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Case Report

Taxane associated subacute cutaneous lupus erythematosus

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Abstract

Numerous medications have been associated with the development of subacute cutaneous lupus erythematosus. A mechanism explaining how unrelated drug classes can lead to subacute cutaneous lupus erythematosus has remained elusive, suggesting that there may be multiple etiologic pathways. Taxanes (docetaxel, paclitaxel, and cabazitaxel) inhibit cell mitosis through microtubule stabilization and their use has uncommonly been associated with subacute cutaneous lupus erythematosus. Recently the antigen recognized by anti-Ro/SS-A antibody (Ro52) has been localized to the cytoplasmic microtubule network. A case report of docetaxel exacerbated subacute cutaneous lupus erythematosus is presented and literature review performed, revealing 11 additional cases of taxane associated subacute cutaneous lupus erythematosus. Taxanes are proposed to exacerbate or induce subacute cutaneous lupus erythematosus in immunogenetically predisposed patients by stabilizing microtubules and affecting Ro/SS-A antigen (Ro52) expression. This may be an under recognized adverse drug reaction because taxanes are used for a defined period and the cutaneous eruption tends to spontaneously improve. Studies analyzing how particular drug classes affect Ro/SS-A antigen expression may be useful in identifying mechanisms of action in drug-induced subacute cutaneous lupus erythematosus.

Introduction

Subacute cutaneous lupus erythematosus (SCLE) is recognized as a subset of cutaneous lupus erythematosus and is characterized by non-scarring, photodistributed, annular or papulosquamous plaques. Patients are often positive for anti-Ro/SS-A antibodies but their presence is not required for diagnosis. A subset of patients with SCLE will meet the American College of Rheumatology criteria for a diagnosis of systemic lupus erythematosus, but they tend to have an overall favorable prognosis. Numerous medications have been associated with development of SCLE with widely variable mechanisms of action. Well-known examples include hydrochlorothiazide, terbinafine, calcium channel blockers, and angiotensin-converting enzyme inhibitors [1]. Taxanes are a class of chemotherapeutic drugs that inhibit cell mitosis through microtubule stabilization. We report a case of docetaxel exacerbated SCLE.

Case synopsis

A 58 year-old female with Stage III right breast ductal carcinoma receiving neo-adjuvant trastuzumab, carboplatin, and docetaxel chemotherapy in preparation for modified radical mastectomy was referred to the dermatology department for new-onset rash. It began a few days after her first carboplatin / docetaxel infusion, spontaneously resolved without treatment, but returned immediately after the second cycle. On examination, the patient had erythematous, slightly scaly papules in a photodistribution on the dorsal forearms and arms, upper chest, neck, and lateral cheeks (Figure 1). A biopsy was performed on the left neck, which demonstrated epidermal atrophy, vacuolar alteration of the basal layer, periadnexal lymphocytic inflammation (Figure 2), and

increased dermal mucin identified by colloidal iron stain. The rash unequivocally flared with each subsequent cycle of carboplatin / docetaxel, only to gradually improve over the following month. Use of topical mid-potency corticosteroids and/or oral prednisone expedited resolution. During her sixth chemotherapy cycle, the patient received carboplatin monotherapy and no flare of her rash occurred, suggestive of docetaxel as the etiology. Other medications temporally associated with her chemotherapy infusions included acetaminophen, dexamethasone, diphenhydramine, famotidine, and fosaprepitant dimeglumine.



