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Markers in Cutaneous Lupus Erythematosus Indicating Systemic Involvement

A Multicenter Study on 296 Patients

BEATE TEBBE[1], ULRICH MANSMANN[2], UWE WOLLINA[3], PIET AUER-GRUMBACH[4], ANGELIKA LICHT-MBALYOHERE[5], MARLIES ARENSMEIER[6] and CONSTANTIN E. ORFANOS[1]

Departments of [1]Dermatology and [2]Medical Informatics and Statistics, University Medical Center Benjamin Franklin, The Free University of Berlin, Berlin, Departments of Dermatology, [3]Friedrich-Schiller University, Jena, [4]University of Graz, Austria, [5]Medical Center, Minden, and [6]Otto-von-Guericke University, Magdeburg, Germany

Lupus erythematosus (LE) is an autoimmune disorder, involving the skin and/or other internal organs. As cutaneous variants, chronic discoid LE (CDLE) and subacute cutaneous LE (SCLE) usually have a better prognosis, however, involvement of internal organs with transition into systemic disease may occur. The aim of this study was to assess the significance of some clinical and laboratory criteria that could serve as markers for early recognition of systemic involvement in cutaneous LE.

Three hundred and seventy-nine patients with LE, seen in five cooperating Departments of Dermatology during the years 1989–1994, were documented by electronic data processing according to a common protocol. Two hundred and forty-five of these patients had cutaneous LE (CDLE or SCLE), and 51 had systemic LE (SLE) and were included in this study. Forty-nine patients with either CDLE/SCLE or SLE were not evaluated because of incomplete documentation; also, 34 patients suffered from other LE subsets and were likewise excluded from the evaluation. Multivariate statistical analysis was used to assess the value of seven selected variables for distinguishing between the CDLE/SCLE and SLE groups: ESR, titers of antinuclear antibodies, anti-dsDNA-antibodies, photosensitivity, presence of arthralgias, recurrent headaches and signs of nephropathy.

Univariate and multivariate analysis of the obtained data showed that signs of nephropathy (proteinuria, hematuria) was the variable with the highest statistical relevance for distinguishing between patients with cutaneous (CDLE/SCLE) and with systemic LE (SLE) in all statistical models tested, followed by the presence of arthralgias and of high ANA titers ($\geq$1:320). In contrast, low ANA titers as well as anti-dsDNA antibodies showed little or no statistical relevance as a criterion for distinction. It seems, therefore, that cutaneous LE patients showing signs of nephropathy, presence of arthralgias and elevated ANA titers ($\geq$1:320) should be carefully monitored, because they may be at risk of developing systemic LE involvement. *Key words: systemic lupus erythematosus; prognosis.*

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B. Tebbe, M.D., Department of Dermatology, University Medical Center Benjamin Franklin, The Free University of Berlin, Berlin, Germany.

Lupus erythematosus (LE) can be classified into 3 major variants: chronic discoid LE (CDLE), subacute cutaneous LE (SCLE) and systemic LE (SLE). As a rule, these entities can be clearly diagnosed by the dermatologist, according to distinct clinical and histological criteria. CDLE is characterized by erythematosquamous, hyperkeratotic plaques mainly located on the face and scalp, whereby the typical skin lesions usually heal with superficial scarring. SCLE has two clinical variants: the *annular type* and the *psoriasiform type,* both distributed mainly over the upper trunk. In typical cases, the SCLE lesions heal without scarring, but they may sometimes lead to hypo- and/or hyperpigmentation. Photosensitivity is a clinical symptom in 40–60% of the patients with cutaneous LE (1–3).

Clinical experience indicates that ca. 5–10% of the patients suffering from CDLE are subject to experience transition into SLE during the course of their disease (4). It is also well established that up to 50–60% of all patients with SCLE may develop systemic involvement over a period of years, in addition to the cutaneous manifestations (1, 5, 6). Other cutaneous LE subsets, such as urticaria vasculitis, bullous LE, LE panniculitis/profundus and hypertrophic LE, are rather rare variants with varying prognosis.

As stated above, CDLE and SCLE can be diagnosed by clinical and histological criteria in most cases. However, it remains difficult to predict which cases will develop visceral involvement with transition into SLE; these should be treated accordingly. SLE itself is defined according to a list of 11 criteria established by the American Rheumatism Association (ARA) (7). This group of patients, however, appears to be inhomogeneous; in particular, the ARA criteria are of limited value for defining patients with cutaneous LE and for determining their further course. Only 20% of all CDLE patients show $\geq$4 positive ARA criteria (8), whereas in most cases only 2–3 criteria are fullfilled. Also, the presence of typical skin lesions for distinguishing between CDLE and SCLE is not included in the list. Altogether, a correct diagnosis or proper evaluation of the course of cutaneous LE is difficult or impossible using the ARA list. The aim of this study, therefore, was to elaborate valuable criteria that distinguish between skin-limited variants and those with SLE and may serve as markers indicating the risk for early systemic involvement, using univariate and multivariate analysis.

