Clinical characteristics of cutaneous lupus erythematosus

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Abstract

Introduction: Lupus erythematosus (LE) shows a wide variety of clinical manifestations, skin involvement being one of the most important.

Aim: To analyze the clinical presentation of cutaneous variants of lupus erythematosus in terms of skin lesion spectrum and extracutaneous involvement.

Material and methods: A total of 64 patients with cutaneous LE (CLE) were included. The study was based on the “Core Set Questionnaire” developed by the European Society of Cutaneous Lupus Erythematosus (EUSCLE). Clinical severity of skin lesions was evaluated with the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI). All results were subjected to statistical analysis.

Results: Fifteen (23.4%) patients had an acute CLE (ACLE), 26 (40.6%) subacute CLE (SCLE) and 21 (32.8%) chronic CLE (CCLE). Two (3.2%) individuals only demonstrated urticarial vasculitis as a cutaneous manifestation of LE and these patients were excluded. Patients with ACLE were characterized by the earliest onset of the disease (mean age of 31.9 ±15.0 years; p < 0.001). On average, 4.8 ±1.8 criteria of systemic LE were found in the ACLE group compared to 2.7 ±1.3 criteria in SCLE and 2.5 ±1.5 criteria in CCLE (p < 0.001). The highest activity of skin lesions according to CLASI was found in the SCLE group (p = 0.002). On the other hand, the most severe skin damage was observed in CCLE (p < 0.01).

Conclusions: Each variant of CLE differs significantly from the others in respect of various aspects of clinical manifestations. Due to a number of different variants of LE skin lesions, a unified classification of CLE still remains a challenge.

Key words: cutaneous lupus erythematosus, diagnostic criteria, CLASI, lupus erythematosus, skin, Core Set Questionnaire.

Introduction

Lupus erythematosus (LE) is a chronic autoimmune disease with a wide spectrum of presenting symptoms ranging from mild cutaneous manifestations in localized cutaneous LE (CLE) to severe, life-threatening internal organ damage in systemic LE (SLE). The etiology of LE remains unknown, although the environmental, genetic, viral and hormonal factors are taken into consideration as probable causes or precipitating factors of this disease [1, 2].

Skin involvement is seen in about 70–85% of all LE patients [3]. Sometimes skin involvement is the only manifestation of LE, while in other cases it could rather be a mild bystander of severe internal involvement. Isolated CLE is a rare disease, albeit it is still about 2 to 3 times more frequent than SLE [4]. Cutaneous features of LE can be classified into LE-specific and LE-nonspecific ones. LE-specific skin lesions usually appear only in patients with LE and thus can be handled as diagnostic ones (e.g. “malar rash”, discoid lupus lesions), while LE-nonspecific skin lesions are not characteristic of LE as they can also be observed in other autoimmune processes. However, the presence of LE-nonspecific skin changes often implies systemic involvement in LE patients. The most common LE-nonspecific skin lesions are livedo reticularis and findings related to thrombophlebitis due to LE-related coagulopathy or secondary cutaneous vasculitis [5–7].

Lupus erythematosus-specific skin lesions are very heterogeneous. The most widely accepted classification of LE-specific cutaneous involvement includes acute CLE (ACLE) with its localized and generalized forms, subacute CLE (SCLE) with its annular and papulosquamous forms and chronic CLE (CCLE) including discoid LE (DLE), lupus panniculitis and chilblain lupus. Some authors postulated to separate an intermittent CLE (ICLE) group covering lupus tumidus, while others handle this subtype as a form of CCLE [8, 9].
A valid assessment of skin involvement in LE patients still remains a challenge in daily clinical settings. Several scoring systems have been proposed, but none was unanimously accepted. Lupus erythematosus skin lesions can be evaluated e.g. by Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), which is a very detailed and accurate measurement of CLE severity, but is also time-consuming and thus seems to be not very feasible for regular use. This scoring system has been designed to measure CLE activity and skin damage [10–12]. Severity of such features like erythema, scaling, hypertrophy, edema and infiltration in different anatomical locations are summed up to assess disease activity. Skin damage considers dyspigmentation, scarring, atrophy and panniculitis [10, 11]. To standardize the assessment of CLE patients the European Society of Cutaneous Lupus Erythematosus developed the Core Set Questionnaire which includes six sections covering patient data, detailed diagnosis, skin involvement, CLASI, laboratory findings and treatment [13]. This questionnaire enables comparison of various CLE subtypes in a standardized and valid way.

