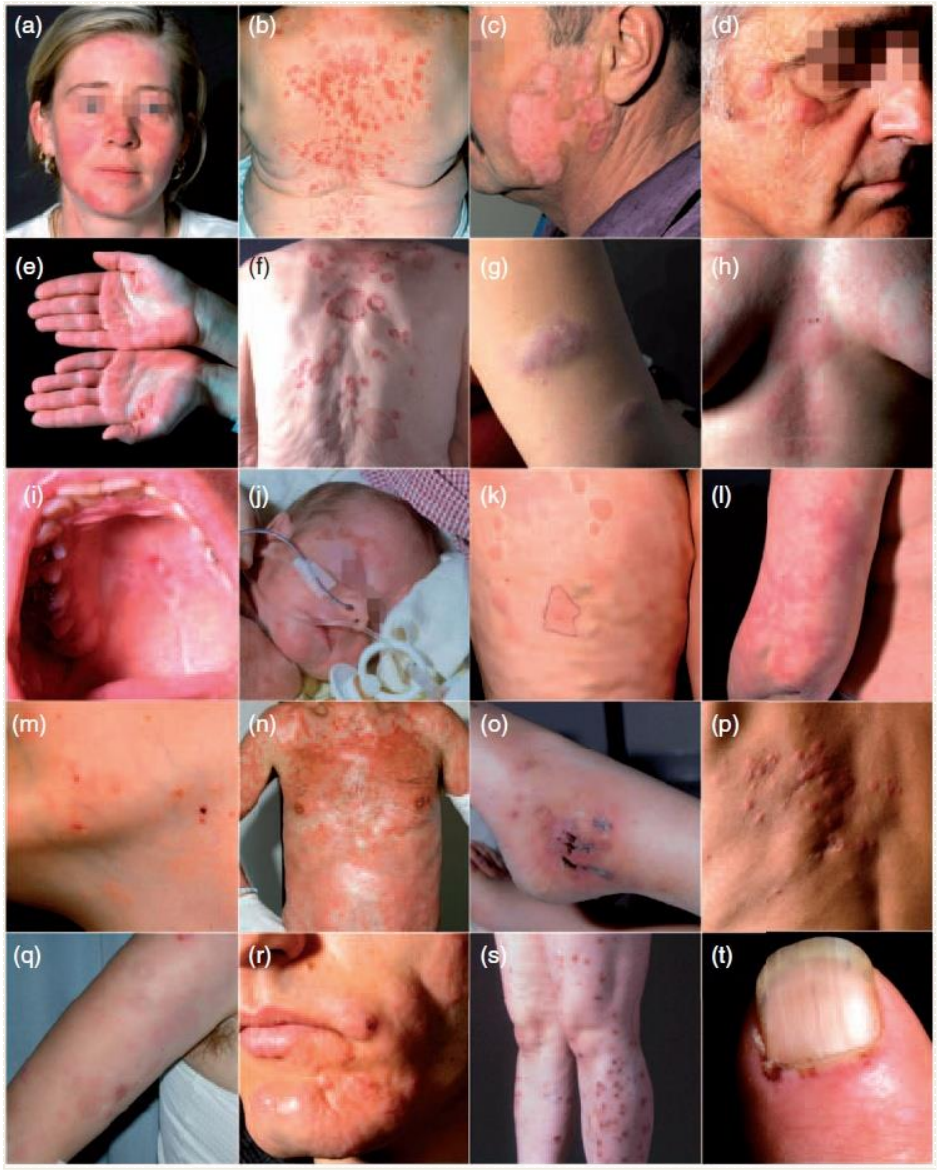
Lupus Eritematoso Cutaneo: Manifestazioni Cliniche e Nuove Linee Terapeutiche

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



CLE: is the polar form of a real **heterogeneous spectrum** of diseases defined as Lupus

Cutaneous Lupus Erythematosus

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

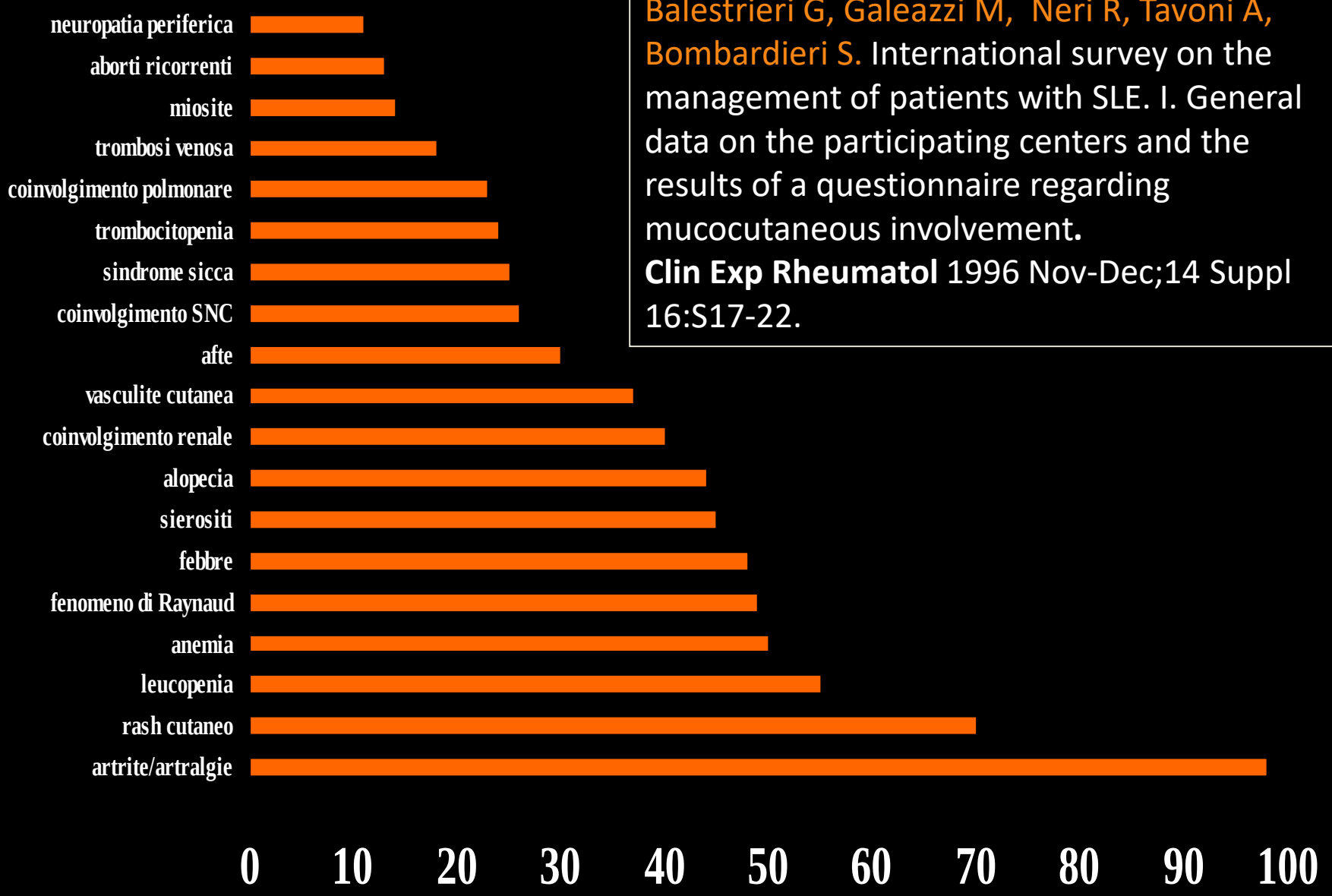
- Lupus Clinic of Florence: In the province of Florence (during the observation period of 2010) considering a population of approx 970.000 inhabitants - the sample studied included primary care patients - SLE incidence was 5,4/100.000 and the prevalence was 75/100.000 (Emmi L et al.)

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

A systematic review and meta-analysis of cutaneous manifestations in late- versus early-onset systemic lupus erythematosus. Semin Arthritis Rheum. 2016 Jan 21.

Cumulative prevalence of clinical manifestations of SLE (704 pz))



Vitali C, Doria A, , Tincani A, Fabbri P, Balestrieri G, Galeazzi M, Neri R, Tavoni A, Bombardieri S. International survey on the management of patients with SLE. I. General data on the participating centers and the results of a questionnaire regarding mucocutaneous involvement**.**
Clin Exp Rheumatol 1996 Nov-Dec;14 Suppl 16:S17-22.

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

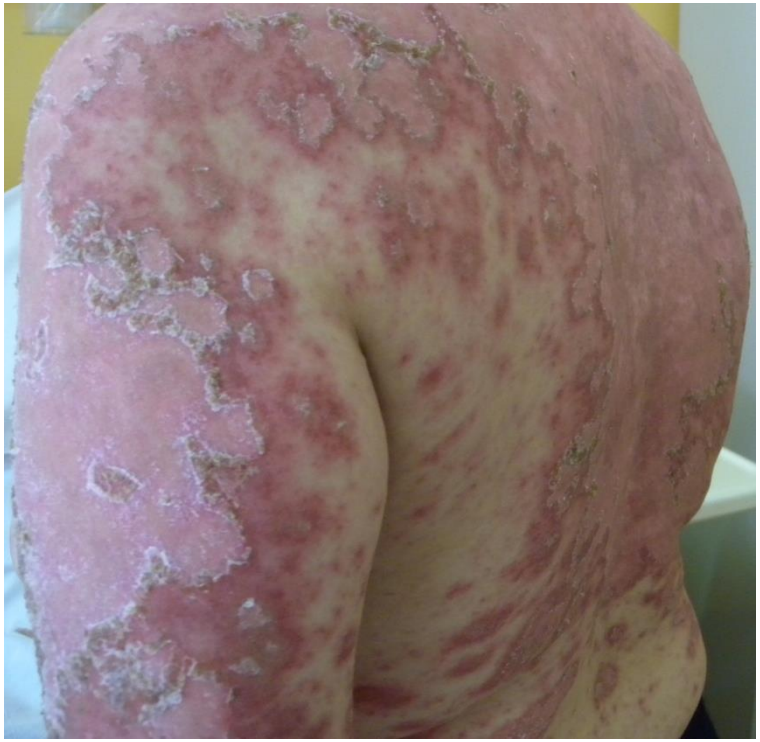
Table 4. Frequency distribution of selected ACR criteria by ethnic group when only a given number of criteria are present*

Number and type of criteria	Hispanic		African American	Caucasian	*P*
	Texas	Puerto Rico			
One criterion, no.	49	35	94	83	
Discoid rash	2.0	2.9	6.4	0	0.0452
Photosensitivity	12.2	51.4	5.3	24.1	< 0.0001
Mucosal ulcers	6.1	0	2.1	15.7	0.0007
Arthritis	42.9	22.9	43.6	24.1	0.0103
Two criteria, no.	16	9	38	31	
Malar rash	25.0	0	10.5	45.2	0.0011
Photosensitivity	12.5	33.3	13.2	54.9	0.0007
Three criteria, no.	12	8	17	7	
Discoid rash	0	0	29.4	0	0.0144
Arthritis	75	25.0	35.3	71.4	0.0449
Four criteria, no.	26	3	27	16	
Renal	34.6	0	51.9	6.3	0.0041
Hematologic	57.7	0	59.3	25.0	0.0200
Immunologic	80.8	33.3	81.5	37.5	0.0064
Total number of patients	103	55	176	137	

* Only those criteria achieving a $P \leq 0.05$ are shown. ACR = American College of Rheumatology.

