Subacute Cutaneous Lupus Erythematosus Exacerbated or Induced by Chemotherapy

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Background: Subacute cutaneous lupus erythematosus (SCLE), characterized by nonscarring, photodistributed, annular or papulosquamous plaques, is occasionally induced by medication. It has been strongly associated with antihypertensive medications and terbinafine hydrochloride.

Observation: We describe 3 women with breast cancer who developed SCLE-like eruptions after being administered doxorubicin hydrochloride and cyclophosphamide. Biopsy specimens of all 3 patients demonstrated an interface dermatitis. Treatment consisted of topical and/or systemic corticosteroids, photoprotection, and switching the chemotherapeutic regimens.

Conclusions: Based on clinicopathologic correlation and timing of chemotherapy exposure, the patients were believed to have drug-induced SCLE. Although cutaneous eruption, pruritus, and photosensitivity are known adverse effects of doxorubicin, to our knowledge there has been only 1 previously reported case of doxorubicin-induced SCLE.

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SUBACUTE CUTANEOUS LUPUS erythematosus (SCLE), first described in 1979,1 is a distinct subset of cutaneous lupus erythematosus characterized by nonscarring, photodistributed, annular or papulosquamous plaques with minimal or no associated systemic findings. It can occasionally be induced by medications, as first reported for hydrochlorothiazide in 19852 and subsequently reported for nearly 30 other medications, including angiotensin-converting enzyme inhibitors, calcium channel blockers, and terbinafine hydrochloride.3 Doxorubicin hydrochloride is a chemotherapeutic agent indicated for a large number of hematologic and solid tumors, and, to our knowledge, there has been only 1 previously reported case of doxorubicin-related SCLE.4 We report 3 cases of SCLE-like eruptions induced or exacerbated by a chemotherapeutic combination of cyclophosphamide and doxorubicin.

REPORT OF CASES

CASE 1

A 44-year-old woman with a history of Sjögren syndrome (positive for anti-Ro/SS-A and anti-La/SS-B antibodies) and no previous photosensitivity was diagnosed as having breast cancer and treated with mastectomy and a combination of cyclophosphamide and doxorubicin. She developed new-onset, photodistributed, erythematous scaly plaques after her third round of chemotherapy with cyclophosphamide and doxorubicin (Figure 1). Her other medications (all part of her chemotherapeutic regimen) included acetaminophen/hydrocodone bitartrate, diphenhydramine hydrochloride, lorazepam, palonosetron hydrochloride, dexamethasone sodium phosphate, and a mouthwash for stomatitis. Laboratory evaluation revealed the following abnormal values: hemoglobin, 9.8 g/dL (reference range, 11.5-15.0 g/dL); hematocrit, 29.6% (34%-44%); differential lymphocyte count, 9% (14%-46%); and differential segmented neutrophil count, 81% (40%-74%) (to convert hemoglobin to grams per liter, multiply by 10; hematocrit and differential counts of lymphocyte and neutrophil to proportions of 1, multiply by 0.01). Her urinalysis results were normal other than showing trace white blood cell esterase and some crystals. Serum protein electrophoresis showed a γ-globulin level of 1.8 g/dL (reference range, 0.5-1.6 g/dL) with no M spike. Serological analysis showed an anti-Ro/SS-A titer of 1174 arbitrary units (AU) per milliliter (reference threshold for positive results, >120 AU/mL) and an anti-La/SS-B titer of 270 AU/mL (positive threshold, >120 AU/mL), whereas
results were negative for anti–double-stranded DNA, anti-U1-ribonucleoprotein, anti-Smith, antiscleroderma-70, antihistone, anti–Jo-1, and anticentromere antibodies. Skin biopsy specimens showed a moderately intense perivascular lymphocytic infiltrate with a scale crust, basal vacuolization, and dyskeratotic keratinocytes consistent with an interface dermatitis. Treatment that included photoprotection, fluticasone propionate lotion, hydroxyzine hydrochloride, and a prednisone taper led to improvement, but the eruption flared during her next round of chemotherapy with a combination of cyclophosphamide and doxorubicin and required additional prednisone therapy. Her regimen was switched to paclitaxel and trastuzumab, but the eruption flared with this regimen as well. She then began treatment with oral hydroxychloroquine sulfate, 200 mg once daily, which led to improvement, but she continued to experience flares of her eruptions with each subsequent administration of paclitaxel. Four weeks after completing chemotherapy, her eruption resolved, and treatment with hydroxychloroquine was tapered and discontinued over several months. At last follow-up, she had had no further skin manifestations.

