Journal of Arthritis
ISSN: 2167-7921

Vera-Recabarren et al., J Arthritis 2016, 5:1
DOI: 10.4172/2167-7921.1000185

Research Article Open access

Comparative Analysis of Acute Cutaneous Lupus Erythematosus with Subacute and Chronic Cutaneous Lupus Erythematosus: Clinical and Immunological Study of 308 Patients

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Rec date: December 21, 2015; **Acc date:** January 08, 2016; **Pub date:** January 18, 2016

Abstract

Background: Patients with acute cutaneous lupus erythematosus (ACLE) usually have systemic manifestations and there is a strong association between ACLE and systemic lupus erythematosus (SLE) involvement. However, there is scarce information on the differences in the systemic manifestations when compared with subacute cutaneous lupus erythematosus (SCLE) and chronic cutaneous lupus erythematosus (CCLE).

Objective: To analyse and compare the prevalence and characteristics of the main clinical and immunological manifestations of patients with ACLE, who were initially attending a Department of Dermatology, with respect to those with SCLE and CCLE.

Methods: A total of 38 patients with ACLE were studied. The clinical and serological characteristics of all the patients were collected in a chart review. These patients were compared to 112 patients with SCLE and 158 with CCLE that were previously reported.

Results: Patients with ACLE had a higher prevalence of mucous membrane ulcers (p=0.012), livedo reticularis (p=0.036), vasculitis (p=0.030), nephropathy (p=0.025) and serositis (p=0.036) compared with patients with SCLE. Patients with ACLE also had a higher frequency of livedo reticularis (P=0.001), mucous membrane ulcers (P<0.001), vasculitis (P<0.001), arthralgias (P<0.001), arthritis (P<0.001), nephropathy (P<0.001) and serositis (P=0.005) compared with patients with CCLE. Furthermore, we detected that patients with ACLE had a higher prevalence of decreased C4 and CH50 levels than SCLE, and a higher frequency of decreased C3, C4 and CH50 levels than CCLE.

Conclusions: In our series, differences in the expression of ACLE, CCLE and SCLE were found with respect to the distribution and type of lesions, the systemic features and the immunological findings.

Keywords: Acute cutaneous lupus erythematosus; Subacute cutaneous lupus erythematosus; Chronic cutaneous lupus erythematosus; Systemic lupus erythematosus

Introduction

Lupus erythematosus (LE) is a chronic autoimmune disease resulting from an interaction of genetic, environmental and hormonal factors and characterized by a spectrum of clinical forms with a variable evolution from a localized cutaneous form to a life-threatening systemic form [1]. Skin involvement occurs in 70-85% of all patients with LE and cutaneous manifestations of LE can be classified as specific or nonspecific. Specific skin lesions of cutaneous lupus erythematosus (CLE) are classified as acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE) and chronic cutaneous lupus erythematosus (CCLE) [2], according to the clinical characteristics of the lesions. ACLE lesions most commonly present as the classic butterfly dermatitis or malar rash localized on the central portion of the face. These lesions generally are characterized by confluent, symmetric erythema and edema centered over the malar eminence. There is a strong association between ACLE and systemic lupus erythematosus (SLE) involvement. The most common form of CCLE is discoid LE, which is characterized by erythema, telangiectasias, atrophy and resolution with scar formation. Discoid LE may be localized or generalized. Widespread DLE has been associated with a higher frequency of laboratorie abnormalities such as anemia, elevated erythrocyte sedimentation rate, high ANA titers and anti-dsDNA antibodies. In addition, widespread disease has been related to a higher prevalence of photosensitivity, panniculitis and systemic involvement [3].

SCLE is an entity described by Sontheimer et al. [4] in 1979, as a distinct subset of CLE, separated from patients with chronic scarring (LE) lesions and characterized by psoriasiform and/or annular lesions

in sun-exposed areas, absent or mild systemic involvement, presence of circulating anti-Ro/SSA antibodies [5], and frequently associated with the presence of human lymphocyte antigen (HLA)-DR3 [6]. SCLE has a predilection for young women with a peak incidence in the fourth decade of life [4]. It is well known that some patients suffering from CLE develop extracutaneous manifestations during the course of disease: up to 5% of patients with discoid LE and up to 30% of SCLE patients meet criteria for SLE [7,8].