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

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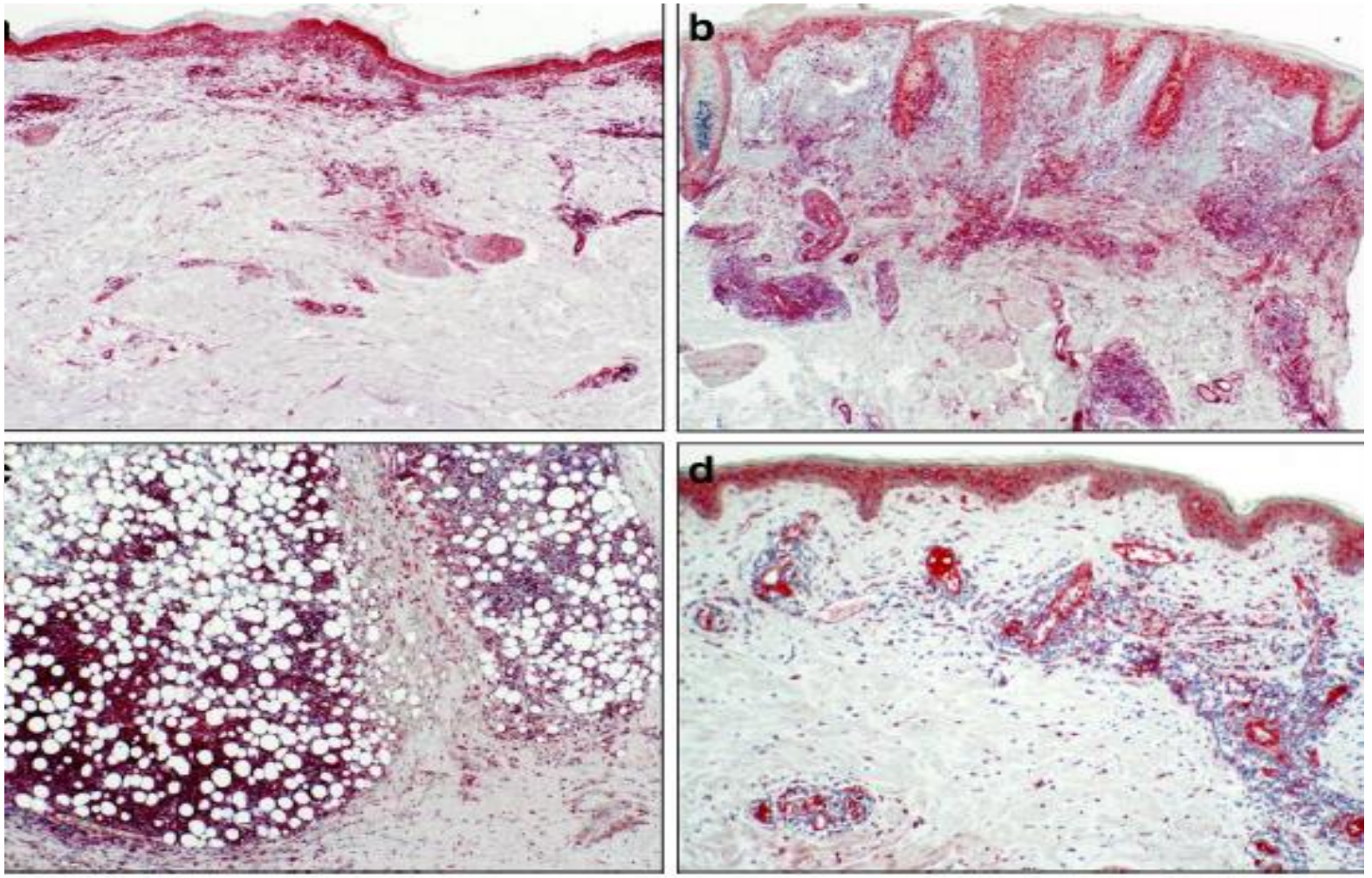
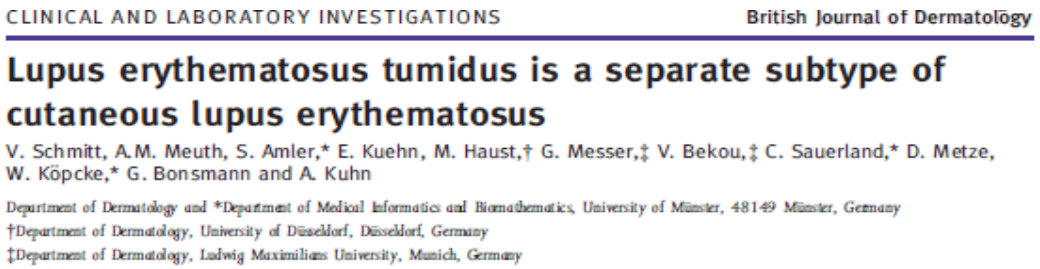


LE-specific manifestations

- 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



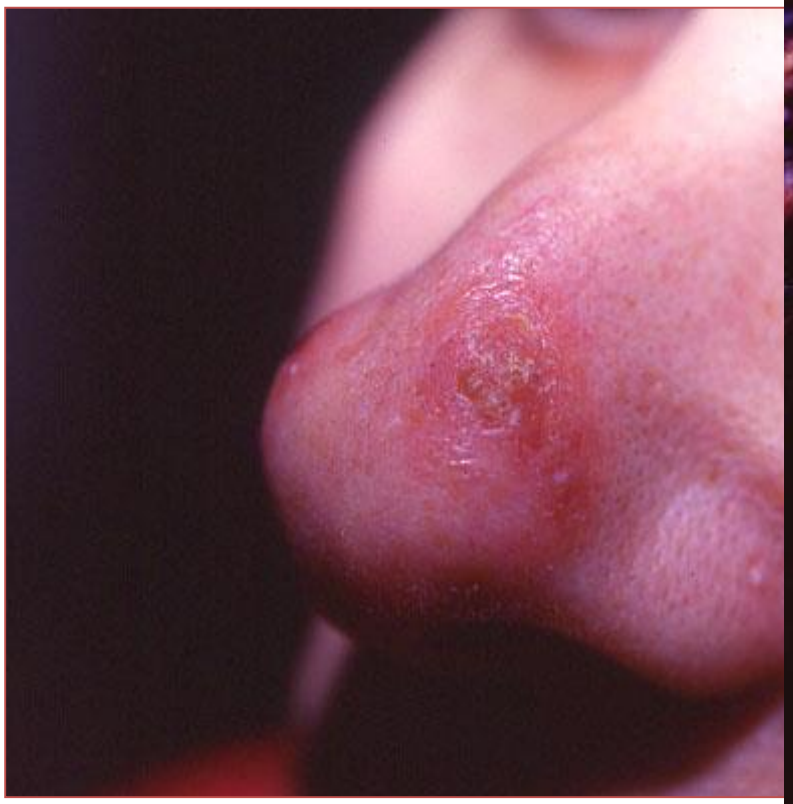
CLINICAL AND LABORATORY INVESTIGATIONS British Journal of Dermatology

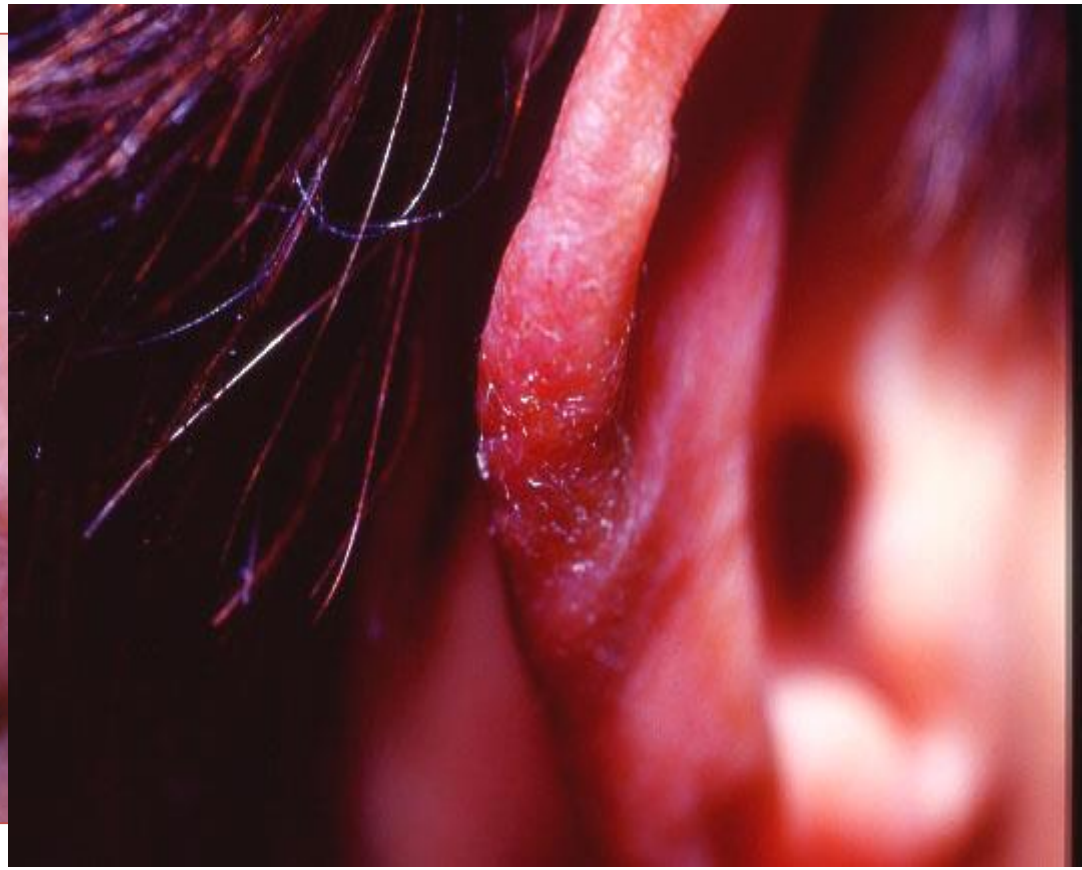
Lupus erythematosus tumidus is a separate subtype of cutaneous lupus erythematosus

V. Schmitt, A.M. Meuth, S. Amler,* E. Kuehn, M. Haust,† G. Messer,‡ V. Bekou,‡ C. Sauerland,* D. Metze, W. Köpcke,* G. Bonsmann and A. Kuhn

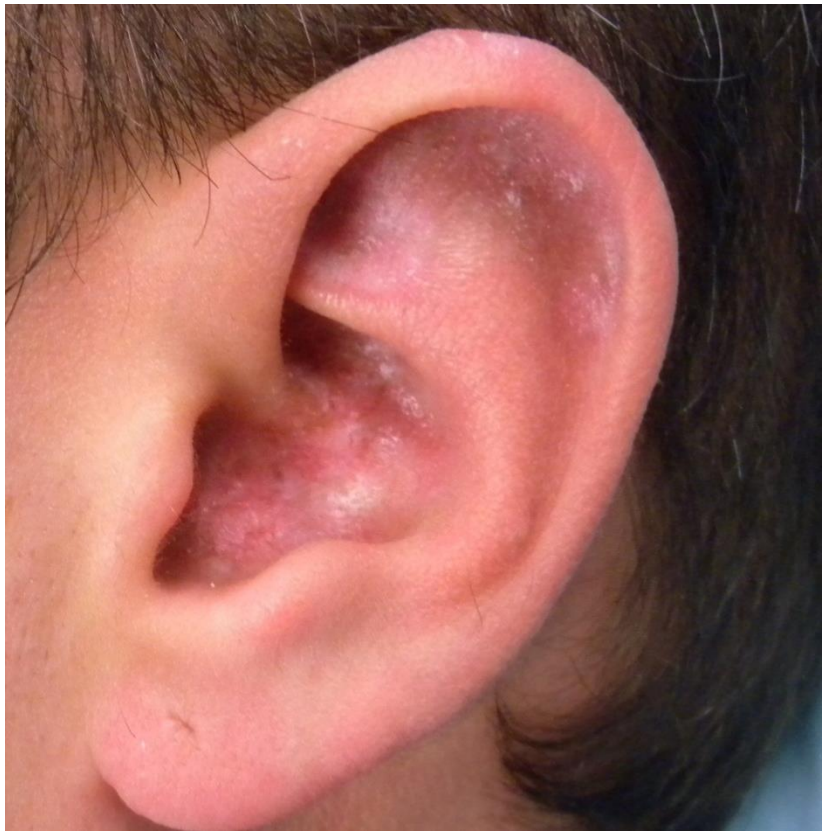
Department of Dermatology and *Department of Medical Informatics and Biomathematics, University of Münster, 48149 Münster, Germany
†Department of Dermatology, University of Düsseldorf, Düsseldorf, Germany
‡Department of Dermatology, Ludwig Maximilians University, Munich, Germany

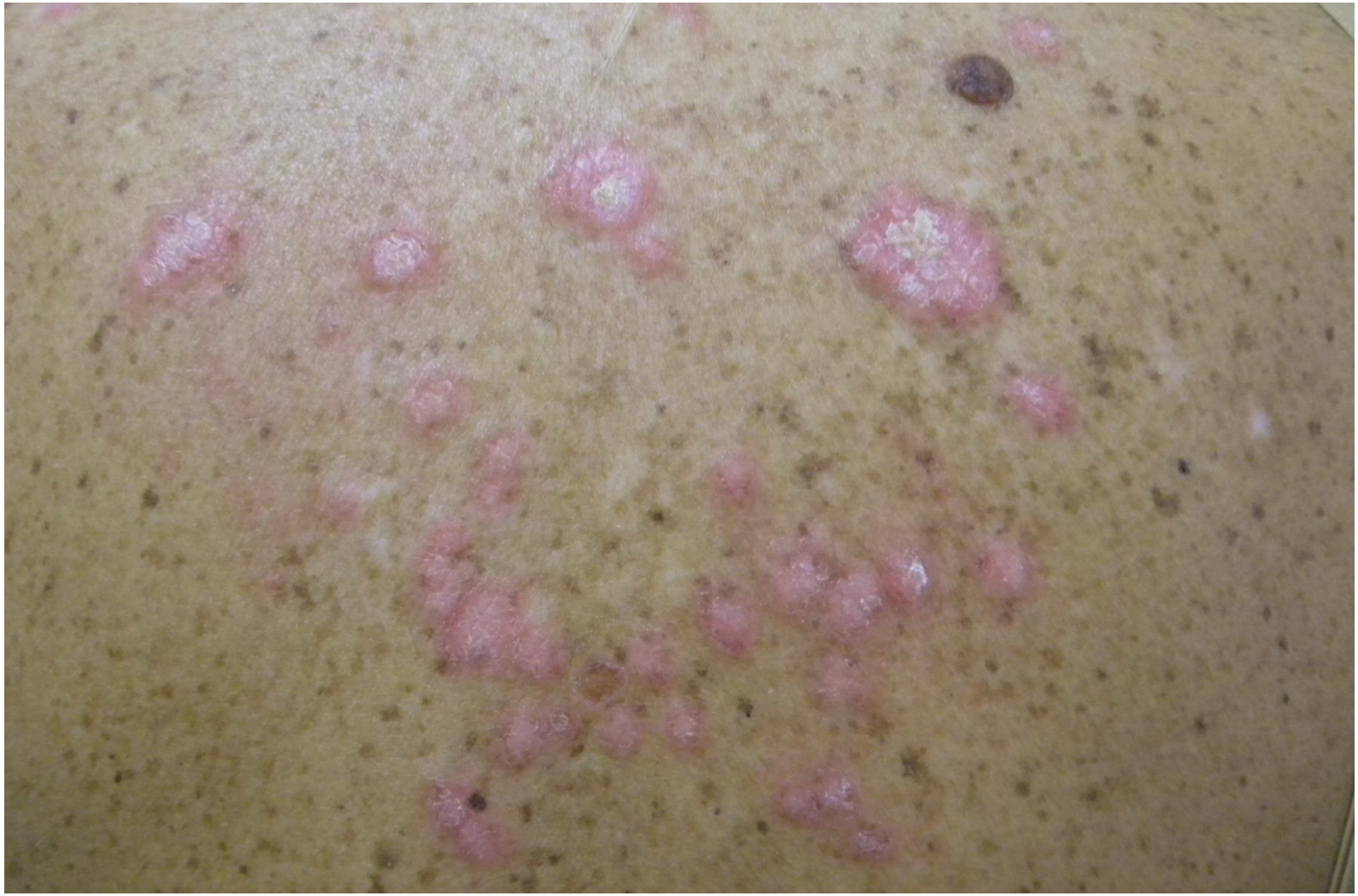
Chronic Cutaneous LE (CCLE)





