Association of discoid lupus erythematosus with other clinical manifestations among patients with systemic lupus erythematosus

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Background: Cutaneous discoid lupus erythematosus (DLE) among patients with systemic lupus erythematosus (SLE) may be associated with less severe disease and with low frequency of nephritis and end-stage renal disease (ESRD).

Objective: We sought to investigate associations between confirmed DLE and other SLE manifestations, adjusting for confounders.

Methods: We identified patients with rheumatologist confirmation, according to 1997 American College of Rheumatology (ACR) SLE classification criteria, more than 2 visits, longer than 3 months of follow-up, and documented year of SLE diagnosis. DLE was confirmed by a dermatologist, supported by histopathology and images. SLE manifestations, medications, and serologies were collected. Multivariable-adjusted logistic regression analyses tested for associations between DLE and each of the ACR SLE criteria, and ESRD.

Results: A total of 1043 patients with SLE (117 with DLE and 926 without DLE) were included in the study. After multivariable adjustment, DLE in SLE was significantly associated with photosensitivity (odds ratio [OR] 1.63), leukopenia (OR 1.55), and anti-Smith antibodies (OR 2.41). DLE was significantly associated with reduced risks of arthritis (OR 0.49) and pleuritis (OR 0.56). We found no significant associations between DLE and nephritis or ESRD.

Limitations: Cross-sectional data collection with risk of data not captured from visits outside system was a limitation.

Conclusions: In our SLE cohort, DLE was confirmed by a dermatologist and we adjusted for possible confounding by medication use, in particular hydroxychloroquine. We found increased risks of photosensitivity, leukopenia, and anti-Smith antibodies and decreased risks of pleuritis and arthritis in patients with SLE and DLE. DLE was not related to anti-double-stranded DNA antibodies, lupus nephritis, or ESRD. These findings have implications for prognosis among patients with SLE. (J Am Acad Dermatol 2013;69:19-24.)

Key words: cutaneous lupus erythematosus; discoid lupus erythematosus; epidemiology; prognosis; systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease of unknown origin. It has been proposed that different clinical subsets of SLE exist, each associated with variable manifestations of the disease.[1-3] Several researchers have observed that chronic cutaneous lupus of the discoid variant (discoid lupus erythematosus [DLE]) occurs infrequently among patients

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with more severe organ involvement, in particular lupus nephritis and end-stage renal disease (ESRD) from nephritis, and seems to impart a better long-term prognosis.[4-9] DLE, a scarring, potentially disfiguring form of cutaneous lupus, is of particular interest to the clinician evaluating a patient with SLE, as it is one of the most outward clinical signs of disease and could provide immediate insight into the clinical prognosis of the patient at the bedside. Furthermore, differing SLE manifestations between patients with and without DLE would suggest different underlying pathophysiology of SLE subtypes and be the basis for future mechanistic study.

In this study, we evaluate the associations between dermatologist-confirmed DLE among patients with SLE and other common clinical and serologic SLE manifestations.

CAPSULE SUMMARY

- Prior studies suggest that discoid lupus erythematosus among patients with systemic lupus erythematosus is a marker for less severe disease, often offered as reassurance.
- We did *not* observe any associations (either positive or negative) with discoid lupus erythematosus and severe lupus manifestations (ie, renal or neurologic).
- These findings have important implications for counseling our patients with systemic lupus erythematosus and discoid lupus erythematosus regarding prognosis.

METHODS

Study population

The Brigham and Women's Hospital Lupus Center, Boston, MA, is staffed by 7 SLE expert rheumatologists and serves over 800 patients with SLE annually. The Brigham and Women's Hospital Lupus Registry contains data from 5030 individuals seen for potential SLE since the 1960s. Medical records have been reviewed by rheumatologists expert in the treatment of SLE for demographic data, date of first symptoms, date of diagnosis, all American College of Rheumatology (ACR) criteria, and serologies.

Inclusion criteria

From the registry, we identified patients who fulfilled the following criteria: (1) definite SLE diagnosis per rheumatologist/SLE expert case review; (2) 1997 ACR classification criteria for SLE[10]; (3) a documented year of SLE diagnosis; and (4) more than 2 visits and longer than 3 months of follow-up between January 1, 1970, and April, 30, 2011.