LE-nonspecific lesions include findings that are not characteristic of, but are frequently seen in SLE. Such lesions include Raynaud's phenomenon, livedo reticularis, periungual telangiectasias and leukocytoclastic vasculitis.

The aim of the current study was to analyse and compare the prevalence and characteristics of the main clinical and immunological manifestations of patients with ACLE, who were initially attending a Department of Dermatology, with respect to those with SCLE and CCLE.

Methods

A total of 38 consecutive Caucasian patients with ACLE attending the Department of Dermatology of the Hospital Clínic of Barcelona were studied retrospectively. Written informed consent was obtained from the patients. The medical records of all patients were reviewed in detail according to a predefined protocol which included inpatient data, records of interval clinic visits, and records from referring institutions. The recorded clinical and serological characteristics of the patients included: (i) type of CLE, based on characteristic specific cutaneous LE lesions; (ii) age at disease onset, defined as the initial manifestation clearly attributable to CLE; (iii) age at diagnosis; (iv) age at protocol, defined as the age when the patient entered the chart review; and (v) immunological features [antinuclear antibodies (ANA), anti-DNA, anti-Ro, anti-La, anti-Sm and antiribonucleoprotein (RNP) antibodies]. All the clinical findings (e.g. Raynaud phenomenon, arthritis, arthralgias, serositis, nephropathy, xerophthalmia, xerostomia and SLE) were routinely recorded.

These patients with ACLE were compared with 112 patients with SCLE and 158 with CCLE, followed at the same Department, whose characteristics were published elsewhere [3]. The diagnosis of specific cutaneous LE lesions where based on the clinical characteristics of the lesions and confirmed by histological and immunofluorescence findings. The distinction between ACLE, SCLE and CCLE was made solely on the basis of the cutaneous clinical findings, according to Gillian and Sontheimer [2]. All the patients were evaluated and followed by one of the authors (CH), who determined the subtype of CLE, for the current study [3,9]. The diagnosis of SLE was based on fulfillment of ≥ 4 of the ACR criteria [10]. Although recent modifications to these criteria have been proposed [11]. The clinical manifestations were defined according to the American Rheumatology Association glossary committee [12].

Laboratory investigations

Standard laboratory definitions were used for this study [3,6,7,9,13,14]. ANA were detected by indirect immunofluorescence using Hep-2 as substrate [ANA (+): ≥ 1/80]. Antidouble-stranded (ds) DNA antibodies (normal: 0-25 U/ml-1) were detected by Farr's ammonium sulphate precipitation technique [14] and indirect immunofluorescence with *Crithidia luciliae* as substrate. Precipitating antibodies to extractable nuclear antigens (ENA), including Ro/SS-A, La/SS-B, U1-snRNP and Sm, were detected by counterimmunoelectrophoresis using calf and rabbit thymus and human spleen extracts. Rheumatoid factor was detected by latex test and Waaler-Rose technique [7]. Complement factors C3 (normal: 50-125 mg/dl-1) and C4 (normal: 19-40 mg/dl -1) were detected by radial immunodifussion assay and CH50 was determined by the haemolytic technique [7]. Biopsy specimens for the histological assessment of skin lesions were fixed in formalin, embedded in paraffin and stained with hematoxylin-eosin and Alcian periodic acid-Schiff stain. The histological criteria for LE proposed by Bangert et al. [15] were used for histological analysis. A direct immunofluorescence examination was performed in sun-exposed lesional and nonlesional skin.

