Docetaxel (Taxotere) Induced Subacute Cutaneous Lupus Erythematosus: Report of 4 Cases

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ABSTRACT. ***Objective.*** We describe 4 patients who developed subacute cutaneous lupus erythematosus (SCLE)-like photodistributed eruptions after ingestion of docetaxel (Taxotere). The development of SCLE-like cutaneous eruptions has been associated with the intake of drugs including thiazide diuretics, calcium channel blockers, angiotensin converting-enzyme inhibitors, phenytoin, etanercept, antihistaminics, interferons, statins, and terbinafine. Docetaxel, a chemotherapeutic drug used in breast cancer therapy, has not to our knowledge been reported to cause SCLE.

Methods. Skin biopsies were obtained from 4 patients with photodistributed rashes while taking docetaxel.

Results. In all patients, skin biopsies were remarkable for an atrophying interface dermatitis associated with mucin deposition. Immunofluorescent testing revealed the characteristic pattern of SCLE, namely, granular epidermal keratinocyte deposition of IgG and C5b-9. The eruptions resolved following cessation of the drug.

Conclusion. Pathogenetically, docetaxel may evoke a lupus-like eruption through its proapoptotic effects on replicating cells, which could in turn provoke the release of nucleosomes postulated to be target antigens in LE. It seems reasonable to postulate that the rapidly replicating keratinocyte, when subjected to the cytotoxic effects of docetaxel, would also manifest nucleosome release followed by a local autoimmune reaction in a genetically predisposed host. (J Rheumatol 2004;31:818–20)

Key Indexing Terms:
DOCETAXEL CUTANEOUS LUPUS ERYTHEMATOSUS NUCLEOSOME

Subacute cutaneous lupus erythematosus (SCLE) is a subtype set of lupus erythematosus (LE) with distinct clinical features comprising an annular eruption of papulosquamous lesions, typically in photodistributed areas[1,2]. Patients with SCLE characteristically express either no or only mild systemic findings in addition to the skin lesions[1,2]. Development of SCLE-like cutaneous eruptions has been associated with the intake of drugs including thiazide diuretics[3-5], calcium channel blockers[6,7], angiotensin converting-enzyme inhibitors[5], phenytoin[8], etanercept[9], antihistaminics[10,11], interferons[5], statins[5], the novel antiangiogenesis factor COL-3[12], and antifungal agents[13,14]. Docetaxel (Taxotere), a chemotherapeutic drug used in breast cancer, has never to our knowledge been implicated as a cause of drug induced SCLE. We describe 4 cases of apparent docetaxel induced SCLE.

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CASE REPORTS

Case 1. A 50-year-old woman was found to have breast carcinoma in 1988 and underwent lumpectomy and axillary node dissection with postoperative chemotherapy and radiation therapy. In January 2002, she developed recurrent breast cancer with liver metastasis. She was treated with docetaxel (Taxotere) and capecitabine (Xeloda), and within a few weeks developed multiple annular, erythematous patches involving sun exposed skin. A biopsied chest lesion showed an atrophying interface dermatitis with mesenchymal mucin deposition. Immunofluorescent analysis showed granular nuclear decoration of epidermal keratinocytes for IgG and C5b-9 along with a negative lupus band test. Serology revealed a markedly positive anti-Ro/SSA assay. Docetaxel was discontinued, although she continued the other drug and was given a tapering dose of prednisone over a course of 3 weeks. The lesions resolved.

Case 2. A 70-year-old woman with carcinoma of the right breast underwent a modified radical mastectomy and was found to have axillary lymph node metastases. She underwent chemotherapy with docetaxel (Taxotere) and gemcitabine. After the first cycle she developed a rash comprising photodistributed erythematous plaques. The docetaxel chemotherapy was temporarily interrupted and the rash improved significantly. She then received additional infusions and the rash flared. Serologic studies showed positive anti-Ro/SSA antibodies. Chemotherapy was again withdrawn and the eruption resolved completely. A skin biopsy revealed an atrophying interface dermatitis with mesenchymal mucin deposition (Figure 1). A second biopsy for immunofluorescence showed prominent fine granular cytoplasmic deposition of IgG and C5b-9 within epidermal keratinocytes (Figure 2).

