

# Paraneoplastic Subacute Cutaneous Lupus Erythematosus: An Underrecognized Entity

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*Subacute cutaneous lupus erythematosus (SCLE) is a form of cutaneous lupus erythematosus that most often presents as scaly, erythematous, papulosquamous, or annular papules and plaques in a photodistributed pattern. Subacute cutaneous lupus erythematosus is classically considered to be either idiopathic or drug induced. There have been few reports of SCLE arising in the setting of malignancy, raising the possibility that paraneoplastic SCLE may be a rare distinct subset of lupus. We report a case of SCLE arising as a paraneoplastic phenomenon in the setting of small cell lung cancer. Given the close temporal proximity of the detection of malignancy and the development of the rash in our patient, we believe this report presents a case of paraneoplastic SCLE. The presentation of new-onset idiopathic SCLE should prompt a careful review of systems and age-appropriate cancer screening, as SCLE may be a sign of an occult malignancy.*

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**L**upus erythematosus is a chronic autoimmune disease with protean manifestations affecting multiple organ systems; 70% to 85% of patients with lupus erythematosus present with skin involvement.<sup>1</sup> Cutaneous lupus erythematosus is classified as acute, subacute, or chronic. These different types of cutaneous lupus erythematosus have classic presentations; subsets are based on duration of skin

lesions, clinical presentation, pathology, and presence of systemic manifestations. Subacute cutaneous lupus erythematosus (SCLE) was described in 1979 by Sontheimer et al<sup>2</sup> as a distinct subset of cutaneous lupus erythematosus.<sup>3</sup> Subacute cutaneous lupus erythematosus manifests as nonscarring, scaly, erythematous papules and plaques, often with either a papulosquamous or annular presentation. It classically has been categorized into 2 groups: idiopathic and drug induced.<sup>4,5</sup> Seventy percent to 90% of patients with SCLE are considered photosensitive because of the photodistribution of lesions on the extensor aspects of the arms, shoulders, neck, upper chest, and back.<sup>1,5</sup> Similar to systemic LE, idiopathic SCLE is most common in young women, though the drug-induced form can occur in older individuals of either sex.<sup>5</sup>

Serology is not specific in SCLE; however, 70% to 90% of patients have positive anti-Ro/Sjögren syndrome antigen A (SS-A), whereas anti-La/Sjögren syndrome antigen B (SS-B) antibodies are found in only 35%.<sup>1</sup> Anti-Ro/SS-A antibodies also may be positive in patients with Sjögren syndrome, systemic lupus erythematosus, neonatal lupus erythematosus, drug-induced lupuslike syndrome, and homozygous C2 and C4 deficiency, indicating that the presence of anti-Ro/SS-A antibodies is not diagnostic of SCLE.<sup>1,5</sup> Patients with drug-induced SCLE often will have positive anti-Ro/SS-A and antinuclear antibodies (ANAs).<sup>3,6</sup> Effective treatments of idiopathic SCLE include photoprotection, topical and systemic corticosteroids, antimalarial agents, thalidomide, retinoids, dapsone, or systemic immunomodulatory therapy.<sup>1,4</sup> Patients with drug-induced SCLE typically improve within weeks of discontinuing the causative medication. Occasionally, however, some cases of SCLE that are considered to be drug induced do not improve on discontinuation of the drug. It is presumed that these cases actually are incidences of idiopathic SCLE that have been triggered by exposure to the medication.

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Most cases of SCLE can be categorized as either idiopathic or drug induced; however, there are some reports in the literature in which SCLE has been associated with malignancies, most notably of the lungs, liver, stomach, head and neck, uterus, and breast, as well as in patients with Hodgkin lymphoma.<sup>7-12</sup> Although this entity is rare, we believe that our patient with SCLE arising in the setting of small cell lung cancer represents a case of paraneoplastic SCLE.

