Subacute cutaneous lupus erythematosus (SCLE) is a subset of cutaneous lupus erythematosus that was first described in 1979 by Sontheimer et al. It typically manifests as annular or papulosquamous eruptions on sun-exposed areas and is frequently associated with anti-Ro (SS-A) antibodies. In 1985, Reed et al described 5 patients with SCLE caused by hydrochlorothiazide use, the first reported cases of drug-induced SCLE (DI-SCLE). Other reports soon followed, implicating drugs in various categories. Up to 38% of SCLE cases are drug induced. The most commonly involved drugs include antifungal medications, hydrochlorothiazide, and calcium channel blockers. Chemotherapeutics are one of several drug classes that have been more recently implicated.

Among the chemotherapeutic agents that have been reported to induce SCLE are docetaxel, paclitaxel, fluorouracil, capecitabine, tamoxifen citrate, and doxorubicin hydrochloride with cyclophosphamide.

Herein, we report a new case of DI-SCLE due to monotherapeutic gemcitabine hydrochloride (hereafter gemcitabine). This agent may be added to the list of chemotherapeutic agents that can cause DI-SCLE.

Report of a Case

A 71-year-old woman with a history of multiple sclerosis was diagnosed as having intraductal carcinoma of the left breast (estrogen receptor negative, progesterone receptor negative, and human epidermal growth factor 2 negative) and was treated with lumpectomy, radiation therapy, and adjuvant chemotherapy with a combination of cyclophosphamide, methotrexate, and fluorouracil (Figure 1). Eleven years later, she underwent a hysterectomy for metastasis to the uterus and was treated with carboplatin and paclitaxel after surgery. She was found 1 year later to have metastasis to the lung, for which she underwent a metastasectomy, revealing a poorly differentiated estrogen receptor–negative, progesterone receptor–negative, and thyroid transcription factor 1–negative carcinoma. She received 2 doses of systemic liposomal doxorubicin, after which she was treated with capecitabine for 20 months. Following a 6-month chemotherapy holiday, a chest radiograph revealed a new pulmonary nodule, for which gemcitabine was started.

After her second weekly dose of gemcitabine, she developed erythematous (2-3 cm) annular patches with scale on her bilateral extensor forearms and upper arms (Figure 2), as well as pink papules (5-9 mm) on her central chest. In addition, the patient soon developed low-grade fevers and profound fatigue. The remainder of the review of systems disclosed no abnormalities. Her other medications included aspirin, fluoxetine hydrochloride, furosemide, gabapentin, zolpidem tartrate, levothyroxine sodium, and calcium with cholecalciferol, all of which had been started at least 6 months before exanthem onset. Laboratory evaluation revealed the following abnormal values: globulin level of 3.8 g/dL (reference range, 2.3-3.5 g/dL), platelet count of 367 × 10^3/μL (reference range, 150-350 × 10^3/μL), total calcium level of 8.4 mg/dL (reference range, 8.8-10.2 mg/dL), and platelet count of 367 × 10^3/μL (reference range, 150-350 × 10^3/μL), total calcium level of 8.4 mg/dL (reference range, 8.8-10.2 mg/dL),

IMPORTANCE Several chemotherapeutic agents have been reported to induce subacute cutaneous lupus erythematosus (SCLE). To our knowledge, this is the first report to date of SCLE induced by monotherapeutic gemcitabine hydrochloride and includes a comprehensive review of all published cases of chemotherapeutic drug-induced SCLE.

OBSERVATIONS We describe a patient who developed a SCLE-like eruption after being administered gemcitabine and discuss 16 other published cases of chemotherapeutic drug-induced SCLE.

CONCLUSIONS AND RELEVANCE This case and a review of the literature call attention to gemcitabine and other chemotherapeutic agents that have been reported to cause drug-induced SCLE. We also discuss the clinical features of the disease.

Published online July 10, 2013.

