Lupus erythematosus: correlation of clinical and histological findings and proposal for a modified disease classification

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Introduction
Lupus erythematosus (LE) is a systemic autoimmune disease of multifactorial genesis. Even today, its pathophysiology is still not fully understood [1]. Given the diverse clinical morphology and the different organ manifestations and severity of the disease, there was an early need to define disease criteria that would allow the diagnosis of patients in a standardized manner. Whereas rheumatological classifications are based on symptomatic views to assess systemic involvement, from a dermatological perspective, classifications have been established that categorize the disease according to the morphology of skin manifestations. Based on acuity, chronic-cutaneous LE variants with chronic-discoid LE (CDLE), lupus profundus and lupus tumidus, subacute-cutaneous LE (SCLE), and acute-cutaneous LE (ACLE) are distinguished [2, 3]. This classification is based on the assumption that LE-specific skin manifestations can be assigned to a specific disease diagnosis. To date, however, no classification has been established that takes both views equally into account. The most recently developed EULAR/ACR criteria from 2018 are a new attempt in this direction.

Due to the different approaches outlined above, however, classification of the disease diagnosis in daily clinical practice is often conflicting.

In recent years, there have been intensive efforts by the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), and the Systemic Lupus...
International Collaborating Clinics (SLICC) to overcome the difficulties of classification. Nevertheless, many problems and inconsistencies of classification remain, especially in patients that do not meet the so-called systemic criteria [4, 5]. In particular, these classifications, including the new EULAR/ACR criteria, consider the disease exclusively from the perspective of systemic LE (SLE) positive for autoantibodies.

A classification that considers the morphology of the skin changes and the clinical diagnosis separately from each other was first proposed by Tsuchida et al. [6]. To this end, the authors created a diagnostic system with two axes. The first axis describes exclusively the morphology of LE-specific skin manifestations. The other axis denotes, dependent on the extent of extracutaneous organ involvement, the final clinical diagnosis: limited-cutaneous LE, intermediate LE, and systemic LE (SLE). The authors were able to show that LE-specific skin manifestations were distributed across all diagnostic groups. It is, therefore, not possible to allocate them reliably to a specific diagnosis [6]. Analogous to this finding, Baltaci et al. showed in their work that in the majority of cases it is also not possible to draw conclusions about the clinical diagnosis of LE solely from histological findings. Rather, the histological classification is performed according to the affected skin compartment (epidermal, epidermo-dermal, dermal, or subcutaneous LE) and must be evaluated in clinical and histopathological context [7, 8].

Methods

Study design, study population, and execution

This work is based on a doctoral thesis that was completed as a monograph. The aim of the work was the retrospective application of the published two-dimensional classification system, which considers disease-specific skin changes and final diagnoses separately, on a collective of our own LE patients, and to compare the revised disease diagnoses with those of the medical records. Furthermore, we wanted to clarify to what extent patients could be grouped by diagnosis based on their LE-specific skin manifestations, corresponding histopathological changes and paraclinical data.

All outpatients and inpatients of the Department of Dermatology, Venereology and Allergology of the University Hospital Leipzig who were encoded within the electronic database of the department (SAP) with the ICD diagnosis L93.x for cutaneous LE and the diagnosis M32.x for SLE were examined retrospectively for the period from 2007 to 2014. Criteria for inclusion in the evaluation were the established clinical diagnosis of LE, available data on clinical history, sufficient description of clinical findings, presence of skin manifestations with corresponding photographs and biopsy, laboratory parameters, such as differential blood count and autoantibodies, and documentation of extracutaneous organ manifestations. Mean age at the time of initial diagnosis was 45 years.

The clinical photographs were evaluated in a standardized manner based on the morphology of skin lesions, their number, distribution, and figuration (Table S1, Online Supplement). The skin biopsies were once again systematically examined by microscopy, and all histopathological changes with respect to epidermis, dermis, and subcutaneous tissue were documented according to uniform criteria (Table S2, Online Supplement).

Based on their paraclinical data and organ manifestations, the patients were then classified into limited-cutaneous LE, intermediate LE, or SLE. In this context, limited-cutaneous LE meets less than four ACR criteria (none of them systemic), limited LE meets also less than four ACR criteria, but at least one of them systemic (for example, corresponding changes in blood counts, arthritis, organ involvement, positive antibodies), and SLE meets four or more ACR criteria [9]. The diagnoses were compared with the original diagnoses of the medical records made according to the ACR criteria valid at the time of examination (at the time of data evaluation, the new EULAR/ACR classification criteria were not yet available) [4, 5].