### Case Report

A 61-year-old man presented with a diffuse photodistributed eruption of 3 months' duration. His medical history was remarkable for carcinoma of the colon, which had been treated 3 years prior via surgical resection and 5-fluorouracil, as well as small cell lung cancer, which was diagnosed 11 months prior. Because of the extent of progression of the lung cancer at the time of diagnosis, surgical resection was not feasible. The patient initially was treated with cisplatin, which was followed by 2 months of radiation therapy. Approximately 2 weeks after completing radiation and 1 day after receiving a dose of intravenous potassium, the patient noted the onset of the eruption. At the time, his medications included gabapentin, omeprazole, acetaminophen, and nitroglycerin. Physical examination revealed multiple annular, erythematous, scaly plaques, some with crusting, on the scalp, arms, chest, abdomen, and back (Figure 1). Biopsy of a lesion on the right upper back showed parakeratosis, focal interface changes at the dermoepidermal junction with basal layer vacuolization, a perivascular and periadnexal (perieccrine) lymphocytic infiltrate, and mucin deposition in the dermis highlighted with a colloidal iron stain (Figure 2). Direct immunofluorescence was negative, but laboratory test results revealed positive serology with an ANA titer of 1:160 in a speckled pattern and an anti-Ro/SS-A antibody of 4.2 (reference range, <1). He also was found to have a zinc level of 46  $\mu\text{g}/\text{dL}$  (reference range, 70–150  $\mu\text{g}/\text{dL}$ ), a hemoglobin level of 12.5 g/dL (reference range, 13.5–17.5 g/dL), and a white blood cell count of  $4.0 \times 10^9/\text{L}$  (reference range,  $4.5\text{--}11.0 \times 10^9/\text{L}$ ). Anti-double-stranded DNA and antihistone antibodies were negative. The patient's metabolic panel and liver function tests were within reference range.

Based on the clinical presentation of photodistributed annular, erythematous, scaly plaques; the positive anti-Ro/SS-A antibody; and the histopathology, the diagnosis of SCLE was rendered. The patient was treated with topical betamethasone dipropionate cream 0.05%, which resulted in only slight improvement of the rash. One month after diagnosis the



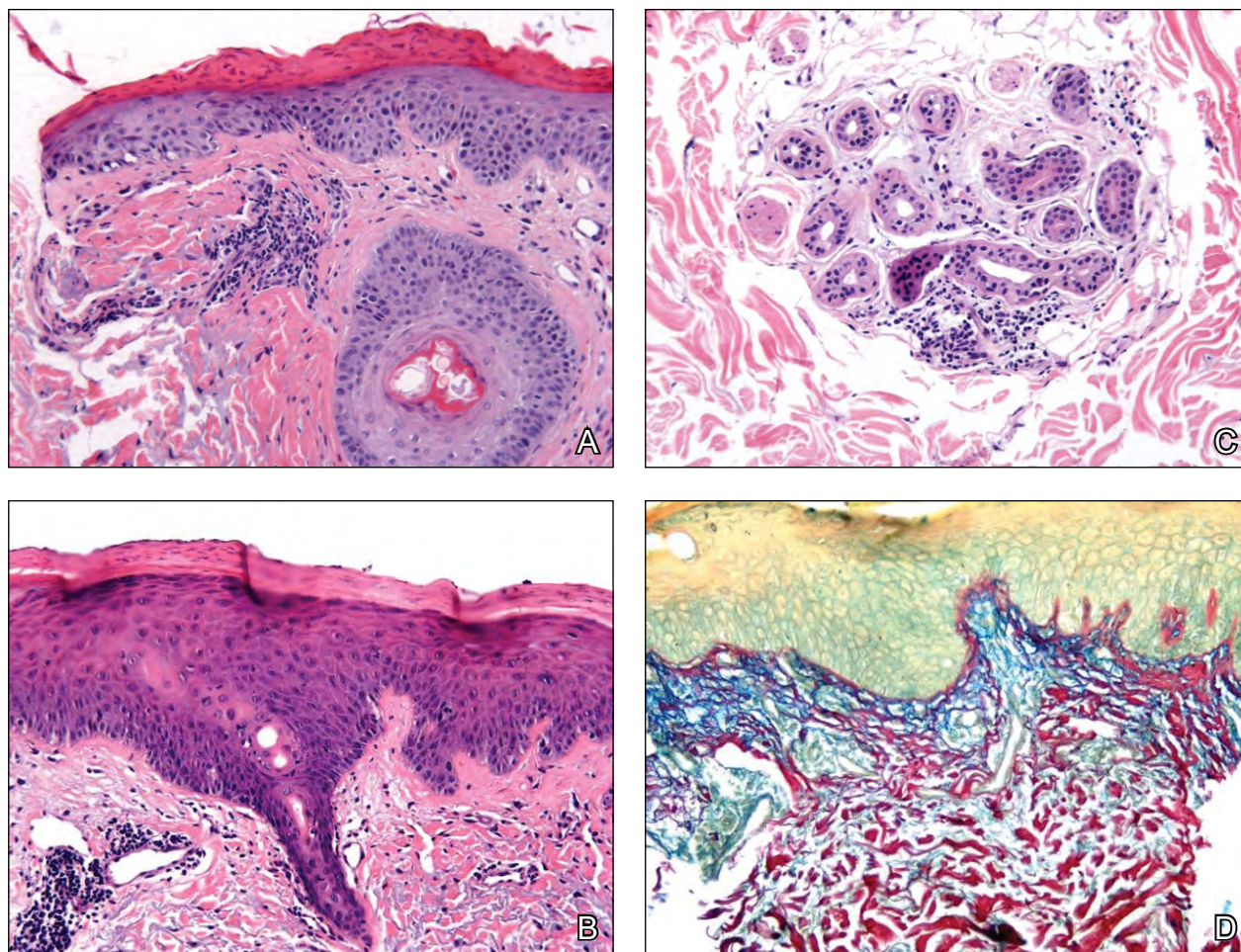
**Figure 1.** The patient presented with multiple annular, erythematous, scaly, and crusted plaques on the back.