Invited Commentary page 1075
Supplemental content at jamadermatology.com

Author Affiliation: Department of Dermatology, Yale University School of Medicine, New Haven, Connecticut.

Corresponding Author: Jennifer N. Choi, MD, Department of Dermatology, Yale University School of Medicine, 333 Cedar St, Laboratory for Medicine and Pediatrics 5040, New Haven, CT 06510 (jennifer.choi@yale.edu).
white blood cell count of 25,000/μL (reference range, 4,000-10,000/μL), and ratio of serum urea nitrogen to creatinine of 8.9 (reference range, 10.0-20.0) (to convert platelet count to $\times 10^9$/L, multiply by 1.0; to convert white blood cell count to $\times 10^9$/L, multiply by 0.001; and to convert total calcium level to millimoles per liter, multiply by 0.25). Serological analysis was positive for anti-Ro (SS-A), anti-La (SS-B), and anti-nuclear antibodies (ANAs), with an ANA titer of 1:640 (reference range, <1:40) and a speckled ANA pattern. Results were negative for anti–double-stranded DNA and anti-Smith antibodies. Skin biopsy specimens showed focal parakeratosis, thinned epidermis, vacuolar alteration along the dermoepidermal junction, and focal pigment incontinence with a superficial and deep perivascular and perianadnexal infiltrate composed predominantly of small lymphocytes, occasional plasma cells, and a few eosinophils (Figure 3). Focal mild follicular infundibular dilatation and focal basement membrane thickening were also seen. A prominent increase in dermal mucin was not seen, nor was morphologic evidence of fungal hyphae observed. Given that gemcitabine was the only medication that had been started in the recent past, it was discontinued. Treatment with desoximetasone, 0.25%, cream twice daily to the affected skin areas was minimally effective, with extension of the exanthem over her thighs and calves, as well as the extensor surfaces of her arms and torso, 2 weeks later. A 20-day prednisone taper led to marked improvement. Within 2 weeks (and 5 weeks after the last dose of gemcitabine), her systemic symptoms and eruption resolved. Subsequently, her chemotherapeutic regimen was switched to cyclophosphamide, fluorouracil, and methotrexate, with no recurrence of the eruption. Anti-Ro autoantibodies remained present 5 weeks after the resolution of cutaneous symptoms. Ten weeks after discontinuing gemcitabine therapy, her ANA screen remained positive, with a titer of 1:640 and a speckled ANA pattern.

Discussion

To our knowledge, this is the first report of monotherapeutic gemcitabine–induced SCLE. In 2004, Chen et al² described a 70-year-old woman who developed photodistributed erythema...
Subacute Cutaneous Lupus Erythematosus

Case Report/Case Series  Research

Figure 3. Skin Biopsy Specimens

A, Epidermal atrophy, vascular ectasia, and superficial and deep dermal inflammatory infiltrate (hematoxylin-eosin, original magnification ×100). B, The inflammatory infiltrate consists predominantly of small lymphocytes, and eosinophils are rare (hematoxylin-eosin, original magnification ×200). C, Mild follicular infundibular dilatation, mild hyperkeratosis, and focal parakeratosis (hematoxylin-eosin, original magnification ×200). D, Highlights focal basement membrane thickening. Basal vacuolar change and pigment incontinence are also present (periodic acid–Schiff, original magnification ×200).

atous plaques after her first cycle of docetaxel and gemcitabine. When docetaxel was temporarily discontinued, the exanthem improved significantly. A rechallenge of docetaxel led to a flare, and when the therapy was again withdrawn, the eruption completely resolved. Although this patient was receiving gemcitabine, her cutaneous symptoms of DI-SCLE coincided with the administration of docetaxel and was not attributed to gemcitabine use. In contrast, our patient’s SCLE outbreak is attributable to gemcitabine because this medication was her only chemotherapeutic agent that was initiated 2 weeks before symptom onset, and her symptoms resolved shortly after gemcitabine discontinuation. Histopathologically, DI-SCLE manifests as an interface dermatitis or lichenoid tissue reaction with focal vacuolization of the epidermal basal layer associated with a perivascular dermal lymphocytic infiltrate.4 Our patient’s skin biopsy specimen was consistent with DI-SCLE.

