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INVESTIGATIVE REPORT

A Database Analysis of Cutaneous Lupus Erythematosus with the EUSCLE Core Set Questionnaire

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The aim of this study was to determine whether the Core Set Questionnaire developed recently by the European Society of Cutaneous Lupus Erythematosus (EUSCLE) is a useful tool to evaluate clinical features and therapeutic strategies in cutaneous lupus erythematosus. Disease characteristics were analysed in 50 patients with different subtypes of cutaneous lupus erythematosus from two European centres (Germany and Sweden). Mean age at onset of disease was 42.0 ± 13.3 years (range: 7–69 years) and this differed significantly between the cutaneous lupus erythematosus subtypes. Moreover, 22 (44.0%) of the patients with cutaneous lupus erythematosus fulfilled four or more of the American College of Rheumatology (ACR) criteria; however, only 7 (14.0%) had severe systemic organ manifestations, such as kidney involvement. The analysis of serological features, such as antinuclear antibodies, revealed further significant differences between the cutaneous lupus erythematosus subtypes. In conclusion, the EUSCLE Core Set Questionnaire provides a useful tool for standardized collection and statistical analysis of data on cutaneous lupus erythematosus in clinical practice. ***Key words: lupus erythematosus; questionnaire; skin; ACR criteria.***

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The clinical expression of skin lesions in lupus erythematosus (LE) presents with a great variety, and, consequently, it has been difficult to develop a unifying concept of the various cutaneous symptoms of the disease. In 1977, Gilliam et al. (1–3) initially proposed a classification system that divided the skin manifestations of LE into those that are specific for LE (i.e. LE-specific skin disease) and those that are not specific for the disease (i.e. LE-non-specific skin disease) by histological analysis of skin biopsy specimens. There are a number of distinctive forms of LE-non-specific manifestations, such as urticarial vasculitis and livedo reticularis, which are mostly associated with systemic LE (SLE), reflecting potentially internal organ involvement and serious complications (4, 5). The LE-specific manifestations encompass the various subtypes of cutaneous LE (CLE), which are subdivided into different categories, as defined by constellations of clinical features, histological changes, serological abnormalities, and average duration of skin lesions: acute CLE (ACLE), subacute CLE (SCLE), and chronic CLE (CCLE). Recently, modification and extension of the Gilliam classification was suggested, with the intermittent CLE (ICLE) subtype, including LE tumidus (LET) as a separate entity of the disease (Duesseldorf Classification 2004) (6).

In all subtypes of CLE, systemic organ manifestations can occur during the course of the disease, but exact population-based data are not currently available in the literature. Overall, epidemiological analyses have rarely been performed; it has been estimated that patients with CLE are two to three times more prevalent than those with SLE (7). In 2007, Popovic et al. (8) reported the prevalence of anti-Ro/SSA-positive SCLE patients in Stockholm County, Sweden, to be 6.2–14.0 per 100,000 persons. Moreover, the European Medicines Agency (EMEA) recently evaluated CLE as a severe and rare disease, which exists in fewer than 5 out of 10,000 citizens in the European Union (9). Moreover, no standardized guidelines exist for the assessment and treatment of patients with CLE. This results in varying diagnostic and therapeutic strategies in the different European centres, which impedes the comparison of patient data.

In order to facilitate data collection in patients with CLE and to enable consistent evaluation, comparison, and statistical analysis throughout Europe, a study group of the European Society of Cutaneous Lupus Erythematosus (EUSCLE) defined a core set of variables for the evaluation of patients with CLE, resulting in the EUSCLE Core Set Questionnaire (10). By collecting data from CLE patients, the non-profit working group EUSCLE aims to achieve a general consensus concerning evidence-based clinical standards for disease assessment and to develop diagnostic and therapeutic guidelines. The main purpose of the current study was to evaluate the recently developed EUSCLE Core Set Questionnaire and the associated database on 50 patients with different subtypes of CLE from two centres

in Germany and Sweden. The results demonstrate that the EUSCLE Core Set Questionnaire enables consistent data collection and statistical analysis of the various clinical features in CLE, providing a useful tool for an extensive and comparative evaluation of data related to the disease.

METHODS

Patients

A total of 50 patients (42 females, 8 males) with different subtypes of CLE was included in the analysis, 40 patients (32 females, 8 males) from the Department of Dermatology, University of Duesseldorf, Germany, and 10 female patients from the Department of Dermatology, Danderyd Hospital, Stockholm, Sweden. The included CLE patients were representative of the patient cohort that was treated at the two centres in the period between July and December 2006. The mean age of the CLE patients at the time of data collection was 51.9 ± 12.6 years, range 19–73 (Germany, mean ± SD age, 53.0 ± 11.6 years; Sweden, mean ± SD age, 47.6 ± 15.8 years). Ten patients (mean ± SD age, 32.8 ± 7.6 years) were ≤ 40 years old and 40 patients (mean ± SD age, 56.7 ± 8.3 years) were > 40 years old. The age of the male CLE patients ranged from 38 to 67 years (mean ± SD age; 54.3 ± 11.5 years), whereas the age of the female patients ranged from 19 to 73 years (mean ± SD age; 51.5 ± 12.8 years).