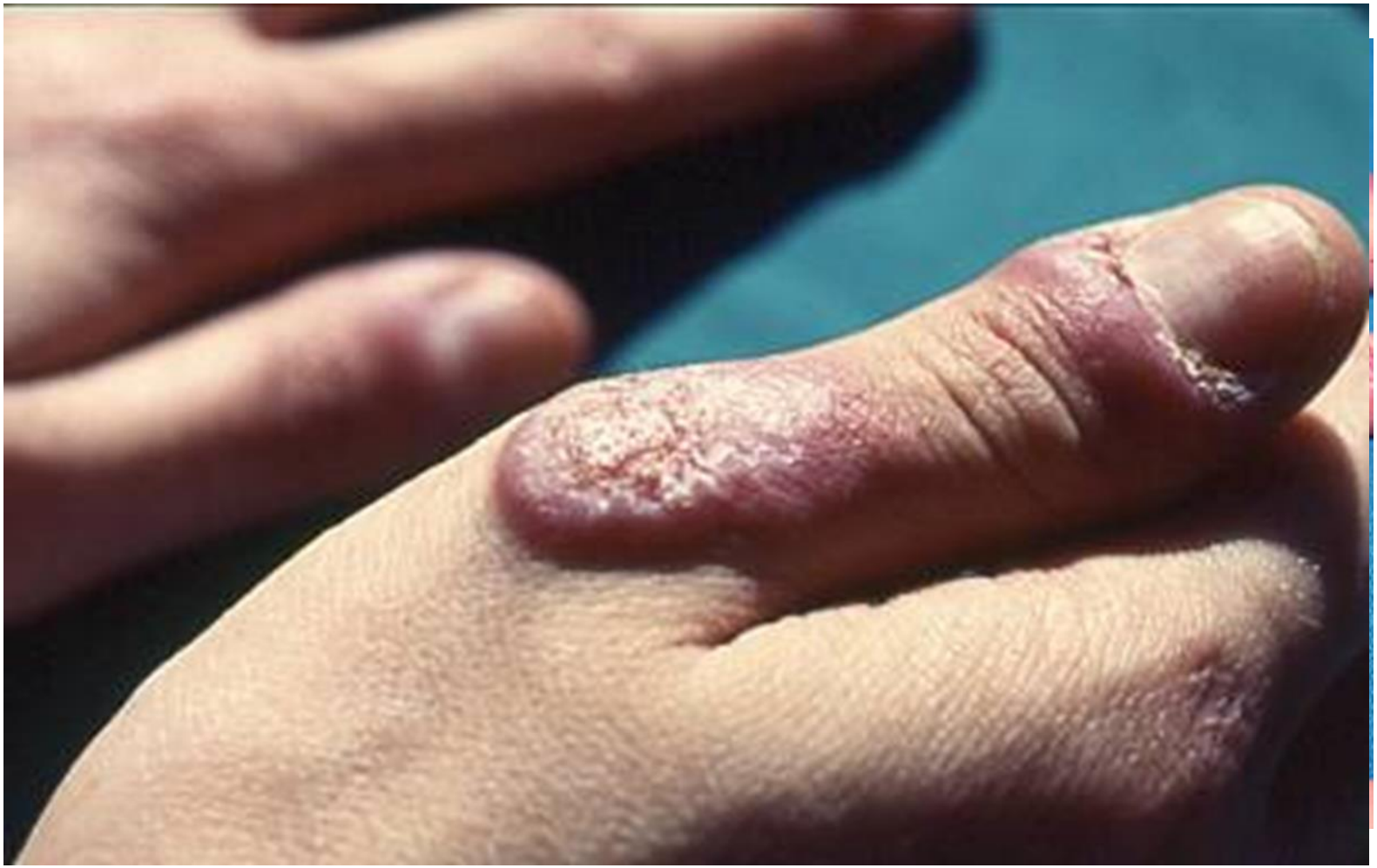
LUPUS ERITEMATOSO DISCOIDE



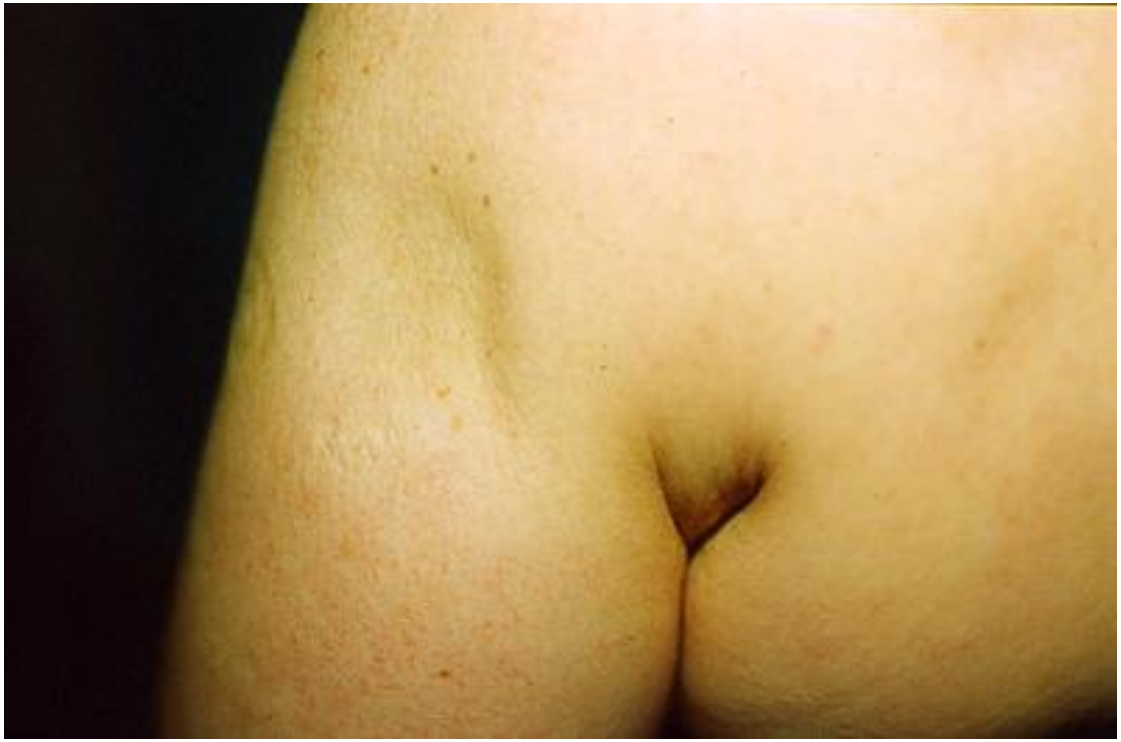


LUPUS ERITEMATOSO DISCOIDE DISSEMINATO Discoid

Lupus Erythematosus Discoid Disseminated



HYPERTROPHIC or VERRUCOUS LE



Lupus Profundus

Autoimmunity Reviews 12 (2013) 444–454

Contents lis

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Review

Cutaneous lupus erythematosus: Fi from the European Society of Cuta

Cyrus Biazar [a], Johanna Sigges [a], Nikolaos Pa
Gisela Bonsmann [a], Annegret Kuhn [a,*]
and the EUSCLE co-authors [1]

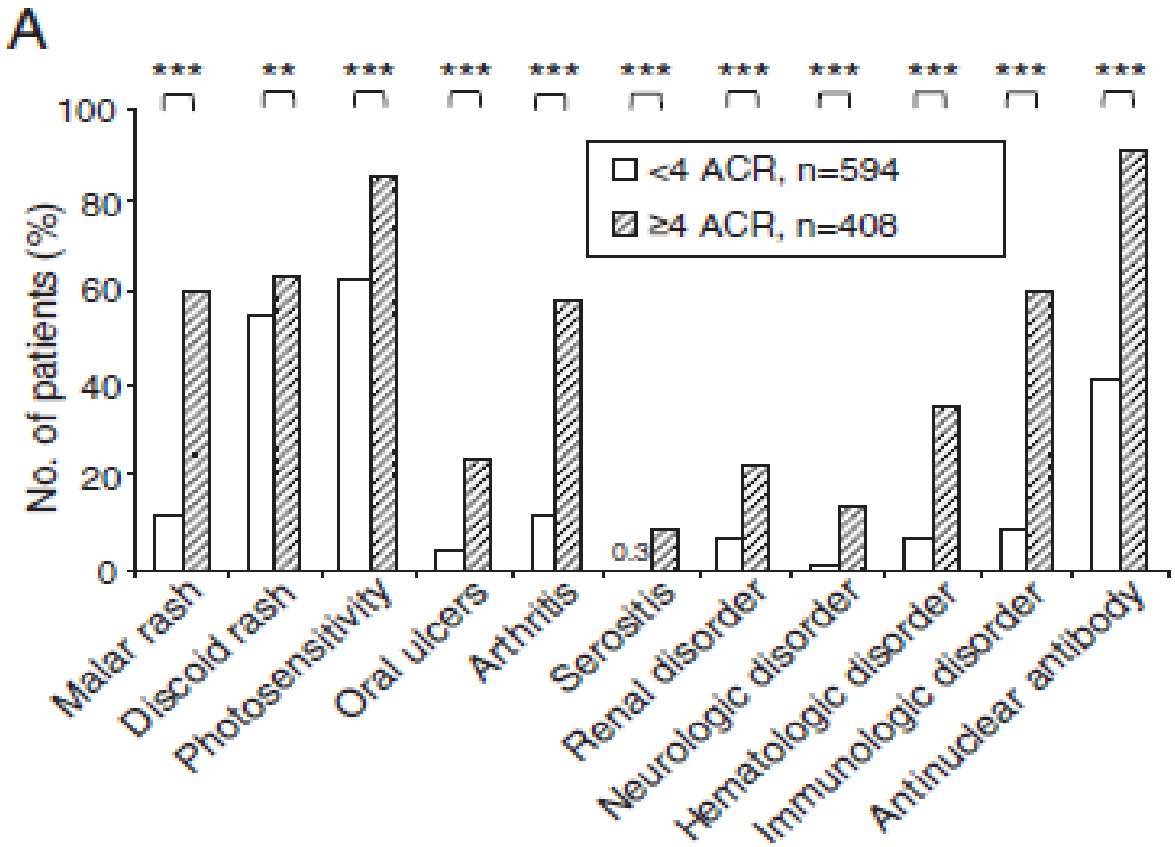


Fig. 3. A) Percentages of patients fulfilling the ACR criteria. The 11 ACR criteria are listed with respect to the percentages of patients who fulfilled each criterion in the subgroup of patients who fulfilled four or more or fewer than four ACR criteria, respectively. **B) Percentages of CLE patients 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

Dermatology

Dermatology 2000:200:6–10

Received: June 2, 1999
Accepted: October 13, 1999

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[c] Cristina Zane[c] Manuela Papini[d]
Farnase Cleto Veller[e] Mario Vaccaro[f] Paolo Fabbri[b]

Table 1. Cutaneous changes in SCLE patients

SCLE	
Annular type	42%
Psoriasiform type	39%
Annular and psoriasiform type	16%
Pityriasiform type	1 patient
Exfoliative erythroderma type	1 patient
Malar eruption	12%
Discoid lupus erythematosus lesions	12%
Non-scarring alopecia	5%
Livedo reticularis	7%
Raynaud's phenomenon	12%
Periungual telangiectasia	3%