Data collection

We collected SLE manifestation, medication, and serologic data from review of electronic medical records. Electronic medical record data have been available since October 1, 1989. From the electronic medical records, we collected the following data for all subjects: age at SLE diagnosis, date of SLE diagnosis, self-reported race/ethnicity (white, African American, Asian, Hispanic, other), sex, duration (months) of follow-up at Brigham and Women's Hospital, number of lupus center visits, all ACR criteria for classification of SLE, DLE (ever), SLE-specific serologies (anti-Ro, anti-La, anti-Smith, anti-U1-ribonucleoprotein, anti-double-stranded DNA [dsDNA], antinuclear antibody initial pattern, anticardiolipin IgM and IgG, lupus anticoagulant), clinical laboratory findings (thrombocytopenia ever, defined as platelet count <100,000; anemia ever, defined as hematocrit <24%; and leukopenia ever, defined as white blood cell count <3000), and medications (use and number of prescriptions for the following medications: steroids [prednisone, prednisolone, methylprednisolone] [ever/never]; hydroxychloroquine [ever/never]; and immunosuppressives [azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil, systemic corticosteroids] [ever/never]). All patients had testing for anti-dsDNA antibodies in our study, performed by enzyme-linked immunosorbent assay in our hospital immunology laboratory.

These data were augmented by individual review of the medical records, in particular for those with dates of diagnoses before 1989 to: (1) recover missing data (including above demographic, serologic, and medication data); and (2) obtain details of diagnosis and treatment. The presence of DLE was confirmed by a board-certified dermatologist (J. F. M.) with review of dermatology/multispecialty notes supported by pathology and digital images, where applicable. DLE is a clinical diagnosis that is further supported by pathology findings. Criteria for confirmation of DLE included a specific diagnosis of "discoid" lupus from a specialist dermatologist AND support from 1 or more of the following: (1) a clinical description consistent with DLE (elements including follicular plugging, dyspigmentation, atrophy, scar formation, scarring-alopecia, telangiectasis, erythema, scale—*with emphasis on chronic scarring changes*); (2) histopathologic results consistent with DLE in the medical records; and/or (3) photographs in the medical records confirming DLE lesions. All aspects of this project were approved by the

Abbreviations used:

ACR:	American College of Rheumatology
DLE:	discoid lupus erythematosus
dsDNA:	double-stranded DNA
ESRD:	end-stage renal disease
OR:	odds ratio
SLE:	systemic lupus erythematosus

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Statistical analyses

We used Fisher exact tests for categorical variables (race/ethnicity), Wilcoxon rank sum tests for continuous variables, and χ^2 tests for medication use among those who had SLE with and without DLE. In univariable, followed by multivariable, logistic regression analyses, we modeled the odds of DLE associated *individually* with each of the ACR SLE criteria, and ESRD. Each individual model was adjusted for age at diagnosis, sex, race/ethnicity, disease duration, and *ever* use of the following medications individually and in combination: steroids (ever/never); hydroxychloroquine (ever/never); and immunosuppressives (azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil, systemic corticosteroids) (ever/never).

Suspected confounders were assessed between the primary predictor of interest and the outcome (DLE) as a more than 10% change in the risk estimate with inclusion of the covariate; problematic collinearity diagnostics such as tolerance and variance inflation factor review in the methods of Belsley et al[11] were used. Each of the ACR criteria and ESRD was re-evaluated in models containing: (1) all *ever-use* medications; (2) manual subtraction of individual medications by level of significance in the model; and (3) individually (azathioprine, cyclophosphamide, hydroxychloroquine, methotrexate, mycophenolate mofetil, systemic corticosteroids). Wald 95% confidence intervals were calculated for odds ratios (OR). All analyses were performed using software (SAS, Version 9.2, SAS Institute, Cary, NC).

RESULTS

Of 1043 patients with SLE who met inclusion criteria, 92% were female and 51% were white; 100% were antinuclear antibody positive and 66% were anti-dsDNA positive. Mean age at diagnosis was 32 years (±13) and mean duration of follow-up was 10 years (±6.5). In all, 117 patients were confirmed to have DLE.

