

## ONLINE FIRST

## Tissue Eosinophilia

## Not an Indicator of Drug-Induced Subacute Cutaneous Lupus Erythematosus

Paul B. Hillesheim, DO; Soon Bahrami, MD; Brooke G. Jeffy, MD; Jeffrey P. Callen, MD

**Objective:** To investigate whether tissue eosinophilia is a differentiating histopathologic feature of drug-induced subacute cutaneous lupus erythematosus (DI-SCLE) compared with non-DI-SCLE.

**Design:** Retrospective medical record review with prospective blinded histopathologic analysis.

**Setting:** University-affiliated dermatology and dermatopathology practice.

**Patients:** Fifty-nine patients with SCLE were divided into DI (n=15) and non-DI (n=44) groups.

**Main Outcome Measures:** A dermatopathologist masked to the etiologic associations reviewed corresponding histopathologic specimens. For each patient, an eosinophil ratio was calculated as the mean eosinophil score (averaging eosinophil counts from 10 high-power histologic fields) divided by the intensity of inflammation. Eosinophil ratios for both groups were compared using the Mann-Whitney test.

**Results:** No significant difference was found in mean eosinophil ratios in the DI vs non-DI groups (0.11 vs 0.004;  $P=.34$ ). Mucin deposition was present in both populations and was not significantly different ( $P=.18$ ). The inflammatory infiltrate was superficial and deep in 10 patients (67%) in the DI group vs 24 (55%) in the non-DI group. Periadnexal inflammation was observed in 12 patients (80%) in the DI group vs 37 (84%) in the non-DI group, and basal layer liquefaction with dyskeratosis was seen in 15 patients (100%) in the DI group and in 37 (84%) in the non-DI group.

**Conclusions:** Tissue eosinophilia is not a differentiating histopathologic feature of DI-SCLE. Careful review of a patient's drug history in correlation with clinical findings remains the standard for identifying a drug as an etiologic or exacerbating factor in patients with SCLE.

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**D**RUG-INDUCED SUBACUTE cutaneous lupus erythematosus (DI-SCLE) was first described in 1985 by Reed et al,<sup>1</sup> who determined that hydrochlorothiazide was the causative agent in 5 patients with a photodistributed papulosquamous eruption. Additional drugs have since been implicated, including angiotension-converting enzyme inhibitors, calcium channel blockers, terbinafine, and, most recently, several chemotherapeutic agents.<sup>2-6</sup> These patients may or may not have a history of SCLE or systemic LE before a new pharmacologic therapy.

### See Practice Gaps at end of article

Clinically, the presentation of DI-SCLE is similar to that of non-DI-SCLE, characterized by nonscarring annular or papulosquamous lesions in a photodistributed pattern. Unlike in non-DI-SCLE, cutaneous lesions in DI-SCLE resolve on with-

drawal of the causative pharmacologic agent.<sup>2</sup> Systemic involvement may be seen in non-DI-SCLE, but it is rare in DI-SCLE.<sup>4</sup> The lateral aspect of the neck, upper back, chest, and dorsal arms are the most common areas involved in both types of SCLE. The legs may also be involved, with clinical features mimicking a small-vessel vasculitis.<sup>2</sup> Laboratory findings associated with both forms include positive antinuclear antibody and anti-Ro/SS-A antibody test results.<sup>3</sup>

The histopathologic findings of DI-SCLE have not been carefully analyzed in a blinded manner using a comparison with the findings in non-DI-SCLE. Typical histopathologic features of SCLE include liquefaction degeneration of the basal layer, a perivascular and periadnexal lymphocytic infiltrate, and dermal mucin deposition. Eosinophils are typically not seen in SCLE. In a previous study,<sup>7</sup> we demonstrated that tissue eosinophilia was predictive of drug-induced cutaneous vasculitis and thought that perhaps their presence in SCLE might also be predictive of DI-SCLE. This study

**Author Affiliations:**  
Department of Pathology and Laboratory Medicine (Drs Hillesheim and Bahrami) and Division of Dermatology, Department of Medicine (Drs Bahrami, Jeffy, and Callen), University of Louisville, Louisville, Kentucky.

attempts to determine whether tissue eosinophilia is a reliable indicator of a DI etiology by comparing patients with known DI-SCLE and those with non-DI-SCLE.