Table 2. Distribution of SCLE lesions

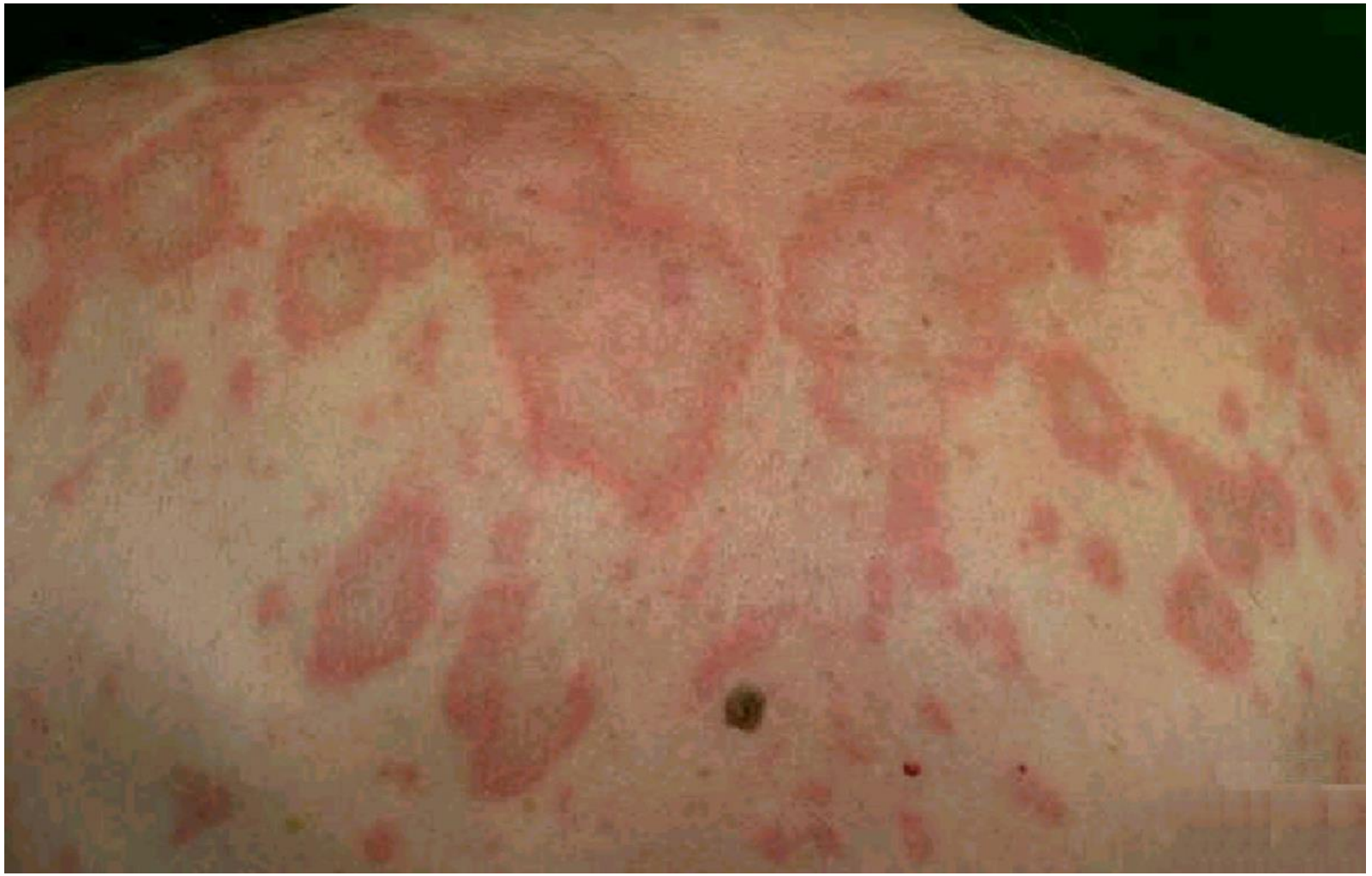
Neck	83%
Face	66%
Arms (extensor surfaces)	39%
Hands (dorsum)	21%
Lower limbs	16%
Scalp	12%

SLE in 30% of the patients 3,4% mammary carcinoma

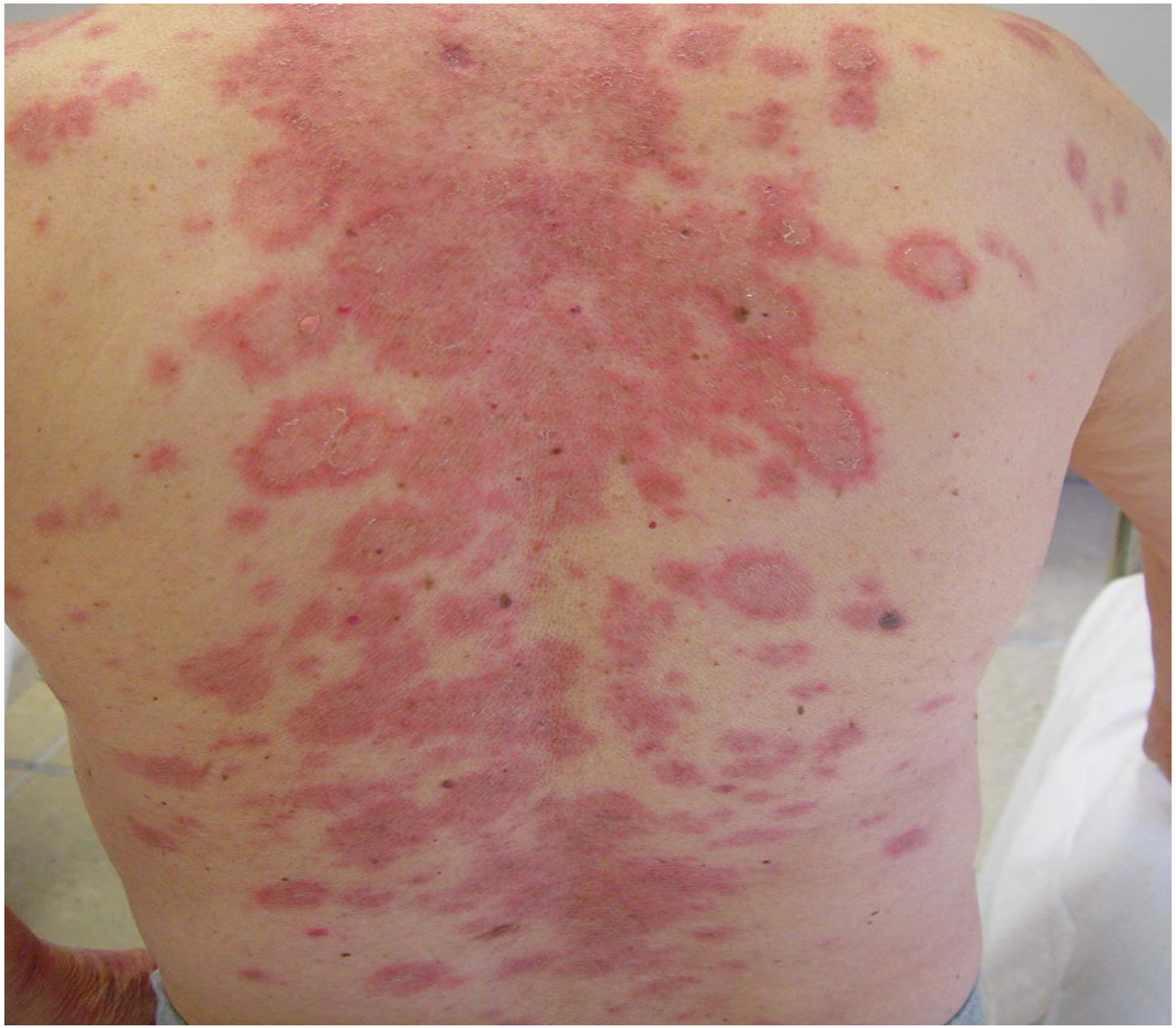
Classical forms of SCLE

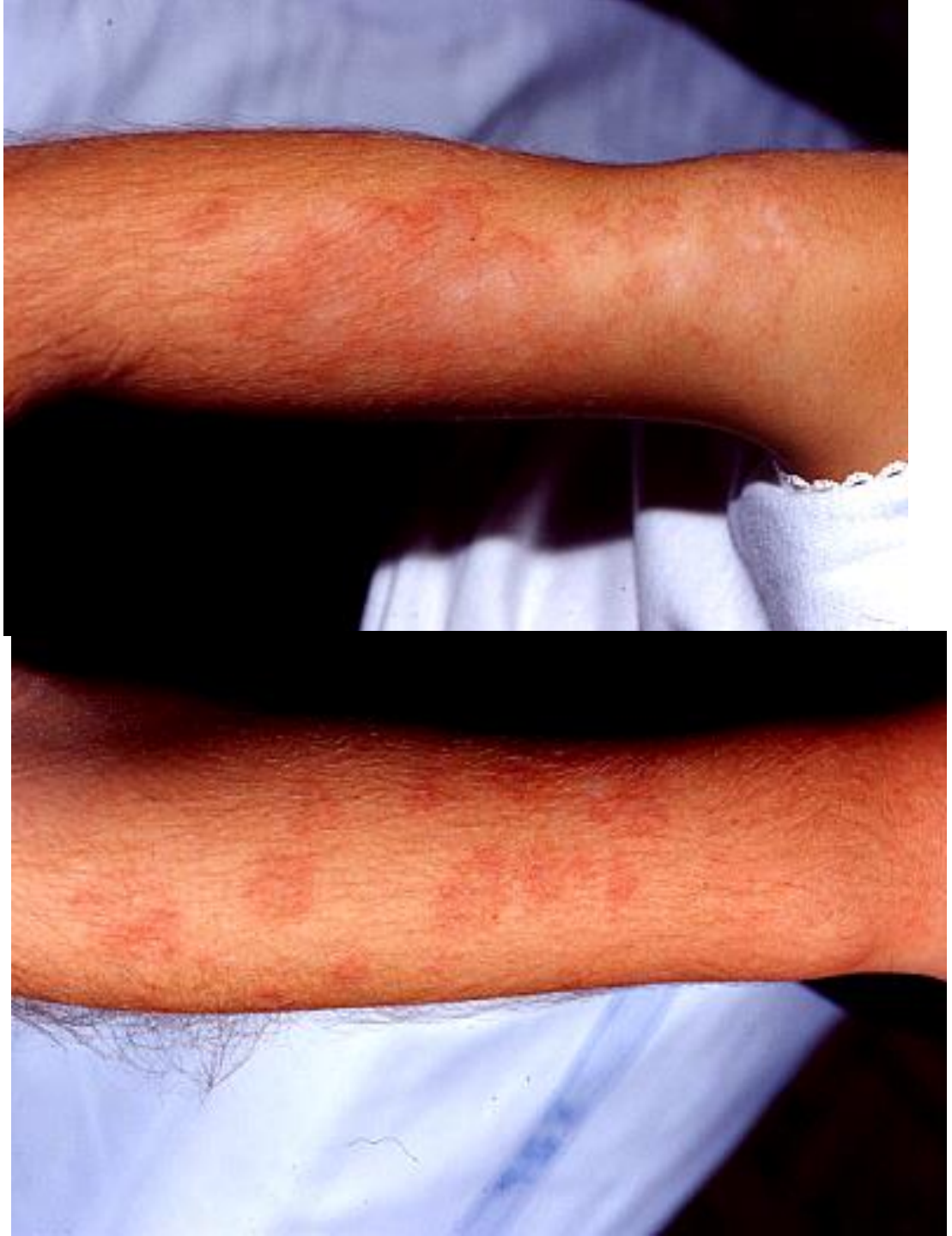
- Annular-polyciclic
- Psoriasiform
- Mixed forms

