Lupus Eritematoso Cutaneo: Manifestazioni Cliniche e Nuove Linee Terapeutiche

Marzia Caproni

SOS Immunopatologia Cutanea e Malattie Rare Dermatologiche
U.O. Dermatologia I - USL Toscana Centro
Università di Firenze
Outline

• Cutaneous Lupus Erythematosus: Definition and Epidemiological nods
• Classification: clinical varieties and differential diagnosis
• Management of LEC patients
Cutaneous Lupus Erythematosus (CLE) is the polar form of a real heterogeneous spectrum of diseases defined as Lupus.
Lupus Erythematosus: the dermatologist’s perspective

Marzia Caproni

Skin Immunopathology and Rare Dermatological Diseases Unit, 1st Dermatological Clinic
ASF-PO Piero Palagi, University of Florence
Florence, Italy

Address for correspondence:
Dr.ssa Marzia Caproni
Skin Immunopathology and Rare Dermatological Diseases Unit, 1st Dermatological Clinic
ASF-PO Piero Palagi
University of Florence
Viale Michelangelo, 41
50125 Florence, Italy
E-mail: marzia.caproni@unifi.it

form of a heterogeneous spectrum of diseases defined as “lupus”.
The prevalence of Systemic Lupus Erythematosus (SLE) is estimated to be approx. 17-48/100,000 in the USA, being threefold higher for cutaneous forms as compared to other clinical manifestations; in the province of Florence (during the observation period of 2010) considering a population of approx. 970,000 inhabitants – the sample studied included primary care patients – SLE incidence was 5.4/100,000 and the prevalence was 75/100,000 (1). Cutaneous manifestations are often the first signs and symptoms of SLE and lead to the consultation of a dermatologist or inspire an internist or rheumatologist to consult a dermatologist for appropriate differential diagnosis with other types of dermatoses. Cutaneous manifestations are present in over 75% of patients with SLE and are the second most frequent
Epidemiological Nods

• 20-150 /100,000 with the highest prevalence reported in Brazil  (Tsokos GC N Enlg J Med 2011)

• The cutaneous variants have been reported to be 2–3 fold more prevalent than SLE

• Lupus Clinic of Florence: In the province of Florence (during the observation period of 2010) considering a population of approx 970.000 inhabitants - the sample studied included primary care patients - SLE incidence was 5.4/100.000 and the prevalence was 75/100.000 (Emmi L et al.)
Cutaneous Lupus Erythematosus

- Cutaneous manifestations are often the first signs and symptoms of lupus erythematosus (LE) and lead to the consultation of a dermatologist or inspire an internist or rheumatologist to consult a dermatologist for differential diagnosis.

- Cutaneous lupus erythematosus (CLE) is present in over 75% of patients at some point during the course of systemic lupus erythematosus (SLE) and it is the second most frequent presenting symptom.

- Overall, 35 studies, representing 11,189 early-onset and 1727 late-onset patients with SLE. Cutaneous manifestations are less common in late-onset SLE patients, except sicca symptoms.

Cumulative prevalence of clinical manifestations of SLE (704 pz)

- neuropatia periferica
- aborti ricorrenti
- miosite
- trombosi venosa
- coinvolgimento polmonare
- trombocitopenia
- sindrome sicca
- coinvolgimento SNC
- aftes
- vasculite cutanea
- coinvolgimento renale
- alopecia
- sierositi
- febbre
- fenomeno di Raynaud
- anemia
- leucopenia
- rash cutaneo
- artrite/artralgie

Cutaneous Lupus Erythematosus

• Correct diagnosis of CLE requires a high level of suspicion and broad understanding of lupus diagnosis
  G Obermoser, RD Sontheimer and B Zelger. Lupus 2010

• DD Difficulties lie not only in differentiating CLE from a wide range of mostly non-autoimmune skin disorders (a typical example would be DLE and rosacea or seborrheic dermatitis)

• Importantly in assessing if CLE is associated with internal organ involvement (which may develop weeks to months later in some patients, necessitating careful patient follow-up)
Cutaneous Lupus Erythematosus

- CLE precedes the clinical onset of systemic symptoms for weeks to months in about 25% of patients
Cutaneous Lupus Erythematosus

• Even if serious skin forms are quite rare cutaneous involvement generally contributes to the burden of disease in terms of personal well-being and psychosocial, occupational disability and then in medical and social costs
Classification of Skin Manifestations

- LE-specific manifestations
- LE-non specific manifestations

LE-specific manifestations

- **Chronic Cutaneous LE (CCLE)**
  - Discoid LE discoide (localized and generalized)
  - Hypertrophic LE
  - Panniculitis LE
  - Chilblain lupus

- **Subacute Cutaneous LE (SCLE)**
  - Annular LE
  - Papular-squamous LE
  - Mixed/rare Formes

- **Acute LE (ACLE)**
  - Localized (butterfly rash)
  - Generalized (maculo-papular rash)
  - TEN-like acute cutaneous LE

- **Intermittent LE = Tumidus LE**
Chronic Cutaneous LE (CCLE)
LUPUS ERITEMATOSOS DISCOIDE
LUPUS ERITEMATOSO DISCOIDE DISSEMINATO Discoid
Lupus Erythematosus Discoid Disseminated
HYPERTROPHIC or VERRUCOUS LE
Lupus Profundus
Fig. 3. A) Percentages of patients fulfilling the ACR criteria. The 11 ACR criteria are listed with respect to the percentages of patients who fulfilled each criterion in the subgroup of patients who fulfilled four or more or fewer than four ACR criteria, respectively. B) Percentages of CLE patients fulfilling the ACR criteria. The total number of patients diagnosed by their physician as CLE fulfilling ≥4 ACR criteria is 212, the total number of patients diagnosed by their physician as CLE fulfilling <4 ACR criteria is 570. C) Significant differences in the ACR criteria between the CLE subtypes. Each bar represents the percentage of patients within each of the four CLE subtypes who fulfilled particular ACR criteria. 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; ***p<0.001.
LE-Specific Manifestations

• LE cutaneo cronico
  – LE discoide (localizzato e disseminato)
  – LE ipertrofico
  – Lupus panniculitis
  – Chilblain lupus
• Subacute Cutaneous LE (SCLE)
  – Annular LE
  – Papular-squamous LE
  – Mixed/rare Formes
• Acute LE (ACLE)
  – Localized (butterfly rash)
  – Generalized (maculo-papular rash)
• LE intermittente = LE tumido
Subacutane Cutaneous LE

• Definition: Subacute cutaneous lupus erythematosus (SCLE) is a distinct subset of cutaneous lupus erythematosus clinically characterized by psoriasiform and/or annular lesions and by a mild or absent systemic involvement.

• ~ 20% of all the forms of CLE
• F/M= 3:1
• Mean age at onset: 52 years
• Photosensitivity: 73.7%

Biazar C, Autoimmun Rev 2013

Development of SLE: 25% after 3 years from the diagnosis

Grönhagen CM, Fored CM, Granath F, Nyberg F. Br J Dermatol 2011
Clinical, Histological and Immunopathological Features of 58 Patients with Subacute Cutaneous Lupus erythematosus

A Review by the Italian Group of Immunodermatology

Aurora Parodi a Marzia Caproni b Carla Cardinali b Elisabetta Bernacchi b Alessandra Fuligni b Giuseppe De Panfilis g Cristina Zane e Manuela Papini d Farnase Cleto Veller e Mario Vaccaro f Paolo Fabbri b

Table 1. Cutaneous changes in SCLE patients

<table>
<thead>
<tr>
<th>SCLE</th>
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<tbody>
<tr>
<td>Annular type</td>
<td>42%</td>
</tr>
<tr>
<td>Psoriasiform type</td>
<td>39%</td>
</tr>
<tr>
<td>Annular and psoriasiform type</td>
<td>16%</td>
</tr>
<tr>
<td>Pityriasisiform type</td>
<td>1 patient</td>
</tr>
<tr>
<td>Exfoliative erythroderma type</td>
<td>1 patient</td>
</tr>
<tr>
<td>Malar eruption</td>
<td>12%</td>
</tr>
<tr>
<td>Discoid lupus erythematosus lesions</td>
<td>12%</td>
</tr>
<tr>
<td>Non-scarring alopecia</td>
<td>5%</td>
</tr>
<tr>
<td>Livedo reticularis</td>
<td>7%</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>12%</td>
</tr>
<tr>
<td>Periungual telangiectasia</td>
<td>3%</td>
</tr>
</tbody>
</table>

Table 2. Distribution of SCLE lesions

<p>| | |</p>
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Neck</td>
<td>83%</td>
</tr>
<tr>
<td>Face</td>
<td>66%</td>
</tr>
<tr>
<td>Arms (extensor surfaces)</td>
<td>39%</td>
</tr>
<tr>
<td>Hands (dorsum)</td>
<td>21%</td>
</tr>
<tr>
<td>Lower limbs</td>
<td>16%</td>
</tr>
<tr>
<td>Scalp</td>
<td>12%</td>
</tr>
</tbody>
</table>

