A RETROSPECTIVE COHORT STUDY OF SUBACUTE CUTANEOUS LUPUS PATIENTS WITH AND WITHOUT SYSTEMIC LUPUS

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# A RETROSPECTIVE COHORT STUDY OF SUBACUTE CUTANEOUS LUPUS PATIENTS WITH AND WITHOUT SYSTEMIC LUPUS

by

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ABSTRACT

# A RETROSPECTIVE COHORT STUDY OF SUBACUTE CUTANEOUS LUPUS PATIENTS WITH AND WITHOUT SYSTEMIC LUPUS

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**Objective:** To compare subacute cutaneous lupus erythematosus (SCLE) patients with systemic lupus erythematosus (SLE) (+SCLE/+SLE) versus SCLE patients without SLE (+SCLE/-SLE) over a period of five years.

**Design:** Retrospective cohort study.

**Setting:** Outpatient dermatology and rheumatology clinics at an academic medical center.

**Patients:** Forty-seven SCLE patients presenting between February 1989 and January 2012 were screened with nineteen meeting inclusion/exclusion criteria.

**Predictive variable:** Anti-nuclear antibodies (ANA).

**Results:** Of the nineteen patients included, thirteen (68.4%) had SCLE only (+SCLE/-SLE) for the majority of the study period and six (31.6%) had both SCLE and SLE

(+SCLE/+SLE). At baseline, +SCLE/+SLE patients were more likely to have a history of discoid lesions, oral ulcers, lupus non-specific findings, and require multiple medications. Over the five year study period, +SCLE/+SLE patients were also more likely to have ANA, immunologic disease (including anti-double-stranded DNA), renal disease, proteinuria, decreased complement, and to complain of arthralgias. Anti-Ro antibodies alone were more common in +SCLE/-SLE patients.

**Conclusions:** Various cutaneous manifestations of lupus are present early in the course of SCLE, but laboratory values in +SCLE/+SLE become more distinct over time. Thus, the aforementioned variables should be tested for evidence of disease involvement and to ensure adequate treatment among +SCLE/+SLE patients. In contrast, +SCLE/-SLE patients may be tested for the development of anti-Ro antibodies but need not be monitored for the other laboratory abnormalities, given their rarity among patients with SCLE only. Larger prospective studies comparing disease course in SCLE patients with and without SLE are needed to verify these findings.

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## PRIOR PUBLICATIONS & PRESENTATIONS

Taylor A, Nguyen R, Glass DA, Agim N. Annular plaques and craniosynostosis. *J Am Acad Dermatol*. (in press)

Taylor A, Shedd A, Cohen J. Linear, sclerotic lesions in a man with Hepatitis C. *Archives of Dermatology*. (in press)

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# LIST OF DEFINITIONS

ACR: American College of Rheumatology

Anti-dsDNA: Anti-double-stranded DNA

ANA: Anti-nuclear antibody

CNS: Central nervous system

C3: Complement 3

C4: Complement 4

CBC: Complete blood count

DI-SCLE: Drug-induced subacute cutaneous lupus erythematosus

ENA: Extractable nuclear antigen

ESR: Erythrocyte sedimentation rate

SCLE: Subacute cutaneous lupus erythematosus

SLE: Systemic lupus erythematosus

+SCLE/-SLE: SCLE only

+SCLE/+SLE: SCLE with concomitant SLE

UTSW: University of Texas Southwestern Medical Center

# CHAPTER ONE
# Introduction

## SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS INTRODUCTION AND RELATIONSHIP TO SYSTEMIC LUPUS ERYTHEMATOSUS

First described in 1979 by Sontheimer, *et al.* [1], subacute cutaneous lupus erythematosus (SCLE) is a relapsing, non-scarring subset of cutaneous lupus with psoriasiform or annular-polycyclic lesions in a sun distribution. About half of affected patients meet criteria for systemic lupus erythematosus (SLE), as defined by the 1982 American College of Rheumatology (ACR) criteria [2, 3]. Patients with SCLE have milder disease and less systemic involvement than those with SLE [1, 4, 5], and SCLE lesions in patients with SLE are thought to portend a more favorable prognosis than those without such lesions [6]. SCLE and SLE, whether independent or concomitant, have a notable impact on health and quality of life for affected patients [7-9].

Both SCLE and SLE are immune-mediated diseases in which an unknown inciting factor induces auto-immunity in genetically susceptible hosts. The two conditions are etiologically linked by their association with HLA-DR3 and complement deficiencies (specifically, C2 and C4) [10]. Similar pathogenic mechanisms of immune complex deposition, direct antibody toxicity, inappropriate homing of activated T cells to the skin, and impaired clearance of apoptotic debris are observed in both diseases [10, 11]. In SLE, B cells produce antibodies (particularly self-destructive auto-antibodies) in excess, and damage is caused primarily by the deposition of immune complexes in various organs, especially the kidney. Similarly, in patients with SCLE,

immunoglobulins form immune complexes with complement, deposit in a granular or "dust like" pattern at the dermal-epidermal junction, and initiate tissue injury [10]. Certain antibodies are associated with specific disease findings in SLE such as congenital heart block in neonatal lupus caused by Ro/SSA antibodies transferred from mother to fetus. It has been shown in SCLE patients that ultraviolet (UV) radiation facilitates Ro/SSA antibody binding to keratinocytes, and in turn, anti-Ro/SSA serves as a phototoxin that commences antibody dependent cell mediated cytotoxicity [10, 12]. The presence of anti-Ro/SSA in both SCLE and SLE helps to explain the sun-sensitivity observed in both diseases.

The similarity in pathogenesis of SCLE and SLE is reflected in the microscopic and immunologic findings common to both disease entities. A superficial perivascular lymphocytic infiltrate, interface changes at the epidermal-dermal junction, and mucin deposition are the histologic findings in all forms of cutaneous lupus erythematosus, any of which may be present in systemic lupus [13].