We explicitly included only LE patients with skin manifestations; drug-induced cases were excluded. It should be noted that the patient population of a dermatological university hospital is selective and may not reflect the entire collective of LE patients. Primarily, LE patients with rather moderate systemic involvement are treated. In case of skin changes, however, it can be assumed that LE patients are presented at least once for co-assessment at the dermatology department of the university by both office-based dermatologists and rheumatologists.

Statistical evaluation

The results were analyzed with the program IBM SPSS Statistics 24.0. The chi-squared test and, if necessary, the Fisher’s exact test were used. For some features significant in the chi-squared test, univariate and multivariate analyses were performed by logistic regression. For all tests, the significance level was set to 5 % (two-sided).

In addition, cluster analyses were performed for the complex data of clinical and histological features in order to identify groups with common features. To this end, hierarchical clustering was performed with the statistics software R v.3.3.1 (function hclust). The results of the analyses were prepared as heatmaps. In two cluster analyses, we examined whether clusters of disease criteria formed in relation to a specific diagnosis. In the first analysis, we included clinical-morphological criteria, laboratory data, and organ
manifestations, in the second analysis histological criteria. Given that only binary and ternary criteria could be included in the cluster analysis, several features were merged. Moreover, criteria with many missing data were excluded to avoid a biased analysis.

**Results**

Between 2007 and 2014, 973 outpatients and inpatients were encoded as LE in various constellations. In one third of these patients, LE was only an excluded diagnosis. Of the remaining 612 patients, 187 and 425 were encoded as cutaneous LE and SLE, respectively. In more than 50 % of the patients encoded as SLE, no skin manifestations were present. Again, one half of the documented skin findings were unspecific changes or dermatologic comorbidities (for example, pruritus, known vitiligo, eczema of the lower leg secondary to chronic venous insufficiency, shingles, hidradenitis suppurativa). For 98 of the remaining 216 patients with LE-specific skin manifestations, the skin biopsy and/or clinical photographs required for the evaluation were missing. After analysis of the usability of biopsies and clinical photographs, 76 patients meeting all inclusion criteria could be included in the final evaluation.

**Diagnostic classification after re-evaluation**

After re-evaluation with the two-dimensional approach, the diagnoses deviated significantly from the original diagnoses in the medical records. After re-evaluation, the percentage of patients with limited-cutaneous LE was markedly reduced (23.7 % vs. 81.6 %). By contrast, patients with intermediate LE presented the majority of all LE cases with 44.7 %. The percentage of SLE patients was also markedly higher in the re-evaluation (31.6 % vs. 18.4 %) (Table S3, Online Supplement). Seven patient examples illustrate the differences of the diagnoses after re-evaluation based on the two-dimensional classification proposal of Tsuchida et al. (Figures 1–7).

![Patient case 1: 70-year-old female patient with generalized, disseminated, annular, polycyclic and confluent erythematous plaques (a, b). Corresponding histopathological findings in a biopsy from the back. Sparse perivascular and periadnexal lymphocytic inflammatory infiltrates in the superficial dermis (c). Focal necrotic keratinocytes and vacuolar degeneration of the epidermo-dermal junction and along the hair follicle epithelium (d) (hematoxylin-eosin stain).](image-url)
Distribution and frequency of LE-specific skin manifestations

The LE-specific skin manifestations were distributed across all three diagnostic groups (Table S3, Online Supplement). CDLE, lupus tumidus, chilblain lupus, and lupus profundus were found regularly in SLE patients, just like, conversely, SCLE or centrofacial erythema in limited-cutaneous LE. It was not possible to allocate skin manifestations to a specific disease diagnosis.

The extent of skin changes was indicative for systemic involvement. For the feature of disseminated skin changes, significant in the chi-squared test, the univariate analysis demonstrated that these changes increase with increasing disease severity of LE (limited-cutaneous LE: 16.7 %, intermediate LE: 58.5 %, systemic LE: 83.3 %).

Histology

The histological characteristics allowed for classification in epidermo-dermal LE, dermal LE, and subcutaneous LE, or showed overlapping features among them. Apart from a few cases of isolated subcutaneous changes that unequivocally corresponded to lupus profundus, it was not possible to allocate the histopathological changes to a specific skin manifestation. Similarly, the histopathological changes without clinical correlation did not permit conclusions about the disease diagnosis.

Cluster analysis

To examine the association of clusters of individual disease features with respect to LE diagnoses (limited-cutaneous, intermediate, and systemic), we performed a cluster analysis (Figures S1 and S2, Online Supplement). The idea was to establish new associations of features with LE diagnoses independent of existing classifications and, thus, without weighting of individual criteria. The cluster analyses of clinical-morphological criteria, laboratory data, and organ manifestations, as well as histological criteria did not form any clusters of common features.
Distribution and frequency of specific LE-related skin manifestations

In our patient collective, CDLE was not a specific indicator of cutaneous-limited LE. After re-evaluation, CDLE was found at the same frequency in patients with limited-cutaneous and intermediate LE (39 % and 38 %), but also at a rate of 54 % in patients with SLE.