SLE in 30% of the patients 3.4% mammary carcinoma
Classical forms of SCLE

- Annular-polycyclic
- Psoriasiform
- Mixed forms
Annular polycyclic variant
Annular polycyclic variant
Subacute cutaneous lupus erythematosus in childhood.
Several erythematous and papulo-squamous elements joining into wider lesions mimic psoriasis vulgaris. Papulo-squamous or Psoariasiform SCLE.
The lesions tend to produce retiform arrays. Papulo-squamous variant or Psoariasiform SCLE
Papulo-sqamous or Psoriasiform SCLE
Hypopigmentation that follows active lesions; it can be considered «a clue» but have to be distinguished from pityriasis versicolor.
Rare SCLE variants

- Erythema multiforme-like (Lyon 1998)
- TEN-like (Caproni 2010)
- Pytiriasiform (Caproni 2001)
- Exfoliative erythroderma-like (Mutasim 2003)
- Exanthematous (Sontheimer, 1985)
- Poikiloderma-like (Pramatarov et al, 2000)
A 69-year-old white man diagnosed as having squamous cell carcinoma of the lung (stage T4N2M0) treated with cisplatinum plus gemcitabine. Thirteen months after surgery (5 weeks after the last adjuvant cycle) developed diffuse eruption with confluent, erythematous-violaceous lesions on the trunk and arms.
These lesions were associated with erosions partially covered by detached epidermal sheets. Mucous membranes were not involved; histologic and immunofluorescence results were compatible with SCLE.
Sontheimer classification on vesicobullous lesions occurring in the setting of LE

Five types of blistering presentations are included:
1. TEN-like acute cutaneous LE: sheet-like cleavage of skin changes rapidly evolving from pre-existing photodistributed confluent acute LE lesions.
2. TEN-like subacute cutaneous LE: sheet-like cleavage of skin changes evolving from otherwise typical photodistributed non-scarring annular or papulosquamous lesions in association with anti-Ro/SS-A: La/SS-B.
3. TEN occurring in SLE patients not having conventional LE-specific skin lesions.
4. Vesiculobullous changes occurring at the active border of advancing of annular SCLE.
5. Vesiculobullous chronic cutaneous LE.
He had a history of lupus without any cutaneous lesions and started with Ten extensive lesions; in this case to make a diagnosis it is essential for the survival of the patient
Rare SCLE variants

- Erythema multiforme-like (Lyon 1998)
- TEN-like (Caproni 2010)
- Pytiriasiform (Caproni 2001)
- Exfoliative erythroderma-like (Mutasim 2003)
- Exanthematous (Sontheimer, 1985)
- Poikiloderma-like (Pramatarov et al, 2000)
• Subacute cutaneous lupus erythematosus with pityriasis-like cutaneous manifestations


On the upper third of the back, she presented a wide patch with irregular borders, due to many coalescing small purplish-red lesions. Each lesion was covered with branny scales and, on palpation, revealed a variable degree of infiltration. Few areas of uninvolved skin could be seen inside the main patch. Beyond this main patch, small individual scattered lesions with a net-like distribution were detected.
Differential Diagnosis

- Psoriasis
- Seborrheic dermatitis
- Pytiriasis rosea
- Tinea corporis
- Annular erythema centrifugum
- Disseminated annular granuloma
Papulo-squamous variant or Psoariasiform SCLE
Psoriasis
Seborrheic Dermatitis
Annular erythema centrifugum
Subacute cutaneous lupus erythematosus and its association with drugs: a population-based matched case–control study of 234 patients in Sweden

C.M. Grönhagen, C.M. Fored, M. Linder, F. Granath and F. Nyberg

1 Division of Dermatology, Department of Clinical Sciences, Karolinska Institutet, Danderyd Hospital, SE-182 88 Danderyd, Sweden
2 Clinical Epidemiology Unit and Centre for Pharmacoepidemiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden
3 Uppsala University Hospital, Uppsala, Sweden

- Terbinafine
- TNF-α inhibitors
- Carbamazepine
- Proton-pomp inhibitors
SCLE and Cancer Risk

Increased risk of cancer among 3663 patients with cutaneous lupus erythematosus: a Swedish nationwide cohort study
C.M. Grönhagen,* C.M. Fored,† F. Granath† and F. Nyberg*†

- Elevated overall cancer risk for patients with CLE
- Buccal cancer, lymphomas, respiratory cancers, NMSC
- SCLE > DLE greater during the first year after CLE diagnosis
- Risk is independent from SLE diagnosis
LE-Specific Manifestations

• LE cutaneo cronico
  – LE discoide (localizzato e disseminato)
  – LE ipertrofico
  – Lupus panniculitis
  – Chilblain lupus

• LE cutaneo subacuto
  – Anulare
  – Papulo-squamoso
  – Forme miste/rare

• Acute LE (ACLE)
  – Localized (butterfly rash)
  – Generalized (maculo-papular rash)

• LE intermittente = LE tumido
Seborrheic Dermatitis
Papular-macular rash

5-10% of SLE patients

Multiple erythematous, infiltrated and purpuric lesions

Face, extensor aspects of the limbs, hands, upper trunk

Oral involvement with erosions/ulcerations

Quick resolution after DDS
Differential diagnosis: **Acute cutaneous lupus erythematosus (ACLE)**

- Localized form: rosacea, seborrheic eczema, perioral dermatitis, tinea faciei, erysipelas
- Generalized form: dermatomyositis, viral and drug-induced rash, erythema multiforme, TEN
Intermittent LE

- “Intermittent" trend
- Absence of atrophic, scarring or discolored outcome
- High light sensitivity (> CCLE)

- LES Incidence very low
- Histological examination not "specific"
- Absence of interface dermatitis
- Absence of hyperkeratosis
- Deposition of very abundant mucin
- DD Jessner-Kanof, pseudolinfomi, etc.
# LUPUS ERYTHEMATOSUS

## ACR Criteria for Diagnosis of SLE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malar rash</td>
<td>A “butterfly rash” of flat or raised fixed erythema tending to spare the nasolabial folds</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>Erythematous raised patches with adherent keratotic scaling and follicular plugging associated with scarring</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>A reaction to sunlight causing rash that may last for several weeks after brief sun exposure</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>Often painless oral or nasopharyngeal ulceration</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Nonerosive arthritis tenderness, swelling, or effusion involving 2 or more peripheral joints</td>
</tr>
<tr>
<td>Serositis</td>
<td>Pleuritis (chest pain on inspiration) or pericarditis; note that premature coronary artery disease is associated with inflammatory conditions like SLE</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>Persistent proteinuria</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>Seizures or psychosis in the absence of offending drugs or known metabolic derangements</td>
</tr>
<tr>
<td>Hematologic disorder</td>
<td>Leucopenia (often an early sign), hemolytic anemia, lymphopenia, thrombocytopenia in the absence of offending drugs</td>
</tr>
<tr>
<td>Immunologic disorder</td>
<td>Positive LE cell preparation, anti-DNA, anti-Sm, or false positive serologic test for syphilis</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>An abnormal titer of antinuclear antibody at any point in time and in the absence of drugs known to be associated with “drug-induced lupus” syndrome</td>
</tr>
</tbody>
</table>

ACR = American College of Rheumatology; LE = lupus erythematosus; SLE = systemic lupus erythematosus. Adapted from references 3, 4, and 7.
Mucosal Membrane Involvement

- Mucous membranes involvement in 24% of DLE patients

- 90.47% patients had oral lesions along with skin lesions with the most common site of oral involvement being labial mucosa (76.19%), vermillion border (71.42%) and buccal mucosa (42.85%). White spots, LP-like were present in 28.6%, ulcers in 19% and central erythema in 52.4% lesions.

CLINICAL ASPECTS OF LUPUS ERYTHEMATOSUS IN THE ORAL MUCOSA/LIPS

Discoid lesions in (A) (B) superior and inferior lips (CLE 3-20%)

(C) Erythematous lesion with central a fissure surrounded by a delicate keratotic border on buccal mucosa.  (D) Erythemato-keratotic lesion on buccal mucosa.

(E) SLE (9-54 %) Erythematous-purpuric lesion on hard palate present in SLE. (F) Bullous lesions and erosions on palate and alveolar border.
It has been suggested that oral lesions may represent the mucosal counterpart to the cutaneous lesions and should be similarly classified.