# CHAPTER TWO
# Background

## SCLE WITH VS. WITHOUT SLE BACKGROUND DATA

Fifty percent of SCLE patients are reported to have SLE [1, 4], and skin findings such as the malar rash characteristic of acute cutaneous lupus erythematosus, papulosquamous SCLE morphology, and lupus non-specific skin lesions such as nail telangiectasias in SCLE patients have been associated with active systemic disease [6, 14, 15]. SCLE patients with SLE more often demonstrate extracutaneous involvement than those with SCLE alone, including higher rates of arthralgias and arthritis (45.7-60.9% vs. 1.5-18.2%), nephropathy (21.7% vs. 0%), and hematologic abnormalities such as lymphopenia (77.8% vs. 13.3%) [6]. SCLE patients meeting criteria for SLE tend to have laboratory abnormalities such as higher ANA titers, positive anti-double-stranded DNA antibody (anti-dsDNA), and hypocomplementemia [1, 6]. Although SCLE patients have higher rates of anti-Ro antibody positivity than those with SLE alone, the prevalence of elevated anti-Ro antibodies is reportedly higher in SCLE patients with (57.1%) than in those without (30.0%) SLE [6, 12].

Previous studies have been helpful in differentiating SCLE patients with and without systemic disease, but there are notable gaps in knowledge, particularly in terms of disease progression. Cross-sectional analysis and lack of minimum follow up period in some studies are not adequate to capture the evolution of disease over time, and the rate at which systemic features, lab abnormalities, and signs or symptoms of disease are accumulated remains unclear [4-6, 12, 16-18]. Most studies failed to exclude drug-induced cases and one grouped SCLE with other forms of cutaneous lupus, making a

heterogeneous cohort [19]. Given the significant overlap between SCLE and SLE, clarification of the natural history of SCLE with and without SLE may help to accurately anticipate disease course and tailor treatment for patients.

We conducted a retrospective cohort study of 19 SCLE patients seen at the University of Texas Southwestern (UTSW) Medical Center and Parkland Health and Hospital System. We required following SCLE patients without SLE for at least two years since the highest risk of developing SLE appears to be within one year of SCLE diagnosis [20]. The primary aim was to compare SCLE patients with (+SCLE/+SLE) and without (+SCLE/-SLE) SLE over a period of at least two but up to five years. We hypothesize that +SCLE/+SLE patients may be differentiated from +SCLE/-SLE patients by the presence or development of serologic abnormalities (particularly ANA positivity), decreased complement levels, renal disease, oral ulcers, and arthralgias.

# METHODS

*Patient Recruitment*

A retrospective cohort study of SCLE patients seen at the outpatient dermatology and rheumatology clinics at the UTSW Medical Center and Parkland Health and Hospital System between February 1989 and January 2012 was performed. Follow-up information of these patients was obtained from the same clinics and North Dallas Dermatology Associates, where one provider (M.C.) had moved her practice from UTSW. SCLE patients were identified from ICD-9 code searches and from the UTSW Cutaneous Lupus Registry. Inclusion criteria were the diagnosis of SCLE by a dermatologist based on clinicopathological correlation and a minimum of two clinic visits within two years with a dermatologist or rheumatologist. Patients lacking sufficient documentation of disease course (such as lab values) and drug-induced SCLE patients were excluded. Patients with SCLE were divided into those who did not meet four out of eleven ACR criteria for SLE [2, 3] (+SCLE/-SLE) over the majority of the study period and those with SLE (+SCLE/+SLE) over the majority of the study period. The study was approved by the UTSW Institutional Review Board.

*Data collection*

Demographics, historical data, physical exam findings, and lab data at initial visit and subsequent visits were gleaned from each patient record. Historical data included: age at SCLE diagnosis, disease duration, ACR SLE diagnostic criteria met, subjective symptoms, personal medical history, and family history. Rash subtype (papulosquamous or annular-polycyclic), presence of other cutaneous lupus, and non-specific lupus

findings (e.g., alopecia, nailfold telangiectasia, Raynaud's, palmar erythema) were identified on documentation of the physical exam. Routine laboratory values such as ANA, complete blood count (CBC), extractable nuclear antigen (ENA) serologies, complement levels, erythrocyte sedimentation rate (ESR), and urinalysis were collected.

The number of prescribed medications per patient was noted as a surrogate marker of disease severity. To quantify medication use, prescriptions for prednisone, methotrexate, mycophenolate, azathioprine, and cyclosporine were each counted as one medication. Anti-malarials (including hydroxychloroquine, chloroquine, and quinacrine), either alone or in combination, were credited as one medication.

The first time point (t=1) was defined as the time of diagnosis or initial presentation. Subsequent time points (t=2, t=3, etc.) were defined in 12 month intervals, plus or minus 3 months. Longitudinal analysis between groups was extended for up to five years of follow-up. Only four +SCLE/-SLE patients did not have data for the whole study duration.

*Statistical analysis*

There was no sample size justification as this was a pilot study. Comparisons were made at the initial visit, and data were accumulated over subsequent yearly visits. At baseline, categorical values were analyzed using Fisher's exact test and continuous variables using Student's t-test or Wilcoxon rank sum test between the +SCLE/-SLE and +SCLE/+SLE groups. Occurrences of individual SLE criteria, abnormal laboratory values, and signs and symptoms were compared between +SCLE/-SLE and +SCLE/+SLE groups with the Logrank test to account for censored observations. Numbers of SLE criteria and medications averaged at each time point were compared

between groups using a Poisson repeated measures analysis. $P < 0.05$ was considered statistically significant.