Case 3. A 63-year-old woman had a history of photosensitive eruption of the arms, legs, and V of the chest. She was diagnosed with breast carcinoma, metastatic to the bone and liver. She was given docetaxel (Taxotere) and trastuzumab (Herseptin) in July 2002. Four to 6 months later, she noted a stinging, pruritic cutaneous eruption. The eruption worsened during the spring and summer months. Clinical examination revealed erythematous

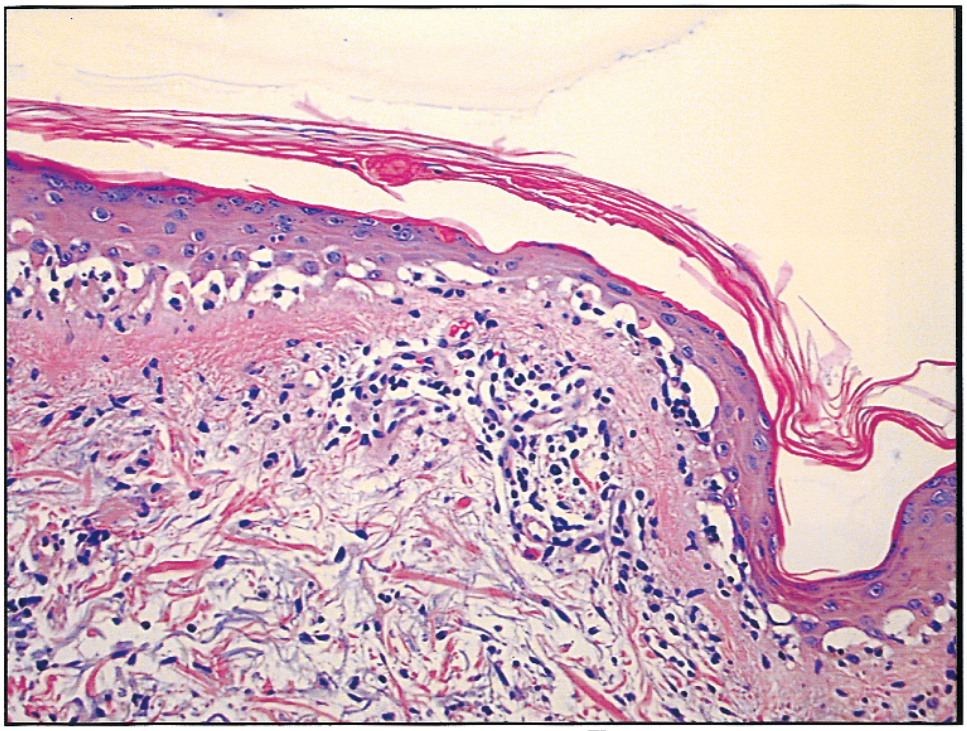

Figure 1. The biopsy was remarkable for an attenuated epidermis revealing a lymphocytic interface dermatitis with suprabasilar keratinocyte necrosis to which there was satellitosis of lymphoid cells. The dermis was remarkable for a modest perivenular lymphocytic infiltrate associated with prominent mesenchymal mucin deposition.