LE-nonspecific manifestations

❖ CUTANEOUS VASCULAR DISEASE
  • Urticaria vasculitis
  • Palpable purpura
  • Periungual teleangiectasia
  • Cutaneous micro-infarctions
  • Periarteritis nodosa-like
  • Ulcerations
  • Livedo reticularis
  • Peripheral gangrena
  • Raynaud’s phenomenon

❖ ALOPECIA
  • Non scarring (lupus hair, telogen efluvinum, alopecia areata)

❖ PIGMENTARY CHANGES

❖ SCLERODACTILY

❖ CALCINOSIS CUTIS
B. Histopathologically non-specific (LE-non-specific) skin lesions

1. Cutaneous vascular disease
   Vasculitis
   (a) Leukocytoclastic 1. Palpable purpura 2. Urticarial vasculitis
   (b) Panarteritis nodosa-like
   Vasculopathy
   (a) Degos disease-like
   (b) Atrophy blanche-like
   (c) Periungual telangiectasia
   (d) Livedo reticularis
   (e) Thrombophlebitis
   (f) Raynaud’s phenomenon
   (g) Erythromelalgia (erythmalgia)

2. Alopecia (non-scarring)
   ‘Lupus hair’
   Telogen effluvium
   Alopecia areata

3. Sclerodactyly

4. Rheumatoid nodules

5. Calcinosis cutis

6. LE-non-specific bullous lesions
   Epidermolysis bullosa acquisita-like bullous LE
   Dermatitis herpetiformis-like bullous LE
   Pemphigus erythematosus Senear–Usher
   Bullous pemphigoid
   Porphyria cutanea tarda

7. Urticaria

8. Papulo-nodular mucinosis

9. Anetoderma/cutis laxa/mid-dermal elastolysis

10. Acanthosis nigricans (type B insulin resistance)

11. Erythema multiforme (Rowell’s syndrome)

12. Leg ulcers

13. Lichen planus
Large vessel vasculitis (LVV)
  Takayasu arteritis (TAK)
  Giant cell arteritis (GCA)

Medium vessel vasculitis (MVV)
  Polyarteritis nodosa (PAN)
  Kawasaki disease (KD)

Small vessel vasculitis (SVV)
  Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis
    (AAV)
    Microscopic polyangiitis (MPA)
    Granulomatosis with polyangiitis (Wegener’s) (GPA)
    Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
      (EGPA)
  Immune complex SVV
    Anti–glomerular basement membrane (anti-GBM) disease
    Cryoglobulinemic vasculitis (CV)
    IgA vasculitis (Henoch-Schönlein) (IgAV)
    Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q
    vasculitis)

Variable vessel vasculitis (VVV)
  Behçet’s disease (BD)
  Cogan’s syndrome (CS)

Single-organ vasculitis (SOV)
  Cutaneous leukocytoclastic angiitis
  Cutaneous arteritis
  Primary central nervous system vasculitis
  Isolated aortitis
  Others

Vasculitis associated with systemic disease
  Lupus vasculitis
  Rheumatoid vasculitis
  Sarcoid vasculitis
  Others

Vasculitis associated with probable etiology
  Hepatitis C virus–associated cryoglobulinemic vasculitis
  Hepatitis B virus–associated vasculitis
  Syphilis-associated aortitis
  Drug-associated immune complex vasculitis
  Drug-associated ANCA-associated vasculitis
  Cancer-associated vasculitis
  Others
VASCULITIS: PALPABLE PURPURA and URTICARIAL VASCULITIS
ULCERATIONS
Our Experience

“AUTOANTIBODY PROFILE AND SPECIFIC CLINICAL PATTERNS IN 619 ITALIAN PATIENTS WITH CUTANEOUS LUPUS ERYTHEMATOSUS”
ITALIAN EXPERIENCE
GIIP 2009-2014

Tot. 619 pt

SUBTYPE

<table>
<thead>
<tr>
<th>SUBTYPE</th>
<th>Percentage</th>
<th>n</th>
</tr>
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<tbody>
<tr>
<td>CLE</td>
<td>49%</td>
<td>303</td>
</tr>
<tr>
<td>SCLE</td>
<td>19%</td>
<td>115</td>
</tr>
<tr>
<td>ICLE</td>
<td>17%</td>
<td>108</td>
</tr>
<tr>
<td>ACLE</td>
<td>10%</td>
<td>62</td>
</tr>
<tr>
<td>LUPUS SINE LUPO</td>
<td>5%</td>
<td>31</td>
</tr>
</tbody>
</table>
Subtypes

- localized DLE
- generalized DLE
- Lupus panniculitis
- Chilblein lupus
- Hypertrophic lupus
- anular SCLE
- Papulous-squamous SCLE
- localized ACLE
- generalized ACLE
- ICLE
Age at Diagnosis

Età media: 45.2 ± 1.2 anni

![Bar Chart showing age at diagnosis for different types of SLE: CCLE, SCLE, ACLE, ICLE. The y-axis represents age in years, and the x-axis represents the different types of SLE.]
Patient Management

Diagnosis Cutaneous form

- history
- clinic
- skin biopsy (Histology, IFD)

Diagnosis of SLE?

- Laboratory / instrumental tests
- ACR criteria / SLICC
- Screening associated diseases
Diagnosi

- Anamnesi
- Clinica
- Esame istologico
- **What do more?**
  - Immunofluorescenza diretta
  - **Clinical Score** Fototest
  - Indagini strumentali
SLICC Classification Criteria for Systemic Lupus Erythematosus

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criterion) OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

### Clinical Criteria

1. Acute Cutaneous Lupus *
2. Chronic Cutaneous Lupus *
3. Oral or nasal ulcers *
4. Non-scarring alopecia
5. Arthritis *
6. Serositis *
7. Renal *
8. Neurologic *
9. Hemolytic anemia
10. Leukopenia *
11. Thrombocytopenia (<100,000/mm³)

### Immunologic Criteria

1. ANA
2. Anti-DNA
3. Anti-Sm
4. Antiphospholipid Ab *
5. Low complement (C3, C4, CH50)
6. Direct Coombs’ test (do not count in the presence of hemolytic anemia)

†SLICC: Systemic Lupus International Collaborating Clinics
* See notes for criteria details

S2 Guideline for Treatment of Cutaneous Lupus Erythematosus -
guided by the European Dermatology Forum (EDF) in cooperation with the European
Academy of Dermatology and Venereology (EADV).

Annegret Kuhn¹, Elisabeth Aberer²*, Zsuzsanna Bata-Csörgő³*, Marzia Caproni⁴*, Andreas
Dreher⁵, Camille Frances⁶*, Regine Gläser⁷*, Hans-Wilhelm Klötgen⁸*, Aysche Landmann⁹,
Branka Marinovic¹⁰*, Filippa Nyberg¹¹*, Rodica Olteanu¹²*, Annamari Ranki¹³*, Jacek C.
Szepietowski¹⁴*, Beatrix Volc-Platzer¹⁵*

European Dermatology Forum (EDF). To achieve a broad consensus on recommendations for
therapeutic strategies in CLE, 15 experts from all over Europe were included in the guideline
subcommittee. At a consensus conference in July 2014, a draft of the guidelines for CLE was
discussed. Moreover, recommendations were defined and a consensus was achieved for each
therapeutic option. The recommendations were validated according to the system developed
by the “Grading of Recommendations Assessment, Development and Evaluation” (GRADE)
and included in the manuscript. In addition to dermatology, the consensus-based guidelines
also address other medical disciplines that diagnose and treat patients suffering from lupus
erythematosus, such as rheumatology.
S2k guideline for treatment of cutaneous lupus erythematosus – guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV)

A. Kuhn,1,2,* E. Aberer,3,† Z. Bata-Csörgő,4,† M. Caproni,5,† A. Dreher,6 C. Frances,7,† R. Gläser,8,† H.-W. Klötgen,9,† A. Landmann,2 B. Marinovic,10,† F. Nyberg,11,† R. Olteanu,12,† A. Ranki,13,† J.C. Szepietowski,14,†, B. Volc-Platzer15,†

Abstract
Cutaneous lupus erythematosus (CLE) is a rare inflammatory autoimmune disease with heterogeneous clinical manifestations. To date, no therapeutic agents have been licensed specifically for patients with this disease entity, and topical and systemic drugs are mostly used ‘off-label’. The aim of the present guideline was to achieve a broad consensus on treatment strategies for patients with CLE by a European subcommittee, guided by the European Dermatology Forum (EDF) and supported by the European Academy of Dermatology and Venereology (EADV). In total, 16 European participants were included in this project and agreed on all recommendations. Topical corticosteroids remain the mainstay of treatment for localized CLE, and further topical agents, such as calcineurin inhibitors, are listed as alternative first-line or second-line topical therapeutic option. Antimalarials are recommended as first-line and long-term systemic treatment in all CLE patients with severe and/or widespread skin lesions, particularly in patients with a high risk of scarring and/or the development of systemic disease. In addition to antimalarials, systemic corticosteroids are recommended as first-line treatment in highly active and/or severe CLE. Second- and third-line systemic treatments include methotrexate, retinoids, dapsone and mycophenolate mofetil or mycophenolate acid, respectively. Thalidomide should only be used in selected therapy-refractory CLE patients, preferably in addition to antimalarials. Several new therapeutic options, such as B-cell- or interferon α-targeted agents, need to be further evaluated in clinical trials to assess their efficacy and safety in the treatment of patients with CLE.

Received: 11 October 2016; Accepted: 26 October 2016
Recommendations

- We recommend performing patient’s past and present drug history, particularly in patients with SCLE (Table 1).
- We recommend to avoid unprotected UV exposure and to use daily preventive (chemical and physical) measures in all patients with CLE.
- Vitamin D supplementation is suggested in all patients with CLE.
- Cessation of smoking (active and passive) is recommended in all patients with CLE.
- We recommend the avoidance of isomorphic trigger factors, especially in patients with DLE.