The diagnosis and classification of CLE were based on clinical and histological criteria, as well as on serological abnormalities according to the Duesseldorf Classification 2004 (6). Patients with the following subtypes of CLE were included in the study: ACLE (5 females, mean ± SD age; 41.6 ± 15.3 years), SCLE (11 females; mean ± SD age, 59.0 ± 9.1 years), CCLE (13 females and 1 male; mean ± SD age, 52.5 ± 12.7 years), and ICLE (13 females and 7 males; mean ± SD age, 50.2 ± 12.0 years). Sub-classification of CCLE into discoid LE (DLE), LE panniculitis (LEP), and chilblain LE (CHLE) was performed, but is only indicated for some clinically relevant aspects. Nine (18.0%) of the 50 patients presented with two different CLE subtypes (Table I); the respective subtype that was initially diagnosed was defined as the main diagnosis in the statistical analysis. Therefore, the CLE subtype analysis always refers to the main diagnosis unless otherwise indicated.

The study was approved by the ethics committee of the University of Duesseldorf (Duesseldorf, Germany) and was conducted according to the ethics guidelines at the institutions and the Helsinki Declaration.

Table I. *Subtypes of cutaneous lupus erythematosus (CLE) occurring simultaneously in patients. The number of CLE patients is indicated, highlighting those who presented with particular combinations of disease subtypes. The main diagnosis (left-hand column) that was primarily seen in the patients was used for further statistical analysis*

	Secondary diagnosis			
Main diagnosis	ACLE	SCLE	CCLE	ICLE
ACLE	–	1	2	–
SCLE	–	–	2	–
CCLE	1	–	–	1
ICLE	2	–	–	–

ACLE: acute cutaneous lupus erythematosus; SCLE: subacute cutaneous lupus erythematosus; CCLE: chronic cutaneous lupus erythematosus; ICLE: intermittent cutaneous lupus erythematosus.

EUSCLE Core Set Questionnaire

The EUSCLE Core Set Questionnaire includes various parameters considered to be the most relevant features of CLE, which were compiled from international literature, clinical praxis, and the long-term CLE experience of the authors (10). Moreover, the 11 clinical and laboratory criteria of the American College of Rheumatology (ACR) for the diagnosis of SLE, which were established in 1971 (11) and revised in 1982 (12) and 1997 (13), are listed in the EUSCLE Questionnaire. For the analysis of disease activity and damage, the recently published and validated disease activity and damage scoring system "Cutaneous Lupus Erythematosus Disease Area and Severity Index" (CLASI) (14, 15) is also included in the EUSCLE Core Set Questionnaire. The compilation of parameters for the evaluation of CLE resulted in the 4-paged EUSCLE Core Set Questionnaire with the following six sections: (A) Patient, (B) Diagnosis, (C) Skin involvement, (D) Activity and damage of disease, (E) Laboratory analysis, and (F) Treatment. The parameters included in the EUSCLE Core Set Questionnaire are defined precisely in an associated glossary that was also distributed to the participating centres.

Statistical methods

Data collection and transformation was performed using SPSS statistical packages version 14.0. A SPSS database was designed to enable a consistent, detailed statistical analysis of the EUSCLE Core Set Questionnaire with the final aim of including a high number of CLE patients from various centres all over Europe. For the conformal transmission of the data, each parameter was assigned a specific name in SPSS, and a standard coding plan for the numerical values was developed. The EUSCLE Core Set Questionnaire is based on a nominal scale level. The structure of the database enables various test application possibilities and different combinations for comparison. Statistical analysis was performed using SPSS and SAS version 9.1. The database-driven analysis was performed primarily with a Fisher's exact test to adjust small case numbers. According to the respective question analysed, a Kruskal-Wallis test, a Mann-Whitney *U* test, or an analysis of variance (one-way ANOVA with Scheffé *post hoc* test) was applied. p-values < 0.05 were considered significant. Means are presented with standard deviations.

RESULTS

Gender and age at onset of disease

In the 50 patients with different subtypes of CLE participating in the study, there was a significant difference with regard to gender ($p = 0.042$). Seven (87.5%) of the 8 male patients presented with ICLE and one (12.5%) presented with CCLE, but none of the male patients presented with any of the other subtypes, i.e. ACLE or SCLE. In the female patients, however, all different CLE subtypes were diagnosed (Fig. 1A). The mean age at onset of disease (42.0 ± 13.3 years, range 7–69) did not differ significantly between male and female patients; it was slightly higher in the male patients aged 44.6 ± 12.6 years (range 29–61) compared with the female patients aged 41.5 ± 13.5 years (range 7–69). However, concerning the mean age at onset of disease in the different CLE subtypes, significant differences were found between ACLE and SCLE ($p = 0.011$) and SCLE and ICLE ($p = 0.038$) being lowest in ACLE

