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Cross-sectional analysis of a collaborative web-based database for lupus erythematosus associated skin lesions: 114 prospectively enrolled patients

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Abstract

Objective—To assess disease severity in subsets of cutaneous lupus erythematosus (CLE) by using outcome and quality of life (QoL) measures, and to determine treatment responsiveness by establishing a web-based database of patients with skin manifestations of lupus.

Design—A prospective, cross-sectional study.

Setting—A university hospital cutaneous autoimmunity outpatient clinic

Patients—One hundred fourteen patients who presented from January 2007 to November 2007 and met the criteria for having CLE or lupus-nonspecific skin disease.

Main Outcome Measures—We used the CLE Disease Activity and Severity index (CLASI) to evaluate cutaneous disease. Patients completed the modified Skindex-29 at each visit.

Results—Seven (6.2%) of the University of Pennsylvania patients presented with ACLE, 21 (18.6 %) with SCLE, 77 (68.1 %) with CCLE, 7 (6.2 %) with SLE and LE-nonspecific skin lesions, and 1 (0.9 %) with LE-nonspecific skin disease only. The mean baseline CLASI activity/damage scores in ACLE, SCLE, and CCLE patients were 6.4/5.1, 11.1, 1.6, 7.5/10.2, respectively. The mean baseline modified Skindex-29 score in ACLE, SCLE, and CCLE patients was 76.3, 79.4, and 82.7, respectively (ns). Eleven of the patients (9.7%) were considered refractory to conventional therapies. The number of patients with positive history of current smoking was significantly higher in the refractory group than the non-refractory group (p=0.006).

Conclusions—This web-based database is the first systematic epidemiologic study of cutaneous LE in the United States, and should allow collection of data related to disease activity, QoL, and response to therapy at multiple centers.

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Introduction

Lupus Erythematosus (LE) is a potentially disabling autoimmune disease that presents clinically as a spectrum ranging from mildly affected patients with only localized discoid skin lesions to those at risk of dying from severe systemic manifestations of LE. While the prevalence of systemic LE (SLE) is 17-48 per 100,000 worldwide, cutaneous LE is estimated to be as much as 2-3 times more frequent than SLE itself.[1] Skin disease is the second most frequent clinical manifestation of LE as well as the second most common primary presenting symptom of LE.2

Skin disease in LE is diagnosed on the basis of clinical, serological and histological criteria, following the Gilliam's or modified Gilliam's classification.3[-4] According to this classification, skin disease in LE can present with either lupus-specific cutaneous LE (CLE) or lupus-nonspecific findings. Lupus-specific skin lesions are seen only in patients with LE. Lupus-nonspecific skin lesions may occur in patients with LE, but also may be present among other disease processes. Lupus-specific skin manifestations are subclassified into chronic CLE (CCLE), subacute CLE (SCLE), and acute CLE (ACLE).[3] The types of skin lesions in an individual patient can provide insight into the likelihood of underlying systemic disease. CCLE and SCLE may persist for many years, and like SLE, may lead to severe disability and limited quality of life. CLE is considered to be the third most common cause of industrial disability from dermatologic disease, with as many as 45% of CLE patients experiencing some form of vocational handicap.5 These data imply considerable societal and medical costs for patients.

The need for high quality, multicenter clinical databases which enable collection and organization of information on specific diseases has been well documented. Databases enable clinicians to conduct research, plan and manage services, and obtain more accurate estimates of care outcomes that can be shared with patients.[6-11] Valid and reliable information is critical in chronic diseases like LE in which patients present with a large spectrum of symptoms requiring management over an extended period of time.[12]

At present, though a few SLE databases exist, including the Cincinnati Children's Hospital SLE Database and the CaNIOS (National Lupus Registry and the 1000 Canadian Faces of Lupus) Database,[13-]14 there has not been a comprehensive prospective collection of data on CLE. Since research projects depend on systematic data collection to determine feasibility and design, medical databases are a valuable tool to support new inquiries and investigations.