**Aim**

The aim of the study was to analyze the clinical presentation of cutaneous variants of lupus erythematosus in relation to skin lesion spectrum and extracutaneous involvement.

**Material and methods**

A total of 64 consecutive patients (45 women and 19 men) diagnosed with cutaneous involvement during LE course were initially included into the study. All subjects were inpatients of the Department of Dermatology, Venereology and Allergology in Wroclaw. Their age ranged between 19 and 87 years (mean: 51.4 ±17.3 years) while the age at the time of disease onset ranged between 16 and 86 years (mean: 45.9 ±18.8 years). The study was conducted in accordance with the Data Protection Act and according to the ethical guidelines of the Declaration of Helsinki. The study was approved by our institutional review board. All patients agreed to participate in the study. Among analyzed subjects, 15 (23.4%) patients were diagnosed as having an acute CLE (ACLE) (8 patients with localized and 7 with generalized form), 26 (40.6%) as having subacute CLE (SCLE) (including 17 patients with annular and 9 with papulosquamous form), and 21 (32.8%) as having chronic CLE (CCLE) – all with discoid LE. Two (3.2%) individuals only demonstrated urticarial vasculitis as a cutaneous manifestation of LE and these patients were excluded from further analysis as urticarial vasculitis is nowadays considered as a LE-nonspecific skin manifestation. The disease was confirmed by histological examination in 41 (66.1%) individuals, while remaining patients (33.9%) had the disease diagnosed solely based on clinical presentation and laboratory abnormalities.

The study was performed between 2007 and 2012. It was based on the “Core Set Questionnaire” of the European Society of Cutaneous Lupus Erythematosus (EUSCLE), which includes data gained during a detailed anamnesis, physical examination and certain laboratory tests [13]. The EUSCLE Core Set Questionnaire was approved by the central Ethical Committee of the University of Muenster in Germany. The study was performed using 1997 update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus [14, 15]. Diagnosis of CLE was based on clinical presentation, histopathology, direct immunofluorescence (lupus band test) and additional laboratory data, if necessary [16, 17]. Severity of skin lesions was evaluated according to the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) [10]. Antinuclear antibodies (ANA) were detected by immunofluorescence on HEp2 cells and immunoblot tests. A titer above 1 : 160 was considered as a positive test result. If indicated, the lupus band test was performed from lesional and/or non-lesional skin.

**Statistical analysis**

All results were analysed statistically using the software package Statistica® 10.0 (Statsoft, Krakow, Poland). The significance of the observed differences between studied groups was determined by analysis of variance (ANOVA), Student t test, and χ² test or two sided Fisher exact test, where appropriate. A p-value lower than 0.05 was considered as statistically significant.

**Results**

**Demographic data**

Patients with ACLE were characterized by the earliest onset of the disease (mean age: 31.9 ±15.0 years), followed by SCLE and CCLE (mean age: 43.9 ±14.2 years and 55.6 ±18.9 years, respectively; p < 0.001). Earlier disease onset also resulted in the younger age of ACLE patients (mean age: 39.0 ±15.5 years) compared to CLE and SCLE individuals (49.1 ±12.8 years and 60.5 ±16.8 years, respectively, p < 0.001). Female predominance was higher in ACLE group (females : males ratio – 4 : 1) than in SCLE (2.2 : 1) and CCLE groups (1.6 : 1), but the difference was not significant (p = 0.51). The highest prevalence of cigarette smoking was observed in CCLE patients (85.7%); followed by SCLE – 57.7%, and ACLE – 53.3% (p < 0.05).

**Severity of cutaneous involvement**

According to CLASI, the highest activity of skin lesions was found in SCLE group (mean: 26.4 ±14.5 points, range: 4–58 points) followed by ACLE (mean: 16.7 ±8.3 points,
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Systemic involvement in CLE patients

Systemic symptoms were present in 14 (93.3%) patients with ACLE, 15 (57.7%) with SCLE and 6 (28.6%) with CCLE ($p < 0.001$). At least 4 out of 11 ACR (American College of Rheumatology) diagnostic criteria indicating the diagnosis of SLE were observed in 12 (80%) subjects with ACLE (mean: 5.1 ±1.7 criteria, range: 3–9 criteria), 7 (26.9%) with SCLE (mean: 3.0 ±1.3 criteria, range: 0–5 criteria) and 7 (33.3%) with CCLE (mean: 2.7 ±1.5 criteria, range: 0–7 criteria) ($p < 0.01$).