## METHODS

Approval for this study was obtained from the human studies committee at the University of Louisville, Louisville, Kentucky. Fifty-nine patients were included in this study. Cases were obtained using the following methods: (1) a computerized medical record search for the diagnosis code for LE between January 1, 2000, and April 15, 2010, was performed on the files at a University of Louisville–affiliated dermatology practice; the records were evaluated further to distinguish SCLE from discoid LE and systemic LE; and (2) a computerized search for the corresponding archived histopathologic slides with the diagnosis of SCLE between January 1, 2000, to April 15, 2010, was performed at a University of Louisville–affiliated dermatopathology laboratory.

## CLINICAL DATA

Medical records were systematically reviewed. The patient inclusion criteria were as follows: (1) clinical evidence of SCLE (ie, annular-polycyclic or papulosquamous erythematous lesions in a photosensitive distribution), (2) skin biopsy findings consistent with SCLE, (3) the presence of a drug history with no previous SCLE or exacerbation occurring with the introduction of a new drug within 6 months, and (4) a physician's diagnosis of DI-SCLE. Patients without a skin biopsy sample or a drug history were excluded.

The medical records of patients who met these criteria were evaluated for the etiology of SCLE, clinical presentation, interval between potential drug administration, development of symptoms, drug identity, and laboratory workup. Based on the previously mentioned criteria, patients were separated into DI-SCLE and non-DI-SCLE groups.

## HISTOPATHOLOGIC ANALYSIS

The corresponding slides were evaluated for the following variables: (1) mucin deposition, (2) periadnexal inflammation, (3) level of dermal inflammation, and (4) liquefaction degeneration at the basal layer with or without dyskeratotic keratinocytes. Slides were randomized using a study number corresponding to a particular patient. Evaluation was performed by a dermatopathologist (S.B.) masked to the ascribed etiology of the SCLE. An eosinophil count was obtained for each histopathologic slide by assessing the number of eosinophils in 10 random high-power fields (original magnification  $\times 400$ ). The raw number of eosinophils was divided by 10 to obtain a mean eosinophil count per high-power field (eosinophil score). To account for the variability in inflammation density, 10 high-power fields were assessed based on a scale from 1 to 4 as follows: 1 indicates that 25% or less of the field has inflammation involvement; 2, 26% to 50%; 3, 51% to 75%; and 4, greater than 75%. The eosinophil score was divided by the inflammation density number to achieve a ratio indicative of the level of tissue eosinophilia. In cases in which there were 2 biopsy specimens for the same patient, a mean tissue eosinophil ratio was computed based on the individual ratios calculated in each biopsy specimen. Additional histopathologic factors were evaluated, including mucin deposition, presence of periadnexal inflammation, depth of dermal inflammation, and basal layer liquefaction degeneration with or without dyskeratosis. Mucin deposition and periadnexal inflammation were noted as present or



**Figure 1.** Representative annular and papulosquamous erythematous lesions in a photosensitive distribution seen in subacute cutaneous lupus erythematosus.

absent. Depth of dermal inflammation was evaluated as superficial vs superficial and deep.

Tissue eosinophilia and inflammation density in the DI and non-DI groups were analyzed using the Mann-Whitney test, with significance set at  $P < .05$ . Peripheral blood eosinophilia, when available, inflammation density, and mucin deposition were analyzed using the same method.

## RESULTS

The study group consisted of 53 females (90%) and 6 males (10%) aged 15 to 87 years (mean age, 56.2 years) at disease onset. All the patients initially had annular-polycyclic or papulosquamous erythematous lesions in a photosensitive distribution (**Figure 1**). Patients were divided into 2 groups: group 1 included 15 patients with DI-SCLE, and group 2 included the remaining 44 patients with non-DI-SCLE.