Table 1  Drugs inducing cutaneous lupus erythematous

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Low Risk (&lt;5%)</th>
<th>High Risk (&gt;5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antifungal agents</td>
<td></td>
<td>Griseofulvin, terbinafine</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>Angiotensin-converting enzyme inhibitors: cilazapril, captopril</td>
<td>Calcium channel blockers: diltiazem, verapamil, nifedipine, nitrendipine, Betablockers: oxprenolol, acebutolol; Diuretics: hydrochlorothiazide, spironolactone</td>
</tr>
<tr>
<td>Chemotherapeutic agents</td>
<td>5-Fluorouracil, capecitabine</td>
<td>Docetaxel</td>
</tr>
<tr>
<td>Antacids</td>
<td>Omeprazole, lansoprazole, ranitidine</td>
<td></td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>Phenytoin, oxcarbazepine</td>
<td></td>
</tr>
<tr>
<td>Immunomodulators</td>
<td>Etanercept, infliximab, efalizumab, IFN-α, leflunomide</td>
<td></td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>Pravastatin, simvastatin</td>
<td></td>
</tr>
<tr>
<td>Anti-inflammatory drugs</td>
<td>Naproxen, piroxicam</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Bupropion</td>
<td></td>
</tr>
<tr>
<td>Antidiabetic drugs</td>
<td>Sulphonylurea (glyburide)</td>
<td></td>
</tr>
<tr>
<td>Antiarrhythmia agents</td>
<td>Procanamide</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Tetrazepam, lometazepam</td>
<td></td>
</tr>
<tr>
<td>Platelet aggregation inhibitors</td>
<td>Ticlopidine</td>
<td></td>
</tr>
</tbody>
</table>
Prevention (sunscreens, cessation of smoking, elimination of photosensitizing drugs)

Local disease

Topical therapy (corticosteroids, CI)

- good response: maintain
- no response: HCQ (or CQ)

HCQ (or CQ)

- good response: maintain
- no response / contraindication: add Quinacrine

Quinacrine discontinued

- no response: maintain
- good response: partial response: add MTX
- no response / contraindication: Retinoids (hypertrophic CLE)

- good response: maintain
- no response / contraindication: Dapsone

- good response: maintain

- no response / contraindication: Other systemic agents or experimental therapy

Severe and widespread skin manifestations

Topical therapy + HCQ (or CQ) + Systemic steroids (active disease)

- no response: good response: maintain

178 A randomized, double-blind, placebo-controlled, open-labelled, dose-ascending phase I study evaluated the safety and pharmacokinetics of multiple intravenous infusions of sirukumab, an anti-interleukin (IL)-6 antibody, in 31 patients with CLE and 15 patients with SLE.179 As evaluated by the CLASI, no

Recommendations

- We recommend antimalarials as first-line and long-term systemic treatment in all CLE patients with severe or widespread skin lesions, in particular in patients with the risk of scarring and development of systemic disease.
- We recommend to apply HCQ in a maximum daily dose of 5 mg/kg real bodyweight or CQ in a maximum daily dose of 2.3 mg/kg real bodyweight. A combination of HCQ with CQ must be avoided due to the risk of irreversible retinopathy.
- In refractory cases, we recommend to add quinacrine to either HCQ or CQ.
- In cases of contraindication for HCQ or CQ (e.g. retinopathy), monotherapy with quinacrine is recommended.
- Ophthalmological consultation is recommended in all CLE patients treated with HCQ or CQ at baseline, annually after 5 years of starting treatment or earlier in the presence of risk factors.
- We suggest to measure HCQ or CQ blood levels in therapy-refractory patients.
- Determination of G6PD activity is suggested before antimalarial treatment.
Recommendations

- In patients with CLE and associated antiphospholipid syndrome, we do not recommend to take **hormonal contraception** containing oestrogen.
- We do not suggest **oestrogen replacement** therapy for patients with CLE.
- In active disease during pregnancy or breastfeeding, we recommend **HCQ** as first-line treatment for CLE at usual dosage.
- We recommend continuing the **maintenance of HCQ treatment during pregnancy**, but we also recommend switching from CQ to HCQ in this period.\(^{31}\)
- In active disease or during flares, we suggest **dapsone** for HCQ-refractory CLE patients as an alternative treatment during pregnancy or breastfeeding.
- We recommend that **systemic corticosteroids** (prednisone and methylprednisolone) should be given in a dose of not more than 10-15 mg per day during pregnancy or breastfeeding.
- We do not recommend **methotrexate** (MTX), mycophenolate mofetil (MMF) or mycophenolate acid (MPA), retinoids and thalidomide or lenalidomide in women of childbearing age without effective contraception.
- We recommend that a pregnant or breastfeeding patient with severe CLE and/or anti-Ro/SSA antibodies should be treated by a **multidisciplinary approach**.
<table>
<thead>
<tr>
<th>Name of Drug/Intervention</th>
<th>Type</th>
<th>Study Design</th>
<th>Condition</th>
<th>Enrolment</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept (intradermal)</td>
<td>anti-TNF-α antibody</td>
<td>Phase II, open-label study</td>
<td>DLE</td>
<td>25 patients</td>
<td>NCT02656082</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Ex vivo expanded human autologous polyclonal regulatory T cells</td>
<td>–</td>
<td>Phase I, open-label, dose escalation study</td>
<td>SLE (ACLE, SCLE, DLE, LET)</td>
<td>18 patients</td>
<td>NCT02428309</td>
<td>Ongoing</td>
</tr>
<tr>
<td>RSLV-132</td>
<td>monospecific nuclease Fc-fusion protein</td>
<td>Phase IIa, randomized, placebo-controlled, double-blind study</td>
<td>SLE (CLE)</td>
<td>50 patients</td>
<td>NCT02660944</td>
<td>Ongoing</td>
</tr>
<tr>
<td>ALX-0061</td>
<td>anti-IL-6 receptor nanobody</td>
<td>Phase II, randomized, placebo-controlled, double-blind study</td>
<td>SLE</td>
<td>300 patients</td>
<td>NCT02437890</td>
<td>Ongoing</td>
</tr>
<tr>
<td>BMS-931699 (riluzumab pegol)</td>
<td>anti-CD28 antibody</td>
<td>Phase II, randomized, placebo-controlled, double-blind study</td>
<td>SLE</td>
<td>350 patients</td>
<td>NCT02265744</td>
<td>Ongoing</td>
</tr>
<tr>
<td>CC-220</td>
<td>small molecule</td>
<td>Phase II, randomized, placebo-controlled, double-blind study</td>
<td>SLE</td>
<td>140 patients</td>
<td>NCT02185040</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Abatacept</td>
<td>fusion protein</td>
<td>Phase II, randomized, placebo-controlled, double-blind study</td>
<td>SLE</td>
<td>60 patients</td>
<td>NCT02270957</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Anifrolumab</td>
<td>type I IFN receptor antagonist</td>
<td>Phase III, randomized, placebo-controlled, double-blind study</td>
<td>SLE</td>
<td>450 patients</td>
<td>NCT02446912</td>
<td>Ongoing</td>
</tr>
<tr>
<td>TAB08</td>
<td>CD28 superagonist</td>
<td>Phase II, randomized, placebo-controlled, double-blind study</td>
<td>SLE</td>
<td>60 patients</td>
<td>NCT02711813</td>
<td>Not yet ongoing</td>
</tr>
<tr>
<td>CC-11050</td>
<td>small molecule</td>
<td>Phase II, randomized, placebo-controlled, double-blind study</td>
<td>DLE, SCLE</td>
<td>48 patients</td>
<td>NCT01300208</td>
<td>Completed, not yet published</td>
</tr>
<tr>
<td>KRP203</td>
<td>S1P1/4/5 agonist</td>
<td>Phase II, randomized, placebo-controlled, double-blind study</td>
<td>SCLE</td>
<td>10 patients</td>
<td>NCT01294774</td>
<td>Completed, not yet published</td>
</tr>
<tr>
<td>Apremilast (CC10004)</td>
<td>phosphodiesterase 4 (PDE-4) inhibitor</td>
<td>Phase II, open-label study</td>
<td>DLE</td>
<td>10 patients</td>
<td>NCT00708916</td>
<td>Published152</td>
</tr>
<tr>
<td>Fumaric Acid Esters</td>
<td>Fumaric acid esters</td>
<td>Phase II, open-label pilot study</td>
<td>CLE (DLE, SCLE)</td>
<td>11 patients</td>
<td>NCT01352988</td>
<td>Published153</td>
</tr>
<tr>
<td>Paquinimod (ABR-215757)</td>
<td>small molecule</td>
<td>Phase II, open-label study</td>
<td>SLE</td>
<td>13 patients</td>
<td>NCT00997100</td>
<td>Published154</td>
</tr>
<tr>
<td>AMG 811</td>
<td>anti-IFN-γ IgG1 antibody</td>
<td>Phase I, randomized, placebo-controlled, double-blind study</td>
<td>DLE</td>
<td>16 patients</td>
<td>NCT01164917</td>
<td>Published155</td>
</tr>
<tr>
<td>PD-0360324</td>
<td>IgG1 antibody</td>
<td>Phase I, randomized, placebo-controlled, double-blind study</td>
<td>DLE, SCLE</td>
<td>28 patients</td>
<td>NCT01470313</td>
<td>Published156</td>
</tr>
</tbody>
</table>