## RESULTS

*SCLE patient characteristics*

Forty-seven SCLE patients were initially screened, but twenty-eight failed to meet inclusion criteria. Seven did not have sufficient physician follow up, two were afflicted with SCLE for less than two years, and another nine had insufficient data available for analysis. Ten patients had confirmed or suspected drug-induced SCLE. Of the nineteen patients included, thirteen (68.4%) were +SCLE/-SLE, including two patients that ultimately met criteria for SLE after four years. Six (31.6%) had both SCLE and SLE, three of which were diagnosed with SCLE prior to the development of systemic disease (median: 3 years between diagnoses, range: 2-21 years), and three were considered to have simultaneous onset, receiving both diagnoses within a one-year timespan. Almost all patients were newly diagnosed at the time of study inclusion, with only two patients being diagnosed more than one year before presentation (Figure 1).

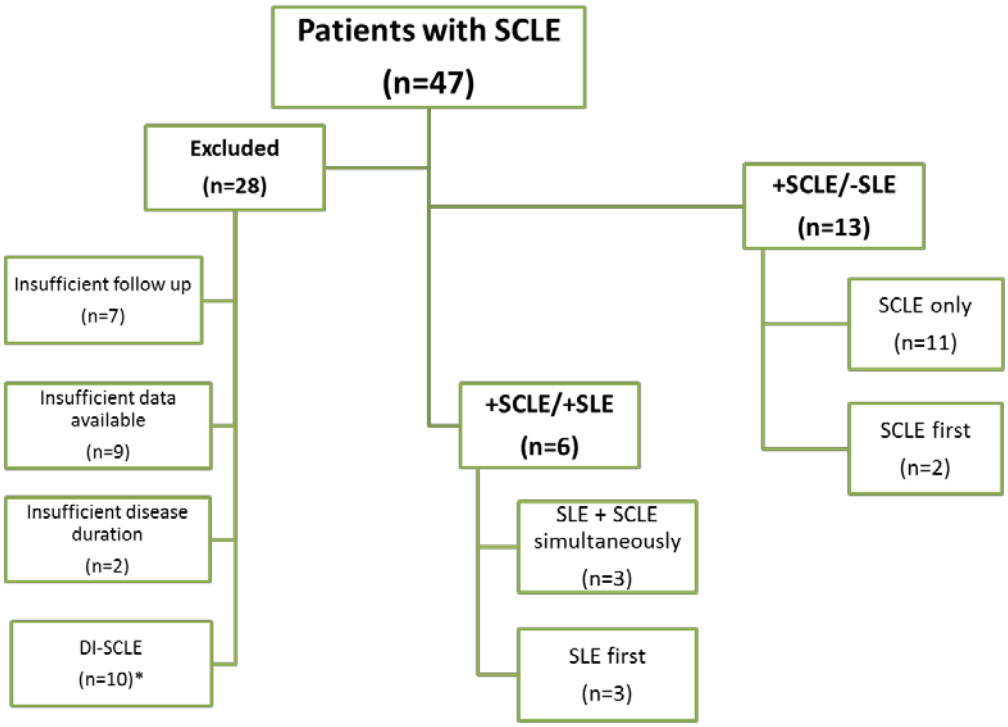


**Figure 1:** Patient classification scheme.

**DI-SCLE: drug-induced subacute cutaneous lupus erythematosus.*

Table 1 summarizes various patient characteristics in the +SCLE/-SLE and +SCLE/+SLE groups. The groups were predominantly female and Caucasian with a median age of onset in the fifth decade. +SCLE/-SLE and +SCLE/+SLE patients had a median duration of follow up of 7 ± 5.9 (range: 2-21 years) and 11 ± 9.3 (range: 5-30 years), respectively. Papulosquamous and annular-polycyclic SCLE subtypes were present in both groups (p=0.14), and there were no differences in personal or family history of specific auto-immune diseases. +SCLE/+SLE patients required a greater number of agents for initial disease control (3.0 ± 1.9 vs. 1.0 ± 0.8, p=0.03).

**Table 1:** Patient characteristics at baseline.

| | +SCLE/-SLE* | +SCLE/+SLE** | P-value*** |
|---|---|---|---|
| **Gender** | | | |
| Female, N (%) | 13 (100) | 5 (83.3) | 0.32 |
| Male, N (%) | 0 (0) | 1 (16.7) | |
| **Ethnicity** | | | |
| Caucasian, N (%) | 12 (92.3) | 5 (83.3) | 0.26 |
| Hispanic, N (%) | 0 (0) | 1 (16.7) | |
| Unknown, N (%) | 1 (7.7) | 0 (0) | |
| **Age at SCLE diagnosis** | | | |
| Median, years (SD) | 49 (16.4) | 47 (13.4) | 0.41 |
| Range, years | 28-82 | 20-56 | |
| **Duration of follow up** | | | |
| Median, years (SD) | 7 (5.9) | 11 (9.3) | 0.18 |
| Range, years | 2-21 | 5-30 | |
| **SCLE subtype** | | | |
| Papulosquamous, N (%) | 4 (30.8) | 4 (66.7) | 0.14 |
| Annular-polycyclic, N (%) | 9 (69.2) | 2 (33.3) | |
| **Personal history** | | | |
| Sjogren's, N (%) | 4 (30.8) | 1 (16.7) | 0.37 |
| Thyroid disease, N (%) | 6 (46.2) | 2 (33.3) | 0.34 |
| Fibromyalgia, N (%) | 3 (23.1) | 0 (0) | 0.30 |
| **Family history** | | | |
| SLE, N (%) | 1 (7.7) | 2 (33.3) | 0.20 |
| Autoimmunity, N (%) | 3 (23.1) | 1 (16.7) | 0.44 |
| **Oral medications** | | | |
| Antimalarials, N (%) | 11 (84.6) | 5 (83.3) | 0.48 |
| Oral steroids, N (%) | 6 (46.2) | 5 (83.3) | 0.14 |
| Methotrexate, N (%) | 0 (0) | 2 (33.3) | 0.09 |
| Azathioprine, N (%) | 0 (0) | 2 (33.3) | 0.09 |
| Thalidomide, N (%) | 0 (0) | 2 (33.3) | 0.09 |
| Cyclophosphamide, N (%) | 0 (0) | 1 (16.7) | 0.32 |
| Acitretin, N (%) | 0 (0) | 1 (16.7) | 0.32 |
| Average no. oral treatments, Median (SD) | 1.0 (0.8) | 3.0 (1.9) | 0.03 |

*Two +SCLE/-SLE patients met criteria for SLE after four years.