## CLINICAL ANALYSIS

Group 1 had a female to male ratio of 6.5 to 1, and group 2 had a ratio of 10 to 1. The mean age in group 1 was 57.9 years (age range, 23-85 years); the mean age in group 2 was 55.6 years (age range, 15-87 years). Peripheral blood eosinophil values, expressed as a percentage of total leukocytes, were available in 13 of 15 group 1 patients and ranged from 0% to 5.9% (mean, 1.9%). In group 2, peripheral blood eosinophil values were available in 31 of 44 patients and ranged from 0% to 6% (mean, 1.9%). Peripheral blood eosinophilia was not significantly different between the 2 groups ( $P = .39$ ).

The drugs most commonly implicated in DI-SCLE were antihypertensive agents ( $n = 3$ ) and chemotherapeutic agents ( $n = 3$ ). Calcium channel blockers were the implicated agents in 2 of the antihypertensive-induced patients; 1 of these was combined with an angiotension-converting enzyme inhibitor. One patient began treatment with 2 chemotherapeutic medications on the same date, and, thus, the exact medication leading to the development of SCLE could not be determined. Other pharmacologic causes of DI-SCLE in the present study included

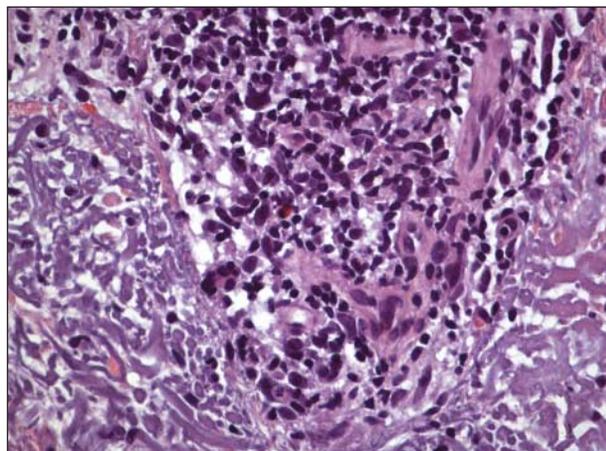
**Table. Drugs Associated With 15 Cases of Drug-Induced Subacute Cutaneous Lupus Erythematosus**

Drug	
Pregabalin	Celecoxib <sup>a</sup>
Rosuvastatin calcium <sup>a</sup>	Paclitaxel
Fenofibrate	Paclitaxel and doxorubicin <sup>c</sup>
Amlodipine besylate and benazepril hydrochloride <sup>b</sup>	Bupropion hydrochloride
Indapamide	Terbinafine <sup>a</sup>
Diltiazem	Bupropion

<sup>a</sup>Two cases.

<sup>b</sup>Combined angiotensin-converting enzyme inhibitor and calcium channel blocker.

<sup>c</sup>Therapy with both medications was started on the same day.