Annular polyciclic variant

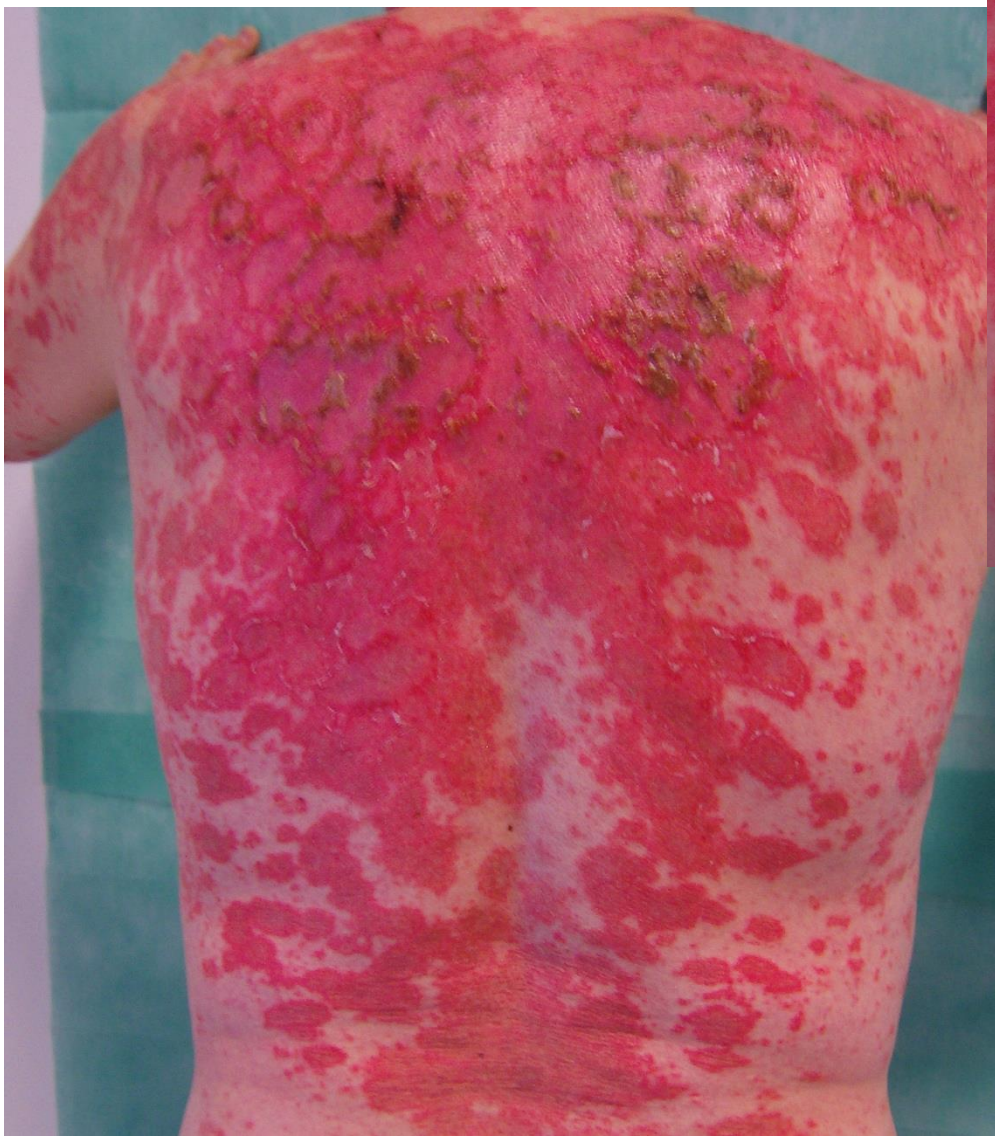


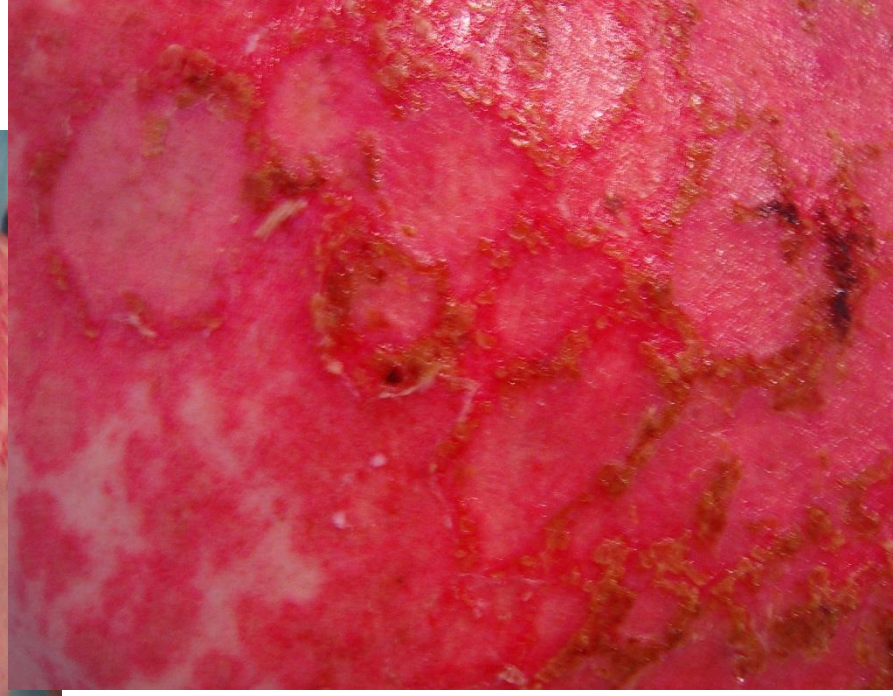
Annular polyciclic variant



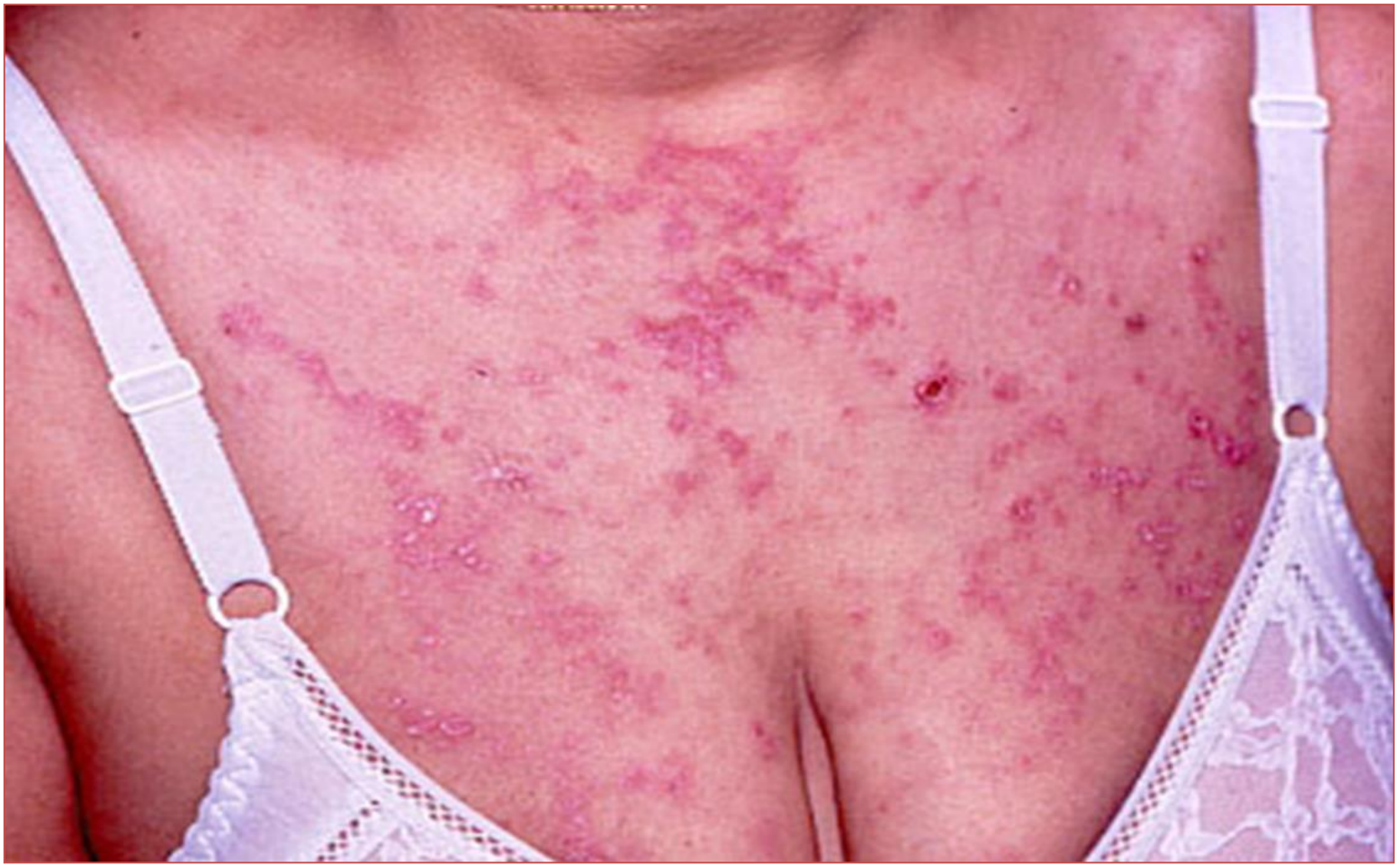


Subacute cutaneous lupus erythematosus in childhood.
Fabbri P et al. Pediatr Dermatol 2003 Jan.-Feb;20(1):31-4.