Arthritis, neurological involvement and oral ulcers more commonly accompanied ACLE (60%, 33.3% and 33.3% of patients, respectively), compared to SCLE (19.2%, 11.5% and 7.7%, respectively) and CCLE (19.0%, 4.8% and 4.8%, respectively) ($p = 0.01$, $p < 0.05$ and $p = 0.02$, respectively). Serositis was only observed in 2 (13.2%) patients with ACLE and 1 (3.8%) with SCLE ($p = 0.18$), renal disease in 3 (20.0%) with ACLE, 1 (3.8%) with SCLE and 1 (4.8%) with CCLE ($p = 0.15$). Hematologic abnormalities were nearly equally frequent in ACLE and SCLE (53.3% and 42.3%, respectively), but were uncommon in CCLE individuals (14.3%, $p < 0.05$) (Table 1).

The secondary Sjögren’s syndrome more often occurred in the SCLE group (23.1%) than in ACLE (13.3%). Interestingly, none of CCLE patients demonstrated symptoms of sicca syndrome ($p = 0.06$). The prevalence of photosensitivity was high in all groups, with the highest prevalence in the ACLE group (93.3%), followed by SCLE (76.9%) and CCLE (71.4%) ($p = 0.27$).

Immunological disturbances in CLE patients

Presence of ANA was confirmed for 86.7% of all patients with ACLE and for 78.6% of patients with SCLE. Regarding ANA subtypes, anti-La (33.3%), anti-Sm (33.3%) anti-RNP (26.7%) and anti-dsDNA (33.3%) antibodies were the most frequent in the ACLE group, while anti-Ro (50.0%) antibodies were most commonly found in SCLE subjects (Table 2). Regarding ACR diagnostic criteria for SLE, presence of anti-Sm and anti-RNP antibodies were

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<th>Table 1. Frequency of American College of Rheumatology diagnostic criteria for systemic lupus erythematosus in different subtypes of cutaneous lupus erythematosus</th>
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| Variable | ACLE (%) | SCLE (%) | CCLE (%) | Value of $p$
| Malar rash | 86.7 | 30.8 | 23.8 | < 0.001
| Discoid rash | 20.0 | 11.5 | 90.5 | < 0.001
| Photosensitivity | 93.3 | 76.9 | 71.4 | 0.02
| Oral ulcers | 33.3 | 7.7 | 4.8 | 0.02
| Arthritis | 60.0 | 19.2 | 19.0 | 0.01
| Serositis | 13.2 | 3.8 | 0.0 | 0.18
| Renal disorder | 20.0 | 3.8 | 4.8 | 0.15
| Neurological disorder | 33.3 | 11.5 | 4.8 | < 0.05
| Hematologic disorder | 53.3 | 42.3 | 14.3 | 0.03
| Immunological disorder | 13.3 | 15.4 | 0.0 | 0.19
| Antinuclear antibodies | 86.7 | 80.9 | 42.9 | < 0.01

ACE – acute cutaneous lupus erythematosus, SCLE – subacute cutaneous lupus erythematosus, CCLE – chronic cutaneous lupus erythematosus; p-values according to $\chi^2$ test.

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<th>Table 2. Presence of various antinuclear antibodies in different subtypes of cutaneous lupus erythematosus</th>
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| Type of antibody | ACLE (%) | SCLE (%) | CCLE (%) | Value of $p$
| Anti-Ro | 46.7 | 50.0 | 4.8 | 0.002
| Anti-La | 33.3 | 26.9 | 4.8 | 0.07
| Anti-Sm | 33.3 | 0.0 | 0.0 | < 0.001
| Anti-RNP | 26.7 | 0.0 | 4.8 | < 0.02
| Anti-histone | 0.0 | 11.5 | 0.0 | 0.24
| Anti-dsDNA | 33.3 | 15.4 | 4.8 | 0.07

ACE – acute cutaneous lupus erythematosus, SCLE – subacute cutaneous lupus erythematosus, CCLE – chronic cutaneous lupus erythematosus; p-values according to $\chi^2$ test.
should be considered as a subtype of CCLE or has to be.