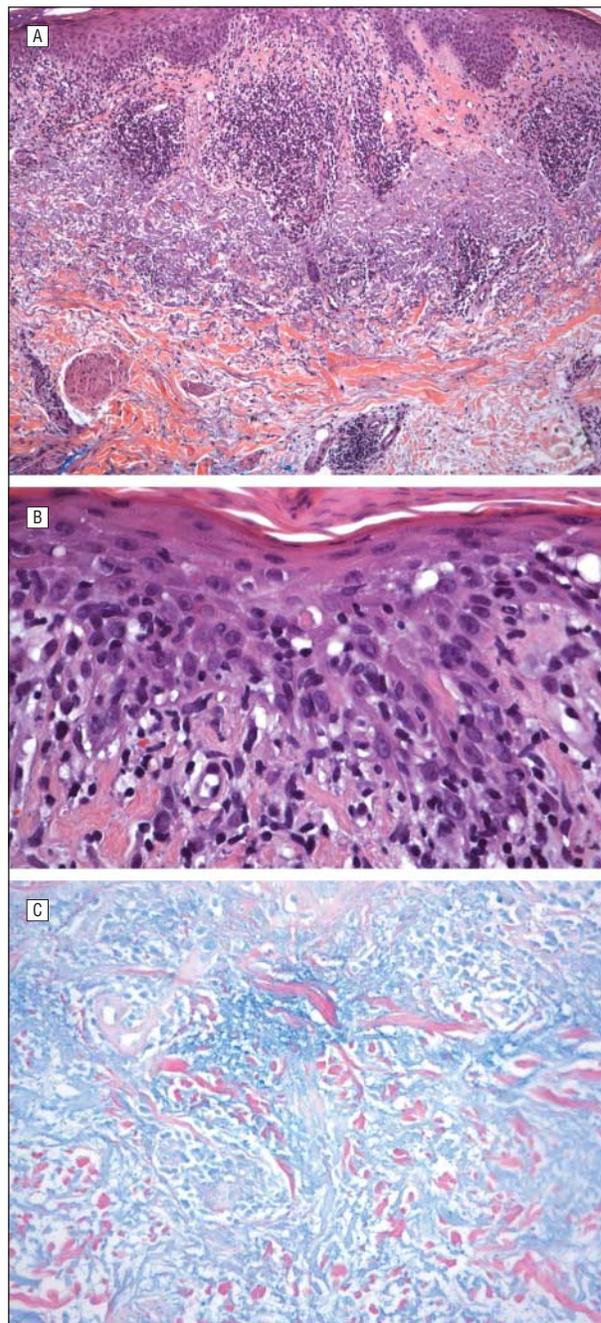


**Figure 2.** Rare eosinophils noted in the dermal inflammation (hematoxylin-eosin, original magnification  $\times 600$ ).

a statin (n=2), a cyclooxygenase 2 selective inhibitor (n=2), an antifungal drug (n=2), an antineurologic pain medication (n=1), an antianxiety drug (n=1), and a smoking cessation/depression medication (n=1). The drugs found to be associated with DI-SCLE in this study are summarized in the **Table**. The development of cutaneous lesions occurred 1 week to 5 months after administration of the drug. Two cases (13%) were found to be exacerbations of SCLE on introduction of a new medication. All 15 cases of DI-SCLE in this study resolved with withdrawal of the offending therapeutic agent. Two cases resolved within an unknown period. The other 13 cases (87%) resolved within a mean of 4.2 months (range, 2-9 months). All the patients were treated with topical corticosteroids, and most were treated with short courses of oral prednisone. Four cases were treated with oral antimalarial therapy (primarily hydroxychloroquine sulfate).

### HISTOPATHOLOGIC ANALYSIS

Tissue eosinophil ratios in group 1 ranged from 0.00 to 0.15 (mean, 0.11) and in group 2 ranged from 0.00 to 0.1 (mean, 0.004) (**Figure 2**). No significant difference was found in mean eosinophil ratios in the DI vs non-DI groups ( $P=.34$ ). Inflammation density between biopsy specimens of the 2 groups was not found to be significantly different ( $P=.14$ ).



**Figure 3.** A, Histopathologic findings in subacute cutaneous lupus erythematosus with superficial and deep dermal and periadnexal inflammation (hematoxylin-eosin, original magnification  $\times 100$ ). B, High-power photomicrograph showing liquefaction degeneration of the basal layer with dyskeratosis (hematoxylin-eosin, original magnification  $\times 600$ ). C, Mucin deposition highlighted by a colloidal iron histochemical stain (original magnification  $\times 400$ ).

The inflammatory infiltrate was identified to be superficial and deep in 10 patients (67%) in the DI group and in 24 patients (55%) in the non-DI group (**Figure 3A**). Additional histologic variables included the presence of periadnexal inflammation in 12 patients (80%) in the DI group and in 37 (84%) in the non-DI group and basal layer liquefaction degeneration with dyskeratosis in 15 patients (100%) in the DI group and in 37 (84%) in the non-DI group (**Figure 3B**). Mucin

deposition present in the biopsy specimens of both populations was not found to be significantly different ( $P=.18$ ) (Figure 3C).