Figure 1: Erythematous, slightly scaly papules on the right forearm

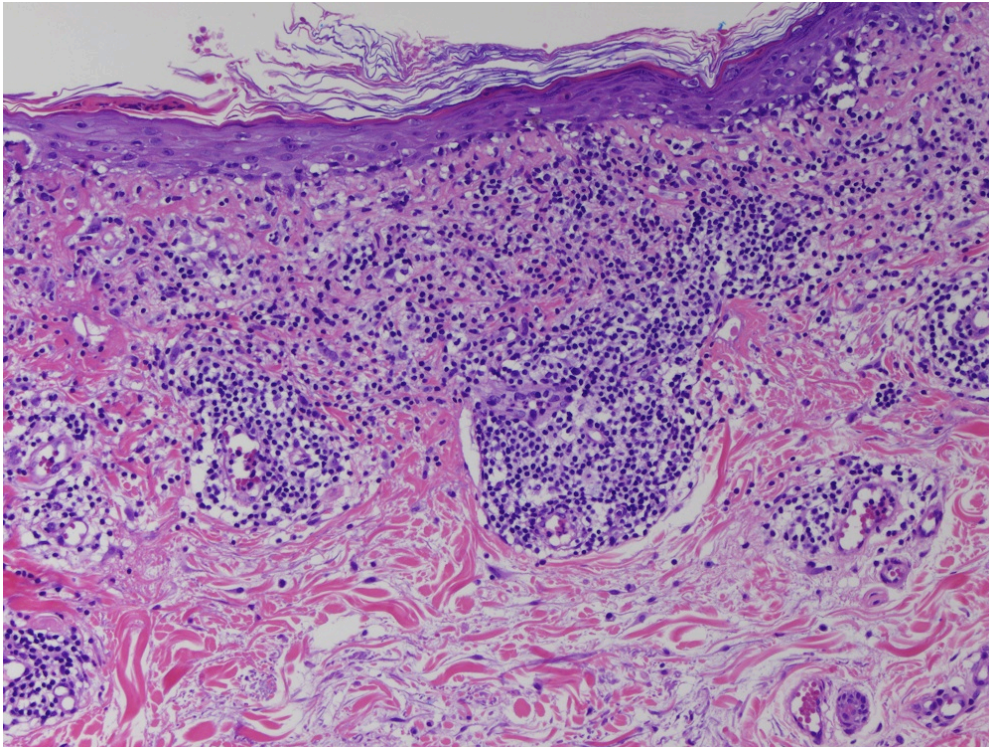


Figure 2: Biopsy of the left neck reveals epidermal atrophy, a lymphocytic band-like infiltrate in the dermis with keratinocyte basal layer vacuolization, and dermal mucin. (Hematoxylin-eosin stain; original magnification: X20)

Review of her medical record subsequently revealed that she had been diagnosed with SCLE approximately twenty years prior. Her serologic profile seven months before chemotherapy initiation included a greater than 1:640 antinuclear antibody (ANA) titer with speckled pattern and high titer anti-Ro/SS-A antibody [>8.0 Antibody Index (AI)]. She had been successfully managed with hydroxychloroquine for many years without any cutaneous disease. In anticipation of chemotherapy, hydroxychloroquine was discontinued because of the risk of myelosuppression.

The patient was diagnosed with docetaxel exacerbated SCLE given the patient's clinical history of SCLE, autoantibody profile, histopathologic features, and temporal disease association with docetaxel, but not carboplatin infusion. Repeat serologies performed four weeks after chemotherapy continued to show greater than 1:640 ANA titer with speckled pattern and high titer anti-Ro/SS-A antibody (>8.0 AI). Quantification of a rise in antibody index could not be performed.

IV. Discussion:

A PubMed literature review reveals seven additional cases of docetaxel associated SCLE and five cases of paclitaxel associated SCLE [1, 2, 3, 4, 5, 6, 7]. Some of these patients had prior diagnoses of SCLE or Sjögren syndrome (with positive anti-Ro/SS-A and/or anti-La/SS-B antibodies) before initiation of taxane chemotherapy. Because the cutaneous eruptions responded to topical and systemic corticosteroids and resolved after completion of chemotherapy, SCLE eruptions occurring in the context of taxane therapy are likely under-recognized. Of note, there are two published cases of doxorubicin-associated SCLE reported with positive anti-Ro/SS-A antibodies whose cutaneous disease did not flare with paclitaxel therapy [1]. Another reported cutaneous lupus reaction associated with taxane therapy is a transient acute lupus-like malar rash related to the diluent cremophor, which is used to solubilize paclitaxel for IV infusion. The transient cremophor response was not linked with ANA, anti-Ro/SS-A, anti-La/SS-B, anti-histone, or rheumatoid factor antibodies [8]. Docetaxel is solubilized in polysorbate-80 and is less often associated with infusion reactions.