Additionally, until recently there have been no adequate disease severity measures available to allow this type of study to be conducted. Skin-specific and systemic clinical outcome and quality of life measures have recently become available to enable clinicians to plan future research projects that can lead to improved patient care and treatment modalities. The CLE Disease Activity and Severity index (CLASI) was designed in 2005 to convert subjective observations seen in CLE into objective data by means of a scoring system.[15] The recent development of this validated skin instrument, which has separate scores for quantifying activity and damage, has made it possible to objectively follow patients' disease course and response to therapy. Since CLE is a relatively rare condition, data collection can be improved by multicenter collaborative efforts.

We established a collaborative, web-based database to collect information on patients with various skin manifestations of LE in order to elucidate certain differences that may exist across disease subtypes. This is the first known systematic epidemiologic study of cutaneous LE in the United States. The primary endpoints of our prospective study were: 1) to establish a web-based database of patients with skin lesions associated with lupus erythematosus, 2) to perform a prospective evaluation of CLE patients in order to assess disease severity, quality of life, and response to therapy, and 3) to determine the prevalence, clinical severity, and characteristics

of refractory cases. Using available and validated clinical outcome measures such as the CLASI and quality of life measures such as the modified Skindex-29, we evaluated the severity of disease as well as the efficacy of currently available treatments in order to assess the need for novel interventions and provide useful data for future clinical trials of new therapies for CLE.

Methods

Subject Selection

Subjects at the University of Pennsylvania were enrolled sequentially during scheduled outpatient clinic visits. All subjects at the University of Pennsylvania who were 18 years of age or older and who were diagnosed with CLE or LE-nonspecific disease by clinico-histopathological correlation were invited to enroll in the database study. Most of these patients were already receiving established medical standard of care at the Hospital of the University of Pennsylvania. All subjects were consented using IRB-approved informed consent and HIPAA forms.

Study Procedures

Information was obtained via history, physical exams, chart reviews, and subject questionnaires. All subjects who agreed to participate were assessed in terms of specific parameters related to their medical history and treatment. Information related to socio-demographics (age, gender), concomitant systemic illness and duration, dermatologic diagnosis and duration, smoking history, medications used, and response to therapies was recorded. The following distinct yet complementary outcome measures of the subject's disease and therapeutic experience were used at each visit: the CLASI; the SLE disease activity index (SLEDAI), which evaluates systemic disease; the modified Skindex-29, a CLE-modified quality-of-life (QoL) measure; and analogue measures of itch, pain, fatigue, general health, and skin assessments. Data were collected in accordance with Good Clinical Practice (GCP) guidelines to ensure accuracy and integrity. Completeness of data and use of explicit definitions for variables were assessed and a constant effort at quality control was maintained. Data were then organized and entered into a collaborative web-based database. Data security and confidentiality were managed carefully to ensure regulatory compliance.

Subjects were categorized into the various subtypes of CLE, namely ACLE, SCLE (annular or papulosquamous), and CCLE (classic DLE [generalized or localized], hypertrophic DLE, tumid LE, chilblains, or lupus panniculitis), according to the modified Gilliams's classification.[4]

Statistical Analysis

Conventional methods were used to generate descriptive statistical results. Groups were compared by using ANOVA, followed by the Student-newman-Keuls Test. P values of less than 0.05 were considered to represent differences among population sets examined.

Results

We sequentially enrolled and followed 114 patients who presented to our outpatient clinic at the Hospital of the University of Pennsylvania from January 2007 to November 2007 and met the criteria for having CLE or lupus-nonspecific skin disease. One of the patients had three types of LE-specific skin disease with ACLE, SCLE, and CCLE skin lesions. CCLE was the most predominant subset seen, with 77 patients (68.1%) carrying that diagnosis. Of these subjects, 26 had generalized DLE, 32 had localized DLE, 2 had hypertrophic DLE, 13 had tumid LE, 1 had chilblains, and 3 had LE panniculitis. Seven (6.2%) of the subjects presented