## COMMENT

Drug-induced SCLE is a type of SCLE characterized by the presence of anti-Ro/SS-A antibodies and an association between the development or exacerbation of cutaneous LE with a new drug exposure of generally less than 6 months. The clinical and laboratory features of DI-SCLE and non-DI-SCLE have been characterized previously in the literature. The most recent report by Marzano et al<sup>8</sup> discussed these differences between the 2 entities. However, few articles are found in the literature comparing the histologic features. Marzano et al<sup>8</sup> described the histopathologic features of DI-SCLE but did not contrast these microscopic findings of DI-SCLE with those of non-DI-SCLE.<sup>8</sup> Another study<sup>3</sup> suggested a possible link between granular IgG deposition in the basal layer and DI-SCLE. To our knowledge, no studies have specifically looked at the relationship between DI-SCLE and the presence of eosinophils as a clue to a DI cause of disease.

A concise method was derived to obtain a ratio using the number of eosinophils and the density of inflammation. This ratio was indicative of tissue eosinophilia in the specimen. A statistical analysis of the inflammation density was performed to ensure that any difference between groups was not secondary to the level of inflammation. Thus, we conclude that tissue eosinophilia is not a statistically significant histopathologic aid in identifying the underlying etiology of SCLE, specifically in DI specimens. In addition, peripheral blood eosinophilia was not statistically significantly different between the 2 groups and was not a helpful clue in the etiologic evaluation of SCLE.

Because tissue eosinophilia is not a reliable finding in DI-SCLE biopsy specimens, this study reaffirms the importance of an accurate history of new medications as the main diagnostic aid in the clinical recognition of DI-SCLE. Identifying and discontinuing the offending therapeutic agent remains the major therapeutic intervention in the treatment of these patients. At least 41 different therapeutic agents have been reported in association with DI-SCLE.<sup>2</sup> Some of the more common agents are antihypertensives, antifungals, and chemotherapeutic agents. It is believed that hydrochlorothiazide is the drug most commonly associated with DI-SCLE, despite terbinafine having the highest number of associated reports.<sup>2</sup> The present study had 1 patient with DI-SCLE caused by a thiazideliike diuretic and 2 patients who developed disease in conjunction with terbinafine use. Two patients developed DI-SCLE associated with a calcium channel blocker (combined with an angiotension-converting enzyme inhibitor in 1 patient) and a chemotherapeutic agent, paclitaxel. Paclitaxel therapy was started the same day as doxorubicin therapy in 1 patient, but both have been described as inciting or exacerbating agents of DI-SCLE.<sup>2</sup> In addition, 2 cases of DI-SCLE were triggered by celecoxib and rosuvastatin calcium. The association of celecoxib has not been formally described in the literature but has been reported in personal observation.<sup>2</sup> Statin drugs were first linked to DI-SCLE by Srivastava et al<sup>3</sup> in 2003 and have since

been described further in the literature.<sup>2</sup> Bupropion was the inciting agent in 1 patient, which has been previously described.<sup>9</sup> Three causative agents (pregabalin, fenofibrate, and buspirone hydrochloride) of DI-SCLE in the present study have not been reported previously in the literature.

In summary, we found that tissue eosinophilia is not a differentiating histopathologic feature of DI-SCLE. This study reinforces the importance of a thorough review of a patient's medical and medication history, especially of drugs that were initially administered within weeks up to 6 months. These findings can then be correlated with the clinical presentation of SCLE to determine whether a drug is the underlying etiologic or exacerbating factor.

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Correspondence: Paul B. Hillesheim, DO, Department of Pathology and Laboratory Medicine, University of Louisville, 530 S Jackson St, Louisville, KY 40202 (pbhill01@louisville.edu).

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