Statistical analysis

Conventional X2 and Fisher's exact tests were used for analysing qualitative differences. The Student t and Mann-Whitney U tests were used to compare the median. A value of $p<0.05$ was taken to indicate statistical significance. Results of the analysis of continuous variables are presented as the mean ± standard deviation. The statistical analysis was performed using the SPSS/PC programs (SPSS inc, Chicago, USA).

Results

Patients characteristics

Of the 38 patients with ACLE, 30 (78.9%) were female and 8 (21.1%) were male (F: M ratio, 3.8:1). The mean age at the onset of symptoms attributable to ACLE was 28.4 ± 16.4 years (range, 0.6-73), and the mean age at the time of diagnosis was 29.1 ± 16.4 years (range, 2-73). The mean age at protocol entry was 29.5 ± 16.5 years (range, 2-73), and the time of evolution of the disease before protocol entry was 1.1 ± 1.7 years (range 0-6).

Significant differences existed between ACLE vs SCLE and CCLE with respect to the mean age at the onset and diagnosis of symptoms, at protocol entry and the evolution of the disease before protocol entry ($p<0.001$) (Tables 1 and 2).

Manifestation	ACLE (n= 38) (%)	SCLE (n=112) (%)3	P value
Age at disease onset	28.4 ± 16.4 years	42.0 ± 17.8 years	<0.001
Age at diagnosis	29.1 ± 16.4 years	43.6 ± 17.9 years	<0.001
Age at protocol	29.5 ± 16.5 years	44.0 ± 17.7 years	<0.001
Evolution	1.1 ± 1.7 years	2.0 ± 3.2 years	<0.001
Site			
Head	38 (100)	90 (80.4)	0.003
Trunk	17 (44.7)	86 (76.8)	<0.001
Arms	11 (28.9)	76 (67.9)	<0.001
Hands	11 (28.9)	37 (33.0)	NS
Lower limbs	6(15.8)	39 (34.8)	0.027
Clinical features			
Alopecia	9 (23.7)	13 (11.6)	NS
Oral ulcers	10 (26.3)	11 (9.8)	0.012

Livedo reticularis	4 (10.5)	2 (1.8)	0.036
Raynaud's phenomenon	2 (5.3)	9 (8.0)	NS
Vasculitis	9 (23.7)	11 (9.8)	0.03
Arthralgia	20 (52.6)	40 (35.7)	NS
Arthritis	13 (34.2)	22 (19.6)	NS
Nephropathy	9 (23.7)	10 (8.9)	0.025
Serositis	4 (10.5)	2 (1.8)	0.036
Xerostomia	3 (7.9)	6 (5.4)	NS
Xerophthalmia	5 (13.2)	11 (9.8)	NS
General laboratory			
Anemia	8/35 (22.9)	13/103 (12.6)	NS
Leukopenia	9/35 (25.7)	25/105 (23.8)	NS
Lymphopenia	15/35 (42.9)	43/105 (41.0)	NS
Trombocytopenia	4/36 (11.1)	6/105 (5.7)	NS
Elevated ESR	17/31 (54.8)	45/100 (45.0)	NS
Immunological findings			
ANA	28/35 (80.0)	53/101 (52.5)	0.004
dsDNA	13/33 (39.4)	16/93 (17.2)	0.01
Anti-Ro/SS-A	2/31 (6.5)	39/92 (42.4)	<0.001
Anti-La/SS-B	0/29 (0)	14/91 (15.4)	0.021
Anti-Sm	8/30 (26.7)	6/89 (6.7)	0.007
Anti-RNP	10/32 (31.3)	7/90 (7.8)	0.002
Low C3	9/28 (32.1)	16/94 (17.0)	NS
Low C4	13/28 (46.4)	19/94 (20.2)	0.006
Low CH50	13/28 (46.4)	20/94 (21.3)	0.009
Rheumatoid factor	6/29 (20.7)	15/84 (17.9)	NS

NS: not significant; ACLE: acute cutaneous lupus erythematosus; SCLE: subcutaneous lupus erythematosus; SLE: systemic lupus erythematosus

Table 1: Comparative clinical features and laboratory values in 38 patients with acute cutaneous lupus erythematosus and 112 with subacute cutaneous lupus erythematosus.