MATERIAL AND METHODS

Patients' collective

In this prospective, observational multicenter study, performed in five Departments of Dermatology in Germany and in Austria, 379 patients with different clinical variants of LE were documented between the years 1989 and 1994. Of these patients 296 were classified into two groups: group I included 245 (82.7%) patients with either CDLE or SCLE, while group II consisted of 51 (17.2%) patients with SLE with well known visceral involvement. In 49 patients with CDLE/SCLE or SLE the documentation remained incomplete, and in another 34 cases rare cutaneous LE subsets were diagnosed; these cases were therefore excluded from evaluation.

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The cutaneous LE variants were diagnosed by clinical criteria and confirmed by routine histology. CDLE was defined as circumscribed erythematosquamous, hyperkeratotic lesions with central atrophy and superficial scar formation, mainly on the face and scalp. SCLE lesions were typically annular or psoriasiform, healing without atrophy or scar formation, and were mostly located on light-exposed areas and the upper trunk. The patients with CDLE/SCLE were evaluated together in one group, since the final diagnosis of the skin lesions remained unclear in some cases. It seems that the distinction between CDLE and SCLE may be occasionally obscured by transitional cases.

Study design

From the wealth of clinical and laboratory data documented in this joint project, 7 major variables were selected for statistical evaluation, based on the high frequency of pathological values and their suspected clinical relevance for indicating systemic involvement.

I. *Laboratory data.* ESR elevation (>40 mm after 2 h), ANA titers (>1:80), presence of circulating anti-dsDNA antibodies, skin hypersensitivity to UV light (UVA/UVB photosensitivity).
II. *Clinical data.* Presence of arthralgias, signs of nephropathy, recurrent headaches.

The laboratory techniques, including photosensitivity testing, were routinely performed in all cooperating departments. Antinuclear antibodies were detected by indirect immunofluorescence with Hep-2-cells, and circulating anti-dsDNA antibodies were measured by a radioimmunoassay technique (Farr). ESR was measured by the Westergren method. The clinical symptomatology was assessed according to the following score to achieve a *yes/no* answer: *arthralgias* were considered for evaluation only if pain in small or large joints had been recorded, at least twice weekly over a period of 3 months; *nephropathy* was considered for evaluation in the presence of 2 of the following 4 signs: proteinuria (≥0.4 g/l), hematuria, increased serum creatinine levels (>100 µmol/l), and decreased creatinine clearance (<50 ml/min). Kidney biopsies were performed for further assessment in only a limited number of these patients, and the results were not evaluated in this study. *Headaches* were registered if recurrent (>once a week) and if diagnosed as LE-related by a neurologist. Other rare neurological manifestations (i.e. seizures, psychosis) were seldom diagnosed and were therefore excluded from statistical analysis.

Univariate statistical evaluation of the above-mentioned variables was carried out using the chi^2 test and the odds ratio (Mantel-Haenzel procedure). Multivariate analysis was made by logistic regression analysis (BMDP LR software) to study the effect of the selected parameters as independent prognostic factors. Four different models have been found which offer a good description of the observed data. These models resulted from different decisions during the model selection process. The odds ratios (OR) and the 95% confidence interval (CI) of the factors of the final models are given. The statistical relevance of a given variable was assessed by a Wald test. To judge statistical relevance according to the Wald test risk factor, one looks at the difference between zero and the boundary closest to zero of the 95% confidence interval of the relevant regression coefficient. The larger the difference the stronger the impact of the considered factor of the overall risk. The Hosmer-Lemeshow test of goodness of fit (GOF) was used to check the appropriateness of the proposed models. The log-likelihoods of the final models were used to calculate the Akaike Information Criterion (AIC). The value of the AIC is calculated as $-LL+2\times$(No. of factors). If several models are available to describe the data the model with the lowest AIC value will be preferred (9).

RESULTS

The sex distribution had a dominance of women in both groups, while the age of onset was about the same in the two groups and varied from 8 to 84 years. The disease duration was on the average 7 years, with a broad distribution in both groups (Table I).

Univariate analysis of 7 selected variables revealed ESR elevation to be the variable with the highest discriminatory power, followed by signs of nephropathy and presence of arthralgias and high ANA titers ≥1:320. If slightly elevated ANA titers ≥1:80 were included in the statistical analysis, this variable still showed a statistical difference but had less discriminatory power than high ANA titers. Variables of only secondary significance were the presence of anti-dsDNA antibodies and/or of recurrent headaches. Photosensitivity was found significantly more often in cutaneous LE than in SLE (Table II).

