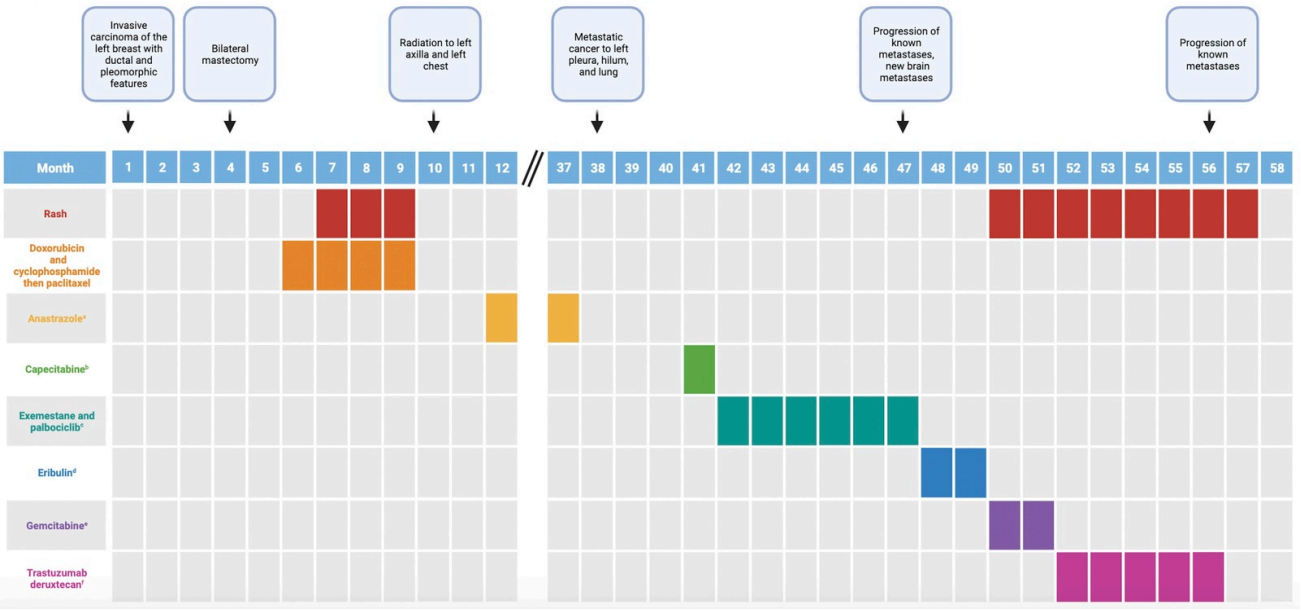


Figure 1. *Timeline of patient's presentation. Created with biorender.com.* ***A)*** *Discontinued due to progression of disease.* ***B)*** *Discontinued due to coronary vasospasm.* ***C)*** *Discontinued due to progression of disease.* ***D)*** *Discontinued due to peripheral neuropathy.* ***E)*** *Discontinued due to rash and thrombocytopenia.* ***F)*** *Discontinued due to the progression of disease.*

She reported a remote history of excessive UV exposure while wearing sleeveless tops in early adulthood. Other medications were longstanding without dose adjustments, including topiramate, levetiracetam, cyclobenzaprine, gabapentin, ocrelizumab, liothyronine, furosemide, spironolactone, and propranolol. Laboratory examination revealed positive antinuclear antibody, positive anti-SS-A antibody (>240 unit/mL), negative anti-SS-B antibody, negative anti-histone antibody, negative anti-double-stranded DNA antibody, erythrocyte sedimentation rate of 115mm/hr, and C-reactive protein of 50mg/L. Testing 10 years prior was notable for negative antinuclear antibody, negative extractable nuclear antigen antibody, negative anti-SS-B antibody, and positive anti-SS-A antibody (titer 1:3).

Physical examination revealed photodistributed, erythematous, scaly papules coalescing into plaques on the chest, back, arms, and face (**Figure 2A-C**), with notable sparing of prior sun-protected areas. Biopsy of the right shoulder revealed atrophic epidermis with slight basement membrane thickening, subtle vacuolar interface change with cytoid bodies, and mild superficial perivascular lymphocytic infiltrate (**Figure 3**).

Gemcitabine was discontinued after two cycles. She was started on trastuzumab deruxtecan every three weeks; however, the rash flared and progressed in body surface area involvement with each dose. Betamethasone dipropionate 0.05% ointment and tacrolimus 0.1% ointment led to no improvement. Initiation of hydroxychloroquine 300mg daily, high dose oral corticosteroids, and twice daily wet wrap topical corticosteroid therapy resulted in mild improvement. Ultimately, discontinuation of trastuzumab deruxtecan after 7 cycles led to significant improvement at 6 weeks post-treatment.