CASE 2

A 42-year-old woman with a known history of SCLE (positive for anti-Ro/SS-A antibodies and negative for anti-La/SS-B antibodies) that was well controlled with photoprotection; hydroxychloroquine sulfate, 200 mg twice daily; thalidomide, 50 mg nightly; and occasional prednisone tapers was diagnosed as having breast cancer. Her treatment included mastectomy and chemotherapy with a combination of cyclophosphamide and doxorubicin and required additional prednisone therapy. Her regimen was switched to paclitaxel and trastuzumab, but the eruption flared with this regimen as well. She then began treatment with oral hydroxychloroquine sulfate, 200 mg once daily, which led to improvement, but she continued to experience flares of her eruptions with each subsequent administration of paclitaxel. Four weeks after completing chemotherapy, her eruption resolved, and treatment with hydroxychloroquine was tapered and discontinued over several months. At last follow-up, she had had no further skin manifestations.

A 73-year-old woman with a history of basal cell skin cancer, hypertension, and hypothyroidism was diagnosed as having breast cancer and treated with lumpectomy and sentinel lymph node biopsy. Her biopsy specimen was positive for cancer, and subsequent axillary dissection revealed several additional lymph nodes positive for cancer. She began therapy with a combination of cyclophosphamide and doxorubicin and developed an eruption of photodistributed, erythematous, flat-topped papules and slightly scaly plaques after the fourth and final round of therapy. Her other medications included levothyroxine sodium, amiodipine besylate/benazepril hydrochloride, ibandronate sodium, calcium, fish oil, vitamin B complex, cholecalciferol, and vitamin E. She was also receiving filgrastim, granisetron hydrochloride, and promethazine hydrochloride as part of her chemotherapeutic regimen. Laboratory evaluation results showed the blood cell count, comprehensive metabolic profile, and erythrocyte sedimentation rate all within reference ranges. Serological analysis showed concentrations of antinuclear antibodies of 464 U/mL (positive threshold, >120 U/mL) and anti-Ro/SS-A of 464 U/mL (positive threshold, >120 U/mL), whereas results were negative for anti-La/SS-B, anti–double-stranded DNA, anti-U1-ribonucleoprotein, anti-Smith, antiscleroderma-70, antihistone, anti–Jo-1, and anticentromere antibodies. A skin biopsy specimen showed partial epidermal necrosis, superficial and deep perivascular and periannexal lymphocytic infiltrate, and basal vacuolization consistent with an interface dermatitis (Figure 3 and Figure 4). Direct immunofluorescence revealed nonspecific 1+ staining of IgG on the cell surface within the upper epidermis. Her eruption was treated with a prednisone taper and continuation of her previous SCLE regimen, and her chemotherapy was switched to paclitaxel and carboplatin, which led to resolution of her bullous lesions and no further recurrences. At last follow-up, her cutaneous lupus continued to be well controlled with thalidomide, 50 mg every third night; hydroxychloroquine sulfate, 200 mg twice daily; and fluticasone propionate lotion for occasional localized flares.
following abnormal values: hemoglobin, 10.3 g/dL (reference range, 11.5-15.0 g/dL); hematocrit, 30.8% (34%-44%); white blood cell count, 35.9 × 10^3/µL (4.0 × 10^3-15.5 × 10^3/µL); differential neutrophil count, 94% (40%-74%); differential lymphocyte count, 2% (14%-46%); glucose level, 52 mg/dL (65-99 mg/dL); alkaline phosphatase, 167 U/L (25-165 U/L); and aspartate aminotransferase, 72 U/L (0-40 U/L) (to convert white blood cell count to cells/µL, multiply by 0.001; glucose to millimoles per liter, multiply by 0.0555; and alkaline phosphatase and aspartate aminotransferase to microkatal per liter, multiply by 0.0167). Urinalysis results were normal. Analysis of antinuclear antibodies with reflex to extractable nuclear antigens was negative; therefore, anti-Ro/SS-A and anti-La/SS-B autoantibodies were not specifically evaluated. A skin biopsy specimen showed focal atrophy of the epidermis, basal vacuolar alteration, scattered dyskeratosis, and a superficial perivascular lymphocytic infiltrate in the dermis consistent with an interface dermatitis. She was initially treated with flu tacson propionate lotion and photoprotection, with minimal improvement. A switch to triamcinolone acetonide cream improved her symptoms, and her eruption resolved within a few weeks. At last follow-up, she had completed a course of dose-dense paclitaxel and radiation therapy with no further eruptions.