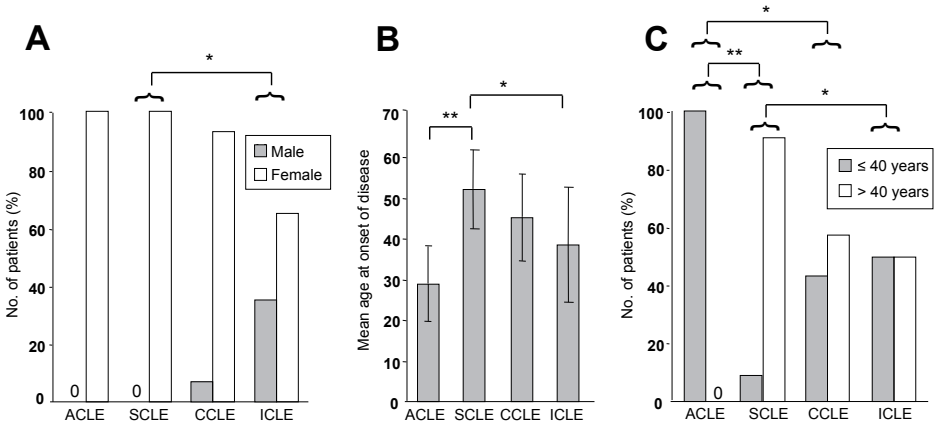

Fig. 1. (A) Male and female patients with different cutaneous lupus erythematosus (CLE) subtypes. The percentage of male ($n=8$) and female ($n=42$) patients is shown with respect to each of the CLE subtype. (B) The mean age at onset in CLE subtypes is presented with standard deviation for each CLE subtype. (C) The percentage of patients with different CLE subtypes is demonstrated with regard to the age at onset of disease (≤40 years or >40 years). ACLE: acute cutaneous lupus erythematosus; SCLE: subacute cutaneous lupus erythematosus; CCLE: chronic cutaneous lupus erythematosus; ICLE: intermittent cutaneous lupus erythematosus. *$p<0.05$; **$p<0.01$.

(28.8 ± 8.6 years, range 17–38) and highest in SCLE (51.4 ± 9.6 years, range 36–69) (Fig. 1B). In all patients with ACLE, the mean age at onset of disease was ≤40 years, whereas in the other CLE subtypes the mean age at onset of disease was primarily >40 years. These differences were significant (Fig. 1C).

ACR criteria

Seven patients with the diagnosis of SLE fulfilled four or more of the ACR criteria at the time of or prior to data collection; 15 patients fulfilled four or more of the ACR criteria, although they had not initially been diagnosed with SLE by the attending physicians. Moreover, there was a significant difference between the number of patients with ACLE and ICLE who fulfilled four or more of the ACR criteria ($p=0.002$) (Fig. 2A). The most frequently fulfilled ACR criterion in CLE was photosensitivity, which was present in 42 of the 50 patients (84.0%) (Fig. 2B). Antinuclear antibodies (ANA) were present in 31 patients (62.0%); discoid rash, malar rash, immunological disorders, and arthritis