The 7 variables selected were then tested in a *multivariate analysis*, using 4 different statistical models. In models 1, 2 and 3, the presence of a low ANA titer ≥1:80 was used as a variable; however, in model 4 only high ANA titers ≥1:320 were studied. In two models, the signs of nephropathy are further specified; model 2 used proteinuria and model 3 hematuria alone as the nephropathy-defining variable.

Model 1

Signs of nephropathy (OR:3.83; CI:1.75–8.40) and arthralgias (OR:4.61; CI:1.92–11.01) were found to be the most significant variables for distinction between cutaneous LE and SLE in this study. In order of statistical relevance they were followed by ESR elevation (OR:3.74; CI:1.35–10.42) and the presence of photosensitivity (OR:0.40; CI:0.12–0.82). An ANA titer ≥1:80 was only at the lowest level of significance (OR:2.60; CI:1.02–6.50). Remarkably, the occurrence of circulating anti-dsDNA antibodies and of recurrent headaches dropped out of this model (AIC value 113.064).

Model 2

If proteinuria was included in the statistical model for signs of nephropathy, it was again the most significant parameter for distinction between the two groups (OR:2.84; CI:1.72–4.69), followed by arthralgias (OR:4.83; CI:2.07–11.25). Although the odds ratio was higher for arthralgias than for proteinuria, the confidence interval of the latter was smaller and therefore of higher statistical relevance. The next important variable was ESR elevation (OR:3.94; CI:1.42–10.87), followed by the presence of photosensitivity (OR:0.41; CI:0.22–0.79) and of ANA titers ≥1:80 (OR:2.6; CI:1.06–6.33). Anti-dsDNA antibodies and recurrent headaches dropped out in this model (AIC value 114.86).

Table I. *Clinical characteristics of the groups evaluated*

	CDLE/SCLE ($n=245$)	SLE ($n=51$)
Male/female	53/192	6/45
Age of onset	8–84 y	12–64 y
(mean age)	38 y (SD 14.9)	36 y (SD 13.4)
Disease duration	<1–46 y	<1–28 y
(mean years)	7 y (SD 9.2)	7 y (SD 7.7)

Table II. *Univariate analysis for the prognostic value of criteria for distinguishing between cutaneous LE and systemic LE*

	Cutaneous LE (CDLE/SCLE) No. of pts. yes/no	Systemic LE No. of pts. yes/no	*p*	Odds ratio	Confidence interval
ESR elevation	137/108	46/5	0.0002	7.25	[2.79–18.88]
ANA titer ≥1:80	150/95	44/7	0.00016	3.98	[1.72–9.20]
ANA titer ≥1:320	72/173	35/16	<0.000009	5.26	[2.74–10.09]
Anti-dsDNA ab	85/160	31/20	0.0005	2.92	[1.57–5.43]
Photosensitivity	166/79	26/25	0.0227	0.49	[0.27–0.91]
Arthralgias	115/130	43/8	<0.000009	6.10	[2.74–13.46]
Signs of nephropathy	22/223	20/31	<0.000009	6.56	[3.21–13.34]
Proteinuria	22/225	14/37	0.00004	4.26	[2.04; 8.90]
Hematuria	11/234	13/38	<0.00001	7.28	[3.20; 17.11]
Recurrent headaches	46/199	17/34	0.0211	2.16	[1.11–4.20]

Model 3

Statistical analysis with hematuria showed the following order of statistical relevance: hematuria was rated first (OR:4.15; CI:2.48–6.99), followed by arthralgias (OR:4.10; CI:1.73–9.71). Photosensitivity was in position 3 before ESR elevation because of its smaller confidence interval (photosensitivity: OR:0.33; CI:0.16–0.67; ESR elevation: OR:4.83; CI:1.76–13.21). Apart from anti-dsDNA antibodies and recurrent headaches, a slightly elevated ANA titer ≥1:80 was also excluded in this model (AIC value 110.201).

Model 4

It appeared of particular interest to us to find out whether elevation of ANA titers ≥1:320 was of greater statistical relevance than all elevated ANA titers. Multivariate analysis revealed that an ANA titer ≥1:320 (OR:3.11; CI:1.49–6.78) ranked below the signs of nephropathy (OR:4.21; CI:1.88–9.38) in position 2 of statistical relevance, followed by arthralgias (OR:3.58; CI:1.49–8.60). These positions are exchangeable because of the negligible difference in the confidence intervals between the two odds ratios. ESR elevation (OR:2.57; CI:0.97–6.78) and presence of photosensitivity (OR:0.44; CI:0.21–0.91) followed in positions 4 and 5, respectively. Again, the presence of anti-dsDNA antibodies and of recurrent headaches dropped out (AIC value 101.842).