Sociodemographic features and medication use of patients with SLE evaluated in subgroups as those with (n = 117) and without DLE are shown in Table I along with medication use between the 2 groups. A statistically significant difference existed between the race/ethnicity of patients who had SLE with DLE and without DLE (P = .02). The number of ACR criteria was higher among patients who had SLE with DLE compared to those without DLE ($P < .01$). Age at diagnosis, SLE disease duration, sex, and medication use was not significantly different between groups. There was, however, a nonsignificant trend toward greater hydroxychloroquine use in patients who had SLE with DLE compared to those without DLE.

In individual multivariable logistic regression models (adjusting for age at diagnosis, sex, race/ethnicity, disease duration, and medication use), among patients with SLE, DLE was significantly associated with the presence of anti-Smith antibodies (OR 2.41, $P < .01$), photosensitivity (OR 1.63, P = .02), and leukopenia (OR 1.55, P = .04) (Table II). DLE was inversely associated with both arthritis (OR 0.49, $P < .01$) and pleuritis (OR 0.56, P = .01). We found no significant associations between DLE and malar rash, oral ulcers, pericarditis, proteinuria, urinary casts, seizure, psychosis, anemia, lymphopenia, thrombocytopenia, anti-dsDNA, antiphospholipid antibodies, nephritis, or ESRD. No significant associations between DLE and World Health Organization class III to IV nephritis (n = 97; DLE + class III/IV nephritis n = 26) were found (OR 0.54, P = .21). Regression models controlling for use of medications individually, or all medications combined in the same model, did not yield significantly different associations (Table II).

COMMENT

It was first reported 30 years ago by Prystowsky et al[7,8] that patients with SLE and DLE had less frequent and less severe systemic organ involvement. Several other authors, including Callen,[4,5] have observed that in the subgroup of SLE with active discoid lesions, patients tended to have a more benign disease course. These studies tended to be of relatively small numbers of patients and observational in nature, with data often gathered in the setting of a dermatology clinic, which may have biased toward a group of patients with less severe systemic disease. It has been noted, in particular, that patients with SLE and DLE had a low prevalence of severe renal disease.[5,6] Based on these earlier observational data, many clinicians have offered prognostic information to the patient with SLE who presents with discoid lesions as part of the SLE clinical phenotype.

More recently, Santiago-Casas et al[9] reported the clinical manifestations and damage accrual

Table I. Sociodemographic features of patients with systemic lupus erythematosus with and without discoid lupus erythematosus

Feature	SLE without DLE, n = 926 (90%)	SLE with DLE, n = 117 (10%)	*P* value*
Female (%)	847 (92)	111 (95)	.28
Race/ethnicity (%)			
White	480 (52)	56 (48)	.02
African American	130 (14)	31 (27)	
Hispanic	41 (4)	6 (5)	
Asian	83 (9)	8 (7)	
Other	10 (1)	1 (1)	
Missing race/ethnicity	182 (19)	15 (12)	.09
Age at diagnosis, y, mean (SD)	32.6 (13.5)	32.0 (12.6)	.91
SLE duration, y, mean (SD)	18.4 (10.6)	18.4 (10.5)	.90
No. of ACR criteria for SLE, mean (SD)	5.2 (1.2)	5.6 (1.4)	<.01
Medications, n (%)			
Hydroxychloroquine	739 (80)	103 (88)	.05
Mycophenolate	178 (20)	24 (20)	.71
Corticosteroids (systemic)	693 (75)	88 (75)	1.00
Methotrexate	101 (11)	18 (15)	.16
Cyclophosphamide	101 (11)	15 (13)	.53
Azathioprine	204 (22)	30 (26)	.41
Rituximab	26 (3)	1 (1)	.35
Leflunomide	22 (2)	2 (2)	1.00

ACR, American College of Rheumatology; *DLE*, discoid lupus erythematosus; *SLE*, systemic lupus erythematosus.
*Fisher exact tests for categorical variables (race/ethnicity). Wilcoxon rank sum tests for continuous variables and χ^2 tests for medications.

among patients with SLE and DLE in the PROFILE multiethnic lupus cohort. This group determined that patients with SLE and DLE were more likely to have malar rash, photosensitivity, oral ulcers, leukopenia, vasculitis, and seizures, while less likely to have arthritis, ESRD, and immunologic abnormalities than patients with SLE without a history of DLE. They did not, however, find an association between DLE and nephritis. Cases of DLE in the PROFILE study were not confirmed or validated by an expert dermatologist, and that study did not assess effects of individual and combinations of medications upon the outcomes of interest.