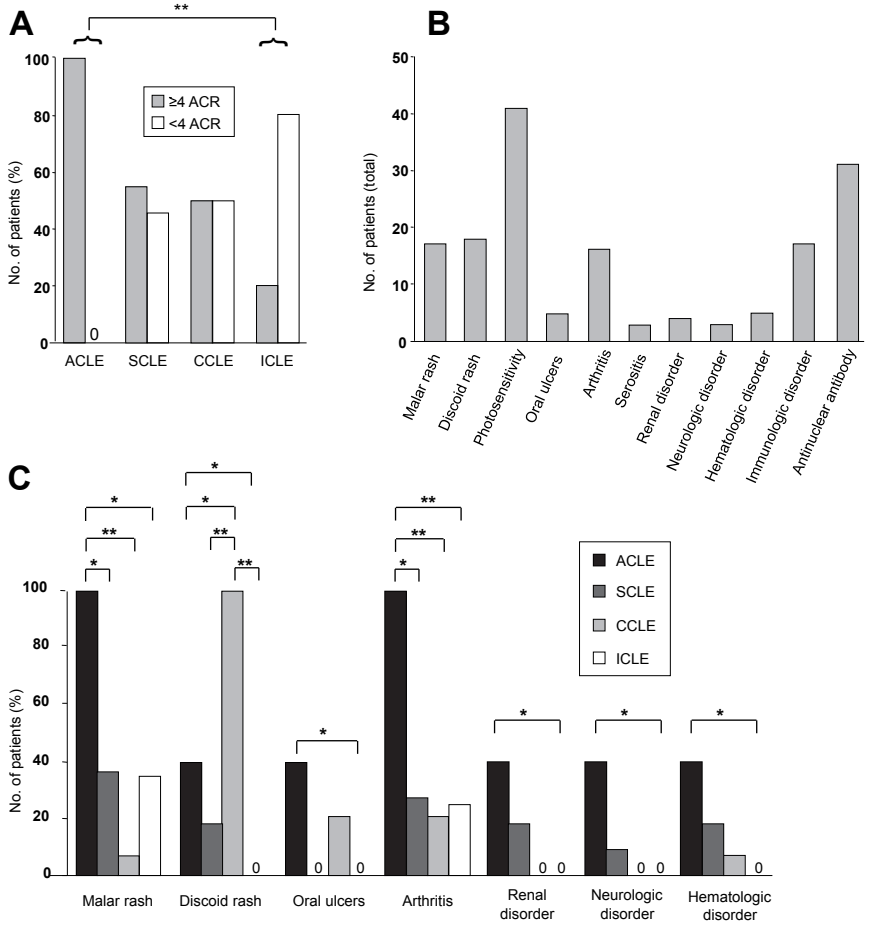

Fig. 2. (A) Presence of four or more of the American College of Rheumatology (ACR) criteria in different cutaneous lupus erythematosus (CLE) subtypes. The percentage of CLE patients with the four subtypes who fulfilled <4 or ≥4 of the ACR criteria is presented. (B) Number of CLE patients who fulfilled the various ACR criteria. The 11 ACR criteria are listed with the respective number of CLE patients who fulfilled any of these criteria. (C) Significant differences of ACR criteria in CLE subtypes. Each bar indicates the percentage of patients within the CLE subtypes who fulfilled the respective ACR criteria, resulting in significant differences. ACLE: acute cutaneous lupus erythematosus; SCLE: subacute cutaneous lupus erythematosus; CCLE: chronic cutaneous lupus erythematosus; ICLE: intermittent cutaneous lupus erythematosus. *$p<0.05$; **$p<0.01$.

were also frequently observed. The presence of several ACR criteria, such as malar rash, discoid rash, and arthritis, differed significantly between the various CLE subtypes (Fig. 2C). Other ACR criteria, such as photosensitivity, serositis, immunological disorder and antinuclear antibodies, did not show significant differences among the CLE subtypes (Table II).

The presence of two of the 11 ACR criteria varied significantly between male and female patients with CLE. Arthritis appeared significantly more often in female patients ($p = 0.043$), in 16 (38.1%) of 42 patients in contrast to none of the 8 male patients. Moreover, ANA were also detected significantly ($p = 0.041$) more often in female patients (29 of 42; 69.0%) compared with 2 of the 8 male patients (25.0%). Overall, the number of CLE patients who fulfilled four or more of the ACR criteria was much higher in female patients (21 of 42; 50.0%) than in male patients (1 of 8; 12.5%), but this difference was not significant. In addition, there was a significant difference in patients with regard to mean age at onset of disease ≤ 40 or > 40 years and malar rash ($p = 0.042$). Only 6 (21.4%) of the 28 patients with an age at onset of disease > 40 years presented with a malar rash, but 11 (50%) of the 22 patients with a mean onset of disease < 40 years presented with a malar rash.

Polymorphous light eruption and Sjögren's syndrome

The occurrence of polymorphous light eruption (PLE) and Sjögren's syndrome (SS) is evaluated in the EUSCLE Core Set Questionnaire as concomitant diseases. The incidence of each disease, however, was not significantly different between the CLE subtypes. Of the 6 patients presenting with PLE, 2 (33.3%) were diagnosed as SCLE and 2 were diagnosed as ICLE; one (16.7%) was diagnosed as DLE and one was diagnosed as LEP. Of the 6 patients with SS, 3 (50.0%) were diagnosed as SCLE; one (16.7%) as ACLE; one as DLE; and one as ICLE. In most patients (5 of 6, 83.3%), the onset of PLE was prior to the diagnosis of LE, whereas SS was not diagnosed in any of the patients prior to the onset of LE. In three cases, SS was diagnosed simultaneously with, or secondarily in the course of the disease.

Table II. *Distribution of further American College of Rheumatology (ACR) criteria in cutaneous lupus erythematosus (CLE) subtypes. The table reveals the presence of the remaining non-significant ACR criteria in the 50 patients with the different CLE subtypes*

	Number (%) of patients			
Subtype	Photosensitivity	Serositis	Immunological disorder	Antinuclear antibody
ACLE	4 (80.0)	1 (20.0)	2 (40.0)	4 (80.0)
SCLE	9 (81.8)	0 (0.0)	4 (36.4)	10 (90.9)
CCLE	12 (85.7)	2 (14.3)	6 (42.9)	8 (57.1)
ICLE	17 (85.0)	0 (0.0)	5 (25.0)	9 (45.0)

ACLE: acute cutaneous lupus erythematosus; SCLE: subacute cutaneous lupus erythematosus; CCLE: chronic cutaneous lupus erythematosus; ICLE: intermittent cutaneous lupus erythematosus.

LE-specific skin lesions

All 8 patients with ACLE lesions presented at the time of data collection or in the past with the localized form as malar rash, and none showed any sign of a generalized manifestation. Of the 12 patients with SCLE, 8 (66.7%) presented with the annular form and 5 (41.7%) presented with the papulosquamous form, with one patient (8.3%) displaying both forms. Within the different subforms of CCLE, all 18 patients were diagnosed as DLE, mostly (13 of 18, 72.2%) presenting with the localized form; 5 (27.8%) of 18 patients presented with the disseminated form; one (5.6%) of the DLE patients additionally had LEP, but none of the patients with CCLE was diagnosed as CHLE.