patient's lung cancer was found to have progressed; he died 3 months later.

### Comment

Subacute cutaneous lupus erythematosus is an autoimmune inflammatory disorder characterized by classic skin findings and a positive anti-Ro/SS-A antibody in the majority of patients. Most cases are either classified as idiopathic or drug induced, but there have been reports in the literature of SCLE arising as a paraneoplastic phenomenon.<sup>7-12</sup>

Rheumatic diseases presenting as paraneoplastic entities have been recognized since the early 1900s.<sup>13</sup> A classic example of a rheumatic disease heralding an occult malignancy is dermatomyositis, with a 6% to 60% incidence of an associated cancer in affected patients.<sup>13</sup> There have been reports of patients with Raynaud phenomenon, scleroderma-like illnesses, lupus-like syndromes, polymyalgia rheumatica, and various arthritides and vasculitides presenting as paraneoplastic diseases.<sup>13,14</sup>



**Figure 2.** Punch biopsy specimen from the right upper back showed parakeratosis, focal interface changes at the dermoepidermal junction with basal layer vacuolization, a perivascular and periadnexal (perieccrine) lymphocytic infiltrate (A–C)(H&E; original magnifications  $\times 20$ ,  $\times 20$ , and  $\times 40$ , respectively), and mucin deposition in the dermis (D) (colloidal iron, original magnification  $\times 20$ ).

Although theories exist, the pathogenesis of paraneoplastic rheumatic disease has not been fully elucidated. Racanelli et al<sup>13</sup> proposed 3 hypotheses: (1) the malignancy and the rheumatic disease are a result of the same inciting factor (eg, a virus); (2) the paraneoplastic disease is a direct effect of an inflammatory toxin that the tumor cells have secreted; or (3) the rheumatic disease represents a hypersensitivity reaction to proteins that are expressed or exposed by the tumor and recognized as antigens by the host.<sup>13,14</sup> Szekanecz et al<sup>15</sup> suggested that hormones, cytokines, peptides, and other humoral factors directly affect the musculoskeletal system and affect immune function, thereby causing the patient with a neoplasm to present with rheumatologic concerns.

Few cases of malignancy-related SCLE have been reported in the literature. Paraneoplastic SCLE has been described in patients with lung, gastric, breast,

uterine, head and neck, and hepatocellular cancers, as well as Hodgkin lymphoma.<sup>7,8,11,16</sup> Few cases of paraneoplastic SCLE arising in patients with small cell lung cancer have been reported.

In 1997, Brenner et al<sup>9</sup> described a patient who initially presented with SCLE and was diagnosed with small cell carcinoma of the lung 3 months later. Similar to our case, the patient had a positive anti-Ro/SS-A antibody, ANA in a speckled pattern, and a negative antihistone antibody. The dermatosis improved when the malignancy was treated.<sup>9</sup> Another case reported by Trüeb and Trüeb<sup>10</sup> in 1999 described a patient who had a latency period of 9 months from the time of tumor diagnosis to the development of SCLE. The patient showed improvement of symptoms on treatment of the tumor but experienced exacerbation of the dermatosis when the tumor recurred. This patient also had a positive

anti-Ro/SS-A antibody.<sup>10</sup> Renner and Sticherling<sup>12</sup> reported another case in 2008. The authors described a patient who was diagnosed with SCLE in 1995 and developed small cell lung carcinoma 9 years later. The patient had elevated ANA and anti-Ro/SS-A, anti-La/SS-B, and antihistone antibodies,<sup>12</sup> but the latency period between the development of the dermatosis and detection of the malignancy raised the concern if it was a true case of paraneoplastic SCLE.