The most frequent non-cutaneous manifestations in patients with ACLE were arthralgias (52.6%) and arthritis (34.2%). Twenty seven (71.1%) patients with ACLE fulfilled criteria for SLE classification at the time of diagnosis. Patients with ACLE fulfilled criteria for SLE more frequently than patients with SCLE (71.1% vs 41.1%, p=0.001) as well as than those with CCLE (71.1% vs 6.3%, p<0.001).

Differences between patients with ACLE and SCLE

Patients with ACLE had a higher prevalence of lesions on the head (p=0.003), oral ulcers (p=0.012), livedo reticularis (p=0.036), vasculitis (P=0.030), nephropathy (p=0.025) and serositis (p=0.036 and a lower frequency of lesions on the trunk (p<0.001), arms (p<0.001) and lower limbs (p=0.027) compared with patients with SCLE. Patients with ACLE also had a higher prevalence of ANA (p=0.004), anti-dsDNA (p=0.010), anti-RNP (p=0.002) and anti-Sm antibodies (p=0.007), and decreased C4 (p=0.006) and CH50 (p=0.009) levels, and a lower frequency of anti-Ro (p<0.001) and anti-La (p=0.021) antibodies compared with patients with SCLE (Table 1).

Differences between patients with ACLE and CCLE

Patients with ACLE had a higher prevalence of lesions on the head (p=0.027) and hands (p=0.019), livedo reticularis (p=0.001), oral ulcers (p<0.001), vasculitis (p<0.001), arthralgias (p<0.001), arthritis (p<0.001), nephropathy (p<0.001), serositis (p=0.005) and xerophthalmia (p=0.040) compared with patients with CCLE. Patients with ACLE also had a higher frequency of anemia (p=0.002), leukopenia (p=0.017), lymphopenia (p=0.035), thrombocytopenia (p=0.007), elevated ESR (p<0.001), ANA (p<0.001), anti-dsDNA (p<0.001), anti-RNP (p<0.001) and anti-Sm (p<0.001) antibodies, and rheumatoid factor (p=0.020), and decreased C3 (p=0.001), C4 (p<0.001) and CH50 (p<0.001) levels compared with patients with CCLE (Table 2).

Discussion

In our series, differences in the expression of ACLE, CCLE and SCLE existed with respect to the distribution and the type of lesions, the systemic features and the immunological findings. ACLE, SCLE and CCLE differed in their course and prognosis. ACLE has a predilection for young subjects and typically presents in the third decade of life. It is frequently associated with active SLE [16,17]. On the other hand, patients with SCLE and CCLE have an age of onset of the disease on the fourth and fifth

Decade [3,4,18-20]. Nevertheless, there is a non-statistical difference between SCLE and CCLE according to the age at disease onset, age at diagnosis, age at protocol and evolution. The difference between SCLE and CCLE is clinical. SCLE is a non-scarring entity separated from patients with chronic scarring lesions and characterized by psoriasiform and/or annular lesions in sun-exposed areas, absent or mild systemic involvement.

Aviles-Izquierdo et al. [21] demonstrated that patients with ACLE were younger than patients with SCLE and CCLE. In our series, we found similar results. Biazar et al. [20] found that in patients with SCLE, the mean age at onset of the disease was significantly higher than in patients with ACLE. In our series, significant differences existed between ACLE vs SCLE and CCLE with respect to the mean age at the onset and diagnosis of symptoms (p<0.001).