with ACLE, 21 (18.6 %) presented with SCLE, 7 (6.2 %) presented with SLE and LE-nonspecific skin lesions, and 1 (0.9 %) presented with LE-nonspecific skin disease only. Of the SCLE patients, 17 (81 %) had predominantly papulosquamous lesions, 2 (9.5 %) had predominantly annular lesions, and 2 (9.5 %) had a combination of both papulosquamous and annular lesions (Table 1). Twenty-five subjects refused to participate in the study. Twenty-two (88 %) of these subjects were female and 3 (12%) of them were male. Race distribution in the non-enrolled subjects was as follows: 52% Caucasian, 44% African-American, and 4% Asian. Twenty-three of the non-enrolled subjects had CCLE (20 female, 3 male; 11 Caucasian, 11 African-American, 1 Asian), 1 had SCLE (female, Caucasian), and 1 had SLE (female, Caucasian).

Demographics

The racial composition of our study population was as follows: 58.4% Caucasian, 36.3% African-American, 0.9% Hispanic, and 4.4% Asian. Thirty-six (46.8 %) CCLE subjects were Caucasian, 37 (48 %) were African-American, 3 (3.9 %) were Asian, and 1 (1.3 %) was Hispanic. Twenty (95.2 %) SCLE subjects were Caucasian, and 1 (4.8 %) was Asian. Three (42.9 %) ACLE subjects were Caucasian, 3 (42.9 %) were African-American, and 1 (14.3%) was Asian. Females comprised the majority of the study population, as ninety-three (82.3 %) of our subjects were female and only 20 (18%) were male. Female-to-male ratio was 3.2:1 in subjects with SCLE and 4.1:1 in subjects with CCLE. Within CCLE subsets, the female-to-male ratio was the highest (4.3) in subjects with localized DLE and the lowest (2.2) in subjects with tumid LE. All of our ACLE subjects were female.

The mean age at onset was the highest in SCLE subjects (48.2 +/- 4.1, $P<0.05$ for SCLE vs. ACLE and SCLE vs. CCLE). The difference between the mean age at onset in ACLE subjects and CCLE subjects was not statistically significant (33.1 +/- 5 vs. 36.1 +/- 1.5, P = NS). Eight (7.6 %) of the CLE subjects were younger than 20 years old at onset of disease and 5 (4.8 %) were older than 60 at the time of onset. 10% of the SCLE subjects were younger than 20 at disease onset, while 20% were older than 60 at the time of onset. 6.9 % of the CCLE subjects were younger than 20 at disease onset and 1.4% were older than 60; however, there was no significant difference in the age at onset between the different subsets of CCLE. Furthermore, in the CCLE subjects, no significant difference at age of onset between genders was found (mean age at onset in our female and male CCLE subjects: 36.5 +/- 1.6 and 33.2 +/- 3.9, respectively, P=0.39 [t test]) (Table 1).

CLASI analysis

Regarding CLASI, modified Skindex-29, and SLEDAI calculations, we used second visit data instead of first visit data in 5 subjects (1 ACLE, and 4 CCLE [1 localized DLE, 2 generalized DLE, 1 tumid LE]) due to the unavailability of first visit data. Four subjects (all with CCLE [1 localized DLE, 1 generalized DLE, 1 tumid LE, 1 LE panniculitis] were excluded from the CLASI, modified Skindex-29, and SLEDAI calculations, and 2 subjects (1 SCLE, and 1 CCLE [tumid LE]) were excluded only from SLEDAI calculations due to unavailability of data. The mean baseline CLASI activity score (performed at the first visit) was the highest in SCLE subjects and higher in CCLE than ACLE subjects; however, none of these differences were statistically significant (P=0.244) (Table 2). The mean baseline CLASI damage score was the highest in CCLE subjects and higher in ACLE than SCLE subjects ($P<0.05$ for CCLE vs. SCLE; NS for CCLE or SCLE vs. ACLE) (Table 2). Within CCLE subsets the mean baseline CLASI activity score was the highest in generalized DLE subjects and similar between tumid LE and localized DLE subjects ($P<0.05$ for generalized DLE vs. localized DLE and generalized DLE vs. tumid LE; NS for tumid LE vs. localized DLE). The mean baseline CLASI damage score was the highest in generalized DLE subjects and higher in localized DLE than in tumid

LE subjects (P<0.05 for generalized DLE vs. tumid LE, generalized DLE vs. localized DLE, and localized DLE vs. tumid LE) (Table 3).