Drug-induced SCLE (DI-SCLE) is an adverse drug reaction that does not differ clinically, histopathologically or immunologically from idiopathic SCLE [9]. Most of these patients do not have a prior diagnosis of SCLE and do not tend to progress to idiopathic SCLE. Withdrawal of the medication usually leads to resolution of cutaneous disease. The multitude of implicated medications across unrelated drug classes has made identifying a unifying pathogenesis of DI-SCLE challenging. Induction of photosensitivity has been proposed as a mechanism of action. Relocation of Ro/SS-A antigen to the cell surface has been detected in cultured keratinocytes subjected to ultraviolet irradiation. This has been proposed to relate to the photosensitivity exhibited by some patients and to explain the mechanism of direct tissue damage [10]. Not all drugs associated with SCLE, however, are recognized as photosensitizers and numerous well-recognized photosensitizing drugs are uncommonly, if at all, associated with SCLE. It seems likely, as in idiopathic SCLE, that multiple disease pathways converge to produce a shared clinical phenotype.

The taxanes, paclitaxel and docetaxel, are widely used in the treatment of solid organ malignancy as inhibitors of cell mitosis. The newer taxane, cabazitaxel, is limited to use in prostate cancer. Unique to the mechanism of action is the promotion and stabilization of microtubule formation [11]. As a result, microtubule bundles and aberrant structures appear in the mitotic phase of the cell cycle.

The antigen recognized by anti-Ro/SSA antibody is Ro52 (also known as TRIM21) and is expressed in most tissues and cells [12]. Ro52 has been shown to function as an E3 ubiquitin ligase, which ultimately leads to the degradation, membrane internalization, or functional alteration of proteins [13]. Ro52 specifically mediates ubiquitination of several members of the interferon regulatory factor (IRF) transcription factor family, thereby regulating cytokine production [13]. Ro52-deficient mice have enhanced production of pro-inflammatory cytokines (specifically cytokines in the Th17 pathway) and go on to develop signs of systemic autoimmunity [14]. In addition, serum from patients with anti-Ro/SS-A antibodies has been shown to inhibit the E3 ligase activity of Ro52, supporting the direct role of anti-Ro/SS-A antibodies in the pathogenesis of autoimmune disease [13].

Using fluorescence microscopy, Ro52 has been shown to localize to the cytoplasmic microtubule network [15]. Of note, Ro52 cytoplasmic bodies are highly motile and are transported along the microtubule network [15]. This intracellular location, coupled with the stabilizing effect of taxanes on microtubules, suggests an etiologic mechanism of taxane associated SCLE. Taxanes allow expression of Ro52 antigen to the immune system through their stabilizing effect on microtubules during mitotic inhibition.

Another oncologic drug class that interacts with microtubules leading to cell mitosis is the vinca alkaloids, which includes vincristine, vinblastine, and vinorelbine. Contrary to taxanes, vinca alkaloids lead to disruption of microtubule assembly and ultimately depolymerization [16]. In a cellular environment devoid of functional microtubules, Ro52 expression would be

expected to decrease. Supporting this hypothesis is that despite widespread clinical use of vinca alkaloids in oncology for over fifty years in a similar patient population to taxanes, vinca alkaloid-associated SCLE has never been reported.

In addition to taxanes and vinca alkaloids, the epothilones and halichondrin class microtubule dynamics inhibitors have recently been added as approved cancer chemotherapeutics, which also act through microtubule alterations. The epothilones bind to the same taxane-binding site on the tubulin heterodimer subunit and, like the taxanes, prevent tubulin dissociation leading to microtubule stabilization [17]. Halichondrin class drugs bind tubulin near the vinca alkaloid binding site and inhibit intra-chain crosslinks between sulfhydryl groups ultimately leading to suppressed microtubule polymerization with no effect on microtubule shortening [18]. The epothilone and halichondrin drugs are only approved for treatment of breast cancer. There are no reports of SCLE with their use, although these drugs have been used in far fewer patients to date than taxanes or vinca alkaloids.

In summary, the clinical use of taxanes in oncology is associated with SCLE. In a patient with the requisite immunogenetic profile, taxanes are hypothesized to lead to the appearance or increase of anti-Ro/SS-A antibody and ultimately cutaneous disease through increased microtubule associated Ro52 immunologic exposure. Microtubule dynamics may be one of many converging cellular pathways leading to drug-induced SCLE. Drugs that work by stabilizing microtubules, such as epothilones (ixabepilone) and halichondrins (eribulin), are predicted to cause a similar effect. Dermatologists and oncologists should be aware of this potential adverse drug reaction, especially in patients with a history of anti-Ro/SS-A antibody.

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