**Three +SCLE/+SLE patients were diagnosed with SLE first (median: 3 years, range: 2-21 years), and three receive both diagnoses within one year.

***P-values were calculated using Fisher's exact test for categorical variables and Student's t-test or Wilcoxon rank sum test for continuous variables.

*+SCLE/-SLE vs. +SCLE/+SLE patients at baseline*

Historical and clinical data in +SCLE/-SLE and +SCLE/+SLE patients at their baseline were compared. In terms of ACR SLE diagnostic criteria, +SCLE/+SLE patients were significantly more likely than +SCLE/-SLE patients to have a history of discoid lesions (p=0.02) and oral ulcers (p=0.04). Patients in the +SCLE/+SLE group met an average of 5.0 ± 1.8 ACR SLE criteria, which was significantly higher than the +SCLE/-SLE group, which averaged 2.0 ± 1.0 criteria (p=0.0003). +SCLE/+SLE patients also showed a propensity towards malar rash, renal disorder, hematologic disorder, and positive ANA (p=0.09 for each). Both groups demonstrated high levels of photosensitivity (p=0.46), whereas arthritis, serositis, neurologic disease, and immunologic disease were rare in both groups (Table 2).

**Table 2:** ACR SLE criteria at baseline.

| | **+SCLE/-SLE** | **+SCLE/+SLE** | **P-value*** |
|---|---|---|---|
| **Malar rash, N (%)** | 3 (23.1) | 4 (66.7) | 0.09 |
| **Discoid lesions, N (%)** | 0 (0) | 3 (50) | 0.02 |
| **Photosensitivity, N (%)** | 11 (84.6) | 6 (100) | 0.46 |
| **Oral ulcers, N (%)** | 1 (7.7) | 4 (66.7) | 0.04 |
| **Arthritis, N (%)** | 1 (7.7) | 2 (33.3) | 0.20 |
| **Serositis, N (%)** | 1 (7.7) | 2 (33.3) | 0.20 |
| **Renal disorder, N (%)** | 0 (0) | 2 (33.3) | 0.09 |
| **Neurologic disorder, N (%)** | 0 (0) | 1 (16.7) | 0.32 |
| **Hematologic disorder, N (%)** | 0 (0) | 2 (33.3) | 0.09 |
| **ANA, N (%)** | 5 (38.5) | 5 (83.3) | 0.08 |
| **Immunologic disorder, N (%)** | 1 (7.7) | 2 (33.3) | 0.20 |
| **Average No. SLE criteria, Median (SD)** | 2.0 (1.0) | 5.0 (1.8) | 0.0003 |

*P-values were calculated using Fisher's exact test for categorical variables and Wilcoxon rank sum test for continuous variables.

There were no statistically significant differences in auto-antibodies, inflammatory markers, or urinalysis, though anti-Sm antibodies, anti-RNP antibodies, and decreased complement 3 (C3) were more prevalent in the +SCLE/+SLE group ($0.05<p<0.10$). Non-significant differences in rates of positive anti-dsDNA, anti-Ro, and anti-La antibodies were found in both groups (Table 3).

**Table 3:** Laboratory data at baseline.

| | **+SCLE/-SLE** | **+SCLE/+SLE** | **P-value*** |
|---|---|---|---|
| **Anti-dsDNA, N (%)** | 1 (7.7) | 2 (33.3) | 0.20 |
| **Anti-Ro, N (%)** | 6 (54.5) | 3 (60.0) | 0.40 |
| **Anti-La, N (%)** | 4 (36.4) | 1 (20.0) | 0.38 |
| **Anti-Sm, N (%)** | 0 (0) | 2 (50.0) | 0.06 |
| **Anti-Scl, N (%)** | 0 (0) | 0 (0) | 1.0 |
| **Anti-Jo 1, N (%)** | 0 (0) | 1 (25.0) | 0.27 |
| **Anti-RNP, N (%)** | 0 (0) | 2 (50.0) | 0.06 |
| **Anti-cardiolipin, N (%)** | 0 (0) | 0 (0) | 1.0 |
| **Decreased C3, N (%)** | 0 (0) | 2 (33.3) | 0.09 |
| **Decreased C4, N (%)** | 3 (23.1) | 3 (50) | 0.21 |
| **Increased ESR, N (%)** | 2 (15.4) | 2 (33.3) | 0.30 |
| **>5 RBC/HPF urine, N (%)** | 0 (0) | 0 (0) | 1.0 |
| **>30 mg/dl proteinuria, N (%)** | 0 (0) | 0 (0) | 1.0 |

*P-values were calculated using Fisher's exact test.

There were no significant differences in complaints of arthralgias, hair loss, fatigue, or sicca symptoms between groups, but +SCLE/+SLE patients tended to manifest other forms of cutaneous lupus (specifically, discoid lesions) ($p=0.09$). While individual lupus non-specific signs were not found to be statistically different between groups, the presence of any lupus non-specific sign (including: alopecia, nail telangiectasia, Raynaud's phenomenon, or palmar erythema) on exam was more likely seen in +SCLE/+SLE patients ($p=0.04$) (Table 4).