Skindex analysis

The mean baseline modified Skindex-29 total score was not significantly different among the subsets of CLE (See Table 2). The mean baseline modified Skindex-29 total score was the highest in generalized DLE subjects and similar in tumid LE and localized DLE subjects (P<0.05 for generalized DLE vs. localized DLE, generalized DLE vs. tumid LE; NS for tumid LE vs. localized DLE) (Table 3).

SLEDAI analysis

The mean baseline SLEDAI total score was the highest in our ACLE subjects and trending to higher in the SCLE than in the CCLE subjects; however, none of these differences were statistically significant (P=0.08) (Table 2).

LE-nonspecific skin lesions

The lowest incidence (23.8%) of LE-nonspecific skin lesions occurred in SCLE subjects, while CCLE subjects had a slightly higher incidence (31.2%) of LE-nonspecific skin lesions. The highest incidence of LE-nonspecific skin lesions was seen among ACLE subjects (57.1%) (p=ns, χ^2).

Refractory Cases

Eleven subjects (9.7%) at the University of Pennsylvania were considered refractory to conventional therapies, meaning that their skin lesions remained active despite aggressive medical treatment. The majority of refractory cases were females. The distribution of subtypes in the refractory group was significantly different from the distribution of subtypes in the whole population, and the number of refractory cases was enriched with generalized DLE relative to localized DLE and SCLE (p=0.036, χ^2). The number of subjects with current history of smoking was significantly higher in the refractory group than the non-refractory group (p=0.006). The race distribution in the refractory group was not significantly different from the race distribution in the whole population (Table 4).

Discussion

Sontheimer et al. found SCLE lesions in 9 % of their study patients,16 and others have found SCLE lesions in 7-27 % of their LE patient populations.17-23 SCLE patients comprised 18.6 % of our LE patient population, similar to previously reported ratios. Most of our SCLE patients had papulosquamous rather than annular-polycyclic lesions, similar to previous reported results.[24] Additionally, most of our CCLE patients presented with DLE (either generalized or localized) or tumid LE.

The majority (82.3%) of our LE patients were female, consistent with previous studies.[25] However, more of our CLE patients were Caucasian rather than African-American (58.4 vs. 36.3). This finding is different from the previously reported higher incidence of systemic LE in African-Americans relative to Caucasians.26-27 The difference implies that there may be a difference between SLE and cutaneous LE and may also reflect the population of patients attending the Hospital of the University of Pennsylvania clinic. The majority of SCLE subjects were Caucasian, which is consistent with an earlier report that indicated that 85% of the involved SCLE population is of Caucasian origin.16 Others have reported similar racial demographic data.17, 20, 21, 23, 28-30 CCLE subjects were evenly divided between Caucasians and African-Americans, which differs from previous reports. Hochberg et al. showed that

African-Americans were seemingly affected more frequently by DLE;[31] however, some earlier studies have found DLE to be more frequent in Caucasians.[32-35] These results likely reflect different populations drawn to clinics.

The mean age at onset was the highest in our SCLE subjects. The mean age of onset was lower in our ACLE than CCLE subjects; however, this difference was not statistically significant. Malar rash, which is the most common pattern of localized ACLE, has previously been suggested to be associated with a younger age of disease onset.[17] There was no significant difference in the age at onset between different subsets of CCLE. The mean age at onset in our CCLE subjects (36.1) was not significantly different between genders. The usual age at onset of DLE has been reported as 20 to 40 years both in male and females.[32-38]

All of our ACLE subjects were female, which is consistent with a previously reported female-to-male ratio in ACLE patients of 8:1.[39] Malar rash has been reported more commonly in women than in men,[17, 40] which correlates with the higher incidence of ACLE in women. The female-to-male ratio was not significantly different between SCLE and CCLE subjects. The female-to-male ratio was 3.2:1 in our SCLE subjects. Earlier studies have shown that there is likewise a female predominance in SCLE, with women affected 3-6 times more frequently than men.[16, 31, 41] The female-to-male ratio in our CCLE subjects of 4.1:1 is somewhat higher than reported ratios of 3:1.[35, 42, 43] Other researchers have reported the female-to-male ratio for DLE to be between 3:2 and 3:1,[33-38, 42, 43] lower than the ratio of females to males with SLE. In CCLE subjects, the female-to-male ratio was the lowest in tumid LE patients. Interestingly, half of our CLE subjects with onset of disease before age 20 were male.