Describing a "pure" subset of patients with DLE in these studies is crucial, as other cutaneous lupus-specific and -nonspecific skin disease may be associated with different SLE phenotypic subsets of disease. The historic reports of less severe organ involvement pertained specifically to patients with DLE seen by expert dermatologists who largely defined this disease entity.[4,5,7,8,12] Of note, Vasquez et al[13] compared patients with DLE only, "borderline" DLE/SLE, and DLE/SLE with regard to several clinical and serologic features. Interestingly, the patients with borderline DLE/SLE and DLE only in their study had low levels of anti-Smith positivity whereas patients with DLE/SLE had relatively elevated anti-Smith levels, complementing our findings of increased anti-Smith positivity among patients with SLE and DLE (compared with patients who had SLE without DLE). Overall, their study concluded that patients with borderline DLE/SLE and DLE only appeared more similar to each other in serology, lesion distribution, and treatment history than did the patients with DLE/SLE.

SLE is clearly a heterogeneous disease but it remains unclear whether SLE subtypes are actually different diseases. Past studies have attempted to distinguish specific subtypes of SLE using clinical observation and description or various statistical clustering techniques.[1-3] Being able to phenotype SLE subsets would have implications for an individual's disease monitoring, offering patients and physicians prognostic and survival information. No specific means of calculating survival of patients with SLE based on presenting features yet exists. In a few past studies, associations, such as that of anti-dsDNA antibodies with lupus nephritis, and "mucocutaneous manifestations and arthritis" with a low incidence of "serositis and hematologic disease," have been reported.[2,14] Our finding that there is no difference in anti-dsDNA between the groups is interesting and not expected given the historic belief that patients with DLE have a lower incidence of severe manifestations, including renal disease and associated serologies such as

Table II. Associations between discoid lupus erythematosus and other American College of Rheumatology criteria for systemic lupus erythematosus and end-stage renal disease

SLE manifestation (n = positive finding of 1043)	SLE without DLE (n = 926), n (%)	SLE with DLE (n = 117), n (%)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	Adjusted OR† (95% CI)
Anti-Smith	201 (21.7)	45 (38.5)	2.25 (1.50-3.38)	**2.27 (1.50-3.45)**	**2.41 (1.58-3.69)**
Photosensitivity	374 (40.4)	60 (51.3)	1.55 (1.06-2.28)	**1.71 (1.15-2.55)**	**1.63 (1.09-2.44)**
Leukopenia	301 (32.5)	50 (42.7)	1.55 (1.05-2.29)	**1.50 (1.01-2.24)**	**1.55 (1.03-2.32)**
Pleuritis	349 (37.7)	31 (26.5)	0.59 (0.39-0.92)	**0.56 (0.36-0.88)**	**0.56 (0.36-0.87)**
Arthritis	738 (79.7)	79 (67.5)	0.53 (0.35-0.80)	**0.51 (0.33-0.79)**	**0.49 (0.31-0.76)**
Lupus nephritis	281 (30.3)	38 (32.5)	1.10 (0.73-1.66)	1.09 (0.71-1.68)	1.33 (0.83-2.14)
Pericarditis	112 (12.1)	10 (8.6)	0.68 (0.35-1.34)	0.68 (0.34-1.36)	0.68 (0.34-1.36)
Proteinuria	256 (27.7)	27 (23.1)	0.78 (0.50-1.23)	0.70 (0.43-1.13)	0.77 (0.47-1.27)
Casts	117 (12.6)	9 (7.7)	0.56 (0.28-1.17)	0.53 (0.26-1.09)	0.57 (0.27-1.20)
End-stage renal disease	48 (5.1)	7 (6.0)	1.16 (0.51-2.64)	0.96 (0.41-2.22)	1.24 (0.50-3.05)
Oral ulcers	240 (25.9)	37 (31.6)	1.32 (0.87-2.00)	1.35 (0.88-2.07)	1.32 (0.86-2.03)
Malar rash	406 (43.8)	46 (39.3)	0.82 (0.56-1.23)	0.86 (0.57-1.30)	0.88 (0.58-1.32)
Seizure	100 (10.8)	14 (12)	1.12 (0.61-2.03)	1.14 (0.62-2.09)	1.20 (0.65-2.21)
Psychosis	16 (1.7)	3 (2.6)	1.50 (0.43-5.21)	1.45 (0.41-5.14)	1.50 (0.42-5.38)
Anemia	181 (19.5)	26 (22.2)	1.17 (0.74-1.87)	1.12 (0.69-1.80)	1.15 (0.71-1.86)
Lymphopenia	340 (36.7)	51 (43.6)	1.33 (0.90-1.96)	1.32 (0.88-1.97)	1.38 (0.91-2.08)
Thrombocytopenia	110 (11.9)	18 (15.4)	1.35 (0.79-2.31)	1.45 (0.83-2.54)	1.54 (0.87-2.71)
Anti-dsDNA	610 (65.9)	83 (70.9)	1.27 (0.83-1.93)	1.25 (0.81-1.93)	1.33 (0.86-2.07)
Antiphospholipid antibodies	225 (24.3)	24 (20.5)	0.80 (0.50-1.29)	0.85 (0.52-1.37)	0.87 (0.54-1.43)