Comparison of the four tested models revealed that nephropathy and proteinuria/hematuria are the most important factors, followed by arthralgias. Among the signs of nephropathy tested, it was shown that proteinuria and hematuria had the same statistical significance as both variables together. The importance of ANA titers depended on the level of the titer elevation. Slightly positive ANA titers had only low significance or none at all. Only ANA titers ≥1:320 were found with a significant difference in the two groups with cutaneous LE and SLE. Remarkably, anti-dsDNA antibodies and recurrent headaches had no significance as a discriminatory marker. The presence of photosensitivity may be regarded as a characteristic marker for patients with cutaneous LE, thus indicating a rather benign prognosis.

DISCUSSION

Recently, in two other studies the differences between cutaneous LE, either CDLE or SCLE, and SLE were analyzed by determining the frequency of several clinical and laboratory parameters in the two groups of patients (3, 8). Both studies showed that parameters including those we analyzed can serve as reliable markers for distingushing between cutaneous LE and SLE. However, these statistical analyses do not give any information about the interrelation between the analyzed parameters as a multivariate analysis can do. In all statistical models applied in our study signs of nephropathy, presence of arthralgias and high ANA titers ≥1:320 were the most significant variables for distinguishing between cutaneous LE and SLE. It seems likely that if one or more of these criteria are detectable in a patient with cutaneous LE, there is a considerable risk for transition into SLE. The individual risk for developing a severe course of the disease should increase with the number of positive variables, as calculated by multiplication of the odds ratios.

In contrast, the occurrence of circulating anti-dsDNA antibodies was not a marker for distinction between cutaneous LE and SLE in our study. The presence of circulating anti-dsDNA antibodies appears highly characteristic for idiopathic SLE and is rarely seen in other related conditions, e.g. drug-induced LE (10). Presence of these autoantibodies, however, has been reported in up to 20% of CDLE/SCLE patients, though at low levels (3, 11, 12), whereas 39–55% of all patients with SLE were shown to be anti-dsDNA-positive (13, 14). SLE patients with high levels of anti-dsDNA antibodies are obviously at risk of developing lupus nephritis (15), but they may not serve as an early marker for the possible transition of cutaneous LE into SLE. In our investigation a rather high percentage of patients with cutaneous LE (53%) were also shown to possess circulating anti-dsDNA antibodies at low levels, possibly due to the highly sensitive detection technique used in this investigation.

The prevalence of clinical and laboratory findings indicating kidney involvement is low in cutaneous LE (3, 16–18), but the prognostic value of parameters such as proteinuria, hematuria, decreased creatinine clearance, hypocomplementemia etc. has often been underestimated. However, kidney involvement has been reported in 8–19% of all SCLE patients (1, 8). Mild

signs of kidney involvement may therefore have prognostic value as a marker for the risk of developing SLE during the course of the disease. Frequent monitoring of these patients is recommended, and severe cases should be submitted for kidney biopsy.

Joint manifestations may often occur in patients with cutaneous LE. Ten to eighty per cent of all CDLE/SCLE patients complain of arthralgias/arthritis (6). As shown here, arthralgias in patients with CDLE/SCLE may obviously indicate a more severe disease course, with possible transition into SLE. Seventy-five to ninety per cent of SLE patients suffer from arthralgias/arthritis (13, 19), whereas severe, disabling arthritis is a rare complication in patients with cutaneous LE.

ANA are regarded as a nonspecific diagnostic tool in LE, in view of the fact that these autoantibodies are also prevalent in other rheumatic and nonrheumatic disorders; in addition, their occurrence in LE patients varies widely and also depends on the method used (20). ANA can be detected in 4–63% of CDLE patients (11, 21), in 60–80% of SCLE patients (1, 8) and in nearly all SLE patients (19). Based on the findings presented here, however, this serological parameter may well serve at high levels as a valuable marker, indicating patients at risk of transition into SLE.

Photosensitivity is frequently found in patients with cutaneous LE (40–60% of all cases; 1, 3) and plays a pathogenetic role in cutaneous LE, as could be demonstrated by in vitro studies (22). In particular, skin lesions can be induced in SCLE by photosensitivity testing in 2/3 of the cases (23, 24). This study suggests that photosensitivity is a marker for cutaneous LE and, therefore, may indicate cases with a more benign prognosis.

In conclusion, extended statistical evaluation of clinical and laboratory data in a large group of patients provided useful new information for physicians dealing with LE. It seems that careful monitoring of a few clinical and laboratory criteria will help to identify early patients with cutaneous LE who are at risk for developing SLE.

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