In 1986, McLean<sup>17</sup> proposed 2 criteria to help define paraneoplastic dermatoses: (1) the dermatosis must arise following the development of the malignancy, and (2) the dermatosis and the malignancy must follow a parallel course. Our patient fulfilled the first criteria in that his dermatosis developed 8 months following the initial diagnosis of the tumor during a recurrence of the malignancy. Because our patient died of lung cancer 4 months after developing SCLE and the cancer never regressed, it is difficult to determine if our patient would have met McLean's<sup>17</sup> second criterion. Although the eruption remained active as the tumor progressed, we were unable to determine if the rash would have resolved with successful treatment of the malignancy.

Funke et al<sup>18</sup> described 3 cases of SCLE in patients with breast cancer who were treated with doxorubicin hydrochloride. Each of the patients developed an eruption shortly after being exposed to the chemotherapeutic agent, making these cases more consistent with drug-induced SCLE rather than paraneoplastic SCLE. The authors suggested that exposure to cytotoxic drugs can lead to the release of substances that may induce SCLE in some patients.<sup>18</sup> Our patient developed SCLE on recurrence of a malignancy more than 2 months after being exposed to cisplatin. Although it is plausible that the eruption was induced by cisplatin, we believe that the close temporal proximity of the dermatosis and the recurrence of the malignancy in our patient are representative of a case of paraneoplastic SCLE in the setting of small cell carcinoma of the lung.

The histopathologic features in our patient were surprisingly subtle given his clinical appearance, which raised the question as to whether it truly was a case of SCLE, a gyrate erythema (such as erythema annulare centrifugum or erythema gyratum repens [EGR]), or a novel SCLE-like eruption related to his malignancy. Our diagnosis was based on the correlation of clinical and pathologic findings in the patient.

Erythema annulare centrifugum presents with a trailing scale in the superficial form, as opposed to the crusting displayed by our patient, which is more characteristic of SCLE. The diagnosis of EGR is based on the wood grain appearance of the eruption, which was not present in our patient who displayed annular

lesions. The serologic findings also supported the diagnosis of SCLE in our patient.

Despite the subtlety of the histopathologic features, the findings were most consistent with the diagnosis of SCLE based on the presence of focal vacuolar alteration at the dermoepidermal junction, the perieccrine inflammation, and the presence of mucin. In our patient, the pathologic evidence did not display the tightly cuffed perivascular lymphohistiocytic ("coat sleeve–like") infiltrate that is classically described in erythema annulare centrifugum. According to *Lever's Histopathology of the Skin*,<sup>19</sup> EGR demonstrates mild acanthosis, spongiosis, focal parakeratosis, and a superficial perivascular lymphocytic infiltrate with the presence of eosinophils, neutrophils, and melanophages. Our histopathology findings showed a perivascular infiltrate and parakeratosis, but acanthosis, spongiosis, eosinophils, neutrophils, and melanophages were absent. Additionally, EGR does not classically present as interface dermatitis with vacuolar change of the basal layer, periadnexal inflammation, or mucin deposition, all of which were present in our patient and supported a diagnosis of SCLE. Although direct immunofluorescence was negative in our patient, false-negative tests may be observed in patients with SCLE.<sup>19</sup> Based on these findings, we prefer to describe our case as paraneoplastic SCLE rather than a paraneoplastic SCLE-like eruption because we believe our patient met adequate criteria to warrant a diagnosis of SCLE.

## Conclusion

Paraneoplastic rheumatic diseases are well-recognized entities; however, malignancies rarely have been reported in patients with SCLE. This case of paraneoplastic SCLE in the setting of small cell lung cancer adds to the small collection of case reports associating SCLE with malignancy. Although SCLE is classically categorized as either idiopathic or drug induced, this report highlights the importance of considering a correlation between SCLE and the presence of a known neoplasm; perhaps more significantly, it also may reveal the presence of an occult tumor or relapse of a previously treated malignancy.<sup>16</sup> Therefore, it is critical for the clinician to perform a careful review of systems, detailed physical examination, and age-appropriate cancer screening in any patient with SCLE, as there is now increasing evidence suggesting that this dermatosis can be a paraneoplastic phenomenon.

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