Notably, the patient had a similar photodistributed rash with pink, scaly papules on the nose, chest, back, arms, and dorsal hands three years prior. This rash began after the third cycle of doxorubicin and cyclophosphamide and flared after each dose. She transitioned to paclitaxel, but the rash persisted. The rash resolved with completion of paclitaxel and tacrolimus 0.1% ointment use.

Case Discussion

Given the rash's predilection for previously irradiated areas, episodic flaring and improvement off chemotherapy, histopathologic interface dermatitis, and positive anti-SSA antibodies, a diagnosis of DI-SCLE to chemotherapy with a component of radiation recall dermatitis was made. SCLE was considered given the patient's prior positive anti-SS-A antibody, low titer, 10 years prior. However, given the patient's lack of photosensitive rash in the absence of offending medications, DI-SCLE was favored with possible predisposing tendency to autoimmune disease. Additionally, anti-SS-A antibodies have been detected in 3-13% of patients with multiple sclerosis (MS) and are often not associated with rheumatologic disease in this patient population.[3] Therefore, her prior positive anti-SS-A antibody in the absence of rash may be related to her MS. Studies have not yet confirmed a higher incidence of autoimmune disease in patients with DI-SCLE, although preexisting autoimmune disease is commonly reported.[4]

Chemotherapy is a common cause of DI-SCLE, thought to relate to chemotherapy-induced apoptosis triggering a dysfunctional immune response to self-antigens.[4,5] In-

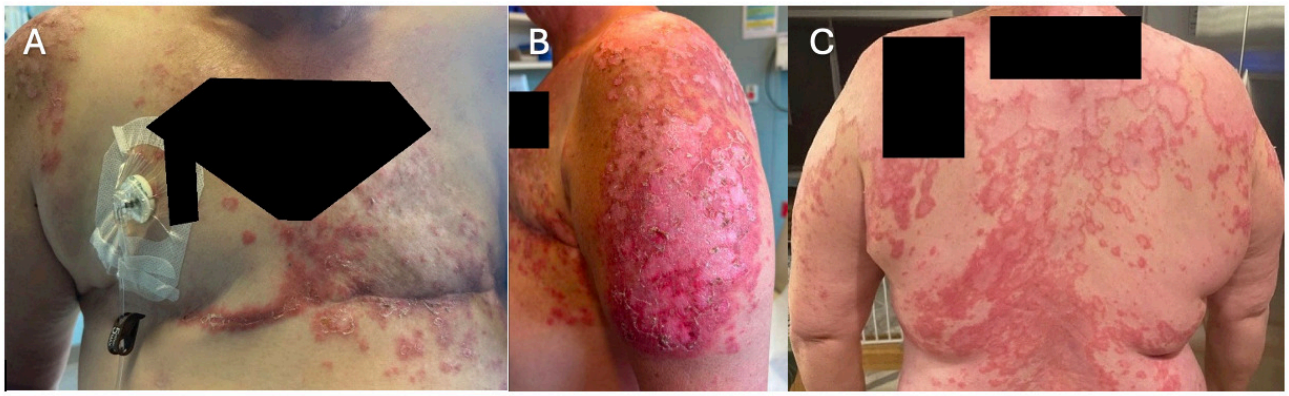


Figure 2. ***A-C)*** *Photodistributed, erythematous, scaly annular papules coalescing into plaques on the shoulders, chest, upper arms, and back.*