The diagnosis of LE-specific skin lesions was confirmed by histological analysis of skin biopsy specimens in all patients, except 2 patients with a butterfly rash consistent with the localized form of ACLE and one patient with ICLE who was only 7 years old at the time of first diagnosis.

LE-non-specific skin lesions

In 19 (38%) of the 50 patients, LE-non-specific skin lesions had been diagnosed during the course of the disease. The majority of cases (12, 63.2%) presented with non-scarring alopecia; 6 of these patients were diagnosed as CCLE, 4 as SCLE, one as ACLE and one as ICLE. We observed significantly less non-scarring alopecia in patients with ICLE than in patients with SCLE ($p = 0.042$) and CCLE ($p = 0.012$). Raynaud's syndrome was the second most frequently diagnosed LE-non-specific skin manifestation, which was present in 8 (16.0%) of the patients: 3 with SCLE, 3 with CCLE, and 2 with ICLE. The other LE-non-specific skin lesions included one case each of urticarial vasculitis, periungual teleangiectasia, livedo reticularis, thrombophlebitis, and calcinosis cutis. Moreover, 5 patients (1 ACLE, 1 SCLE, 2 CCLE, 1 ICLE) were evaluated as having "other non-specific lesions", which were not further specified.

Photosensitivity and photoprovocation test

Of the 50 patients with CLE, 49 (98.0%) presented with skin lesions in sun-exposed areas; only one patient with ICLE had lesions exclusively on the back in non-sun-exposed areas. Photosensitivity by patient's history was reported by 37 of the 49 patients (75.5%) with lesions in sun-exposed areas; however, 12 patients (24.5%) with lesions in sun-exposed areas denied any photosensitivity. With regard to CLE subtypes, patients with ACLE and ICLE were most frequently (80.0% and 84.2%, re-

spectively) photosensitive by patient's history, whereas patients with CCLE (64.3%) presented least frequently with photosensitivity by patient's history.

Phototesting was performed, according to a standardized protocol (16), in 42 of the 50 patients (84.0%) with CLE. Only one of the 5 patients with ACLE underwent phototesting, which yielded a negative result. In the other subtypes, the majority of photoprovocation test results were positive, ranging from 63.2% in ICLE to 69.2% in CCLE. In many cases, photoprovocation test results did not correspond to photosensitivity by patient's history; 5 (45.5%) of the 11 patients, who denied any history of photosensitivity, displayed positive photoprovocation test results. In contrast, 9 (29.0%) of the 31 patients who reported a positive history of photosensitivity displayed negative photoprovocation test results.

Moreover, photoprovocation test results and photosensitivity by patient's history also differed in patients with concomitant PLE disease. Although all 6 CLE patients with associated PLE were photosensitive by patient's history, only 2 (50%) of the 4 tested patients displayed positive photoprovocation test results.

Laboratory analysis

In comparison with all laboratory analyses reported in the EUCLE Core Set Questionnaire, ANA were most frequently found to be positive (with a titre of > 1:160 using HEp-2 cells), in more than half of the patient cohort (29 (58.0%) of the CLE patients) (Table III). The presence of specific antibodies, such as anti-Ro/SSA, anti-La/SSB and anti-dsDNA antibodies, differed significantly among the CLE subtypes, while the differences regarding ANA were remarkable, but not significant (Fig. 3). Thirteen (28.9%) of the 45 tested patients were positive for anti-Ro/SSA and 10 (22.2%) were positive for anti-La/SSB antibodies. If one of these two antibodies was positive in a CLE patient, the other one was also positive in most cases: 8 (17.8%) of the 45 tested patients were positive for both anti-Ro/SSA and anti-La/SSB antibodies, representing 61.5% of the patients with anti-Ro/SSA antibodies and 80.0% of the patients with anti-La/SSB antibodies.

Anti-Sm antibodies were not positive in any of the 37 tested patients, and similarly anti-histone antibodies were not positive in any of the 36 analysed patients. The erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) were found to be increased in 9 (21.4%) of 42 tested patients and in 10 (25.0%) of 40 tested patients, respectively. Of the complement factors, C3 was most often found to be decreased (in 8 (19.0%) of 42 tested patients), whereas C4 was decreased in 4 (9.5%) of 42 tested patients. C1q was found to be decreased in only one (4.2%) patient; however, only 24 patients were tested. Anti-dsDNA antibodies were positive in 8 (17.0%) of 47 tested patients. Anti-cardiolipin antibodies (IgG) were positive in only 2 (5.9%) of 34 tested patients, and anti-cardiolipin antibodies (IgM) were positive in 3 (8.8%) of 34 tested patients (Table III). Leukopenia was detected in 5 (11.4%) of 44 tested patients and proteinuria in 4 (9.1%) of 44 tested patients. Significance was found concerning the age at onset of disease and the current presence of proteinuria, suggesting that proteinuria correlated negatively with the age at onset of disease points to a greater chance that patients with an age at onset of disease ≤40 years will be more likely to exhibit renal involvement ($p = 0.018$). Of the 44 CLE patients for which we analysed urine for the presence of albumin, 4 (9.1%) were diagnosed as having proteinuria; interestingly, all of them presented with a mean age at onset of disease ≤40 years.