It is still no agreement if lupus erythematosus tumidus
CLE still remains a matter of debate. For instance, there
been differentiated, however, the clinical classification of
skin manifestations, various clinical subtypes of CLE have
specific and LE-unspecific lesions [18]. Based on LE-specific
skin abnormalities, which usually are divided into LE-spe-
tifications.

conducting future studies on different patient popula-
ies which might be useful in
seems to be a valuable tool for a standardized clinical
porting data that the EUSCLE "Core Set Questionnaire"
ies on CLE subjects [13]. Our study provides further sup-
data on CLE subjects collected from different European
centers and different patient populations. To standardize
data on CLE subjects collected from different European
countries, EUSCLE has recently developed a structured
questionnaire, which, in our opinion, might be very help-
ful in conducting cross-sectional, population-based stud-
ies on CLE subjects [13]. Our study provides further sup-
porting data that the EUSCLE “Core Set Questionnaire”
seems to be a valuable tool for a standardized clinical
assessment of CLE patients which might be useful in
conducting future studies on different patient popula-
tions.

Another important clinical issue of CLE evaluation is
the assessment of the severity of skin lesions. In 2005,
Albrecht et al. [10] validated the CLASI – a new measure-
ment instrument for CLE that can be used in clinical tri-
als. It was demonstrated that the activity scoring system
of CLASI very well correlated with the general assess-
ment of the global skin health performed by physicians
and by patients [19]. Our study also showed that CLASI
is a valid method of CLE assessment, which also enables
differentiation of different CLE subtypes. However, this
scale is time consuming and requires some clinical ex-
pertise to be properly scored, and thus is not well suited
for daily clinical practice. Furthermore, it is still unknown
if it is feasible for rare variants of CLE, like LE panniculitis or chilblain LE. Some modifications of CLASI have been
proposed, but to date no instrument assessing CLE se-
verity really overcame previous shortcomings [20, 21].
Furthermore, to the best of our knowledge, no currently
available CLE severity scoring system takes into consid-
eration subjective symptoms and patient’s perspective
of having skin lesions in LE. Remarkably, it has recently
also been shown that damage domain of CLASI did not correlate with overall health-related quality of life of CLE
patients [22].

In the current study we have observed that systemic
symptoms of LE may be found in all analyzed CLE sub-
types, albeit with different prevalence. We have found
this observation important, as some subtypes of CLE, like
e.g. SCLE, were not included in the original ACR diagnos-
tic criteria of SLE, which might lead to underrecognition
of SLE [14, 15]. It might also cause a misconception that
SCLE is a CLE variant without systemic involvement. On
the other hand, photosensitivity, i.e. “unusual reaction to
sunlight by a patient’s history or by physician observa-
tion”, was considered as a separate diagnostic criterion
of SLE [14, 15], which might lead to a faulty increase in
the number of positive SLE criteria in selected patients,
as “malar rash” is often indistinguishable from photo-
sensitivity, and therefore these criteria were not indepen-
dent [23]. These shortcomings have been substantially
improved in the new diagnostic criteria proposed by Petri
et al. [24], as they recognized many previously excluded
cutaneous LE manifestations, including SCLE and LE tu-
midus.

It must be underlined that the current study was
performed on patients treated in the dermatology de-
partment, which might differ from LE subjects treated
by rheumatologists regarding the distribution pattern of
cutaneous manifestations. Having only patients
from dermatology department might be considered as
a limitation of our study. Thus, it would be interesting
to perform a similar study on LE individuals from the
rheumatology department to test whether these pa-
tients indeed have different skin problems than those
from dermatology.

Lupus erythematosus is often accompanied by ANA
directed against various nuclear antigens. These anti-
bodies have crucial diagnostic and prognostic meaning,
however, no ANA subtype could be solely linked with one
clinical subtype of CLE, albeit some of them may be more
common in certain CLE variants. Interestingly, it seems
that some ANA subtypes may predispose patients to
particular systemic manifestations of LE, e.g. antibodies
anti-Ro were found to be related to a higher prevalence
of oral ulcers and hematological disturbances.
Conclusions

It can be concluded that each variant of CLE differs significantly from the others in respect of various aspects of clinical manifestations. Due to a number of different variants of LE skin manifestations, a unified classification of CLE still remains a challenge. We do believe that EUSCLE Core Set Questionnaire might be helpful in a standardized assessment of clinical characteristics of different CLE subtypes. However, future attempts should be concentrated on the development of better instruments for CLE severity assessment, which will also consider patient perspective on skin lesions and will be simple enough to be used in daily clinical practice.

Conflict of interest

The authors declare no conflict of interest.

References