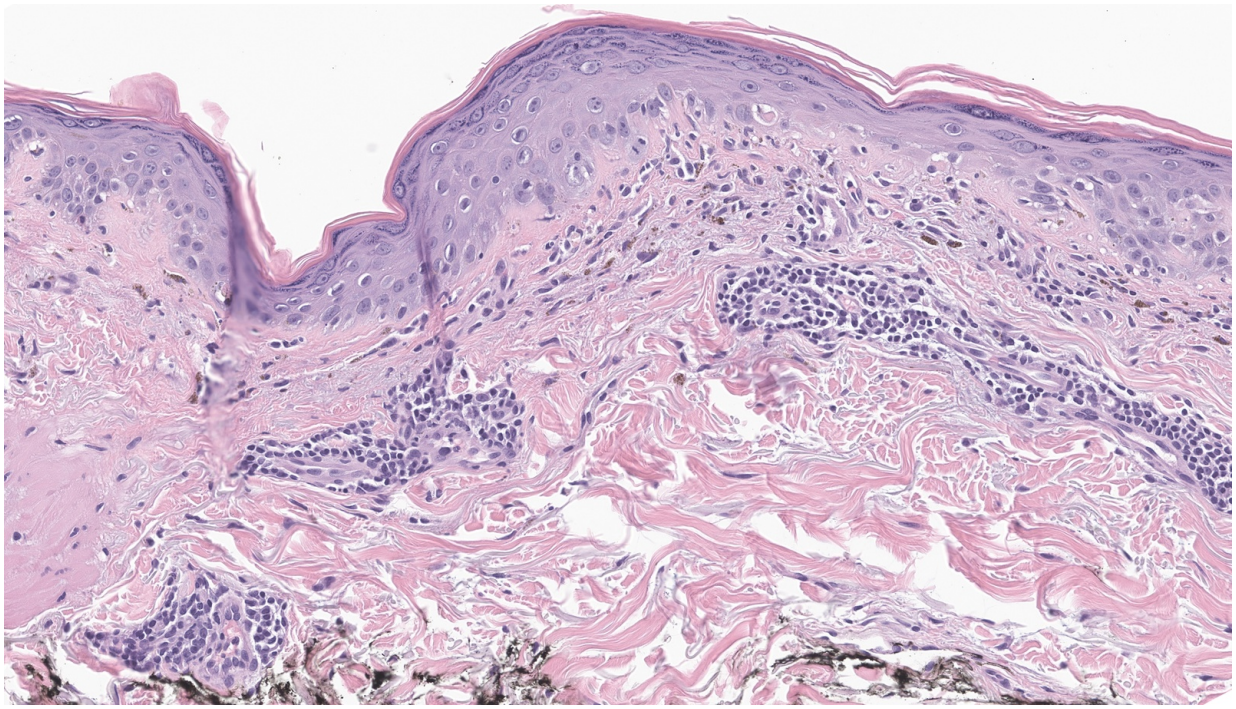


Figure 3. *Hematoxylin and eosin (H&E) stained shave biopsy of the right shoulder showing atrophic epidermis with mild hyperkeratosis, slight basement membrane thickening, subtle vacuolar interface change with cytoid bodies, and mild superficial perivascular lymphocytic infiltrate (H&E, 100×).*

terestingly, this patient experienced DI-SCLE triggered by several different chemotherapeutic agents. Although a biopsy was not performed of the initial rash, clinical morphology was also consistent with DI-SCLE. Cases of patients developing multiple episodes of DI-SCLE associated with different medications have previously been reported.[2] Median onset of DI-SCLE after drug initiation is 8 weeks,[1] though some chemotherapeutics have an incubation period of days,[5] whereas median time to resolution following drug discontinuation is 9 weeks.[6] Rapid cycling through different chemotherapy regimens for cancer management may preclude identification of a causative agent. For the first DI-SCLE eruption, possible culprits include doxorubicin, cyclophosphamide, and paclitaxel. For the second eruption, potential culprits include eribulin, gemcitabine, and trastuzumab deruxtecan. The second eruption started one week after initiating gemcitabine and persisted on trastuzumab deruxtecan, with increased flaring and progression with each dose of both therapies. These flares may have been a result of prolonged time to resolution after discontinuation of eribulin or gemcitabine, or a new reaction to trastuzumab deruxtecan. Taxanes, gemcitabine, combination trastuzumab and paclitaxel, combination doxorubicin and cyclophosphamide, and doxorubicin monotherapy have all been reported to induce DI-SCLE.[2,5,7,8] To the best of our knowledge, this case highlights the

first reported association of DI-SCLE with trastuzumab deruxtecan.

The additional unique component to this patient's presentation, beyond a likely multidrug trigger of DI-SCLE, is the feature of radiation recall dermatitis. Radiation recall dermatitis is a cutaneous eruption in previously irradiated skin following drug exposure, especially chemotherapeutic agents or antibiotics.[9] Radiation may alter the skin's immune response, possibly making the skin more susceptible to SCLE.[9] Although cases of eribulin-associated DI-SCLE have not yet been reported, evidence exists for radiation recall dermatitis triggered by eribulin.[9]

Prompt diagnosis of DI-SCLE is critical in oncology as cancer patients are at elevated risk for cutaneous reactions that impair quality of life, often requiring changes to chemotherapeutic regimens.[10] Early use of immunomodulating agents like hydroxychloroquine could be considered for patients with a history of moderate to severe DI-SCLE to chemotherapy as they continue to undergo anti-cancer treatment, similar to the use of prophylactic minocycline for estimated glomerular filtration rate (EGFR) inhibitor-induced acneiform eruption.[11] Further investigation into the benefit of early immunomodulation in patients at risk for autoimmune drug reactions is warranted.

Conclusion

Patients with treatment-resistant cancer may experience multiple episodes of drug-induced subacute cutaneous lupus erythematosus (DI-SCLE) to different chemotherapeutic agents. Newer agents, like trastuzumab deruxtecan, may also trigger DI-SCLE. For patients with a history of DI-SCLE who continue to undergo treatment, early initiation of immunomodulating agents like hydroxychloroquine may be beneficial and warrants further investigation.

Potential conflicts of interest

The authors declare no conflicts of interest.

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