

BRIEF ARTICLES

Capecitabine-induced subacute cutaneous lupus erythematosus in a patient with systemic lupus erythematosusAlyx Rosen MD^a, Evan Darwin BS^a, Jennifer N. Choi MD^b^aUniversity of Miami Miller School of Medicine, Department of Dermatology and Cutaneous Surgery, Miami, FL^bNorthwestern University Feinberg School of Medicine Department of Dermatology, Chicago, IL

ABSTRACT

Capecitabine is a fluoropyrimidine chemotherapy prodrug of 5-fluorouracil (5-FU) used in the treatment of metastatic breast and colorectal cancers. Drug-induced subacute cutaneous lupus erythematosus (DI-SCLE) is a rare side effect of capecitabine therapy, with eight cases previously reported. We report a case of DI-SCLE in a patient with a documented history of systemic lupus erythematosus (SLE). This is the second documented case of DI-SCLE in a patient with a past medical history of SLE, and provides evidence that there may be an increased risk of DI-SCLE in these patients. Further research should examine whether patients with SLE are at greater risk for this adverse event.

INTRODUCTION

Drug-induced subacute cutaneous lupus erythematosus (DI-SCLE) is characterized by histopathological and immunopathological features of typical SCLE that are induced by a drug, dissipate with the drug's removal, and recur with re-exposure to the agent.¹ Capecitabine is a fluoropyrimidine chemotherapy prodrug of 5-fluorouracil (5-FU) used for the treatment of metastatic breast and colorectal cancers.² Dermatologic conditions commonly associated with capecitabine include palmar-plantar erythrodysesthesia, photoeruption, dermatitis, leopard-like vitiligo, erythematous rash, and onycholysis.³ Here we present a case of DI-SCLE in association with capecitabine in the setting

of known systemic lupus erythematosus (SLE).

CASE REPORT

A 68-year-old female with colon adenocarcinoma presented to the dermatology clinic with a photosensitive rash without pain or pruritus on her upper body that began eight weeks after initiating capecitabine therapy. Her past medical history was significant for SLE diagnosed 16 years prior, which was well-controlled with hydroxychloroquine. The patient denied a history of skin lesions with her lupus. On examination, the patient had several 0.5-2

cm thin pink annular scaly papules and plaques on her forearms, posterior neck, and anterior chest in a photodistribution [Fig. 1]. Patchy scarring alopecia was noted on the scalp, along with several 0.5-1 cm pink scaly papules and plaques on her upper cutaneous lip and bilateral cheeks. The oral mucosa was clear. Review of systems revealed no associated systemic symptoms, such as fevers, fatigue, arthralgias, chest pain, or neurologic symptoms.

A biopsy was obtained from the patient's left forearm. Histopathology showed an interface lymphocytic infiltrate with basal vacuolar changes and necrotic keratinocytes, telangiectasias with a perivascular lymphocytic infiltrate, and dermal edema. The patient's laboratory values showed a positive ANA titer of 1:640 and an anti-dsDNA antibody level of 498, up from 396 immediately prior to starting

capecitabine. C3 complement levels fell from 79 to 66, and C4 dropped from 14 to 10. She was weakly positive for anti-SSA/Ro, anti-Smith, and anti-histone antibodies; however, baseline levels of these antibodies were not performed prior to capecitabine therapy. All other laboratory data were unremarkable.

The patient was prescribed triamcinolone 0.1% cream twice daily and strict sun protection. Due to her symptoms and histologic and laboratory results, she was diagnosed with DI-SCLE and capecitabine was discontinued. At two-week follow-up, the rash had significantly improved, with decreased erythema and scaling of the lesions. Two months after drug discontinuation, the rash had completely resolved [Fig. 2]. Four months after drug discontinuation, the patient's ANA titer fell to 1:320.



Figure 1. Annular scaly pink papules and plaques on the bilateral forearms.



Figure 2. Resolution of rash two months after drug discontinuation.