**Table 4:** Signs and symptoms of disease at baseline.

| | +SCLE/-SLE | +SCLE/+SLE | P-value* |
|---|---|---|---|
| **Arthralgias, N (%)** | 6 (46.2) | 4 (66.7) | 0.28 |
| **Hair loss, N (%)** | 3 (23.1) | 3 (50.0) | 0.21 |
| **Fatigue, N (%)** | 2 (15.4) | 2 (33.3) | 0.30 |
| **Sicca symptoms, N (%)** | 3 (23.1) | 1 (16.7) | 0.44 |
| **Other cutaneous lupus, N (%)** | 0 (0) | 2 (33.3)** | 0.09 |
| **Lupus non-specific signs,*** N (%)** | 2 (15.4) | 4 (66.7) | 0.04 |

*P-values were calculated using Fisher's exact test.

** Patients had discoid lesions.

** Alopecia, nail telangiectasia, Raynaud's phenomenon, and palmar erythema were considered lupus non-specific signs.

*+SCLE/-SLE vs. +SCLE/+SLE patients over five-years of follow-up*

Regarding ACR SLE criteria, discoid lesions (50% vs. 7.7%, p=0.02) and oral ulcers (66.7% vs. 7.7%, p=0.008) remained more common in the +SCLE/+SLE group over the follow-up period. Over time, the +SCLE/-SLE and +SCLE/+SLE patients groups appeared to diverge, with +SCLE/+SLE patients being significantly more likely to develop renal disease (50.0% vs. 0.0%, p=0.006) and to demonstrate immunologic disease, particularly anti-dsDNA antibodies (66.7% vs. 15.4%, p=0.03). +SCLE/+SLE patients also maintained a higher average number of SLE criteria (median 5.5 ± 1.3 vs. 2.0 ± 0.6, p<0.0001) (Figure 2).

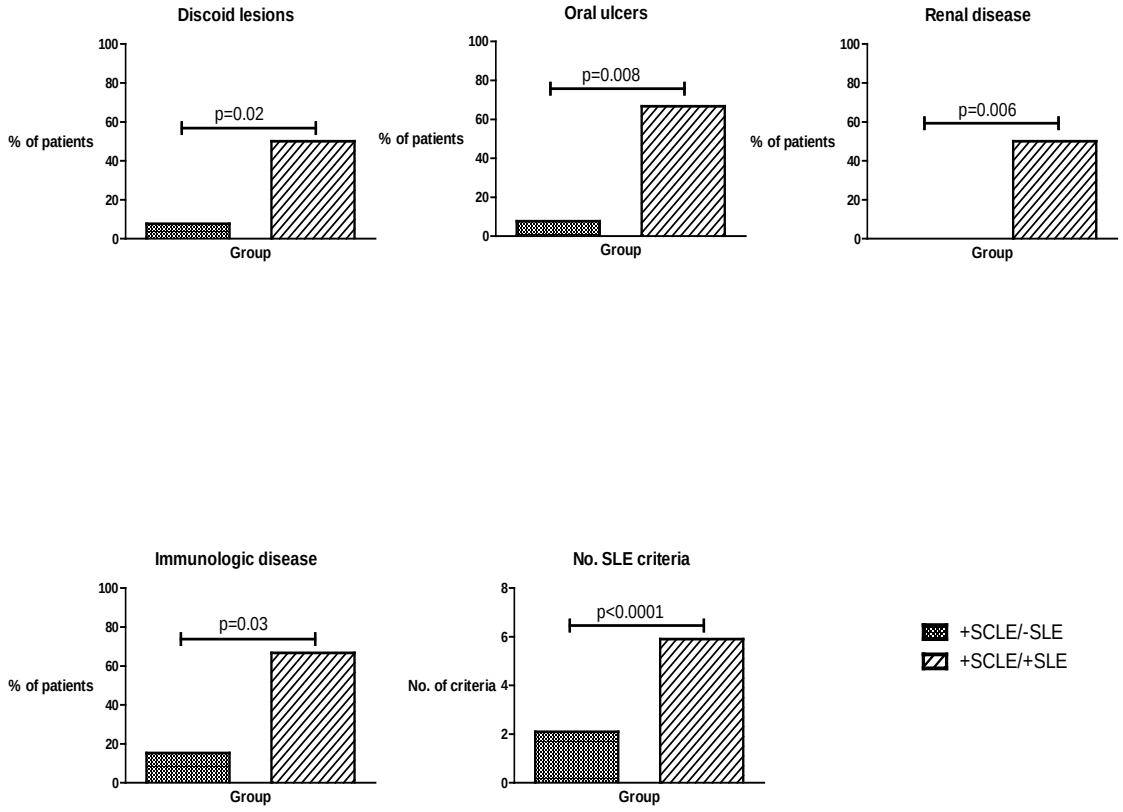


**Figure 2:** ACR SLE criteria accumulated over five years significantly different between +SCLE/-SLE (dotted bar) vs. +SCLE/+SLE (cross-hatched bar).

The +SCLE/+SLE group also demonstrated higher rates of various laboratory abnormalities over the study period. The presence of ANA positivity increased in both cohorts but was statistically more prevalent among +SCLE/+SLE patients (100.0% vs. 61.5%, p=0.04). More +SCLE/+SLE patients developed anti-dsDNA antibodies (66.7% vs. 15.4%, p=0.03). Anti-Sm antibodies and anti-RNP antibodies did not increase among +SCLE/+SLE patients but cumulative data showed significant differences between groups (50.0% vs. 0.0% (p=0.01) and 50.0% vs. 9.1% (p=0.05), respectively). In contrast, more +SCLE/-SLE patients were found to have anti-Ro antibodies (72.7% vs.

60.0%, p=0.01) (Figure 3). Decreased C3 (66.7% vs. 15.4%, p=0.009) and proteinuria (33.3% vs. 0.0%, p=0.04) were noted more often in +SCLE/+SLE patients (Figures 4).