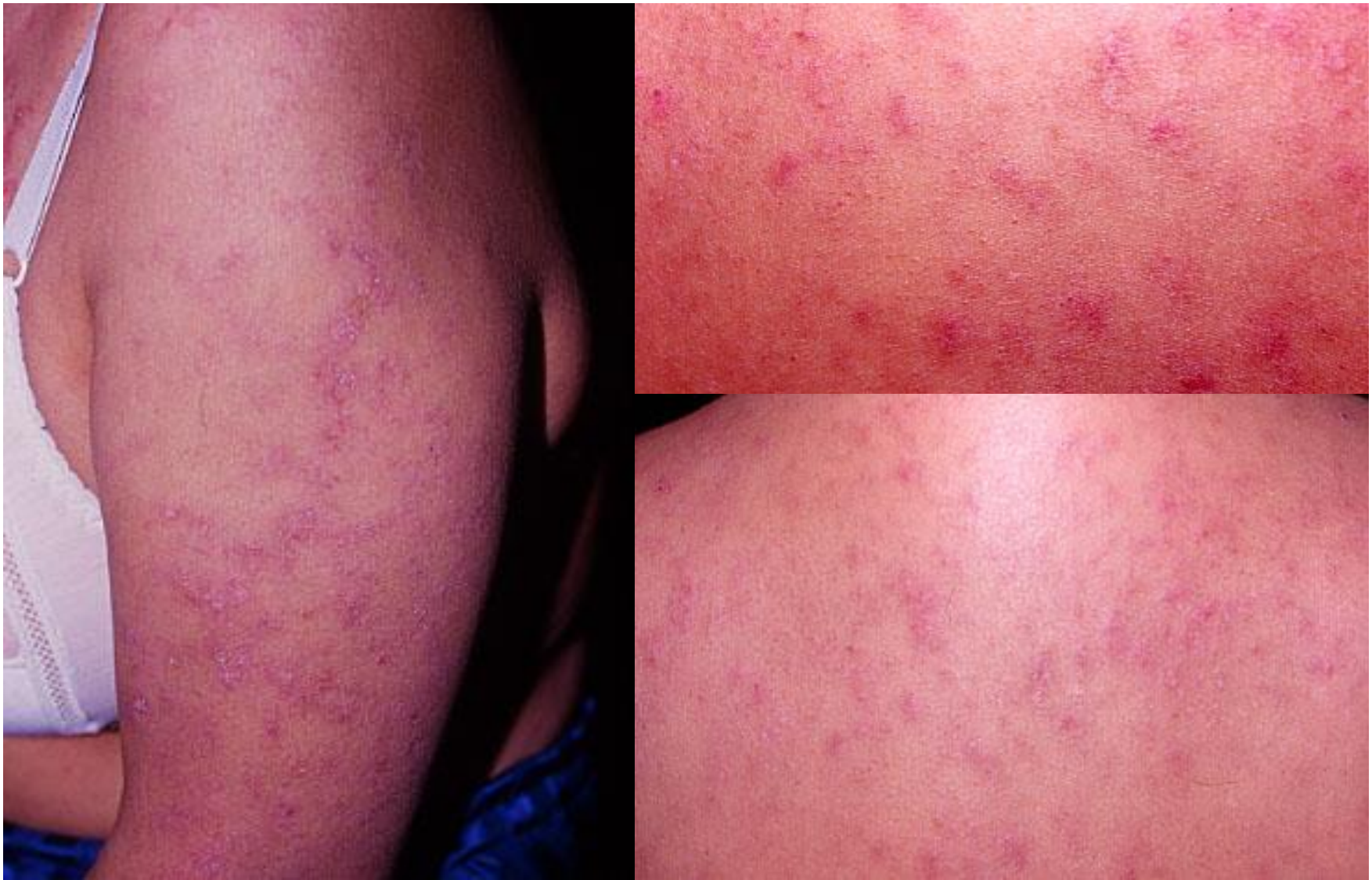




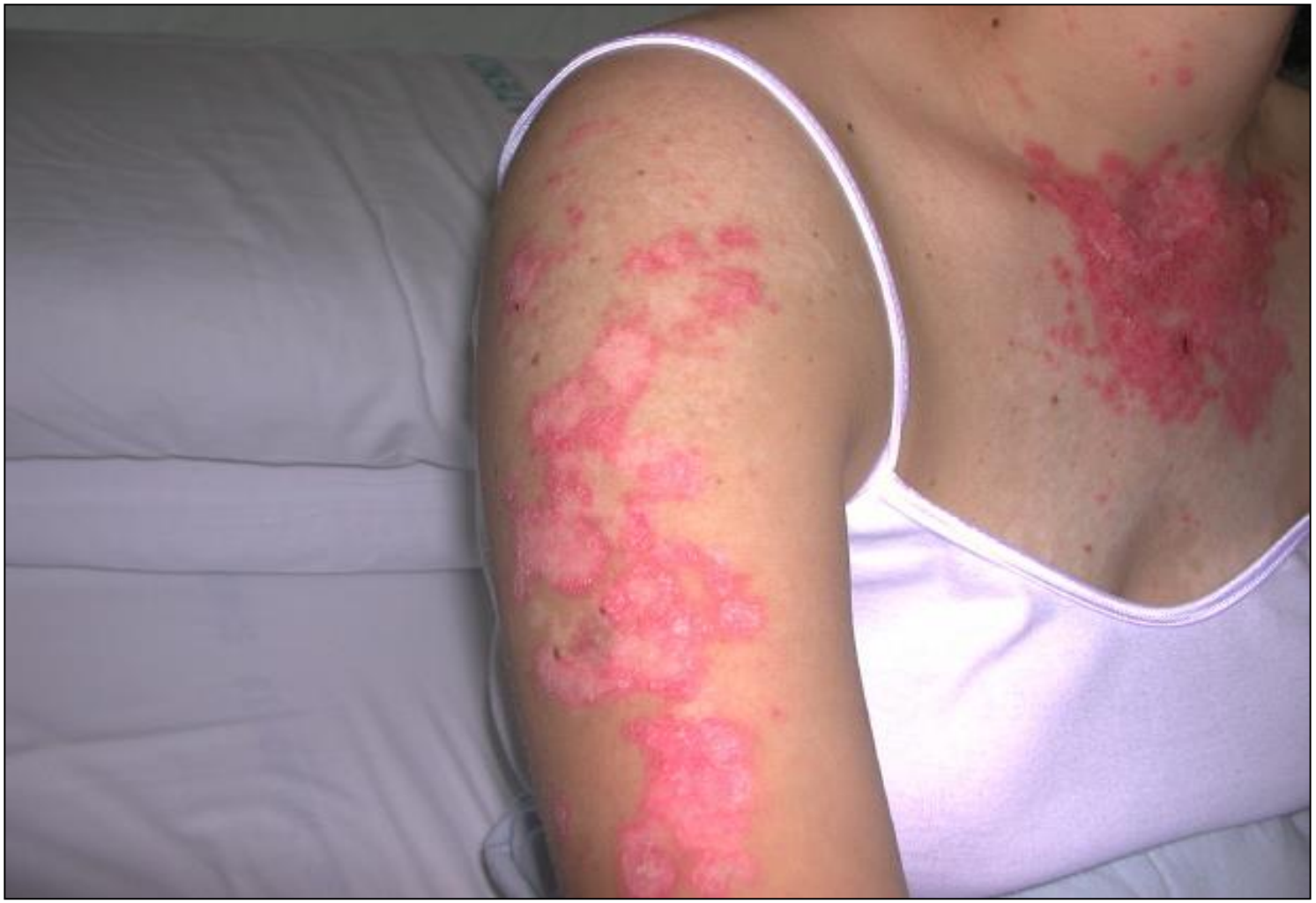
Papulo-squamous or Psoariasiform SCLE



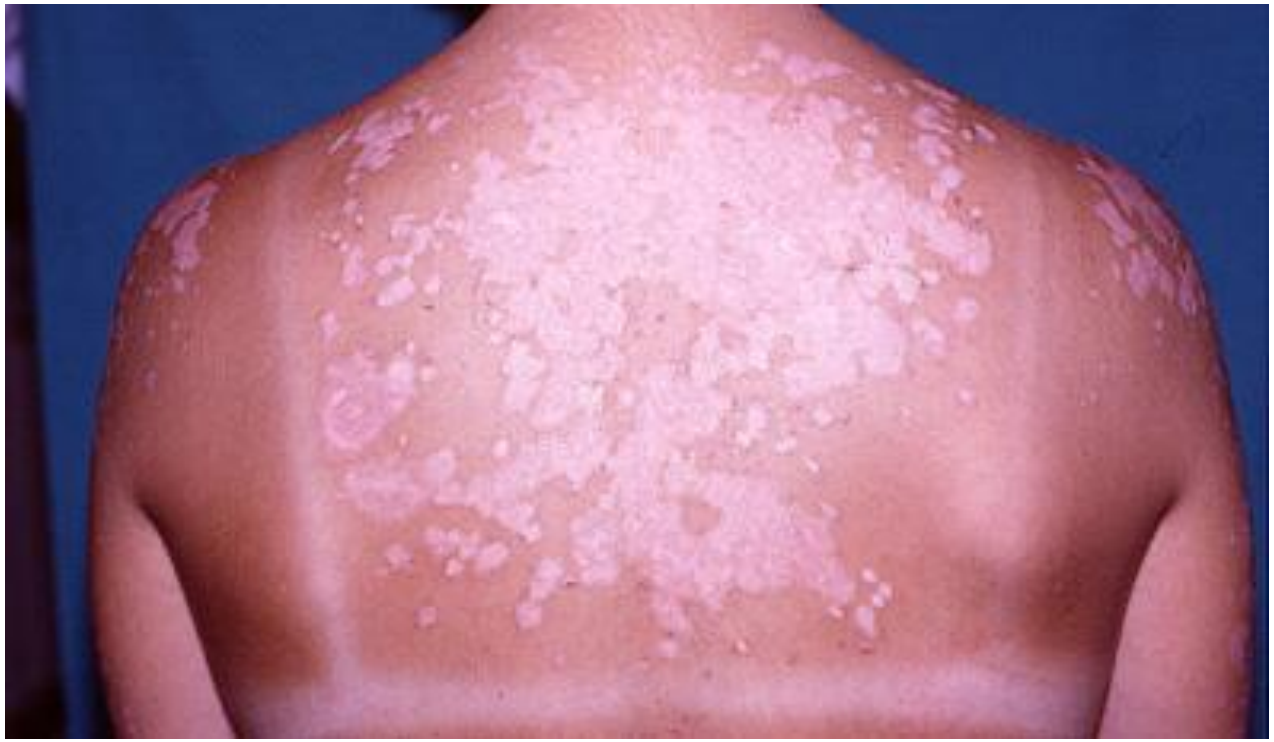
Papulo-squamous variant or Psoariasiform SCLE



Papulo-sqamous or Psoriasiform SCLE



Hypopigmentation



Hypopigmentation that follows active lesions; it can be considered «a clue» but have to be distinguished from pitiriasi versicolor

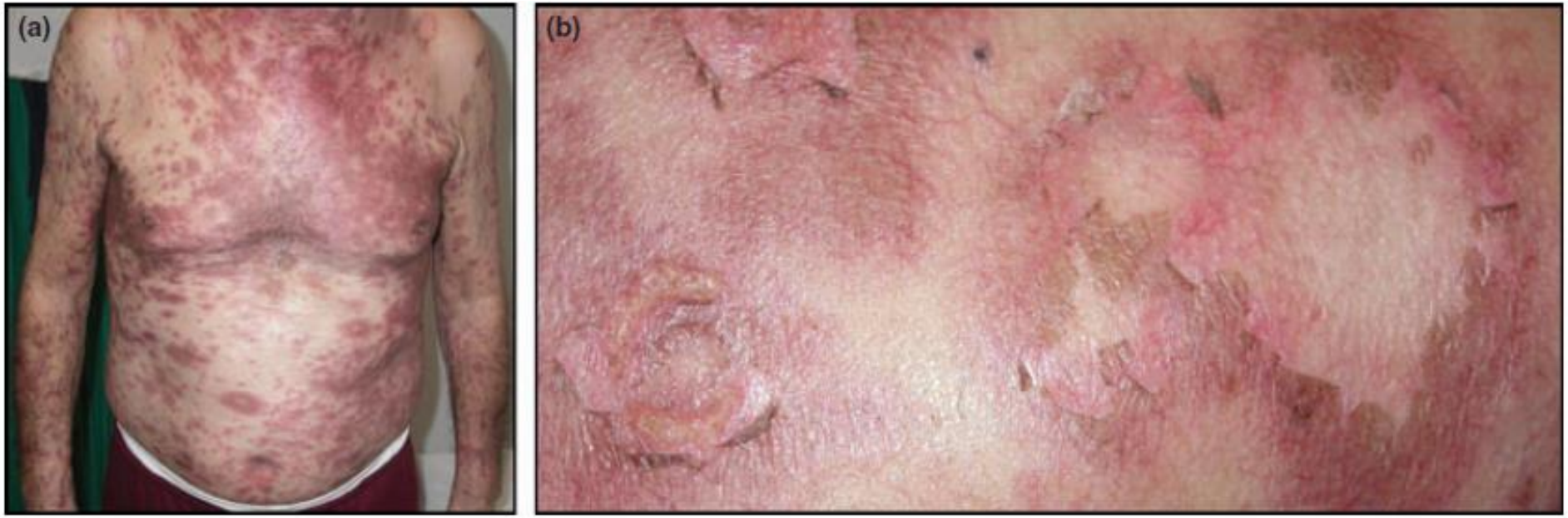
Rare SCLE variants

- 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)

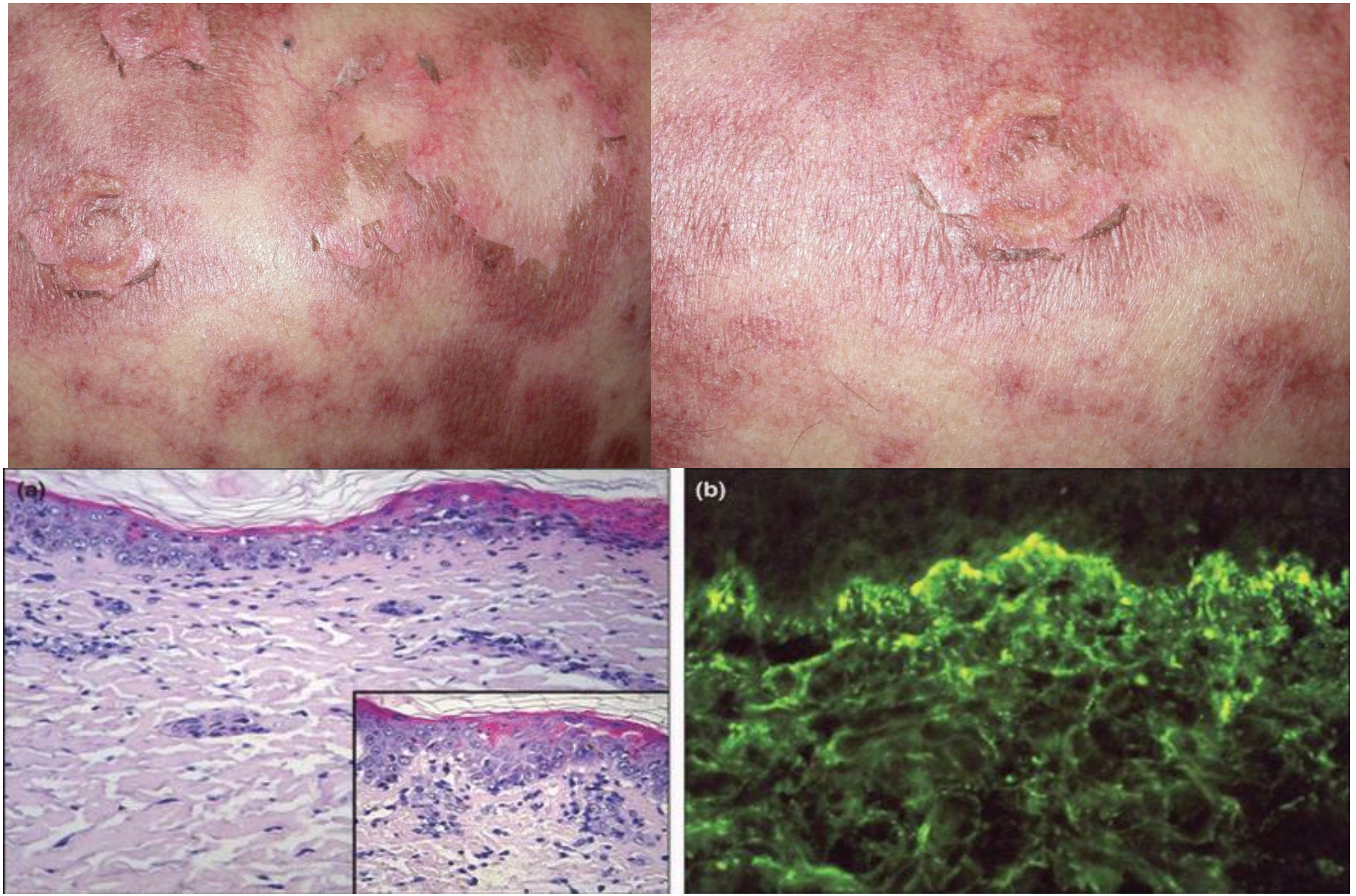
Paraneoplastic toxic epidermal necrolysis-like subacute cutaneous lupus erythematosus

D. Torchia,*,† M. Caproni,* D. Massi,‡ A. Chella§ and P. Fabbri*

*Departments of *Dermatological Sciences, †Experimental Pathology and Oncology, and ‡Human Pathology and Oncology, University of Florence, Florence, Italy; and §Cardio-Thoracic Department, University of Pisa, Pisa, Italy*