Manifestation	ACLE (n= 38) (%)	CCLE (n=158) (%)3	P value
Age at disease onset	28.4 ± 16.4 years	41.3 ± 14.7 years	<0.001
Age at diagnosis	29.1 ± 16.4 years	43.6 ± 15.0 years	<0.001
Age at protocol	29.5 ± 16.5 years	44.1 ± 14.9 years	<0.001
Evolution	1.1 ± 1.7 years	2.8 ± 4.3 years	<0.001
Site			
Head	38 (100)	140 (88.6)	0.027

Trunk	17 (44.7)	52 (32.9)	NS
Arms	11 (28.9)	26 (16.5)	NS
Hands	11 (28.9)	21 (13.3)	0.019
Lower limbs	6(15.8)	9 (5.7)	NS
Clinical features			
Alopecia	9 (23.7)	40 (24.8)	NS
Oral ulcers	10 (26.3)	3 (1.9)	<0.001
Livedo reticularis	4 (10.5)	0 (0)	0.001
Raynaud's phenomenon	2 (5.3)	3 (1.9)	<0.001
Vasculitis	9 (23.7)	3 (1.9)	<0.001
Arthralgia	20 (52.6)	12 (7.6)	<0.001
Arthritis	13 (34.2)	7 (4.4)	<0.001
Nephropathy	9 (23.7)	2 (1.3)	<0.001
Serositis	4 (10.5)	1 (0.6)	0.005
Xerostomia	3 (7.9)	2 (1.3)	NS
Xerophthalmia	5 (13.2)	6 (3.8)	0.04
General laboratory			
Anemia	8/35 (22.9)	6/137 (4.4)	0.002
Leukopenia	9/35 (25.7)	12/140 (8.6)	0.017
Lymphopenia	15/35 (42.9)	34/140 (24.3)	0.035
Trombocytopenia	4/36 (11.1)	2/140 (1.4)	0.007
Elevated ESR	17/31 (54.8)	24/130 (18.5)	<0.001
Immunological findings			
ANA	28/35 (80.0)	24/138 (17.4)	<0.001
dsDNA	13/33 (39.4)	5/130 (3.8)	<0.001
Anti-Ro/SS-A	2/31 (6.5)	5/136 (3.7)	NS
Anti-La/SS-B	0/29 (0)	0/136 (0)	NS
Anti-Sm	8/30 (26.7)	1/128 (0.8)	<0.001
Anti-RNP	10/32 (31.3)	2/127 (1.6)	<0.001
Low C3	9/28 (32.1)	9/133 (6.8)	0.001
Low C4	13/28 (46.4)	8/133 (6.0)	<0.001
Low CH50	13/28 (46.4)	17/132 (12.9)	<0.001
Rheumatoid factor	6/29 (20.7)	6/109 (5.5)	0.02

NS: not significant; ACLE: subacute cutaneous lupus erythematosus; CCLE: chronic cutaneous lupus erythematosus; SLE: Systemic lupus erythematosus

Table 2: Comparative clinical features and laboratory values in 38 patients with acute cutaneous lupus erythematosus and 158 with chronic cutaneous lupus erythematosus.

The overall female:male ratio in patients with CLE varies between 1:1 and 6:1 [20,22]. In a recently published study, the female to male ratio have been shown to be 3:1 for both DLE and SCLE, mean age for being diagnosed with CLE was around 54 years in that study [18]. A recent study in 2228 patients with SLE, the mean age at diagnosis was 34,3 years [23]. In our series, female patients with ACLE are more frequent than males (F:M=3.8:1) than other type of CLE [3] (F:M=2.2:1 in SCLE and F:M=1.6:1 in CCLE), thus confirming the predominance of SLE in females [9].

Patients with SCLE are characterized by a higher prevalence of cutaneous lesions on the body and extremities with respect to patients with ACLE. On the other hand, patients with ACLE have a higher frequency of lesions on the face. They also had a higher prevalence of oral ulcers, livedo reticularis, vasculitis, serositis and nephropathy than patients with SCLE.