Statistically significant findings are listed in bold.

CI, Confidence interval; *DLE*, discoid lupus erythematosus; *dsDNA*, double-stranded DNA; *OR*, odds ratio; *SLE*, systemic lupus erythematosus.

*Multivariable logistic regression analyses modeling OR of DLE associated with each SLE manifestation or laboratory finding *individually*, adjusted for age at diagnosis, sex, race/ethnicity, and disease duration.

†Multivariable logistic regression analyses modeling OR of DLE associated with each SLE manifestation or laboratory finding *individually*, adjusted for age at diagnosis, sex, race/ethnicity, disease duration, and medication use: steroids (ever/never); hydroxychloroquine (ever/never); and immunosuppressives (azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil, systemic corticosteroids) (ever/never).

anti-dsDNA. A multicenter study of 513 Danish patients with SLE evaluated disease manifestations and attempted to define clinical subsets.[1] The rate of nephritis among patients meeting ACR criteria for the classification of SLE was 45% with a mean duration of follow-up of 8.2 years from diagnosis and 12.8 years from first symptom. This group identified 3 clinical clusters: (1) predominantly discoid disease with notable absence of malar rash and nephritis; (2) predominant nephritis, serositis, and lymphopenia; and (3) malar rash and photosensitivity. Work by To et al[2] in a Chinese SLE population supports the concept that clinical manifestations and severity of SLE cluster into 3 groups: (1) mucocutaneous/arthritis-predominant with low nephritis incidence; (2) nephritis/hematologic-predominant with low mucocutaneous; and (3) heterogeneous (consisting of all manifestations in no clear cluster). Although these studies have attempted to predict clinical subsets and organ damage with some success, they have not been able to provide practical clinical prognostic information for patients and clinicians.

In this large cohort of patients with SLE, we have found an increased frequency of photosensitivity, leukopenia, and anti-Smith antibodies among patients with SLE and DLE and an inverse association of DLE with both pleuritis and arthritis, after adjusting for multiple covariates including medication exposures, individually and as a group. We did *not* observe the inverse associations of DLE with anti-dsDNA antibodies, lupus nephritis, or ESRD that have been noted in other studies. This finding will no doubt have an impact on the information we provide to patients presenting with features of DLE as part of their systemic disease.

Limitations of our study include the cross-sectional and partially retrospective nature of data collection with its inherent risk of missing data. Furthermore, our study is only able to determine the *associations* between DLE and other SLE manifestations and cannot temporally relate these clinical features or imply a causal relationship. Regression models were performed as independent tests, and we are aware of the possibility of issues surrounding multiple testing and that future studies may be performed to reproduce our individual findings.

In summary, our findings could have important implications for prognosis among patients with DLE

and possibly for different underlying pathophysiology of SLE subtypes.

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