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

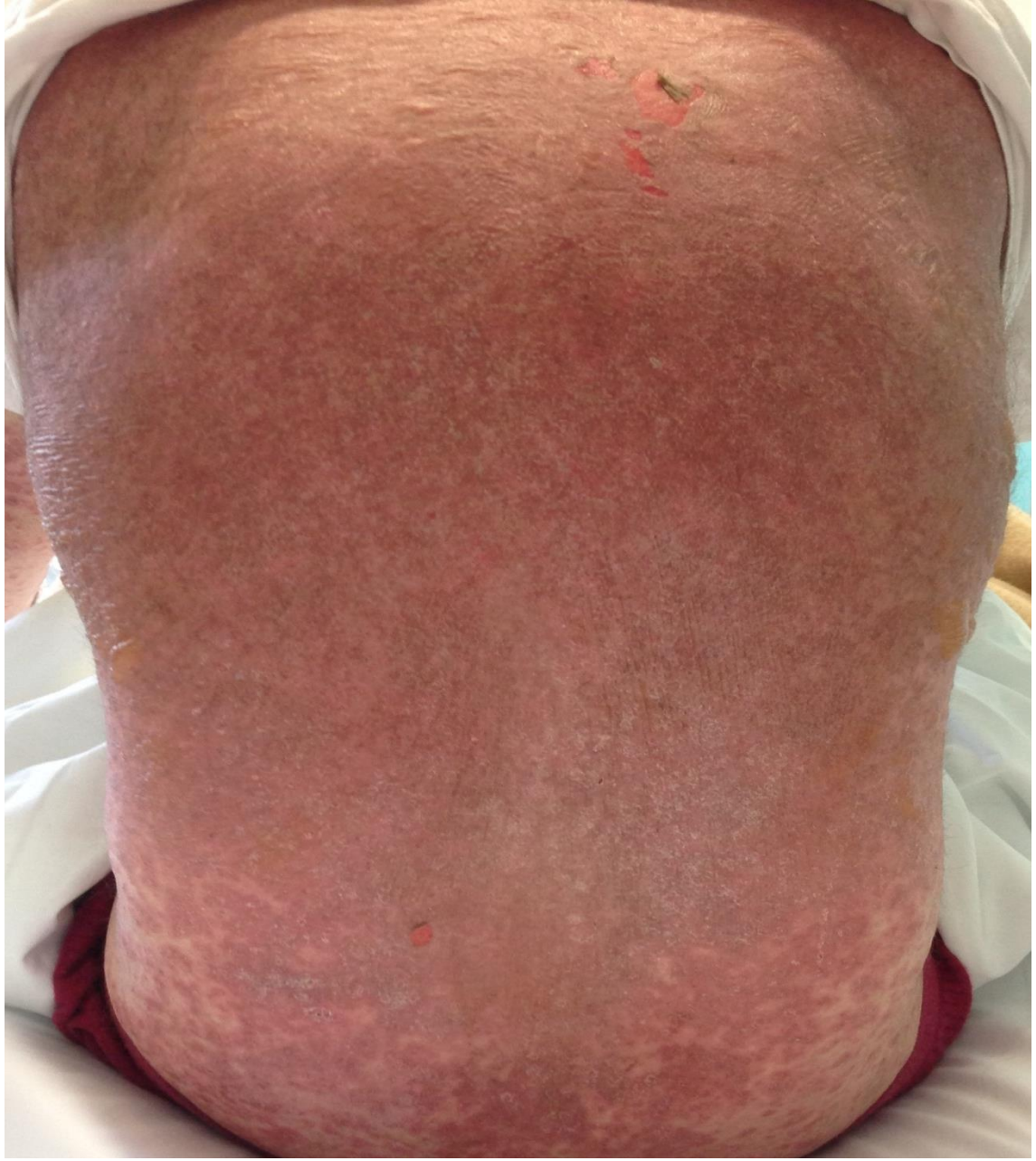


These lesions were associated with erosions partially covered by detached epidermal sheets. Mucous membranes were not involved; histologic and immunofluorescence results were compatible with SCLE

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.



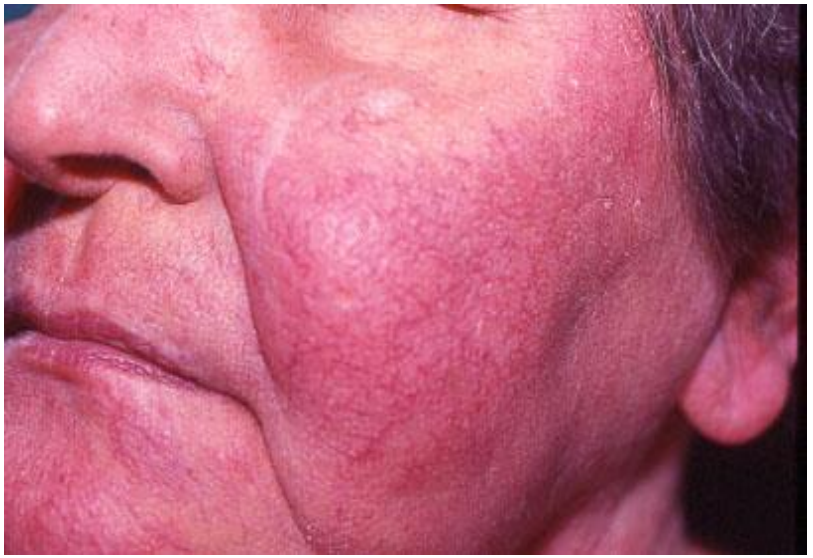
He had a history of lupus without any cutaneous lesions and started with Ten extensive lesions; in this case to make a diagnosis it is essential for the survival of the patient

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)

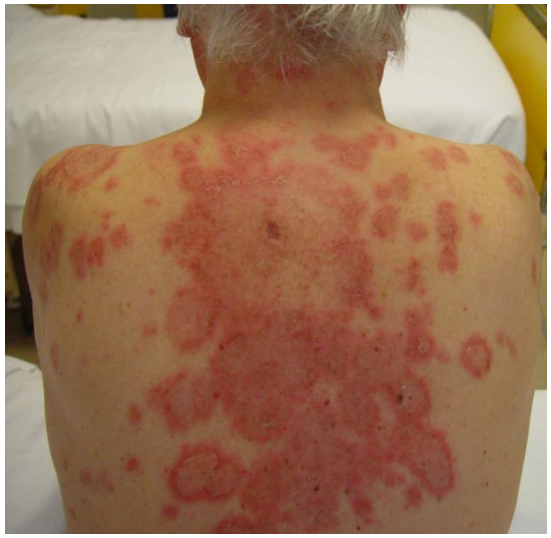
- Subacute cutaneous lupus erythematosus with pityriasis-like cutaneous manifestations
- **Caproni** M, Cardinali C, Salvatore E, Fabbri P. Int J Dermatol. 2001 Jan;40(1):59-62.

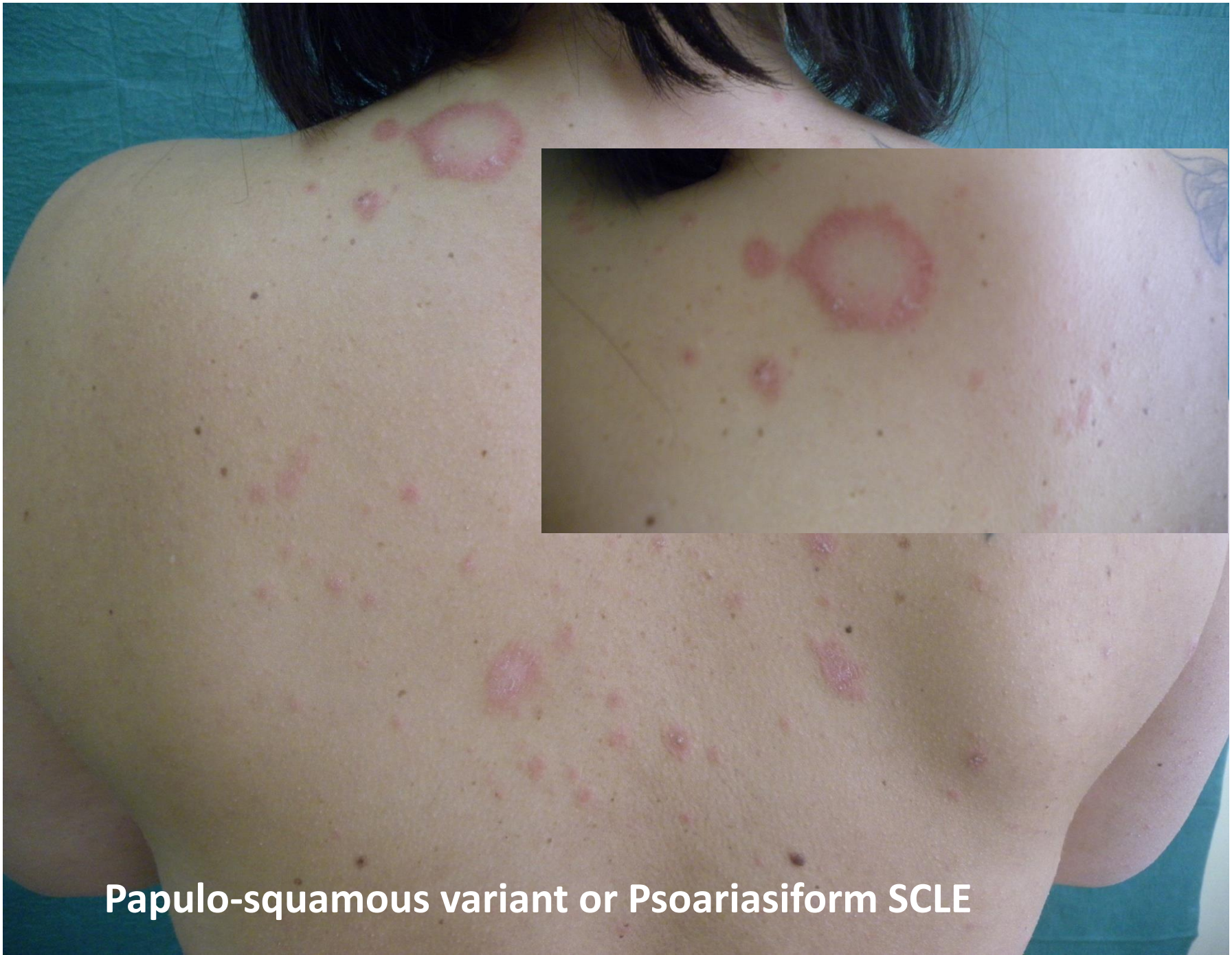
On the upper third of the back, she presented a wide patch with irregular borders, due to many coalescing small purplish-red lesions. Each lesion was covered with branny scales and, on palpation, revealed a variable degree of infiltration. Few areas of uninvolved skin could be seen inside the main patch.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



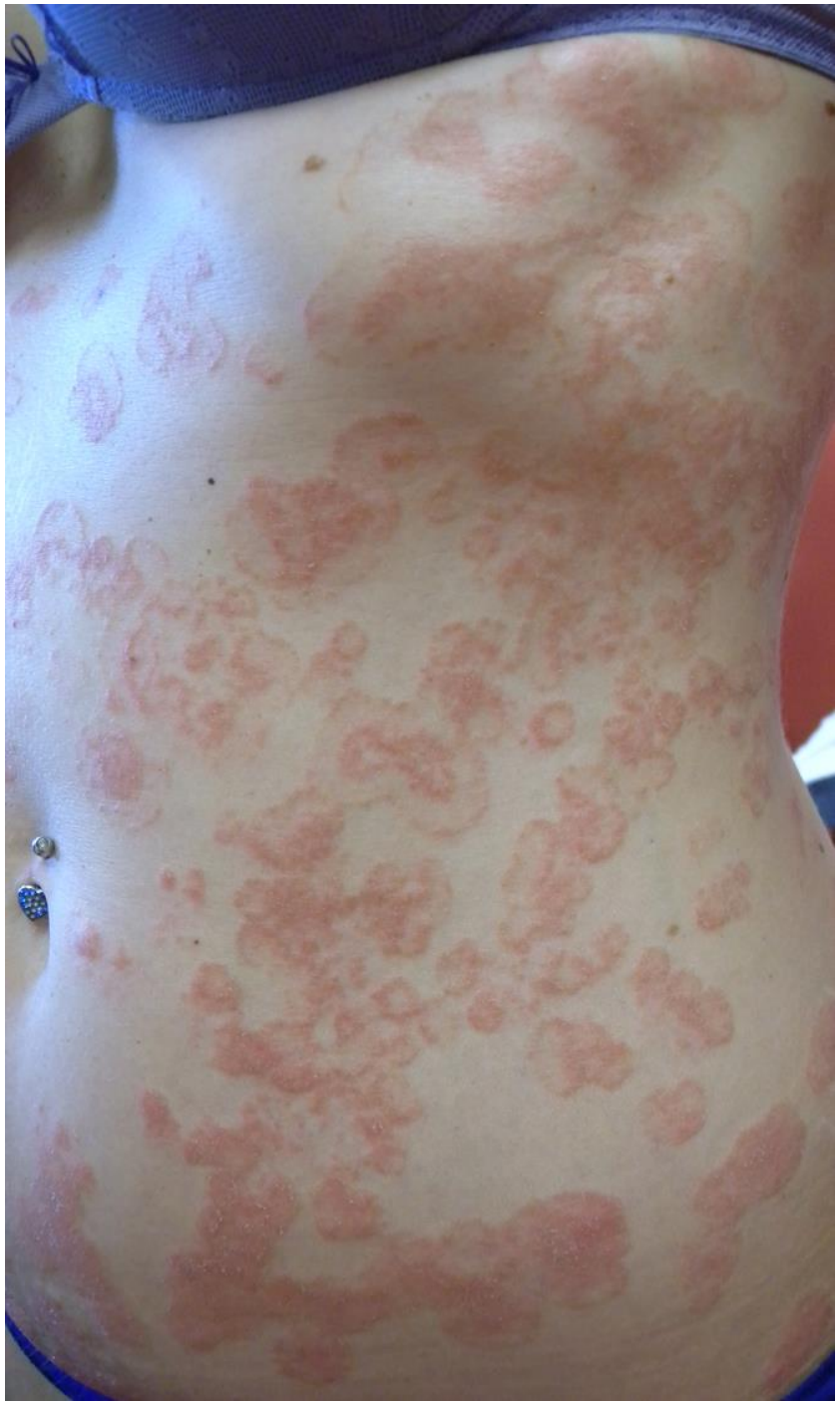
Differential Diagnosis

- Psoriasis
- Seborrheic dermatitis
- Pytiriasis rosea
- Tinea corporis
- Annular erythema centrifugum
- Disseminated annular granuloma