DI-SCLE from capecitabine therapy is rare. In addition to our patient, eight other cases of capecitabine-induced SCLE have been reported [Table 1]. While the antibody profile varied slightly between cases, every patient had an elevated ANA and positive anti-SSA/Ro antibodies, and most demonstrated negative anti-histone and anti-dsDNA autoantibodies.¹⁻⁸ One other patient also had a history of SLE, making this the second case of DI-SCLE from capecitabine in the setting of underlying SLE and

highlighting a potential association.⁶ Additionally, no other cases of DI-SCLE from other chemotherapies in patients with underlying SLE have been described; however, cases of idiopathic SCLE exacerbated by either docetaxel or doxorubicin have been reported.⁹⁻¹⁰ The patients in these cases had well-controlled disease and positive serology for anti-SSA/Ro antibodies prior to the onset of chemotherapy, and their skin rash resolved with cessation of the causative drug.⁹⁻¹⁰

Table 1. Cases of Subacute Cutaneous Lupus Erythematosus from Capecitabine

Author and year	Age/sex	ANA	Anti-dsDNA	Anti-Ro/SSA	Anti-histone	Medical History of SLE or other rheumatic disease
Weger <i>et al.</i> 2008 ³	77/female	+	-	+	-	No
Fernandes <i>et al.</i> 2009 ⁷	49/female	+ 1:640	-	+	+	No
Floristan <i>et al.</i> 2009 ⁸	66/female	Before therapy 1:160 After therapy: 1:1280	Not reported	+	-	Seronegative polyarthritis with occasional positive ANA
Kindem <i>et al.</i> 2013 ²	78/female	+ 1:640	-	+	-	No
Ko <i>et al.</i> 2013 ¹	72/female	+ >1:2560	-	+	-	No
Fongue <i>et al.</i> 2014 ⁶	50/female	Not reported	Not reported	+	Not reported	SLE
Kim <i>et al.</i> 2016 ⁵	67/female	+ >1:320	-	+	-	No
Li <i>et al.</i> 2016 ⁴	74/female	+ 1:1000	-	+	-	No
Our case 2017	68/female	+ 1:640	+	+	+	SLE

One possible explanation for DI-SCLE in association with SLE is the presence of preexisting anti-SSA/Ro antibodies in SLE patients, which may be a risk factor for the development of SCLE in the correct setting, such as exposure to a chemotherapeutic agent. A large multicenter cohort study demonstrated that 32% of childhood-onset SLE patients had positive anti-SSA/Ro antibodies.¹¹ Additionally, 5-FU may translocate SSA/Ro antigens to the surface of keratinocytes, leading to lupus-like eruptions and possibly higher rates of SCLE in patients with underlying SLE and elevated autoantibodies.^{11,12} Alternatively, one case showed a patient who developed DI-SCLE from capecitabine that did not recur with subsequent administration of 5-FU.⁵ This suggests a novel pathophysiology for the induction of SCLE from capecitabine that is distinct from 5-FU, although the mechanism is still unclear.

While the pathophysiology of DI-SCLE requires further investigation, it is also important to differentiate DI-SCLE from other diagnoses such as DI-SLE or a flare of underlying SLE. DI-SCLE is distinguished from DI-SLE by its clinical characteristics and immunologic profile. DI-SCLE will typically present as a skin rash and patients have positive anti-SSA/Ro antibodies.² The cutaneous lesions of DI-SCLE classically present as generalized annular polycyclic or papulosquamous plaques.³ Conversely, DI-SLE patients present more often with systemic symptoms, such as arthralgias and serositis, than with a skin rash and can have anti-histone antibodies.²

DI-SCLE is distinguishable from a flare of underlying SLE based on the disease time course. If the rash begins with onset of the drug, subsides with the drug's cessation, and recurs with re-exposure, it is likely DI-SCLE. Additionally, if the new rash is

substantively different from the patient's typical SLE presentation, then the presence of the rash in the setting of a new drug exposure most likely represents a drug adverse event.

Our patient presented with a new-onset rash that was clinically, immunologically, and histopathologically consistent with SCLE several weeks after starting capecitabine therapy while on oral hydroxychloroquine therapy for her SLE. Her rash improved with topical steroids and ultimately resolved with cessation of capecitabine. No systemic symptoms suggestive of an SLE flare occurred simultaneously.

In conclusion, this case highlights an occurrence of DI-SCLE secondary to capecitabine therapy in a patient with SLE. This is the second case of a patient on capecitabine that developed DI-SCLE with a documented history of SLE and raises concern that SLE in the setting of capecitabine or possibly other chemotherapeutic agents may predispose patients to this reaction. Patients receiving capecitabine should be monitored for the development of SCLE during treatment, with clinicians having a low threshold to perform a skin biopsy and laboratory work-up for possible SCLE if a patient develops new pink scaly papules in a photodistributed pattern. More research should be undertaken to determine the pathophysiology of DI-SCLE in patients with underlying SLE.

Conflict of Interest Disclosures: none.

Funding: none.

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