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# Widespread subacute cutaneous lupus erythematosus in a patient receiving checkpoint inhibitor immunotherapy with ipilimumab and nivolumab

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## Abstract

Checkpoint inhibitor immunotherapy, including ipilimumab and nivolumab, is associated with numerous immune-related adverse events including dermatitis, pruritus, hepatitis, diarrhea, and hypophysitis. As the number of patients undergoing immunotherapy treatment increases, however, rare and unusual immune-related adverse events are observed. Many of these resemble known autoimmune phenomenon, such as subacute lupus erythematosus and myositis. Herein, we report a patient with metastatic serous ovarian carcinoma undergoing treatment with combination ipilimumab and nivolumab who developed subacute cutaneous lupus erythematosus (SCLE). Recent case reports have documented SCLE as a novel immune-related adverse event. In our case, she was able to successfully restart immunotherapy after a course of oral corticosteroids and maintenance oral hydroxychloroquine and topical corticosteroid therapy.

*Keywords: immunotherapy, subacute lupus erythematosus, SCLE, checkpoint inhibitor, immune-related adverse event*

## Introduction

Checkpoint inhibitor immunotherapy is used in the treatment of numerous malignancies, including in trials for ovarian cancer, and is associated with immune-related adverse events (irAEs), [1]. Different immunotherapy classes, such as cytotoxic T

lymphocyte-associated antigen 4 and programmed cell death 1 receptor inhibitors, vary in rates of irAEs and affect nearly every organ system [1, 2]. Risk of irAEs is higher when immunotherapies are used in combination [1]. Dermatologic reactions are the most common and often earliest to appear [3]. We report a case of drug-induced subacute cutaneous lupus erythematosus (SCLE) in the setting of combination immunotherapy with ipilimumab and nivolumab.

## Case Synopsis

A 75-year-old woman was diagnosed with metastatic, high grade, serous ovarian carcinoma in 2011. The patient underwent numerous treatments, including combination docetaxel, carboplatin, bevacizumab; gemcitabine; pegylated liposomal doxorubicin (discontinued due to hand foot syndrome); etoposide; topotecan; tamoxifen; pemetrexed; anastrozole; and niraparib. Owing to progression of disease, combination ipilimumab and nivolumab was initiated in May 2018. She developed fatigue and a few days after receiving cycle two, she developed a pruritic eruption on her arms, thighs, and abdomen. Treatments that yielded only mild improvement in her symptoms included hydroxyzine, triamcinolone 0.1% cream, and gabapentin 200mg three times daily. A prednisone taper starting at 40mg daily improved her pruritus and leg lesions. After receiving the next cycle of immunotherapy, her eruption flared, prompting her oncology team to hold immunotherapy, increase the

prednisone dose, and request a dermatology consultation.

Examination demonstrated bilateral cheek erythema and erythematous, red-brown, scaly plaques with an arcuate appearance widespread on the back, abdomen, arms, and legs (**Figure 1**). Punch biopsy of the thigh showed interface lymphocytic infiltrate with focal basal vacuolar change (**Figure 2**). Serum studies revealed an elevated anti-nuclear antibody (ANA) at 1:160 with speckled pattern, and elevated Sjögren syndrome-A (SS-A or Ro) antibody at >8.0 AI (normal 0-0.9 AI). Remaining autoimmune panel, including SS-B/La, anti-dsDNA, and anti-Smith antibodies was negative. Other concurrent medications were albuterol, ascorbic acid, cetirizine, cholecalciferol, cyclosporine, desipramine, eletriptan, gabapentin, hydroxyzine, levetiracetam, levothyroxine, metoclopramide, metoprolol, niraparib, ondansetron, prochlorperazine, and prednisone 10 mg daily. She denied a history of autoimmune disease, xerostomia, and xerophthalmia. A diagnosis of drug-induced SCLÉ secondary to immunotherapy was made.