*Only studies are listed, in which a skin score is applied to evaluate cutaneous manifestations, modified after157
ACLE, acute cutaneous lupus erythematosus; CLE, cutaneous lupus erythematosus; DLE, discoid lupus erythematosus; LET, lupus erythematosus tumidus; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus.
CONCLUSION

• Being the largest organ of the human body, skin is frequently affected in many rheumatic diseases

• It can serve as an important indicator for the correct diagnosis of a rheumatic disease and also as a marker of disease activity in distinct rheumatic disorders
CONCLUSION

• The skin is the second most frequently affected organ system in lupus erythematosus
• Since several manifestations are closely associated with the presence and activity of systemic lupus erythematosus, prompt and accurate diagnosis of cutaneous lupus erythematosus is essential
• In the context of a multidisciplinary approach, the management of these diseases should be shared for all-round treatment of our patients
THANKS FOR YOUR ATTENTION

Emiliano Antiga
Beatrice Bianchi
Diletta Bonciani
Elena Del Bianco
Veronica Bonciolini
Roberto Maglie
Alessandra Ninci
Lavinia Quintarelli
Alice Verdelli
Walter Volpi

Serpula vermicula
Capraia Isola
Toxic Epidermal Necrolysis-like Rash of Lupus: A Dermatologist's Dilemma

Brahmita Monga, Sangita Ghosh, VK Jain

The points which favor TEN-like rash of LE over drug-induced TEN are:
1) Lack of evidence of ingestion of high-risk drugs
2) Photodistribution of TEN-like lesions
3) Subacute presentation over weeks
4) Recent exacerbation of SLE
5) History of painless oral ulcer associated with malar or discoid rash
6) Distinctive serologic profile, including a strongly positive ANA and positive anti-dsDNA, suggestive of underlying connective tissue disease

A unifying concept of 'acute syndrome of apoptotic pan-epidermolysis (ASAP)'

### Table I. Characteristics of three patients with toxic epidermal necrolysis-like lupus erythematosus. All patients had normal kidney function and serum complement levels

<table>
<thead>
<tr>
<th>Patient/age/sex</th>
<th>Initial presentation</th>
<th>Serological abnormalities</th>
<th>Haematological abnormalities</th>
<th>Previous treatment</th>
<th>Mucosal lesions</th>
<th>Time</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/23/F SCLE</td>
<td>ANA-1:320 nucleolar</td>
<td>rbc 3920</td>
<td>Chlor. 250 mg/day</td>
<td>No</td>
<td>45 days</td>
<td>Chlor. 250 mg/day</td>
<td>Improved</td>
<td></td>
</tr>
<tr>
<td></td>
<td>anti-RO +</td>
<td>wbc 2400</td>
<td>Pred. 40 mg BID pulse</td>
<td></td>
<td></td>
<td>Pred. 60 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>anti-LA +</td>
<td></td>
<td>Pred. 40 mg BID pulse</td>
<td></td>
<td></td>
<td>Aza. 150 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/19/F ACLE</td>
<td>ANA-1:1280 homogenous</td>
<td>rbc 3900</td>
<td>Chlor. 250 mg/day</td>
<td>No</td>
<td>3 months</td>
<td>Chlor. 250 mg/day</td>
<td>Improved</td>
<td></td>
</tr>
<tr>
<td></td>
<td>anti-DNA +</td>
<td>wbc 3770</td>
<td>Pred. 40 mg/day</td>
<td></td>
<td></td>
<td>Pred. 60 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/17/F SCLE</td>
<td>ANA-1:1280 speckled</td>
<td>rbc 3600</td>
<td>Chlor. 250 mg/day</td>
<td>Yes</td>
<td>1 year</td>
<td>Chlor. 250 mg/day</td>
<td>Death from sepsis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>anti-DNA +</td>
<td>wbc 3460</td>
<td>Pred. 40 mg/day</td>
<td></td>
<td></td>
<td>Pred. 60 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>anti-Sm +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>anti-RNP +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Definitive differential diagnosis may be impossible, since histopathological, serological, and immunofluorescence markers were almost identical in all cases.
Fig. 3. A) Percentages of patients fulfilling the ACR criteria. The 11 ACR criteria are listed with respect to the percentages of patients who fulfilled each criterion in the subgroup of patients who fulfilled four or more or fewer than four ACR criteria, respectively. B) Percentages of CLE patients fulfilling the ACR criteria. The total number of patients diagnosed by their physician as CLE fulfilling ≥4 ACR criteria is 212, the total number of patients diagnosed by their physician as CLE fulfilling <4 ACR criteria is 570. C) Significant differences in the ACR criteria between the CLE subtypes. Each bar represents the percentage of patients within each of the four CLE subtypes who fulfilled particular ACR criteria. 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; ***p<0.001.
Our Experience
Diagnosi

• Anamnesi
• Clinica
• Esame istologico
• **What do more?**
  – Immunofluorescenza diretta
  – Esami ematici
  – **Phototest**
  – Indagini strumentali
RINGRAZIAMENTI

Emiliano Antiga
Beatrice Bianchi
Elena del Bianco
Diletta Bonciani
Veronica Bonciolini
Alice Verdellli
Walter Volpi
Review

Cutaneous lupus erythematosus: First multicenter database analysis of 1002 patients from the European Society of Cutaneous Lupus Erythematosus (EUSCLE)

Cyrus Biazar a, Johanna Sigges a, Nikolaos Patsinakidis a, Vincent Ruland a, Susanne Amler b, Gisela Bonsmann a, Annegret Kuhn a,.*
and the EUSCLE co-authors 1

a Department of Dermatology, University of Muenster, 48149 Muenster, Germany
b Institute of Biostatistics and Clinical Research, University of Muenster, 48149 Muenster, Germany

Fig. 1. A) Male and female patients with different CLE subtypes. The percentage of males (n=234, 23.4%) and females (n=768, 76.6%) is itemized by the four subtypes of the disease. B) Mean age at onset of disease in CLE subtypes (main diagnosis). The data present the mean age at onset of disease ± SD in the four subtypes of the disease. 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; ***p<0.001.
Malattie associate

160 pazienti con malattie associate (53%)

<table>
<thead>
<tr>
<th>Malattie autoimmuni</th>
<th>81 (27%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Tiroidite</td>
<td>38 (12,5%)</td>
</tr>
<tr>
<td>- Sindrome di Sjogren</td>
<td>21 (7%)</td>
</tr>
<tr>
<td>Ipertensione, ipercolesterolemia, DM II</td>
<td>48 (16%)</td>
</tr>
<tr>
<td>Malattie cutanee (psoriasi, vitiligine, LP, DA)</td>
<td>23 (7,5%)</td>
</tr>
<tr>
<td>Infezioni</td>
<td>17 (5,5%)</td>
</tr>
<tr>
<td>Neoplasie</td>
<td>11 (3,5%)</td>
</tr>
<tr>
<td>S. Ansioso-depressiva</td>
<td>6 (2%)</td>
</tr>
</tbody>
</table>

*Koskenmies et al, Lupus 2008*
Phototest

- Differential diagnosis (EPL)
- photosensitivity level
- radiation responsible (photoprotection strategies)
Photoprotection

Key role in preventing exacerbations (also systemic) disease

Most photosensitive forms:
- Subacute cutaneous lupus erythematosus
- Lupus erythematosus
Photosensitivity in CLE

• It is commonly accepted that ultraviolet light (UV) exposure can induce and exacerbate skin lesions in patients with all subtypes of CLE, supporting the role of UV light in the pathogenesis of the disease

• Skin lesions often occur in sun-exposed areas

• Photosensitivity in CLE subtypes:
  • SCLE: 27-100 %
  • DLE: 25-90 %
  • LET: 43-71 %

Kuhn et al, Clin Rev Allergy Immunol 2014
ITALIAN EXPERIENCE
GIIP 2009-2014

Tot. 619 pt

SUBTYPE

CCLE
n=303
49%

SCLE
n=115
19%

ICLE
n=108
17%

ACLE
n=62
10%

LUPUS SINE LUPO
n=31
5%
PHOTOSENSITIVITY

Tot. 619 pt

- CCLE n=303: 39.3%
- SCLE n=115: 87%
- ICLE n=108: 73%
- ACLE n=62: 85%
- LUPUS SINE LUPO n=31: 44%
Photosensitivity in SLE

- Sun exposure can lead to exacerbation of organ involvement in SLE, such as lupus nephritis. 
  Schmidt et al, Ann NY Acad Sci 2007

- Photosensitizing drugs can induce LE (thiazide diuretics, sulfonylureas)

- Seasonal variation in SLE incidence and activity

Photosensitivity as a criterion for SLE
<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malar rash</td>
<td>Fixed erythema over malar areas, sparing nasolabial folds</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>Erythematous raised patches with keratotic scaling and follicular plugging</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Skin rash after exposure to sunlight (history or physical exam)</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>Oral or nasopharyngeal, painless, by physical exam</td>
</tr>
<tr>
<td>Nonerosive arthritis</td>
<td>Tenderness, swelling, effusion in 2 or more peripheral joints</td>
</tr>
<tr>
<td>Pleuritis or pericarditis</td>
<td>Convincing history or physical exam or ECG or other evidence</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>&gt;0.5g protein/d or 3+ or cellular casts</td>
</tr>
<tr>
<td>Seizures, psychosis</td>
<td>Not due to drugs, metabolic derangement, etc.</td>
</tr>
<tr>
<td>Hematologic disorder</td>
<td>Hemolytic anemia or leukopenia (&lt;4000 twice) or lymphopenia (&lt;1500 twice) or thrombocytopenia (&lt;100,000) without other causes</td>
</tr>
<tr>
<td>Immunologic disorder</td>
<td>Anti-dsDNA or anti-Sm or antiphospholipid antibodies (anticardiolipin, LAC, or false positive test for syphilis)</td>
</tr>
<tr>
<td>Positive ANA</td>
<td>Not drug-induced</td>
</tr>
</tbody>
</table>
Photosensitivity in ACR criteria

• The term “photosensitivity” is poorly defined by the ACR: “Skin rash as a result of unusual reaction to sunlight by patient history or physician observation”
However, objective evaluation of photosensitivity may be helpful for the management of the patient:

- Education
- Photoprotection
- Vitamin D status
- ...