There are no formal criteria for diagnosing drug-induced SCLE (DI-SCLE); however, the best evidence implicating the involvement of a medication includes resolution of the eruption after treatment with the suspected medication has been discontinued.⁶ The clinical, serological, and histological features of DI-SCLE are similar to the idiopathic variant. The cutaneous eruption usually occurs within a few months of beginning treatment with the suspected drug; in a review of 71 published cases of DI-SCLE, the time to eruption ranged from 2 weeks to 3.2 years. That same report found that the mean time to clearance after discontinuing the causative medication was 5.8 weeks (range, 1-24 weeks).⁷ Since the first published case of hydrochlorothiazide-induced SCLE by Reed et al in 1985,⁸ numerous other medications have been reported to cause or exacerbate SCLE, including antifungals (terbinafine and griseofulvin), angiotensin-converting enzyme inhibitors, calcium channel blockers, spironolactone, taxanes (docetaxel and paclitaxel), tumor necrosis factor inhibitors, and statins.⁹ Generally, medications are implicated in about 10% of SCLE cases; however, in a study by Srivastava et al, medications were responsible in 15 of 70 cases (21%). Patients are often positive for anti-Ro/SS-A antibodies but, as in idiopathic SCLE in which anti-Ro/SS-A is found in about 75% of patients, it is not required for the diagnosis.⁶ Doxorubicin is a cytotoxic anthracycline isolated from cultures of Streptomyces species. It is both cytotoxic and cytocidal and indicated for a number of malignant neoplasms, including as adjuvant therapy in women with axillary lymph node involvement following resection of breast cancer. Common adverse effects include cardiotoxic effects, myelosuppression, secondary leukemia, and tumor lysis syndrome. Previously reported cutaneous adverse effects include alopecia, hyperpigmentation, extravasation-related necrosis, hand-foot syndrome (palmar-plantar erythrodysesthesia syndrome, cutaneous eruptions, and pruritus), and photosensitivity. All 3 women in this series were treated with free doxorubicin hydrochloride rather than the pegylated liposomal formulation, which has decreased cardiotoxicity and myelosuppressive properties but increased cutaneous toxicity.¹⁰ Chemotherapeutic agents (including taxanes,¹¹ fluorouracil,¹² and capecitabine⁹,¹³) have been implicated in DI-SCLE, and we found 1 previously reported case of SCLE induced by treatment with a combination
of cyclophosphamide and doxorubicin. In that report, the eruption occurred in a 58-year-old woman after she received her second dose of cyclophosphamide and doxorubicin. Because the eruption persisted despite the completion of chemotherapy, she required hydroxychloroquine sodium and thalidomide to control her cutaneous-limited disease.

All 3 women in this series had cyclophosphamide as part of their therapeutic regimen. Cutaneous adverse effects, including alopecia, hyperpigmentation, cutaneous eruptions, stomatitis, and, rarely, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported after treatment with cyclophosphamide, but photosensitivity has not. Cyclophosphamide, a well-recognized chemotherapeutic agent, is also used to treat a number of autoimmune conditions, including systemic lupus erythematosus, without exacerbating photosensitivity or cutaneous lesions. Because cyclophosphamide is not known to cause photosensitivity and does not cause exacerbation of cutaneous lupus lesions, we do not believe that it was the cause of the eruption seen in our patients.

Paraneoplastic SCL is a reported, with lung cancer being the most common association, but there are rare reports attributed to breast cancer. Because all 3 of our patients had breast cancer, we considered the possibility of a paraneoplastic process; however, unlike the patients in those reports, our patients did not meet the McLean criteria for a paraneoplastic dermatosis because their eruptions did not develop until after initiation of treatment.

The mechanism of DI-SCL might be related to photosensitivity caused by medication in a genetically predisposed patient. As reviewed by Sontheimer et al, most of the implicated medications are reported to produce photosensitive reactions. Two of our patients were known to be anti-Ro/SS-A positive, and the status of the third patient was unknown because analysis of antinuclear antibodies with reflex to extractable nuclear antigens was negative and therefore anti-Ro/SS-A was not specifically evaluated. Proposed mechanisms of action of previously reported chemotherapy-induced SCL include apoptosis due to taxanes resulting in nucleosome release initiating an autoimmune response and, similarly, destruction of basal layer keratinocytes by fluorouracil or capetitabine in combination with UV-B exposure. It is possible that the cytotoxic effects of treatment with cyclophosphamide and doxorubicin in our patients led to increased release of nucleosomes and, in particular, that doxorubicin, a known photosensitizing agent, resulted in the induction of SCL in 2 and exacerbation of SCL in 1 of these susceptible patients.

In conclusion, the clinical presentation, histopathologic findings, and resolution after a change in or completion of chemotherapy are consistent with doxorubicin-related SCL. To our knowledge, there has been only 1 previously reported case of doxorubicin-associated SCL, which is further supported by these 3 additional cases. We believe that dermatologists should be aware of this possible adverse effect.

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