This underscores the results of a separate study in which systemic symptoms were identified in 28.6 % of patients with CDLE while 33 % were even diagnosed with SLE according to ACR criteria [10]. In this context, the presence of disseminated skin changes may be an indication for the existence of SLE.

Anti-SSA antibodies are considered highly specific for SCLE [2]. In our study population, anti-SSA and anti-SSB antibodies were found significantly more often in patients with SCLE morphology with 84 % ($P < 0.000267$) and 42 % ($P < 0.028$), respectively. The majority of these patients were positive for antinuclear antibodies (ANA). In the current EULAR/ACR classification, antinuclear antibodies are now a mandatory entry criterion for SLE, thus supporting our hypothesis [5].

In our patient collective, skin changes typical of SCLE were found after re-evaluation predominantly in patients with intermediate LE (68 %), but also with SLE (42 %). While a specific allocation was again not possible, the presence of skin changes typical of SCLE would appear to make a limited-cutaneous LE unlikely.

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Patient case 5: 48-year-old female with centrofacial erythema (a), disseminated, maculo-papular exanthema (b) and violaceous indurated plaques on the left lower leg (c).

**Figure 5**

Additional skin findings:
- Erythema with ill-defined borders on the décolleté, solitary erythematous papules on forearms and décolleté

**Organ findings and paraclinical data:**
ANA 1:80, anti-histone and anti-SSA antibodies, fatigue and exhaustion, musculoskeletal symptoms

| Diagnosis according to medical records | SCLE, lupus profundus |
|----------------------------------------|-----------------------|
| Diagnosis after re-evaluation based on two-dimensional classification according to Tsuchida |
| Morphological diagnosis of skin manifestations | ACLE, lupus profundus |
| Clinical diagnosis | Intermediate LE |

**Figure 4** Patient case 4: 23-year-old female with a solitary discoid plaque on her left upper arm with scarring and central crust (a). Corresponding histopathological findings in a biopsy from the left upper arm. Superficial and deep dermal as well as subcutaneous lymphocytic infiltrates (b, c). Periadnexal and perivascular lymphocytic infiltrates with pronounced hair follicle-associated vacuolar interface dermatitis (d) (hematoxylin-eosin stain).
In clinical classification systems from a dermatological perspective, chilblain lupus, lupus tumidus and lupus profundus are predominantly classified as cutaneous-limited LE. Our data show, however, that they occur also in intermediate LE (chilblain LE: 5.9 %, lupus tumidus: 8.8 %, lupus profundus: 11.8 %) and SLE (chilblain LE: 4.2 %, lupus tumidus: 13 %, lupus profundus: 8.3 %). Although lupus tumidus should never be present in SLE, according to the literature [3], in our study it is evident in 13 % of SLE patients. In the past, the possibility of a systemic manifestation in lupus tumidus resulted in a modification of the Düsseldorf classification. Whereas Gilliam and Sontheimer classify lupus tumidus as chronic-cutaneous LE [11], in the Düsseldorf classification it is described as distinct intermittent cutaneous LE [12].

Histological findings

Histology is an essential component for confirming the diagnosis of LE. However, histopathological changes cannot be assigned to a specific diagnosis, as was illustrated by the results of Baltaci et al [7]. The histomorphologic overlap of the clinical variants is due to the fact that similar inflammatory patterns underlie the different cutaneous LE manifestations [13]. Correlation of clinical and histological findings is essential for the final diagnosis.

Diagnostic classification after re-evaluation

After re-evaluation of the diagnoses based on the two-dimensional approach, intermediate LE emerged as largest group in our cohort with 45 %. This finding demonstrates that the majority of LE patients have symptoms or clinical characteristics beyond the purely cutaneous manifestations and emphasizes the systemic character of the disease. It is possible that a certain degree of systemic involvement is underestimated from the dermatological perspective. It is known from the literature that in up to 48 % of cases patients with more than four ACR criteria are still not diagnosed as SLE [14, 15].