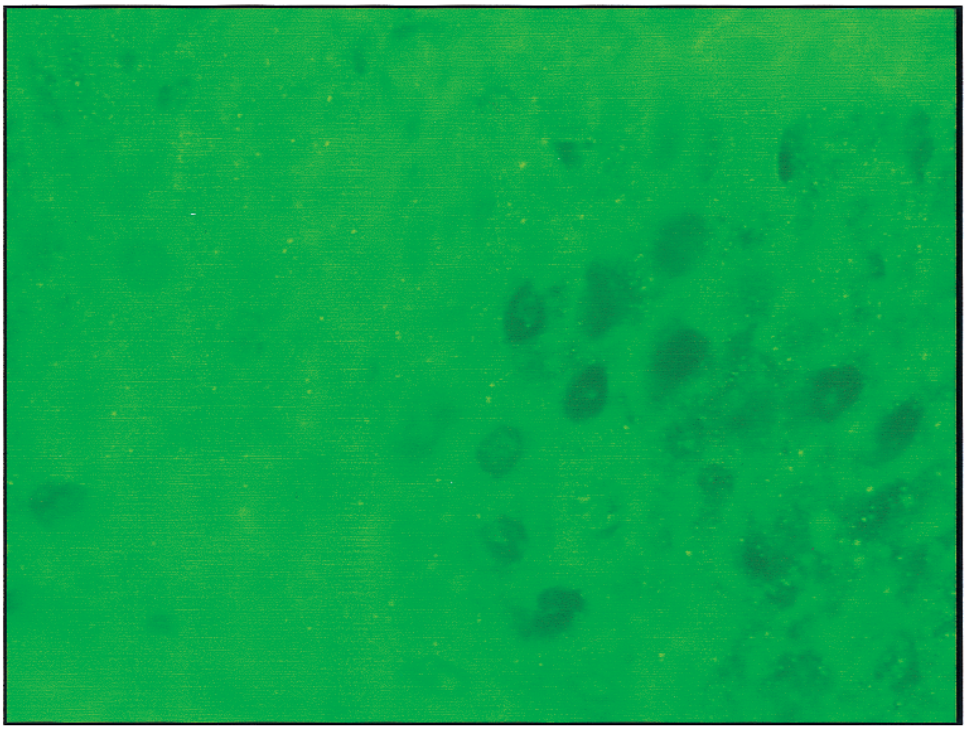

Figure 2. There was prominent fine granular deposition of IgG within epidermal keratinocytes, corroborating a diagnosis of SCLE.

papules, some with annular configuration, of the arms, legs, and V of the chest. Serologic studies were positive for SSA and SSB antibodies as well as positive antinuclear antibody (ANA; 1:160, speckled pattern). A biopsy revealed an atrophying interface dermatitis characterized by epithelial attenuation with lymphocyte tagging along the dermal-epidermal junction accompanied by basilar vacuolar change with keratinocyte necrosis. In addition there was splaying of the dermis by abundant mesenchymal mucin. Direct immunofluorescent testing showed prominent granular deposition of IgG and Cb-9 within epidermal keratinocytes. Withdrawal of the docetaxel and application of triamcinolone acetonide 0.1% to lesions resulted in resolution of lesions.

Case 4. A 69-year-old woman was diagnosed with adenocarcinoma of the lung in May 2003. She began chemotherapy consisting of carboplatin and paclitaxel (Taxol) in July 2003. She tolerated the initial 4 treatments. However, 7 days after receiving her fifth treatment she developed an erythematous, mildly scaling eruption involving the V of the chest, right arm, and upper back. Histopathologic examination revealed an atrophying interface dermatitis with concomitant mesenchymal mucin deposition compatible with SCLE. Her clinical lesions resolved within 4 weeks after discontinuation of paclitaxel. Direct immunofluorescent studies revealed weak staining of epidermal keratinocytes for C5b-9, corroborating the diagnosis of partially treated drug induced SCLE.

DISCUSSION

Idiopathic SCLE occurs most often in women aged 15 to 40 years[1,2]. There appears to be a genetic contribution to pathogenesis, as patients with anti-Ro positive SCLE manifest an increased frequency of HLA-DR2 and -DR3 expression. While renal, vascular, and central nervous system complications are unlikely, half of all patients with SCLE develop arthralgia, fatigue, leukopenia, or other signs that are more typically associated with SLE[1]. Roughly 60–80% of the patients will have a positive ANA and anti-Ro/SSA antibody; they may or may not be positive for anti-dsDNA[1]. A variety of drugs have been reported to cause or to exacerbate SCLE, but these are the first cases of docetaxel induced SCLE to our knowledge. Evidence to implicate docetaxel includes the temporal association between administration of the drug and onset of lesions, resolution upon drug withdrawal, and exacerbation and recurrence upon rechallenge.

Docetaxel is a chemotherapeutic agent used as first-line treatment in metastatic breast carcinoma. Taxotere targets actively replicating cells by disrupting microtubule assembly and disassembly (tubulin polymerization), bcl-2 phosphorylation inactivation, and CPP32 cleavage[15]. The cycling cells are arrested in the G2/M phase and subsequently die by apoptosis[15]. It is possible that docetaxel induces SCLE through its proapoptotic effects on replicating cells. Apoptosis results in release of nucleosomes postulated to be target antigens in LE[15]. The treatment of LE-prone mice with docetaxel has been associated with an increase in circulating nucleosomes followed by aggravation of glomerulonephritis[15]. It seems reasonable to postulate that rapidly replicating keratinocytes, when subjected to the cytotoxic effects of docetaxel, would also manifest a nucleosome release followed by a local autoimmune reaction.

The treatment of idiopathic SCLE is typically low dose systemic steroids and/or photoprotection. In cases of drug based etiology, drug cessation is critical for resolution of lesions.

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