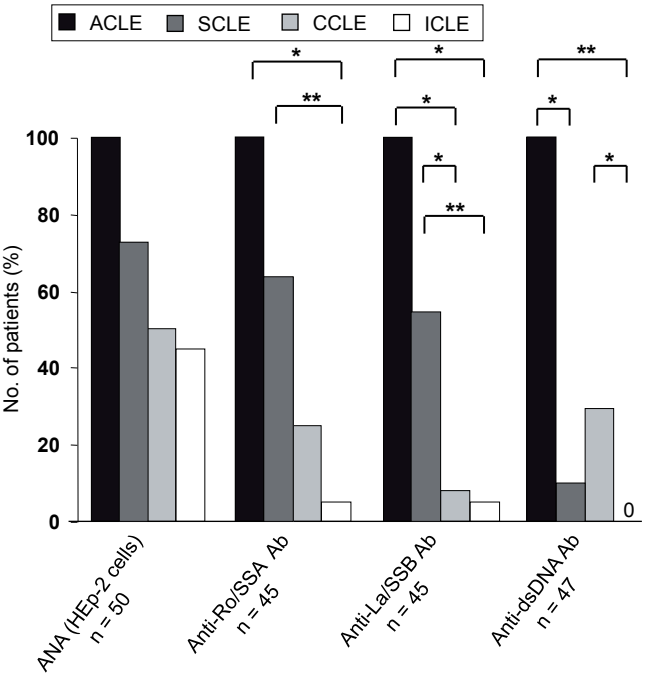

Fig. 3. Autoantibodies in different cutaneous lupus erythematosus (CLE) subtypes. Bars represent the percentage of patients with positive antibodies including anti-Ro/SSA, anti-La/SSB, and anti-dsDNA antibodies within the patients of the respective CLE subtype. Differentiation of antibodies was primarily performed if ANA were positive; therefore, not all patients were evaluated for anti-dsDNA and anti-Ro/SSA and anti-La/SSB antibodies. Numbers of tested patients for each antibody are indicated. Ab: antibodies; ACLE: acute cutaneous lupus erythematosus; ANA: antinuclear antibodies; SCLE: subacute cutaneous lupus erythematosus; CCLE: chronic cutaneous lupus erythematosus; ICLE: intermittent cutaneous lupus erythematosus. *$p < 0.05$; **$p < 0.01$.

Treatment

Forty-seven (94.0%) of the 50 CLE patients had applied sunscreen at the time of the study or at some time in the past. In 36 (76.6%) of the 47 patients, sunscreens were recorded as being successful in prevention of skin lesions. In 2 (4.3%) CLE patients, sunscreens were evaluated as not being successful; the success of prevention was unknown in the remaining 9 (19.2%)

Table III. *Laboratory analysis in patients with cutaneous lupus erythematosus (CLE).*

	Positive patients (%)	Positive patients, number/total tested patients
ANA (HEp-2)	58.0	29/50
Anti-Ro/SSA Ab	28.9	13/45
Anti-La/SSB Ab	22.2	10/45
Anti-cardiolipin (IgG) Ab	5.9	2/34
Anti-cardiolipin (IgM) Ab	8.8	3/34
Anti-dsDNA Ab	17.0	8/47
C3 (decreased)	19.0	8/42
C4 (decreased)	9.5	4/42
C1q (decreased)	4.2	1/24
ESR (increased)	21.4	9/42
CRP (increased)	25.0	10/40
Leukopenia	11.4	5/44
Proteinuria	9.1	4/44

ANA: antinuclear antibodies; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

patients. Application of topical glucocorticosteroids was evaluated as successful in 26 (56.5%) of 46 CLE patients; however, there was also a comparatively high number of patients (10 (21.7%)) in whom the treatment did not show any success. In the remaining 10 (21.7%) patients with CLE, the success of topical glucocorticosteroids was unknown. Topical calcineurin inhibitors had been applied at the time of the study or at some time in the past by 22 CLE patients (44.0%); in 13 (59.1%) of these patients, the agents were also recorded as successful.

Overall, systemic treatment was applied in 33 (66.0%) of the 50 patients included in the EUSCLE Core Set Questionnaire. In contrast to the other CLE subtypes, all patients with ACLE received systemic agents due to the frequent involvement of internal organs. Systemic glucocorticosteroids were recorded as a successful treatment in 12 (80.0%) of 15 treated patients and as not successful in one patient with CLE. Of the antimalarial agents, chloroquine showed the highest success rate, with 19 (86.4%) of 22 patients being recorded as treated successfully; treatment failed in only one patient with DLE. Treatment with hydroxychloroquine was rated as successful in 11 (68.8%) of 16 and not successful in 4 (25.0%) of the CLE patients. In one patient, quinacrine was applied in addition to chloroquine, but the treatment did not prove successful. This might be due to the fact that the patient was a regular smoker. Of 4 CLE patients who received systemic retinoids, treatment was evaluated as successful in 2 patients and one patient showed no response. Other treatments recorded in the EUSCLE Core Set Questionnaire, e.g. thalidomide, were applied only in a very low number or not applied in any of the participating patients.