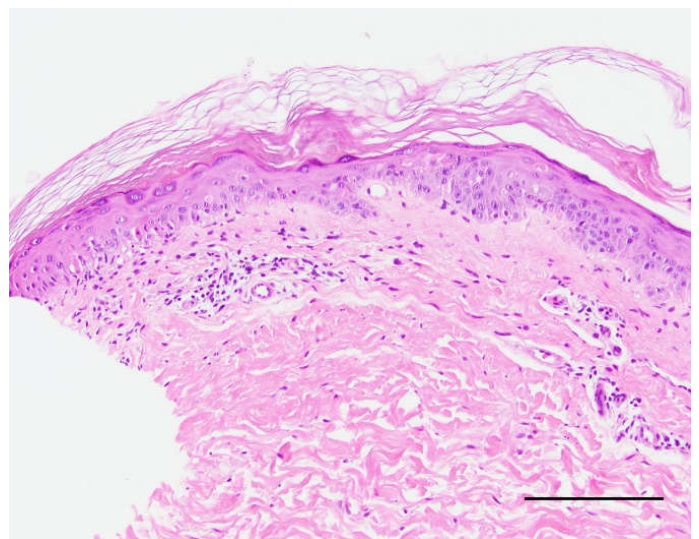


**Figure 1.** *Clinical Appearance.* Numerous scattered erythematous papules and plaques with scale, many with an annular configuration, over the bilateral lower extremities. Similar papules and plaques were found on the back, abdomen, and upper and lower arms.

The prednisone dose was increased back to 40mg daily and hydroxychloroquine 200mg twice daily was initiated. Within one week the eruption largely resolved into hyperpigmented patches. Two weeks later she restarted immunotherapy with nivolumab and ipilimumab and experienced recurrence of a mild facial eruption, which quickly resolved with triamcinolone 0.1% cream. Prednisone was discontinued after six weeks. The patient's treatment course was then switched to pembrolizumab monotherapy, which triggered a slight flare in her SCLÉ eruption on her chest and back. Hydroxychloroquine, along with all her other medications was continued, while quinacrine 100mg daily was added, which led to improvement of her rash. She has not had a significant flare of the eruption with subsequent pembrolizumab cycles.

### Case Discussion

Subacute cutaneous lupus erythematosus is an autoimmune disease that can occur spontaneously, in conjunction with systemic lupus erythematosus or Sjögren syndrome, or as a reaction to medication [4]. It presents with a characteristic cutaneous eruption often in photoexposed areas and is frequently associated with predisposing HLA haplotypes or SS-



**Figure 2.** *Histopathologic Appearance.* Hematoxylin and eosin stained skin biopsy demonstrated a lymphocytic interface and perivascular dermatitis with basal vacuolar change and hyperkeratosis. 200x, scale bar=100µm.

A/Ro antibodies [4]. Drug-induced SCLE (DI-SCLE) is most frequently reported in association with thiazide diuretics, calcium channel blockers, and antifungals, as well as numerous other drugs. In recent years, there have also been rising reports of DI-SCLE occurring secondary to proton pump inhibitors [5]. The most effective treatment for DI-SCLE is discontinuation of the offending drug [4]. Besides nivolumab, none of the patient's medications were new to her and have not been reported to cause DI-SCLE [4]. SCLE has recently been reported to occur during anti-PD-1 and anti-PD-L1 immunotherapy [6-8]. In these cases, most resolved with topical corticosteroids whereas two required hydroxychloroquine and one a short course of oral corticosteroids.

It is unclear whether immunotherapy-induced SCLE represents cutaneous toxicity or unmasking of subclinical disease, like immunotherapy-induced psoriasiform eruptions or dermatomyositis [3]. Histopathologic differences between DI-SCLE and classic SCLE have been reported to include increased dermal mucin deposition with IgM and C3c on direct immunofluorescence in classic SCLE [9]. Although DI-SCLE was reported to have an increased presence of

leukocytoclastic vasculitis, it was present in only about 10% of DI-SCLE samples and was also absent in our patient [9]. Results of testing for ANA, anti-Ro/La, anti-ds DNA, and histones could not distinguish between patients with DI-SCLE or idiopathic SCLE [9]. As in many other autoimmune phenomenon, the presence of autoantibodies suggests a B cell response to immunotherapy [3].

## Conclusion

The appearance of a dermatologic toxicity to checkpoint inhibitor immunotherapy warrants prompt referral to an appropriate specialist for management. Early identification and treatment of immunotherapy-induced SCLE can possibly prevent treatment interruption or discontinuation of life-saving immunotherapy. Immunotherapy-induced SCLE can be managed with a combination of topical corticosteroids, hydroxychloroquine and/or quinacrine, and a short course of oral corticosteroids to obtain rapid disease control.

## Potential conflicts of interest

The authors declare no conflicts of interests.

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