Photoprovocation test
Photoprovocation test

- Different protocols (UVA1, UVA2, UVB)
- Positivity: 24-93%
- Lesion development: after 1-3 weeks
- Duration: up to several months
- Discrepancies between phototest result and patient history
Photoprotective effects of a broad-spectrum sunscreen in ultraviolet-induced cutaneous lupus erythematosus: A randomized, vehicle-controlled, double-blind study

Annegret Kuhn, MD, Kristina Gensch, MD, Merle Haust, MD, Anna-Maria Meuth, MA, France Boyer, MD, Patrick Dupuy, MD, Percy Lehmann, MD, Dieter Metze, MD, and Thomas Ruzicka, MD

Muenster, Duesseldorf, Wuppertal, and Munich, Germany; and Toulouse, France
<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Country</th>
<th>Tested LE patients</th>
<th>LE patients with a positive photoprovocation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>Lehmann et al. [20]</td>
<td>Germany</td>
<td>67</td>
<td>27 (40 %)</td>
<td>First publication on a photoprovocation protocol for CLE including long-wave UVA irradiation</td>
</tr>
<tr>
<td>1989</td>
<td>Wolska et al. [147]</td>
<td>Poland</td>
<td>202</td>
<td>49 (24 %)</td>
<td>Observation of prolonged persistence of erythema after UVB irradiation in CLE compared to healthy controls</td>
</tr>
<tr>
<td>1989</td>
<td>Van Weelden et al. [148]</td>
<td>Netherlands</td>
<td>24</td>
<td>20 (83 %)</td>
<td>Photoprovocation of CLE with UVA, UVB and visible light</td>
</tr>
<tr>
<td>1990</td>
<td>Lehmann et al. [21]</td>
<td>Germany</td>
<td>128</td>
<td>55 (43 %)</td>
<td>Induction of skin manifestations in CLE with UVA, UVB and combined UVA/UVB irradiation</td>
</tr>
<tr>
<td>1991</td>
<td>Beutner et al. [149]</td>
<td>USA</td>
<td>115</td>
<td>90 (78 %)</td>
<td>Persistence of positive reactions in CLE for 10 days</td>
</tr>
<tr>
<td>1993</td>
<td>Kind et al. [150]</td>
<td>Germany</td>
<td>150</td>
<td>81 (54 %)</td>
<td>Review on photoprovocation procedures and results, associated with clinical correlations in CLE</td>
</tr>
<tr>
<td>1993</td>
<td>Nived et al. [151]</td>
<td>Sweden</td>
<td>23</td>
<td>6 (26 %)</td>
<td>Pathological skin reaction is SLE patients after standardized exposure to UVA and UVB wavelengths</td>
</tr>
<tr>
<td>1995</td>
<td>Bensaid [152]</td>
<td>France</td>
<td>19</td>
<td>12 (63 %)</td>
<td>No correlation of photoprovocation results, presence of systemic involvement or anti-Ro/SSA antibodies in CLE</td>
</tr>
<tr>
<td>1997</td>
<td>Walchner et al. [153]</td>
<td>Germany</td>
<td>68</td>
<td>29 (43 %)</td>
<td>Overview on photoprovocation and photoprotection in CLE</td>
</tr>
<tr>
<td>1997</td>
<td>Hasan et al. [154]</td>
<td>Finland</td>
<td>67</td>
<td>46 (69 %)</td>
<td>Induction of PLE- and LE-like skin lesions in CLE and SLE after UV-irradiation</td>
</tr>
<tr>
<td>1999</td>
<td>Leenutaphong [155]</td>
<td>Thailand</td>
<td>15</td>
<td>6 (40 %)</td>
<td>Photoprovocation in oriental LE patients</td>
</tr>
<tr>
<td>2001</td>
<td>Kuhn et al. [9]</td>
<td>Germany</td>
<td>323</td>
<td>175 (54 %)</td>
<td>Summary of 15-years experience with photoprovocation in different subtypes of CLE</td>
</tr>
<tr>
<td>2001</td>
<td>Kuhn et al. [156]</td>
<td>Germany</td>
<td>60</td>
<td>43 (72 %)</td>
<td>Classification of LET as the most photosensitive subtype of CLE</td>
</tr>
<tr>
<td>2003</td>
<td>Sanders et al. [157]</td>
<td>Netherlands</td>
<td>100</td>
<td>93 (93 %)</td>
<td>No correlation of photosensitivity, CLE subtype, presence of antibodies or medical history</td>
</tr>
<tr>
<td>2004</td>
<td>Choonhakarn et al. [158]</td>
<td>Thailand</td>
<td>10</td>
<td>5 (50 %)</td>
<td>Assessment of different clinical parameters in LET patients</td>
</tr>
<tr>
<td>2011</td>
<td>Kuhn et al. [24]</td>
<td>Germany, Poland, Sweden, UK</td>
<td>47</td>
<td>22 (47 %)</td>
<td>Multicenter study evaluating no significant differences in photoprovocation of CLE patients between seven European study sites</td>
</tr>
<tr>
<td>2013</td>
<td>Ruland et al. [25]</td>
<td>Germany</td>
<td>431</td>
<td>266 (62 %)</td>
<td>Study with &gt;400 CLE patients suggesting that the reaction to UV light may change during the course of the disease</td>
</tr>
</tbody>
</table>
Photoprovocation test: summary

Provocative phototesting is an objective means of demonstrating whether a patient has an abnormal response to UV exposure; however, phototesting does not play a role in the routine assessment or diagnosis of a patient with CLE. Indications for phototesting in patients with LE include (a) the objective demonstration of photosensitivity where there is doubt about the history and where such demonstration would support a diagnosis of LE; (b) the exclusion of other causes of photosensitivity, such as PLE, chronic dermatitis, solar urticaria, and drug-induced phototoxicity; and (c) use of the photoprovocation test as a useful research tool with which to study the immunopathology of evolving lesions of LE-specific skin disease.

Lehmann et al, Autoimmun Rev 2009
Phatophysiology of photosensitivity

• Increased apoptosis of keratinocytes
• Increased autoantigens
• Production of chemokines and leukines (IL8) by keratinocytes
• Accumulation of plasmocitoid DC (↑ IFN-α)
• Increasing and binding of autoantibodies and antigen
Ultraviolet light

Keratinocytes

Apoptotic cells

Small apoptotic blebs
Ro (52 kD), ribosomal P, calreticulin, fodrin, Jo-1

Large apoptotic blebs
Nucleosomes, Ro (60 kD), La, Sm, PARP, U1 (70 kD), Mi-2

UV-injury

Apoptosis and necrosis of keratinocytes

Extracellular self-DNA

Autoantigens

LL37

Autoantibodies

Production and release of chemokines

CXCL9
CXCL10
CXCL11

CCL5
CCL20
CCL27

CXCL12

T cell and PDC recruitment / activation

IFN-α and IFN-γ production

UV-induced cutaneous LE phenotype
Fig. 1 Clearance of UV-induced apoptotic cells in autoimmunity. Under physiological conditions, apoptotic cells are efficiently cleared by phagocytes such as antigen presenting cells (APC). Various molecules on the surface of apoptotic cells and corresponding receptors on the APC mediate phagocytosis and anti-inflammatory effects of apoptotic cells (see text for details), maintaining tolerance to apoptotic cell-derived self-antigens. At different levels, excessive apoptosis through UV irradiation as well as autoantibodies and cytokines present in microenvironment can interfere with the anti-inflammatory removal of apoptotic cells and cause autoimmunity. (C, complement proteins; CR3, complement receptor 3; Gas6, growth arrest-specific 6 protein; MerTK, Mer tyrosine kinase; Anx1, annexin 1; AnxR, annexin 1 receptors; MFG-E8, milk fat globule-EGF factor 8; \( \alpha_{v}\beta_{3}, \alpha_{v}\beta_{5} \) integrin; PS, phosphatidylserine; PSR, phosphatidylserine receptors)
Unanswered question

• UV linked to LE development (and not only to exacerbation)?
• UV act as an instantaneous hazard or with cumulative exposure?
• Role of vitamin D?
• Role of phototherapy?
Hypovitaminosis D and lupus flare