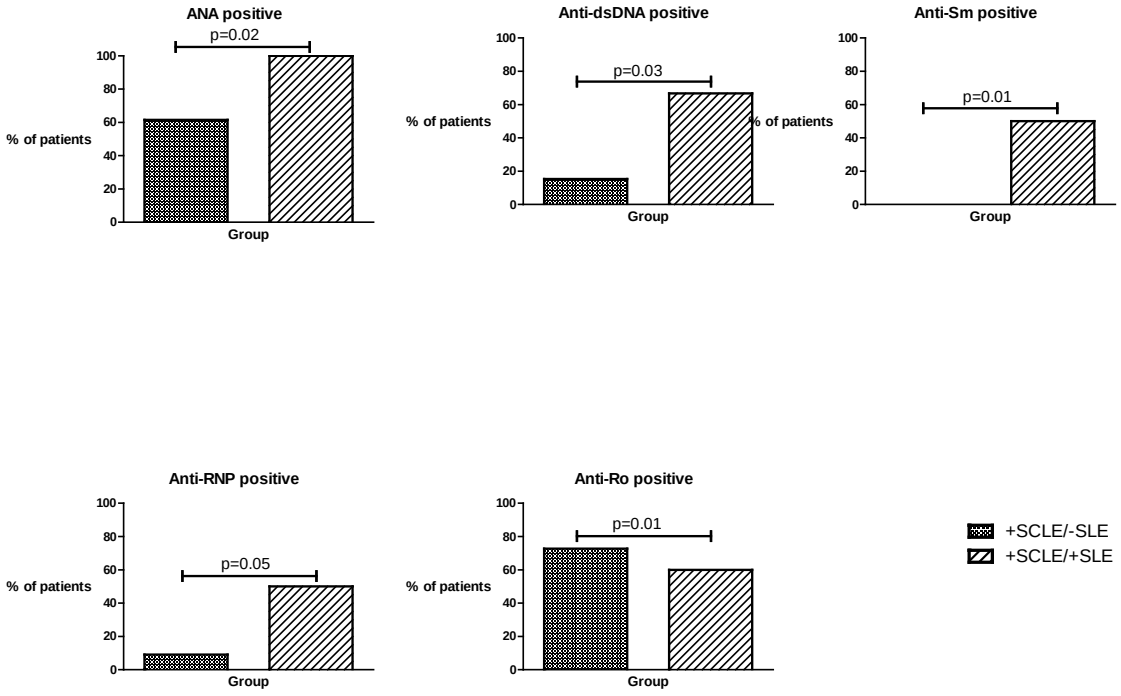


**Figure 3:** Autoantibodies accumulated over five years significantly different between +SCLE/-SLE (dotted bar) vs. +SCLE/+SLE (cross-hatched bar).

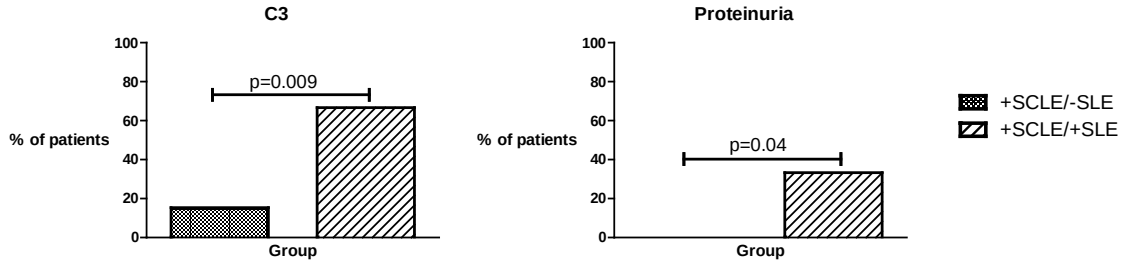


**Figure 4:** Other laboratory data accumulated over five years significantly different between +SCLE/-SLE (dotted bar) vs. +SCLE/+SLE (cross-hatched bar).

+SCLE/+SLE patients further differentiated themselves with higher rates of lupus non-specific findings (83.3% vs. 23.1%, p=0.02), increasing complaints of arthralgias (100.0% vs. 61.5%, p=0.03), and by receiving a higher average number of oral medications (median 3.0 ± 0.6 vs. 2.0 ± 0.5, p<0.0001) (Figure 5).