All English-language PubMed and MEDLINE reports of chemotherapeutic drug–induced SCLE were reviewed for commonalities among cases and potential differences across drug types (eTable in the Supplement). To date, the following 7 chemotherapeutic agents have been previously reported to induce SCLE: docetaxel,5 paclitaxel,5-7 tamoxifen,8 fluorouracil,1,9 capecitabine,1,2,10 and doxorubicin with cyclophosphamide.7,11 Several reports described patients receiving 2 concomitant chemotherapeutic agents; for each case, only one agent was thought by the authors to have induced DI-SCLE. For example, in 4 cases reported in association with doxorubicin and cyclophosphamide, doxorubicin was thought to have been the inducer.7,11

Patients in the reported cases ranged in age from 42 to 84 years, with a mean age of 62 years and a median age of 64 years. All patients were female, with 12 of 17 having new-onset, metastatic, or recurrent breast cancer. Other malignant neoplasms included new-onset and metastatic lung, hepatic, gastric, and colorectal cancers. All patients had histopathological findings consistent with DI-SCLE. Cutaneous symptoms of DI-SCLE developed from days to 4 to 6 months after the initial chemotherapeutic treatment, although these data were reported for only 15 of 17 cases.
Anti-Ro (SS-A) antibodies are regarded as the most common serum marker for SCLE and are present in up to 90% of cases. Although most patients with either form of SCLE (idiopathic or drug induced) are positive for anti-Ro (SS-A) antibodies, their presence is not pathognomonic. Anti-La (SS-B) autoantibodies are positive in fewer patients with SCLE. It has been shown that UV-B radiation induces translocation of the Ro/SS-A antigen from the nucleus and cytoplasm of cultured keratinocytes to the cellular membrane. Such cell membrane antigen expression may lead to the production of autoantibodies seen in these patients. Adachi and Horikawa have speculated that chemotherapeutic agents, including paclitaxel, docetaxel, and fluorouracil, may also induce translocation of the Ro/SS-A antigen to the cell surface of keratinocytes in a manner similar to that of UV-B radiation.

All the reported cases of DI-SCLE showed resolution of cutaneous symptoms on withdrawal of the offending agent and, in some cases, with corticosteroid therapy. The time to resolution after drug discontinuation ranged from 2 weeks to 6 months in 13 cases that reported these data. Seven of 17 cases showed resolution of cutaneous symptoms with drug discontinuation and no additional therapy. The 10 other cases required drug discontinuation and corticosteroid administration. Five of these reports noted sun protection as a measure taken in addition to corticosteroid use. Four cases reported the use of topical corticosteroids, with improvement. Several cases reported resolution after systemic corticosteroids were used.

Mitotic inhibitors, specifically docetaxel and paclitaxel, have been implicated in DI-SCLE. By inhibiting mitosis, these drugs prevent cells from replication and can cause dividing cells to become apoptotic. Docetaxel arrests cycling cells in the interphase and mitosis phase, and the cells subsequently die by apoptosis. Nucleosomes released as a result of apoptosis have been postulated to be lupus erythematosus target antigens. Chen et al hypothesized that the cytotoxic effects of a chemotherapeutic agent that disrupts actively replicating cells might lead to such a nucleosome release and autoimmune reaction and proposed that rapidly replicating keratinocytes would manifest a similar nucleosome release, followed by an autoimmune response when subjected to docetaxel. Perhaps this reasoning can be extended to other chemotherapeutic agents that interfere with the cell cycle and induce replicating cells to apoptosis. Of 7 chemotherapeutic drugs that have been reported to induce DI-SCLE, 6 prevent DNA synthesis and cell replication, the result of which could be apoptosis (Table).