Organ findings and paraclinical data:

ANA 1:640, anti-nucleosome antibodies, arthritis, anemia

| Diagnosis according to medical records | Lupus panniculitis* |
|----------------------------------------|---------------------|
| Diagnosis after re-evaluation based on two-dimensional classification according to Tsuchida | Morphological diagnosis of skin manifestations CDLE |
| | Clinical diagnosis SLE |

*histologically profound panniculitis

Figure 6 Patient case 6: 33-year-old female with a discoid erythema-to-squamous cicatricial plaque on the left cheek with central crust.
the same time, this indicates the limits of the applicability of the ACR criteria for evaluating the degree of systemic involvement; criteria that were originally developed not for the diagnosis of SLE, but for the differentiation from other autoimmune diseases [16]. Compared to the ACR criteria, SLICC and EULAR/ACR criteria provide useful new features, but do not solve the controversial issues. While the EULAR/ACR classification from 2018, in particular, includes more forms of cutaneous manifestation, it remains unclear on which basis the selection was made and why some were included but others not. The classification redefines the weighting of individual criteria, specifically to achieve a more cautious diagnosis of SLE based on a predominance of cutaneous criteria. However, both classifications still refer exclusively to SLE [4, 5]. A definition of LE patients whose disease cannot (yet) be considered as SLE remains open.

In conclusion, disease-specific skin changes are not specifically diagnostic. Skin manifestations alone are not the key to diagnosis. A two-dimensional approach can overcome the difficulties of classification, as skin-related morphological and symptomatic aspects can be considered separately.

Figure 7 Patient case 7: 25-year-old female with a discrete centrofacial erythema (a), erythematous-to-viole- lanceous papules, plaques and nodes on the right gluteal region (b) as well as edematous erythematous-to-violaceous partially squamous plaques on fingers and toes (c, d).

| Diagnosis according to medical records | Chilblain lupus, SLE suspected |
|----------------------------------------|-------------------------------|
| Diagnosis after re-evaluation based on two-dimensional classification according to Tsuchida | Morphological diagnosis of skin manifestations | ACLE, lupus profundus und chilblain lupus |
|                                         | Clinical diagnosis             | Intermediate LE, SLE suspected (assessment of kidneys needed) |
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References

1 Kuhn A, Wenzel J, Bijl M. Semin Lupus erythematosus revisited. Immunopathol 2016; 38(1): 97–112.
2 Alniemi DT, Gutierrez A, Drage LA et al. Subacute cutaneous lupus erythematosus: clinical characteristics, disease associations, treatments, and outcomes in a series of 90 patients at Mayo Clinic, 1996–2011. Mayo Clin Proc 2017; 92(3): 406–14.
3 Alexiades-Armenakas MR, Baldassano M, Bince B et al. Tumid lupus erythematosus: Criteria for classification with immunohistochemical analysis. Arthritis Rheum 2003; 49(4): 494–500.
4 Petri M, Orbai AM, Alarcón GS et al. Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012; 64: 2677–86.
5 Aringer M, Costenbader K, Daik D. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Ann Rheum Dis 2019; 78(9): 1400–12.
6 Tsuchida T. Classification of lupus erythematosus based upon Japanese patients. Autoimmun Rev 2009; 8(6): 453–5.
7 Baltaci M, Fritsch P. Histologic features of cutaneous lupus erythematosus. Autoimmun Rev 2009; 8(6): 467–73.
8 Lipsker D. The need to revisit the nosology of cutaneous lupus erythematosus. Lupus 2010; 19: 1047–9.
9 Tan EM, Cohen AS, Fries JF et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25(11): 1271–7.
10 Szczecisiak J, Rutka M, Samotij D et al. Clinical characteristics of cutaneous lupus erythematosus. Adv Dermatol Allergol 2016; 33(1): 13–7.
11 Sontheimer RD. The lexicon of cutaneous lupus erythematosus – A review and personal perspective on the nomenclature and classification of the cutaneous manifestations of lupus erythematosus. Lupus 1997; 6: 84–95.
12 Kuhn A, Ruzicka T. Classification of cutaneous lupus erythematosus. In: Kuhn A, Lehmann P, Ruzicka T (eds): Cutaneous Lupus Erythematosus. Springer, Berlin, Heidelberg 2005: 53–7.
13 Ackerman AB, Böer A, Benin B et al. Histologic Diagnosis of Inflammatory Skin Diseases. An Algorithmic Method Based on Pattern Analysis, 3rd Edition. New York City: Ardor Scribendi Ltd., 2005.
14 Biazar C, Sigges J, Patzianakis N et al. Cutaneous lupus erythematosus: First multicenter database analysis of 1002 patients from the European Society of Cutaneous Lupus Erythematosus (EUSCLE). Autoimmun Rev 2013; 12(3): 444–54.
15 Parodi A, Rebora A. ARA and EADV Criteria for Classification of Systemic Lupus Erythematosus in Patients with Cutaneous Lupus Erythematosus. Dermatology 1997; 194: 217–20.
16 Larosa M, Iaccarino L, Gatto M et al. Advances in the diagnosis and classification of systemic lupus erythematosus. Expert Rev Clin Immunol 2016; 8(40): 1–12.