DISCUSSION

In this first retrospective analysis, we tested the feasibility and validity of the EUSCLE Core Set Questionnaire in two centres and found significant differences with regard to gender and mean age at onset of disease among the different subtypes of CLE. All patients with ACLE participating in this study were female and presented with a mean age ≤40 years at onset of disease. This might be due to the fact that ACLE usually occurs in association with SLE, preceding the onset of a multisystem disease (17). In most studies, the percentage of females with SLE ranges from 78% to 96%, with a female:male ratio of approximately 10:1 (18). Moreover, the symptoms of patients with SLE appear between the ages of 15 and 40 years, with a mean age at onset of disease of 29–32 years. In contrast to ACLE, the other subtypes of CLE have been shown to appear at a later age and the male:female ratio has been reported to vary between 1:3 and 1:6 in SCLE and CCLE patients (7). ICLE has been reported to be equally frequent in both groups (19); however, a systematic epidemiological analysis of the various CLE subtypes has not been performed. In a recent population-based study from Minnesota, USA, the overall male:female ratio of CLE was 1:1.79 between 1965 and 2005 (20).

The ACR criteria include 11 clinical and laboratory features and are the only universally accepted criteria for the classification of SLE, providing some degree of uniformity to the patient populations of clinical studies

Table IV. *Ranking of the most frequently applied treatments in cutaneous lupus erythematosus (CLE) subtypes. Treatments which were applied in CLE subtypes at the time of the study or ever in the past are listed, ranked according to the number of patients in whom they have been applied. Steroids refer to glucocorticosteroids*

ACLE	Applied *n* (%)	SCLE	Applied *n* (%)	CCLE	Applied *n* (%)	ICLE	Applied *n* (%)
Topical steroids	5 (100.0)	Sunscreens	10 (90.9)	Sunscreens	14 (100.0)	Sunscreens	19 (95.0)
Chloroquine	4 (80.0)	Topical steroids	10 (90.9)	Topical steroids	14 (100)	Topical steroids	17 (85.0)
Sunscreens	4 (80.0)	Chloroquine	6 (54.5)	Calcineurin inhibitors	10 (71.4	Calcineurin inhibitors	8 (40.0)
Systemic steroids	3 (60.0)	Systemic steroids	4 (36.4)	Chloroquine	6 (42.9)	Hydroxychloroquine	8 (40.0)
Retinoids	2 (40.0)	Calcineurin inhibitors	4 (36.4)	Hydroxychloroquine	6 (42.9)	Chloroquine	6 (30.0)
Methotrexate	2 (40.0)	Hydroxychloroquine	1 (9.1)	Systemic steroids	4 (28.6)	Systemic steroids	4 (20.0)

ACLE: acute cutaneous lupus erythematosus; SCLE: subacute cutaneous lupus erythematosus; CCLE: chronic cutaneous lupus erythematosus; ICLE: intermittent cutaneous lupus erythematosus.

(11–13). In the present study, 22 (44.0%) of the 50 CLE patients fulfilled 4 or more of the ACR criteria for the classification of SLE; only 7 (14.0%) of them had severe systemic organ manifestations, such as kidney involvement. The proportion of patients with ACLE who fulfilled four or more of the ACR criteria was significantly greater than among patients with ICLE. Malar rash and arthritis were significantly more frequent in patients with ACLE than in the other CLE subtypes. However, only a low number of ACLE patients are included in the present study, and thus statistical analysis and comparison among the different disease subtypes were limited in some aspects. Discoid rash was obviously present in all DLE patients in contrast to other subtypes of CLE, such as ACLE and SCLE, unless there is a secondary diagnosis of DLE. These data suggest that the fulfilment of specific ACR criteria is dependent on the disease subtype, and thus patients with a "malar rash" (ACLE) or a "discoid rash" (DLE) may more frequently be classified as SLE according to the ACR criteria than patients with other CLE subtypes.

Moreover, Albrecht et al. (21) recently criticized that "malar rash" is often indistinguishable from photosensitivity, and therefore these criteria are not independent. "Photosensitivity" is poorly defined in the ACR criteria as "a result of an unusual reaction to sunlight by patient's history or physician's observation" (12). In 1986, phototesting with different wavelengths was developed better to define sensitivity to ultraviolet (UV) light in patients with a photosensitive form of CLE (22). Meanwhile, a standardized protocol for phototesting has been developed for patients with CLE by considering multiple factors such as light source, test area, dose of UV exposure, and frequency of UV irradiation (16). Interestingly, the history of photosensitivity does not necessarily predict a positive phototesting result. In the present study, 45.5% of the CLE patients who denied any effect of sun exposure on their disease showed a positive reaction to UVA and/or UVB radiation in phototesting. This might be due to the latency period of developing skin lesions after UV exposure in CLE and the difficulty for the patients to realize a relationship between sun exposure and exacerbation of their disease (16). Altogether, the ACR criteria are unspecific or assign too much weight to the skin as one expression of a multi-organ disease (21, 23). As a consequence, patients without severe systemic involvement are frequently classified as SLE according to the ACR criteria.