The CLASI was developed due to a need for skin-based outcome measures for clinical trials in CLE. It allows for detailed measurement of the extent and severity of skin involvement. The mean baseline CLASI activity score was the highest in our SCLE subjects and was similar between our ACLE and CCLE subjects. The mean baseline CLASI damage score was the highest in our CCLE subjects, which is not surprising since CCLE lesions typically can produce scarring and dyspigmentation as they resolve. The mean baseline CLASI damage score was higher in ACLE than SCLE subjects. This may reflect that there are African Americans who pigment with ACLE, while SCLE subjects are Caucasian.

CLASI can document the distribution and severity of cutaneous symptoms in a way that allows comparison between groups of patients. In our CCLE patients, the mean baseline CLASI activity score was the highest in generalized DLE subjects and was similar between localized DLE and tumid LE subjects. As mentioned before, the majority of patients with CCLE lesions tend to suffer an indolently progressive disease that can spread to scarring and dyspigmentation. The mean baseline CLASI damage score was the highest in generalized DLE subjects and was higher in localized DLE than tumid LE subjects.

QoL assessment in dermatology has become a major focus for researchers. The development of new therapeutics is dependent upon meeting the needs of patients. Therefore, using patient-rated outcome measures is one of the best methods of understanding this need. The Skindex is a commonly used index of QoL in dermatology. Since CLE is exacerbated with sun exposure, three questions related to photosensitivity were added to create the modified Skindex-29. The modified Skindex-29 total score was not significantly different among the ACLE, SCLE, and CCLE subsets of CLE.

In our CCLE subjects, the mean baseline modified Skindex-29 total score was the highest in generalized DLE subjects and was similar between localized DLE and tumid LE subjects. Future studies will correlate QoL findings with elements of activity and damage in the CLASI, given the trend to worse QoL in generalized DLE.

The mean baseline SLEDAI total score was the highest in our ACLE subjects and was higher in our SCLE than CCLE subjects, but these differences were not statistically significant. Our subjects were at the mild end of the SLE spectrum.

Almost 10% of our patients were considered refractory to current therapies, with a disproportionate number (54.5 %) of these cases having generalized DLE. Other studies have suggested that patients with generalized DLE have more resistant disease and involvement of cytotoxic T cells.[44] DLE has previously been associated with smoking.45 Smoking has been also shown to interfere with efficacy of antimalarials in CLE.46-47 Our data regarding the higher number of smokers in the refractory group suggest that smoking may be a risk factor for refractory CLE. This highlights the importance of smoking cessation in CLE.

Interest in CLE by pharmaceutical and biotechnology companies has increased and in preparation for future clinical trials of new therapies for CLE, it is crucial that the prevalence, clinical severity, and characteristics of refractory cases be measured and evaluated. This target population of refractory patients will benefit the most from new therapies and assessment of their prevalence will assist in planning future studies.

Conclusions

This pilot study demonstrates the ability to collect data prospectively using a web-based design. Our data suggest significant numbers of both generalized and localized DLE subjects relative to SCLE and ACLE subjects. Our data showed higher CLASI scores in generalized versus localized patients, with a trend to higher modified Skindex-29 scores in generalized DLE. Our future goals are to follow treatment responsiveness and disease severity prospectively, to assess feasibility of using instruments to measure CLE flares, to compare skin-specific vs. general QoL measures in CLE, and to expand use of the web-based database to incorporate participation from additional sites.