Different authors [24,25] suggested that the nature of LE is nonstatic, as evidenced by the progression of a patient's disease through the spectrum of LE. Patients do not drift into a relatively fixed position within the LE spectrum. The group of patients who "progress" from cutaneous disease to SLE tended to have symptoms and/or persistent laboratory abnormalities, including arthritis, persistently active widespread cutaneous disease, a persistently elevated ESR, a persistently positive ANA, and/or the presence of anemia [24]. Other authors [3,15,24,26] found that laboratory abnormalities were substantially more common in patients with widespread skin disease than in patients with localized skin disease. Elevated ESR were frequently present in SCLE patients [3,26]. Studies have shown that 75% of patients with newly diagnosed CLE do not already have an SLE diagnosis [27]. A subset of these patients goes on to develop SLE at a later time, and there have been mixed reports on the percentage that experience a transition from CLE to SLE [28]. Wieczorek et al. [28] prospectively follow 77 patients with CLE and determine that 17% eventually met criteria for SLE diagnosis. These 13 patients mostly fulfilled mucocutaneous criteria and a minority of these (38%) displayed new moderate to severe systemic disease. These findings underscore that CLE progress for SLE in a significant minority of patients and suggest that most patients with CLE who progress to SLE do not experience the severity of manifestations of lupus. These authors state that most of these patients have mild systemic disease, with all patients developing SLE more than 6 months after their CLE diagnosis [28].

A Swedish study demonstrated that the probability of being diagnosed with SLE during the first 3 years after SCLE diagnosis was 24.7% and for DLE the probability was 16.7% [18]. This study showed a 3-year cumulative risk of receiving an additional diagnosis of SLE of 18.1%.

In one study [29] of 191 patients with CLE, it was reported that 5% of patients with localized DLE, 20% with generalized DLE, 50% with SCLE and 72% with ACLE met criteria for SLE. Patients with generalized DLE are more likely to progress to systemic disease, compared to patients with localized DLE [3]. Biazar et al. [20] reported that 408 of the 1002 (40.7%) patients with CLE fulfilled four or more ACR criteria for SLE. Recent review reports that the risk of SLE is highest in ACLE, followed by SCLE and lowest in CCLE [30]. In our series, patients with ACLE fulfilled criteria for SLE more frequently than patients with SCLE (71.1% *vs* 41.1%, p=0.001) as well as than those with CCLE (71.1% *vs* 6.3%, p<0.001).

In some SLE reports [31-34], arthritis was observed in 62.5% to 84%. The most frequent initial manifestations were arthritis, malar rash, fever and photosensitivity. During the evolution of the disease, arthritis appeared in the vast majority of patients (84%). In our series, patients with ACLE had a higher prevalence of arthritis (34.2% *vs* 4.4%, p<0.001) and arthralgias (52.6% *vs* 7.6%, p<0.001) compared with patients with CCLE. So, in general, the presence of articular involvement in patients with CLE could be used to differentiate ACLE from CCLE. Nevertheless, the final distinction has to be made solely on th basis of the cutaneous clinical findings.

The identification of nonspecific, but disease-related skin lesions is important because their presence implies systemic disease [3,12,26,35] and they are often useful indicators of systemic disease activity. A recent study in 260 patients with SLE showed that LE-non-specific cutaneous manifestations were present in 43% of the patients. Of the LE-non-specific skin manifestations Raynaud's phenomenon was the most common (25%), followed by non-scarring alopecia (9%) and vasculitis (8%) [27]. Biazar et al. [20] reported that patients with ACLE exhibited LE-nonspecific skin lesions significantly more often than patients with SCLE, but the incidence of LE-nonspecific skin lesions in patients with ACLE was not significantly different from that in patients with CCLE.

Livedo reticularis presents more commonly in both juvenile and adult patients who are diagnosed with anti-phospholipid syndrome [35]. It is characterized by erythematous or cyanotic discoloration of the skin with reticulated (net-like) pattern, usually on the lower extremities. The etiology and correlation with systemic disease are unknown, but vascular obstruction and blood viscocity may be the cause [36]. Biazar et al. [20] reported that livedo reticularis was significantly more frequent in patients with ACLE than in patients with CCLE, but they did not find significant differences in patients with SCLE. In our series, we found a higher prevalence of livedo reticularis in patients with ACLE (10.5%) compared with patients with SCLE (1.8%, p=0.036) and CCLE (0%, p=0.001).