While the common presumption is that the chemotherapeutic drug itself is the culprit, a recent study showed that a patient who developed a cutaneous lupus–like reaction with the administration of paclitaxel showed no such reaction with 4 subsequent administrations of albumin-bound paclitaxel, which does not contain a polyoxymethylated castor oil emollient (called Cremophor EL) in its formulation. The authors propose that other reports of paclitaxel-induced SCLE may in fact be due to this polyoxymethylated castor oil emollient and not the chemotherapeutic agent.

Others have hypothesized and rejected the idea that SCLE observed in their patients receiving chemotherapy was paraneoplastic, because symptoms began after the initiation of therapy and not before, a characteristic excluded from the criteria of paraneoplastic dermatoses by McLean. To date, 12 cases of paraneoplastic SCLE have been published.

Lowe et al noted that of 41 drugs identified as causative of DI-SCLE, 13 were known to be capable of producing photosensitivity. One of those 13 was the chemotherapeutic agent docetaxel, which Chen et al have reported in association with 3 cases of DI-SCLE. Fluorouracil and doxorubicin, other chemotherapeutic agents for which reports of inducing DI-SCLE have been published, are also known for having photosensitivity as an adverse effect. The role of photosensitivity in inducing DI-SCLE has been called into question by Callen, who noted that not all drugs implicated in DI-SCLE are photosensitizers and that some patients with DI-SCLE can be treated with alternate drugs that are also photosensitizers, without recurrence of symptoms.

Gemcitabine is a nucleoside analogue that, like fluorouracil and other pyrimidine analogues, replaces cytidine during DNA replication, leading to apoptosis. Gemcitabine also inactivates ribonucleotide reductase, further resulting in apoptosis. Although the mechanism by which gemcitabine may induce SCLE remains to be elucidated, its induction of apoptosis likely leads to a release of nucleosomes, which may lead to an autoimmune response.

Drug-induced SCLE is a reversible condition with mild to moderate symptoms. Offending drug cessation and the administration of topical corticosteroids generally lead to the resolution of both cutaneous and serological features. Chemotherapeutic and other drugs that have been reported to induce DI-SCLE are given to hundreds of thousands of patients, with proportionately few documented cases of DI-SCLE. As the number of patients diagnosed as having cancer and the use of chemotherapeutic agents increase, reports of chemotherapy-induced DI-SCLE will also likely become more prevalent.
Subacute Cutaneous Lupus Erythematosus

PRACTICE GAPS

Drug-Induced Subacute Cutaneous Lupus Erythematosus—Filling the Gap in Knowledge

Jeffrey P. Callen, MD

The year 1979 marked the first publication that used the term subacute cutaneous lupus erythematosus (S克莱).2 Six years later, in 1985, Reed et al2 first linked a drug to the onset of the disease, namely, hydrochlorothiazide. During almost 3 decades since that publication, multiple drugs have been linked to this phenomenon, now numbering more than 100 agents, and the occurrence of a drug as a cause or as an exacerbating agent represents roughly 20% of newly diagnosed cases of S克莱.3

There is a lack of understanding about the difference between drug-induced S克莱 (DI-S克莱) and drug-induced systemic lupus erythematosus (S克莱) (DI-S克莱). A misunderstanding about the serologic profile of DI-S克莱 also exists. Furthermore, there is a lack of consensus on the timing for development of the reaction for the onset of the therapy, with some investigators suggesting that this phenomenon might occur even in patients who have been receiving long-term therapy with a potential agent.

Wiznia and colleagues4 present a typical patient with DI-S克莱 who developed disease shortly after exposure to a new chemotherapeutic agent. Their patient was not taking other medications that might be implicated as causes. The eruption occurred within 1 week of the administration of gemcitabine hydrochloride but took several weeks for resolution, inciting her physician to use a short course of systemic corticosteroids.