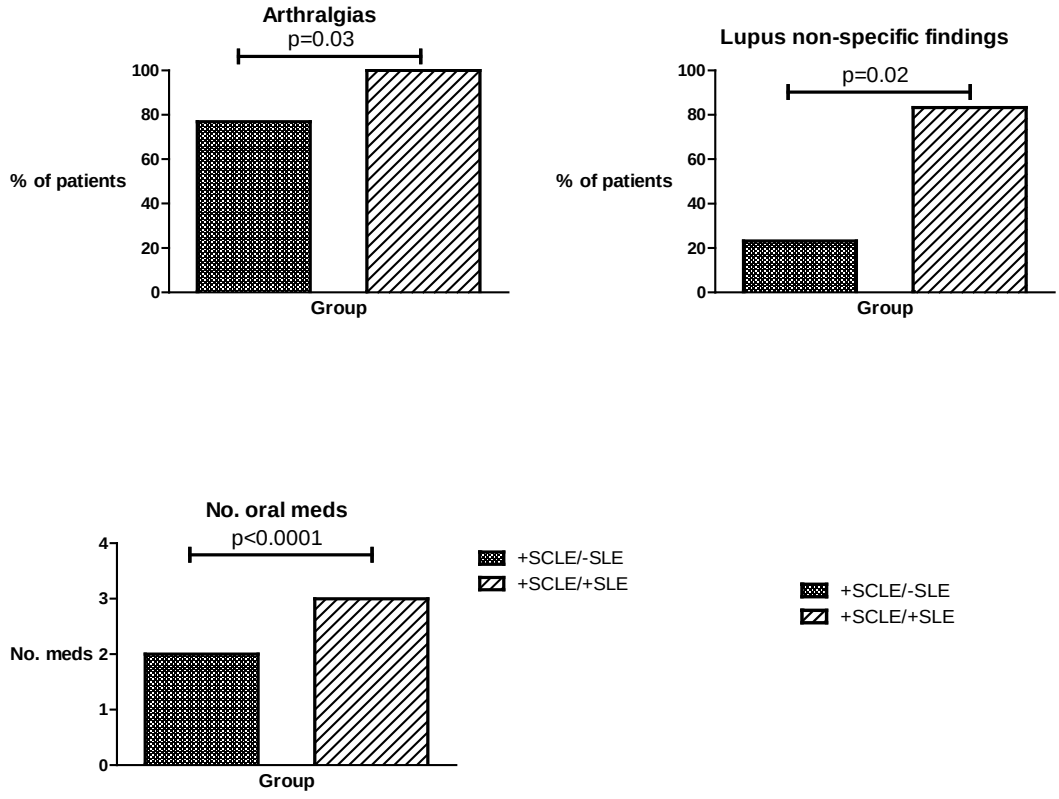


**Figure 5:** Signs and symptoms of disease accumulated over five years significantly different between +SCLE/-SLE (dotted bar) vs. +SCLE/+SLE (cross-hatched bar).

## DISCUSSION

In this study, we attempted to compare the disease courses of SCLE patients with and without SLE over a period of five years. By accumulating data over time and requiring minimum follow-up, we hoped to identify the timing of clinical and laboratory changes, to avoid cross-sectional analysis at one time point, and to ensure proper classification of SCLE subjects. We found that SCLE patients with SLE were more likely to have a history of discoid lesions and oral ulcers, to display lupus non-specific findings, and to require more medications than their SCLE only counterparts at baseline. We further found that SCLE patients with SLE were more likely to have ANA, have other serologic abnormalities (specifically, antibodies to dsDNA, Sm, and RNP antigens), renal disease (especially proteinuria), have low complement levels, and complain of arthralgias when taken cumulatively. Of note, anti-Ro antibodies alone were found more often in +SCLE/-SLE patients. These findings are similar to previous studies but notable in that this is the first study that required a minimum follow up, ensuring that SCLE only patients were designated correctly.

The rates of individual ACR SLE criteria among SCLE patients and the significant differences in specific criteria between SCLE patients with and without SLE that are shown here correspond with prior studies [1, 6, 14], but these data importantly illustrate that the criteria remain relatively stable over time. The development of statistical significance for renal disease, immunologic disease, and ANA positivity observed is partly due to the accumulation of data over time and reflects the addition of these criteria in only a few patients. As expected, +SCLE/+SLE maintained a

significantly higher average number of criteria over time, which indicates greater severity of disease among SCLE patients with SLE and is accompanied by greater medication requirements (and as previously noted) [1, 4].

Sontheimer, *et al.* documented that up to 20% of SCLE patients will manifest discoid lesions or malar rash and that discoid lesions often precede SCLE [1, 14, 21]. Others have noted a higher incidence of discoid lesions among patients with SLE [4, 22]. Here, we report 21.1% (4/19) SCLE patients with discoid lesions, many occurring before SCLE diagnosis, as well as a correlation between discoid lesions and systemic disease. The prevalence of other skin findings (including malar rash, oral ulcers, and lupus non-specific signs) was consistent with previous reports [1, 4, 6, 22, 23], and we support the association between these distinctive findings and systemic disease, as previously suggested [1, 4, 6, 14, 22]. Of note, lupus-related vasculitis, which has been reported to occur in up to 21.7% of SCLE with SLE patients [6], was not observed in our cohort.

As data were accumulated over time, ANA and anti-dsDNA antibodies increased to a greater extent among +SCLE/+SLE patients and were associated with systemic disease in SCLE, as previously reported [6, 19]. Anti-Sm, anti-RNP auto-antibodies, decreased C3, and proteinuria (though correlated with systemic involvement [6] over this 5-year period) only rarely developed in +SCLE/-SLE patients, making these laboratory tests unnecessary for patients with SCLE only.

Although the rate of arthralgias rose in both groups, it rose to a greater extent in the +SCLE/+SLE group, consistent with the hypothesis that arthralgias may signify underlying disease [6, 19]. The value of this finding lies in the ease of obtaining subjective complaints on patient follow up.

Previous studies associated Ro/SSA antibodies with the presence of SCLE lesions in patients with SLE [18, 24], and others found higher levels of Ro/SSA in patients with +SCLE/+SLE versus those with +SCLE/-SLE [6, 12]. In contrast, the data presented here show higher rates of anti-Ro positivity in SCLE patients without SLE relative to those with SLE. This may be due to differences in study designs, as our study has taken into account multiple follow up visits. Our results suggest that +SCLE/-SLE patients can still develop significant anti-Ro antibody levels over time.

Relatively high rates of anemia (27.9%), leukopenia (42.2%), and thrombocytopenia (4.4%) have been reported in SCLE with SLE patients [6], but these features were not found in our patient population, likely because hematologic abnormalities attributable to other causes (i.e., immunosuppressant use, iron-deficiency anemia, etc.) could not be excluded. Our study also failed to show significant differences in the rate of photosensitivity between groups [6], possibly due to variability in reporting these subjective symptoms. While increased rates of xerostomia and xerophthalmia have been reported in SCLE with SLE patients [6], we could not show significant differences between groups in sicca symptoms.

Although the papulosquamous subtype has been suggested to be associated with more severe systemic disease [14, 17, 21], this finding has not been consistent [5, 25]. The data presented here corroborates other studies [5, 6, 18] that find similar rates of papulosquamous and annular-polycyclic subtypes in SCLE patients that meet criteria for SLE and those that do not.