• Vitamin D is an immunomodulator
• Patients with SLE are prone to hypo-vitaminosis D (↓ sun exposure? Disease itself?)
• Hypo-vitaminosis D may induce (or may be a consequence of) lupus flares
• Role for vitamin D supplementation in patients with lupus

Dall’Ara et al, Clin Exp Rheumatol 2015
UVA1-phototherapy in SLE

• Effect on lymphocites (↑ apoptosis)
• ↓ of cytokines such as IFN-γ
• Some studies reported favourable outcome

Kim et al Photodermatol Photoimmunol Photomed 2013

<table>
<thead>
<tr>
<th>Disease</th>
<th>Treatment modality</th>
<th>Level of evidence^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus erythematosus</td>
<td>Phototheraphy</td>
<td>Ib</td>
</tr>
<tr>
<td></td>
<td>UVA1</td>
<td>Ib</td>
</tr>
<tr>
<td></td>
<td>Photodynamic therapy</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>Photopheresis</td>
<td>IIIb</td>
</tr>
</tbody>
</table>

Gordon Spratt et al, Br J Dermatol 2015
Table 2. UVA-1 radiation trials for lupus patients

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>N</th>
<th>Study type</th>
<th>UVA-1 regimen</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>Sönntichsen et al. (46)</td>
<td>1</td>
<td>Case report</td>
<td>186.1 J/cm² over 9 weeks</td>
<td>Clinical improvement in a 71-year-old female with SCLE having contraindications to corticosteroid and immunosuppressive therapy</td>
</tr>
<tr>
<td>1994</td>
<td>McGrath et al. (47)</td>
<td>15</td>
<td>Open-label</td>
<td>6.5 J/cm²/day: 5 days/wk × 3 weeks</td>
<td>Disease activity scores decreased</td>
</tr>
<tr>
<td>1994</td>
<td>McGrath (48)</td>
<td>10</td>
<td>Open-label</td>
<td>6 J/cm²/day: 5 days/wk × 3 weeks</td>
<td>Disease activity scores decreased, and one SCLE patient’s skin lesions improved</td>
</tr>
<tr>
<td>1996</td>
<td>McGrath et al. (37)</td>
<td>26</td>
<td>DB-RCT (crossover)</td>
<td>6 J/cm²/day: 5 days/wk × 3 weeks (or visible light)</td>
<td>SLAM scores and dsDNA autoantibodies significantly decreased with UVA-1 radiation group</td>
</tr>
<tr>
<td>2001</td>
<td>Polderman et al. (40)</td>
<td>11</td>
<td>DB-RCT (crossover)</td>
<td>6 J/cm²/day: 5 days/wk × 3 weeks (or visible light)</td>
<td>SLAM and SLEDAI scores decreased in both groups, but no significant difference between groups</td>
</tr>
<tr>
<td>2003</td>
<td>Menon et al. (38)</td>
<td>1</td>
<td>open-label</td>
<td>16 J/cm²/day: 3 days/wk × 24 weeks (minus 12–14)</td>
<td>Clinically significant improvement seen by week 2–3 of UVA-1 treatment, brain function improvement on PET paralleled reversal of cognitive dysfunction</td>
</tr>
<tr>
<td>2004</td>
<td>Polderman et al. (41)</td>
<td>12</td>
<td>DB-RCT (crossover)</td>
<td>12 J/cm²/day: 5 days/wk × 3 weeks</td>
<td>SLAM and SLEDAI scores significantly decreased in UVA-1 group vs. placebo group, one SCLE patient’s skin lesions improved</td>
</tr>
<tr>
<td>2005</td>
<td>Szegedi et al. (39)</td>
<td>9</td>
<td>Open-label</td>
<td>6 J/cm²/day: 5 days/wk × 3 weeks, then 3 days/wk × 3 weeks then 4 days/wk × 3 weeks</td>
<td>SLEDAI scores declined significantly, decrease in IFN-γ producing T₇₁ and T₇₂ cells, decreased ratio of T₇₁:T₇₂ and T₉₁:T₉₂</td>
</tr>
<tr>
<td>2005</td>
<td>McGrath (49)</td>
<td>1</td>
<td>Case report</td>
<td>10 J/cm²/day: 2 days/wk × 30 weeks</td>
<td>Elimination of anticardiolipin antibodies and termination of cognitive decline in SLE patients</td>
</tr>
<tr>
<td>2010</td>
<td>Jabara et al. (50)</td>
<td>1</td>
<td>Case report</td>
<td>8 J/cm²/day: 2 days/wk × 5 years</td>
<td>Incidental improvement of interstitial lung disease and pulmonary hypertension</td>
</tr>
</tbody>
</table>

DB-RCT, double-blinded randomized control trial; SCLE, subacute cutaneous lupus erythematosus; SLAM, systemic lupus activity measure; SLEDAI, SLE disease activity index.
Take home messages

• Photosensitivity: pathogenetic role in LE
• Need for objective assessment
• Implication for patient management
  – Photoprotection
  – Role for vitamin D supplementation
  – Role for phototherapy in patients with LE
Review

Therapeutic strategies evaluated by the European society of cutaneous lupus erythematosus (EUSCLE) core set questionnaire in more than 1000 patients with cutaneous lupus erythematosus

Annegret Kuhn a,*; Johanna Sigges a; Cyrus Biazar a; Aysche Landmann b; Vincent Ruland a; Nikolaos Patsinakidis a; Susanne Amerl c; Gisela Bonsmann a
and the EUSCLE Co-Authors 1

a Department of Dermatology, University of Muenster, 48149 Muenster, Germany

b Division of Immunogenetics, Tumorimmunology Program, German Cancer Research Center, 69120 Heidelberg, Germany

c Corresponding author at: Department of Dermatology, University of Muenster, Von-Esmarch-Strasse 58, D-48149 Muenster, Germany. Tel.: +49 251 8352210; +49 6221 423773; fax: +49 251 8358947; +49 6221 423749.

E-mail addresses: kuhn@uni-muenster.de (A. Kuhn), johanna.sigges@gmx.de (J. Sigges), cyrusbiazar@gmail.com (C. Biazar), a.landmann@dkg.de (A. Landmann), vru@landlee@gmail.com (V. Ruland), nikos.patsinakidis@uni-muenster.de (N. Patsinakidis), susanne.amerl@ukmuenster.de (S. Amerl), gisela.bonsmann@ukmuenster.de (G. Bonsmann).

1 M. Haust, Department of Dermatology, University of Duesseldorf, Duesseldorf, Germany; F. Nyberg, Department of Dermatology, University of Uppsala, Uppsala, Sweden; Z. Beta, L. Mihályi, Department of Dermatology, University of Szeged, Szeged, Hungary; R. Otteau, Colentina Hospital, Dermatology, Bucharest, Romania; R. M. Pujol, J. M. Sánchez-Schmidt, Department of Dermatology, Parc de Salut Mar-IMAS, Barcelona, Spain; L. Medenica, D. Skiljic, Department of Dermatovenerology, School of Medicine, University of Belgrade, Clinic of Dermatovenerology, Clinical Centre of Serbia, Belgrade, Serbia; A. Reich, J. C. Szeplétei, Department of Dermatology, Venerology and Allergology, Wroclaw Medical University, Wroclaw, Poland; C. Dalle Vedova, G. Grokoma, Department of Dermatology, University of Verona, Verona, Italy; T. Hawro, A. Zelewska-Janowska, Psychodermatology Department, Clinical Immunology and Microbiology, Medical University of Lodz, Lodz, Poland (the study was conducted at the Department of Dermatology and Venereology, Medical University of Lodz, Lodz, Poland); R. Glaeser, R. Hugel, Department of Dermatology of the University Hospital of Schleswig-Holstein, Campus Kiel, Kiel, Germany; H. Jedlicková, Department of Dermatology, St. Anna University Hospital Brno, Czech Republic; A. Bygum, R. Lurarinaevi, Department of Dermatology and Allergy Centre, Odense University Hospital, Odense C, Denmark; S. Benoit, E. Broecker, Department of Dermatology, Venerology and Allergology, University Hospital Wuerzburg, Wuerzburg, Germany; F. A. Bahmer, Department of Dermatology, Hospital Bremen-Mitte, Bremen, Germany; E. Aberer, N. Wutte, Department of Dermatology, Medical University Graz, Graz, Austria; J. Lipozencic, B. Marinovic, University Hospital Centre Zagreb, Department of Dermatology, School of Medicine University of Zagreb, Zagreb, Croatia; M. Sárdy, V. Bekou, T. Ruzicka, Department of Dermatology and Allergology, Ludwig Maximilian University, Munich, Germany; C. Frances, B. Soutou, Tenon Hospital, Department of Dermatology, Paris, France; H. Lee, M. Worm, Department of Dermatology and Allergy, Charité Campus Mitte, Universitätsmedizin Berlin, Berlin, Germany; A. Grauchke, N. Hunzelmam, Department of Dermatology and Venerology, University Hospital Cologne, Cologne, Germany; K. Steinhbrink, Department of Dermatology, University Medical Centre Mainz, Mainz, Germany; R. Romiti, Department of Dermatology, University of Sao Paulo, Sao Paulo, Brazil; M. Sticherling, C. Erfurt-Berge, Department of Dermatology, University Erlangen, Erlangen, Germany; G. Agerinou, D. Papafragkakis, Department of Dermatology, University of Athens, A. Sygros Hospital, Athens, Greece; E. Antiga, M. Caproni, Department of Dermatology Sciences, University of Florence, Florence, Italy; B. Mayer, B. Volc-Platzer, Department of Dermatology, Donauesch-Wien, Vienna, Austria; A. Kreuter, C. Tigges, Department of Dermatology, Venereology and Allergology, Ruhr University Bochum, Bochum, Germany; P. M. Heil, G. Stingl, Division of Immunology, Allergy and Infectious Diseases, Department of Dermatology, Medical University Vienna, Vienna, Austria.
The image contains three bar charts with the following data:

1. The left chart shows the number of people with a score of 81.0, 85.5, and 77.8 for a condition categorized as <4 ACR.
2. The middle chart includes categories for Sunscreens (yes, no) and Topical Agents (yes, no), with corresponding score comparisons.
3. The right chart lists systemic agents (sunscreens, topical treatment, and systemic treatment) used in relation to CLASI activity and damage scores.