Biazar et al. [20] reported that Raynaud's phenomenon was present significantly more often in patients with ACLE than in patients with CCLE. Nevertheless, they did not find significant differences in patients with SCLE. In our series, we found similar results.

It has been reported that aproximately 10-20% of patients with LE present with some form of vasculitis [37]. Cutaneous vasculitis usually affects small blood vessels (leukocytoclastic vasculitis. These lesions are characterized as petechiae or palpable purpura, and may occasionally blister. The lesions are induced by the formation of immune complexes and neutrophilic infiltration, and the presence of vasculitis strongly relates to systemic disease activity [38]. In our series, we found a higher prevalence of vasculitis in patients with ACLE (23.7%) compared with SCLE (9.8%, p=0.030) and CCLE (1.9%, p<0.001).

Most studies have focused on SLE, and epidemiological analyses of the different subtypes of CLE have rarely been performed. Avilés et al. [21] found that patients with ACLE had a higher prevalence of ANA, anti-DNA, anti-Sm and anti-RNP antibodies with respect to the other CLE subsets. In our series, we found similar results. Furthermore, we detected that patients with ACLE had a higher frequency of decreased C4 and CH50 levels than SCLE, and a higher prevalence of decreased C3, C4 and CH50 levels than CCLE. Thus, it is possible to use the type of CLE to predict the likelihood of having underlying systemic disease. Those patients with either ACLE or LE-nonspecific skin lesions more frequently have systemic disease [3,9,37].

It is important to confirm a CLE diagnosis histopathologically by a punch biopsy since the disease is chronic and sometimes need systemic treatment and careful advice concerning triggering factors [39]. Diagnosis of CLE requires proper classification of the subtype, which is best accomplished by a focus on the clinical and histological findings. Nevertheless, direct immunofluorescence of lesional biopsies can supplement non-definitive histological findings. Biazar et al. [20] reported that the diagnosis of their patients with CLE was confirmed by histological analysis of skin biopsy specimens in 148 (47%) with ACLE, in 306 patients (90.8%) with SCLE and in 476 (72.2%) with CCLE. In our series, all our patients with CLE were confirmed by histopathology. However, we have to consider that our study had some limitations. Firstly, it was a retrospective study. Also, we should address the possibility that some of our patients with CLE referred to our hospital-based dermatology group might have been more severely affected or more resistant to treatment than those managed in office-based practices in the Barcelona area.

To summarize, differences in the expression of ACLE, SCLE and CCLE existed with respect to the distribution and the type of lesions, the systemic features and immunological findings. ACLE, SCLE and CCLE differed in their course and prognosis. Our data suggest that patients with ACLE are characterized by a higher prevalence of articular involvement, oral ulcers, livedo reticularis, vasculitis, serositis and nephropathy. In addition, patients with ACLE have a higher frequency of ANA, DNA, anti-Sm and anti-RNP antibodies, and decreased C4 and CH50 levels. In other words, livedo reticularis, vasculitis and a decreased C4 and CH50 levels are more prevalent in patients with ACLE compared with patients with SCLE and CCLE. This group of patients should be carefully monitored because even if they do not fulfil 4 or more classification criteria for SLE at the beginning of their illness, they may be at risk of developing SLE in some moment of the disease. Health care clinicians need to remain vigilant for concerning systemic symptoms and signs by conducting a complete review of systems at each clinic visit and ordering periodic laboratory test such as complete blood cells counts with differentials and urinalysis at least once annually [40]. A positive review of systems would prompt additional serologic tests. Also we have to aware about specific risk factors for progression such as positive antinuclear antibodies, widespread discoid lesions, female sex, and increased numbers of SLE criteria. This form of personalized medicine can revolutionize treatment of patients with CLE because those at high risk for progression to SLE could be promptly started on anti-malarial therapy, which can delay the onset of SLE [40].

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