We report that 15.4% (2/13) of SCLE patients progressed to SLE. This rate of progression confirms findings from Grönhagen *et al.*, who found that 22.0% of their

SCLE patients met criteria for SLE within one year and another 2.7% garnered an additional diagnosis of SLE by the third year [20]. A small study of 8 patients with SCLE noted that 62.5% had received a diagnosis of SLE by year 5 [26]. The discrepancy between the studies may be due to our classification scheme, which segregated patients diagnosed with SLE within one year of SCLE to account for delays in diagnosis due to physician wait times from those with mainly SCLE that later met criteria for SLE.

Limitations of this study are inherent to its retrospective design, such as ascertainment bias, missing data, variable follow-up times, recall bias, and laboratory variability of antibody tests. In addition, clinical severity scores such as the Cutaneous Lupus Erythematosus Disease Area and Severity Index and Systemic Lupus Erythematosus Disease Activity Index [27, 28] were not performed during these visits and could not be done retrospectively. There was also a small sample size because of the rigorous inclusion and exclusion criteria established to address limitations of other studies. In particular, we required follow up of SCLE patients for at least two years for accurate classification. Inadequate follow-up and disease duration excluded over a third of all screened SCLE patients.

# CHAPTER THREE
# Conclusions and Recommendations

## SCLE with vs. without SLE

Conclusions:

ACR SLE criteria are relatively stable among SCLE patients, but +SCLE/+SLE patients are more likely than +SCLE/-SLE patients to have specific skin findings including discoid lesions, oral ulcers, and lupus non-specific findings at baseline. +SCLE/+SLE and +SCLE/-SLE patients become more disparate over time with +SCLE/+SLE patients being more likely to have positive serologies including: ANA, anti-dsDNA, anti-Sm, and anti-RNP; decreased C3; proteinuria; and arthralgias. In contrast, +SCLE/-SLE patients may be more likely to demonstrate anti-Ro antibodies.

Recommendations:

Cutaneous manifestations of lupus present early in SCLE but since laboratory profiles become more dissimilar over time, +SCLE/+SLE patients may be tested for auto-antibodies, decreased complement, proteinuria, and arthralgias with the goal of anticipating disease progression and tailoring treatment. +SCLE/-SLE patients need not be monitored for these laboratory abnormalities since they are rare among patients with SCLE only, but testing for the development of anti-Ro antibodies may be considered. Large prospective studies comparing disease course in SCLE patients with and without SLE are needed to verify these results. Prospective studies evaluating SCLE patients that do and those that do not develop SLE are also needed for risk factor assessment.

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# CURRICULUM VITAE

## Education

**Ballet training:**

Aug 01-May 03 School of American Ballet, New York, NY

Jun 03-Jul 03 Maly Theater, St. Petersburg, Russia

**Universities attended:**

Aug 05-May 08 University of Texas at Dallas • **BS Neuroscience**

Aug 05-Aug 07 Collin County Community College (no major)

Jan 06-May 06 University of New Orleans (no major)

**Medical school:**

Aug 08-Jun 12 University of Texas Southwestern Medical Center at Dallas • **MD with Distinction in Research (**Expected Graduation: 6/1/2012)

## Research

**UT Southwestern Medical Center:**

May 09-Aug 09 The Charcot-Marie-Tooth N. American Database•**Susan Iannaccone, MD**
Performed a retrospective chart review of 305 Texas Scottish Rite, Children's Medical Center, and UT Southwestern patients with Charcot-Marie-Tooth disease to update, refresh, and complete the pre-existing database of patients. Patients were grouped based on inheritance pattern, electrophysiologic characteristics of demyelination or axonopathy, gene mutation identified, and the diagnostic certainty of their disease (definitive or working diagnosis). The information will be used to facilitate further investigation of the disease's natural history, underlying mechanisms, and experimental treatments such as high dose vitamin C, trophic factors, and even gene therapy.

Aug 11-Apr 12 Retrospective cohort of subacute cutaneous lupus patients with and without systemic lupus • **Benjamin F. Chong, MD**
Performed an observational, retrospective cohort study of patients with subacute cutaneous lupus erythematosus. Cohorts were followed over time and compared based on ANA positivity and various historical, clinical, and lab data.

Sept 11-Jan 12 Keloid study • **Donald A. Glass, II, MD, PhD**
Assisted in fielding phone calls and attending home visits for blood draws.

## Awards

Junior member of AOA

1st place Student Case Report poster. **Texas Academy of Family Physicians' Annual Session and Scientific Assembly**, Dallas, TX, 29 Jul 2011.

1st place Student Case Report poster. **5th Annual Health Research Forum**, Waco, TX, 19 Apr 2011.

## Leadership

| | |
|---|---|
| Aug 08-Jun 12 | St. Basil Society: Vice-president/Core member |
| Aug 09-Jun 12 | LIFE (Leaders in the Fight for Every patient): President/Vice-president |
| May 11-Jun 12 | AOA: Organizer for high school sports physicals volunteer event |
| Aug 11-Jun 12 | Colleges peer mentor |
| Aug 08-Aug 09 | Southwestern Student Connection: Vice-president |

## Service

| | |
|---|---|
| Mar 09, Mar 10 | Student Christian Fellowship: medical mission trip, El Paso, TX |
| Aug 09-Jun 12 | Monday Clinic/Agape Clinic: volunteer, Dallas, TX |

## Work/Personal

| | |
|---|---|
| Jul 03-Jun 04 | Boston Ballet II: ballet dancer, Boston, MA |
| Jul 04-May05 | Oregon Ballet Theatre: ballet dancer, Portland, OR |
| Jun 04-Jul 08 | New Orleans Ballet Theater: ballet dancer, New Orleans, LA |
| Aug 06-Jun12 | Telos Fitness Center, Pilates Connection, UT Southwestern Student Center: Pilates instructor, Dallas, TX |