The bars are labeled for various treatments and conditions. The text mentions that the terms "yes" and "no" refer to the presence or absence of treatments, as described in Fig. 2A.
Take-home messages

- Sunscreens were applied by 84.0% of the CLE patients and showed a high efficacy in preventing skin lesions in all disease subtypes, correlating with a lower CLASI activity score.
- Topical steroids were used in 81.5% of the study cohort, with an efficacy of 88.4%, whereas calcineurin inhibitors were only applied in 16.4% of the study population and showed an efficacy of 61.7%.
- Systemic agents including antimalarials and several immunomodulating drugs, such as systemic steroids and methotrexate, were used in 84.4% of the 1002 patients, particularly in cases of acute CLE.
- The CLASI activity and damage score was higher in treated CLE patients as compared to untreated patients, regardless of therapy with topical or systemic agents.
RINGRAZIAMENTI

Emiliano Antiga
Beatrice Bianchi
Elena del Bianco
Diletta Bonciani
Veronica Bonciolini
Lavinia Quintarelli
Roberto Maglie
Alice Verdellli
Walter Volpi

Gruppo di Immunopatologia Cutanea
della Società Italiana di Dermatologia
Medica, Chirurgica, Estetica e delle
Malattie Sessualmente Trasmesse
<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malar rash</td>
<td>A “butterfly rash” of flat or raised fixed erythema tending to spare the nasolabial folds</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>Erythematous raised patches with adherent keratotic scaling and follicular plugging associated with scarring</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>A reaction to sunlight causing rash that may last for several weeks after brief sun exposure</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>Often painless oral or nasopharyngeal ulceration</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Nonerosive arthritis tenderness, swelling, or effusion involving 2 or more peripheral joints</td>
</tr>
<tr>
<td>Serositis</td>
<td>Pleuritis (chest pain on inspiration) or pericarditis; note that premature coronary artery disease is associated with inflammatory conditions like SLE</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>Persistent proteinuria</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>Seizures or psychosis in the absence of offending drugs or known metabolic derangements</td>
</tr>
<tr>
<td>Hematologic disorder</td>
<td>Leucopenia (often an early sign), hemolytic anemia, lymphopenia, thrombocytopenia in the absence of offending drugs</td>
</tr>
<tr>
<td>Immunologic disorder</td>
<td>Positive LE cell preparation, anti-DNA, anti-Sm, or false positive serologic test for syphilis</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>An abnormal titer of antinuclear antibody at any point in time and in the absence of drugs known to be associated with “drug-induced lupus” syndrome</td>
</tr>
</tbody>
</table>

ACR = American College of Rheumatology; LE = lupus erythematosus; SLE = systemic lupus erythematosus. Adapted from references 3, 4, and 7.
OBJECTIVES:
Although systemic lupus erythematosus (SLE) most commonly occurs in reproductive-age women, some are diagnosed after the age of 50. Recognizing that greater than one-third of SLE criteria are cutaneous, we undertook a systematic review and meta-analysis to evaluate differences in cutaneous manifestations in early- and late-onset SLE patients.

METHODS:
We searched the literature using PubMed, CINAHL, Web of Science, and Cochrane Library. We excluded studies that did not include ACR SLE classification criteria, early-onset controls, that defined late-onset SLE as <50 years of age, or were not written in English. Two authors rated study quality using the Newcastle Ottawa Quality Scale. We used Forest plots to compare odds ratios (95% CI) of cutaneous manifestations by age. Study heterogeneity was assessed using $I^2$.

RESULTS:
Overall, 35 studies, representing 11,189 early-onset and 1727 late-onset patients with SLE, met eligibility criteria. The female:male ratio was lower in the late-onset group (5:1 versus 8:1). Most cutaneous manifestations were less prevalent in the late-onset group. In particular, malar rash [OR = 0.43 (0.35, 0.52)], photosensitivity [OR = 0.72 (0.59, 0.88)], and livedo reticularis [OR = 0.33 (0.17, 0.64)] were less common in late-onset patients. In contrast, sicca symptoms were more common [OR = 2.45 (1.91, 3.14)]. The mean Newcastle Ottawa Quality Scale score was 6.3 ± 0.5 (scale: 0-9) with high inter-rater reliability for the score (0.96).

CONCLUSIONS:
Overall, cutaneous manifestations are less common in late-onset SLE patients, except sicca symptoms. Future studies should investigate etiologies for this phenomenon including roles of immune senescence, environment, gender, and immunogenetics.

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Cutaneous Involvement and skin photosensitivity in SLE

Marzia Caproni

SOS Immunopatologia Cutanea e Malattie Rare Dermatologiche
U.O. Dermatologia I – P.O. Piero Palagi  USL Toscana Centro - Università di Firenze
<table>
<thead>
<tr>
<th>Criteri ACR 1997</th>
<th>Criteri SLICC 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRITERI CLINICI</strong></td>
<td></td>
</tr>
<tr>
<td>1  Rash malare</td>
<td>1  Lupus cutaneo acuto o LECS</td>
</tr>
<tr>
<td>2  Rash discoide</td>
<td>2  Lupus cutaneo cronico</td>
</tr>
<tr>
<td>3  Fotosensibilità</td>
<td></td>
</tr>
<tr>
<td>4  Ulcere orali e nasofaringee</td>
<td>3  Ulcere orali o nasali</td>
</tr>
<tr>
<td>5  Artriti non erosive di 2 o più articolazioni</td>
<td>4  Alopecia non cicatriziale</td>
</tr>
<tr>
<td>(iperfiche)</td>
<td></td>
</tr>
<tr>
<td>6  Sierositi (pleurite o pericardite)</td>
<td>5  Sinovite o dolorabilità</td>
</tr>
<tr>
<td>7  Disturbi renali (proteinuria &gt;0.5 g/die o 3+</td>
<td>6  Sierositi</td>
</tr>
<tr>
<td>oppure cilindri cellulari)</td>
<td></td>
</tr>
<tr>
<td>8  Disturbi neurologici (crisi convulsive oppure</td>
<td>7  Manifestazioni renali (Proteinuria 500mg/24h</td>
</tr>
<tr>
<td>psicosi)</td>
<td>oppure cilindri urinari)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8  Disturbi neurologici (Epilessia, psicosi,</td>
</tr>
<tr>
<td></td>
<td>mononeurite multipla; mielite periferica o neuropatia</td>
</tr>
<tr>
<td></td>
<td>nervi cranici; stato confusione)</td>
</tr>
<tr>
<td></td>
<td>Disordini ematologici (anemia emolitica con reticolocitosi, oppure leucopenia &lt;4000/(\mu)l in due occasioni, oppure linfopenia &lt;1500/(\mu)l in due occasioni, oppure trombocitopenia &lt;100000/(\mu)l)</td>
</tr>
<tr>
<td>---</td>
<td>-----------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>9</td>
<td>Anemia emolitica</td>
</tr>
<tr>
<td>10</td>
<td>Leucopenia &lt;4000/(\mu)l almeno una volta, oppure linfopenia &lt;1500/(\mu)l almeno una volta</td>
</tr>
<tr>
<td>11</td>
<td>Trombocitopenia &lt;100000/(\mu)l almeno una volta</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CRITERI IMMUNOLOGICI</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Disordini Immunologici (anticorpi anti-dsDNA, oppure anticorpi anti-Sm, oppur positività di anticorpi antifosfolipidi, LAC o falsa positività al test sierologico per la sifilide</td>
</tr>
<tr>
<td>11</td>
<td>Anticorpi antinucleo</td>
</tr>
<tr>
<td>1</td>
<td>Anticorpi antinucleo</td>
</tr>
<tr>
<td>2</td>
<td>Anticorpi anti-dsDNA</td>
</tr>
<tr>
<td>3</td>
<td>Anticorpi anti-Sm</td>
</tr>
<tr>
<td>4</td>
<td>Positività per anticorpi antifosfolipidi</td>
</tr>
<tr>
<td>5</td>
<td>Riduzione del complemento (C3, C4, CH50)</td>
</tr>
<tr>
<td>6</td>
<td>Positività del test di Coombs diretto</td>
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