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Table 1

Demographics of the patients recruited at the University of Pennsylvania

Type of LE skin manifestations		Number of cases	Age at onset (mean+/- SEM; range)	F/M ratio	Race distribution			
					African-American	Caucasian	Hispanic	Asian
ACLE		7	33.1+/-5.0; 17-56)	7/0	3	3	0	1
SCLE		21	48.2+/-4.1; 15-82	16/5 (3.2)		20		1
CCLE		77	36.1+/-1.5; 12-65	62/15 (4.1)	37	36	1	3
CCLE Subclassifications	DLE generalized	26	32.6+/-1.9 ;19-57	21/5 (4.2)	17	8		1
	DLE localized	32	39.1+/-2.8; 12-65)	26/6 (4.3)	17	14		1
	DLE hypertrophic	2	24.5+/-5.0; 21-28)	2/0		2		
	Tumid LE	13	37.4+/-3.4; 19-60)	9/4 (2.2)	2	9	1	1
	Chilblains	1	46	1/0		1		
	LE panniculitis	3	36.3+/-14.3; 20-59)	3/0	1	2		
SLE		7	34.5+/-4.1; 24-45)	7/0	1	6		
Only LE non-specific disease		1	23	1/0		1		

Table 2

CLASI, modified Skindex-29, and SLEDAI in the CLE patients recruited at the University of Pennsylvania

Type of LE skin manifestations	ACLE	SCLE	CCLE
CLASI Activity (mean+/-SEM; range)	6.4+/-3.3; 0-19	11.1+/-2.5; 0-41	7.5+/-1; 0-32
CLASI Damage (mean+/-SEM; range)	5.1+/-2; 0-11	1.6+/-0.9; 0-17	10.2+/-1.2; 0-40
Modified Skindex-29 (mean+/-SEM; range)	76.3+/-12.1; 43-120	79.4+/-6.9; 33-137	82.7+/-3.3; 34-142
SLEDAI (mean+/-SEM; range)	4.3+/-1.5; 0-10	2.2+/-0.8; 0-10	1.7+/-0.3; 0-11

Table 3

CLASI and modified Skindex-29 in the CCLE patients recruited at the University of Pennsylvania

Type of LE skin manifestations	Generalized DLE	Localized DLE	Tumid LE
CLASI Activity (mean+/-SEM; range)	13.3+/-2.2; 0-32	4+/-0.8; 0-17	5+/-0.9; 2-12
CLASI Damage (mean+/-SEM; range)	19.2+/-2.4; 0-40	6.6+/-0.9; 0-18	1.9+/-1; 0-10
Modified Skindex-29 (mean+/-SEM; range)	93.6+/-5.6; 40-141	74.2+/-3.6; 41-110	75.7+/-9.1; 43-141

Table 4

Characteristics of refractory cases recruited at the University of Pennsylvania (HCQ=hydroxychloroquine, CQ=chloroquine, Q=quinacrine)

Diagnosis	Sex	Ethnicity	Age at onset	Medication History
Generalized DLE	F	African-American	33	HCQ, CQ, Q, immunosuppressives, systemic steroids, thalidomide
Generalized DLE	F	African-American	30	HCQ, Q, immunosuppressives, systemic steroids
Generalized DLE	F	Caucasian	28	HCQ, CQ, Q, immunosuppressives, thalidomide, dapsone
Generalized DLE	F	African-American	28	HCQ, CQ, Q, immunosuppressives, systemic steroids, thalidomide
Generalized DLE	F	African-American	35	HCQ, CQ, Q, immunosuppressives, systemic steroids, thalidomide
Generalized DLE	F	African-American	39	HCQ, Q, immunosuppressives, systemic steroids
Localized DLE	F	African-American	32	HCQ, immunosuppressives, systemic steroids
Localized DLE	F	Caucasian	58	HCQ, CQ, Q, immunosuppressives, thalidomide
Hypertrophic DLE	F	Caucasian	28	HCQ, CQ, Q, immunosuppressives, systemic steroids, thalidomide
Hypertrophic DLE	F	Caucasian	21	CQ, Q, immunosuppressives, systemic steroids, thalidomide
SCLE	M	Caucasian	37	HCQ, CQ, Q, immunosuppressives, thalidomide