ANA evaluated with HEp-2 cells proved to be reliable and important indicators of the disease as they were positive in 58% of the CLE patients. The high proportion (100%) of positive ANA (with a titre of >1:160) in ACLE patients compared with the other CLE subtypes can be explained by the high association of ACLE and systemic organ involvement. Moreover, anti-dsDNA antibodies, anti-Ro/SSA and anti-La/SSB antibodies were also positive in all tested ACLE patients and revealed further significant differences between the various CLE subtypes. In ICLE patients, ANA were detected in only a small number of patients, which is in agreement with the literature (19, 24). Of the complement factors, C3 was most often found to be decreased (in 8 (19.1%) of 42 tested patients), whereas C4 was decreased in 4 (9.5%) of 42 tested patients. Further laboratory parameters, such as C1q, ESR, and CRF, as well as leucopaenia and proteinuria, were analysed by the EUSCLE Core Set Questionnaire; however, only single patients showed pathological results and no significant differences were detected between the various CLE subtypes.

The analysis of treatment strategies in the present study resulted in an overview of the frequency of therapeutic strategies, which were applied in CLE patients; the respective success rates were also evaluated. Most (94.0%) of the 50 patients (distributed among all the different subtypes of CLE) listed sunscreen application as the most frequently applied treatment. Sunscreens were further recorded as being successful in prevention of skin lesions in 76.6% of the patients; therefore, sunscreens were the most successfully applied preventive treatment overall. In other studies, it has been shown that consistent sunscreen photoprotection in patients with SLE is associated with significantly better clinical outcome, such as less frequent renal involvement and a decreased need for immunosuppressive treatment (25, 26). Therefore, it is very important to provide instructions concerning methods of protection from sunlight and artificial sources of UV radiation (27). Consistent sun protection can be provided by photoresistant clothing and applying sunscreens with highly potent chemical or physical UVA- and UVB-protective filters (28). These substances should be applied in sufficient amounts (~2 mg/cm^2) and with a high protection factor (SPF 50) at least 15–30 min before sun exposure in order to avoid induction and exacerbation of cutaneous lesions (29).

Topical glucocorticosteroids have proven to be a very effective treatment for skin lesions in all subtypes of CLE, reducing symptoms such as redness and scaling (30). In the present study, the most frequently successful treatment was topical glucocorticosteroids, yielding successful results in 56.5% of patients. Due to the well-known local side-effects (e.g. atrophy, telangiectasia, dyspigmentation), treatment with topical glucocorticosteroids is usually limited and preferably intermittent. Application twice daily for a few days, followed by a reduction in the frequency of application (with the interruption of treatment lasting a few weeks), may help to minimize the risks of local side-effects; however, this practice might also limit the efficacy. Moreover, recent reports have demonstrated the efficacy of topical calcineurin inhibitors in CLE, which down-regulate T-cell activity by inhibiting the calcineurin phosphatase

responsible for dephosphorylation of the nuclear factor in activated T cells (31). In the present study, tacrolimus and pimecrolimus ointment were applied in 44% of the patients. In 59.1% of the CLE patients, these topical agents were reported as being a successful and therefore promising treatment.

The application of systemic agents becomes necessary to alleviate and prevent the development of widespread skin lesions and life-threatening symptoms in CLE patients. However, only a few randomized, double-blind, placebo-controlled, multicentre trials are available and topical and systemic agents are used "off-label" in most cases (32, 33). In the present study, we demonstrated that antimalarial agents were the most frequently applied and also the most effective systemic drugs in CLE. The value of the study is limited by its small sample size; however, with the inclusion of more patients in future studies, the analysis of the EUSCLE Core Set Questionnaire might serve to improve therapeutic strategies for the different CLE subtypes.

In summary, this study suggests that the EUSCLE Core Set Questionnaire is a useful tool to provide an expedient compilation of parameters for a comprehensive collection and evaluation of clinical data of the different CLE subtypes from various centres. Furthermore, it provides a basis for the development of standardized diagnostic and therapeutic guidelines to improve the outcome of patients with CLE. For example, the finding that proteinuria correlated negatively with the age at onset of disease points to a greater chance that patients with an age at onset of disease ≤ 40 years will be more likely to exhibit renal involvement. This may imply that CLE patients with an age at onset of disease ≤ 40 years should be followed with special attention regarding the potential development of proteinuria. Future and follow-up studies with a higher number of patients from several centres throughout Europe will support the analysis of further prognostic clinical and laboratory parameters and the improvement of therapeutic strategies for patients with CLE.

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