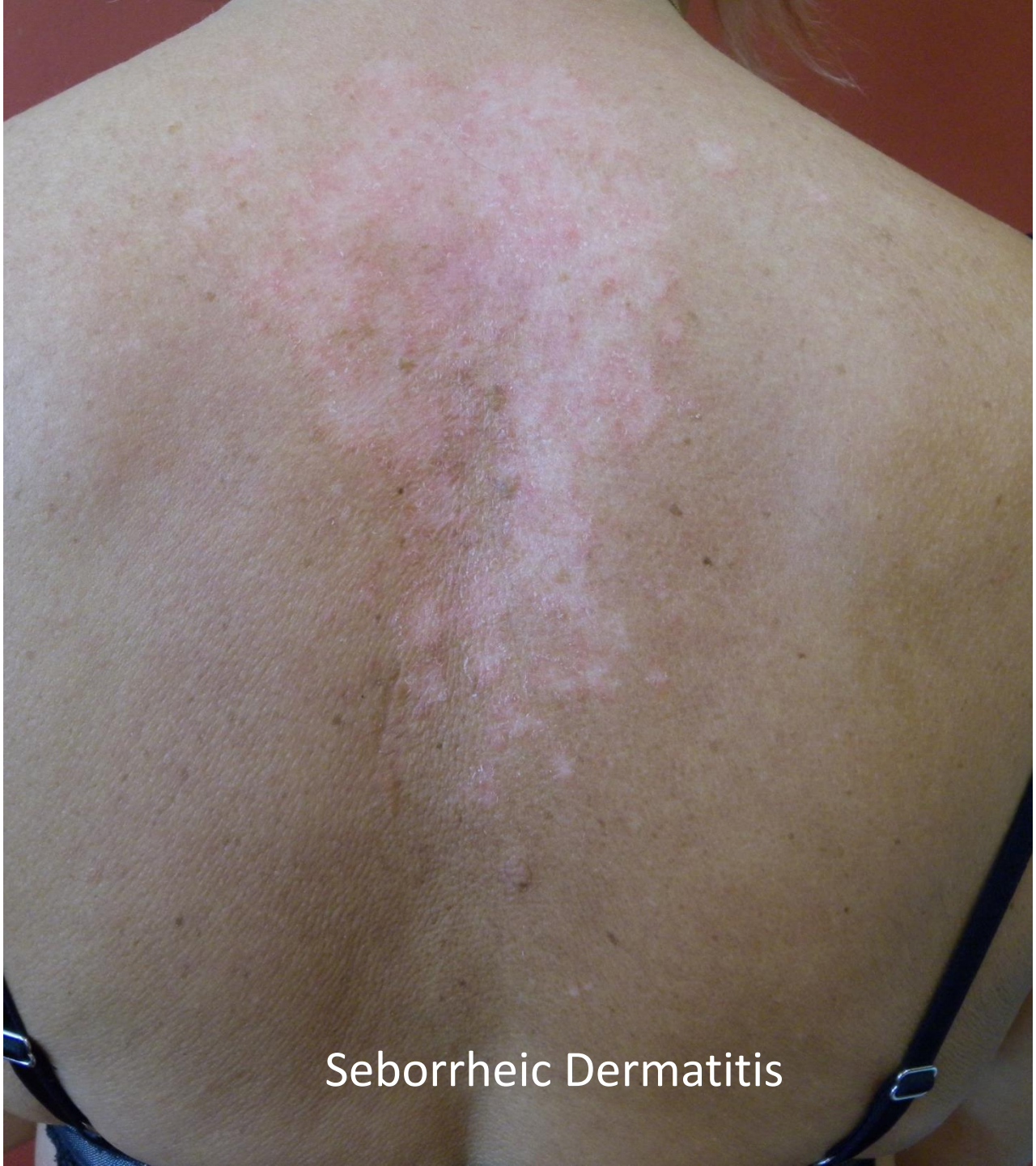




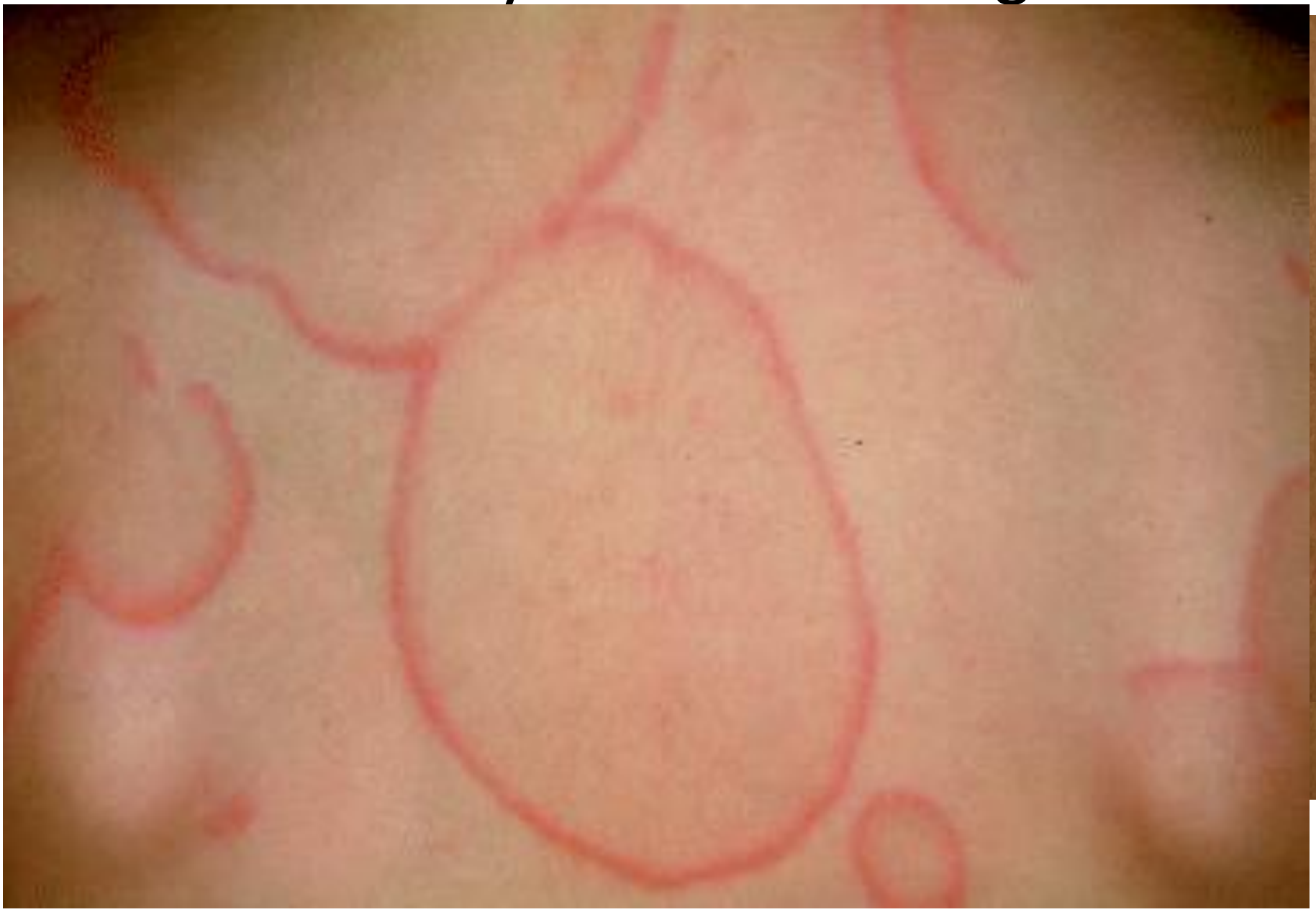
Papulo-squamous variant or Psoariasiform SCLE



Psoriasis


Seborrheic Dermatitis

Annular erythema centrifugum



CLINICAL AND LABORATORY INVESTIGATIONS

BJD
British Journal of Dermatology

Subacute cutaneous lupus erythematosus and its association with drugs: a population-based matched case–control study of 234 patients in Sweden

C.M. Grönhagen,[1] C.M. Fored,[2] M. Linder,[2] F. Granath[2] and F. Nyberg[1,3]

[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

EPIDEMIOLOGY AND HEALTH SERVICES RESEARCH

BJD
British Journal of Dermatology

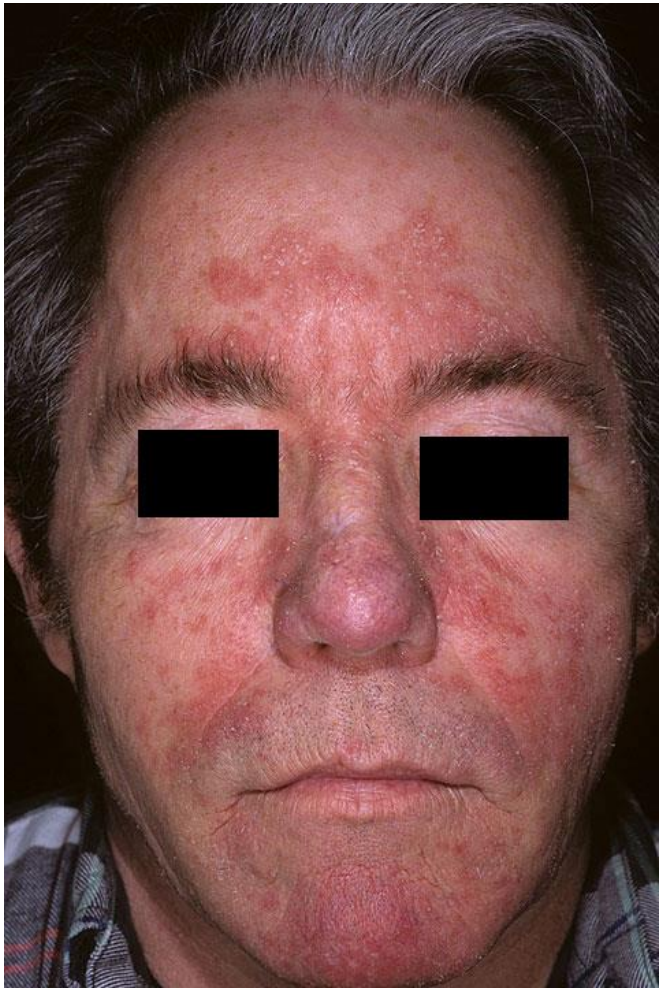
Increased risk of cancer among 3663 patients with cutaneous lupus erythematosus: a Swedish nationwide cohort study

C.M. Grönhagen,* C.M. Fored,† F. Granath† and F. Nyberg*‡

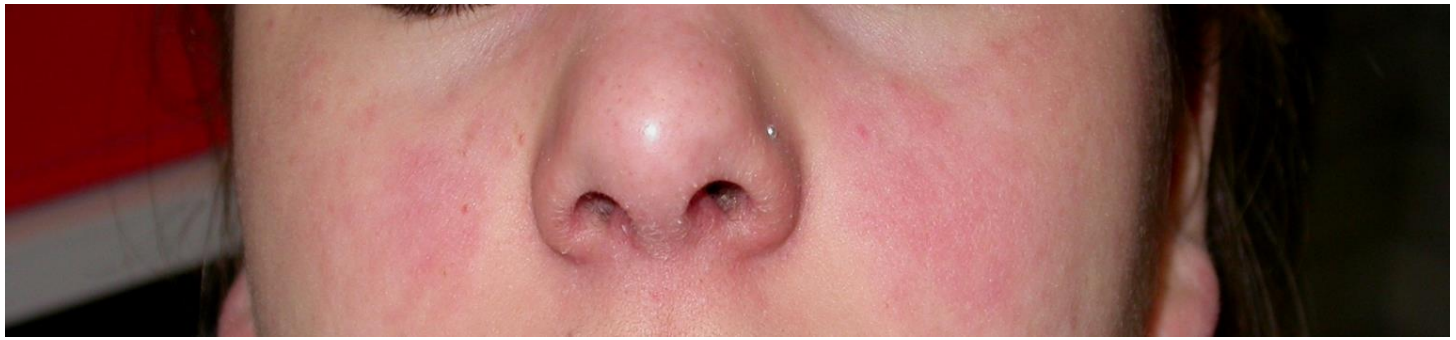
- Elevated overall cancer risk for patients with CLE
- Buccal cancer, lymphomas, respiratory cancers, NMSC
- SCLE > DLE greates during the first year after CLE diagnosis
- Risk is independent from SLE diagnosis

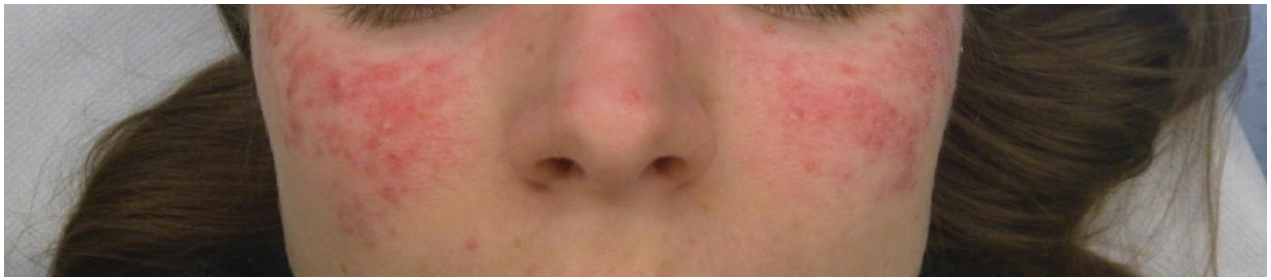
LE-Specific Manifestations

- 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





Rosacea

Papular-macular rash

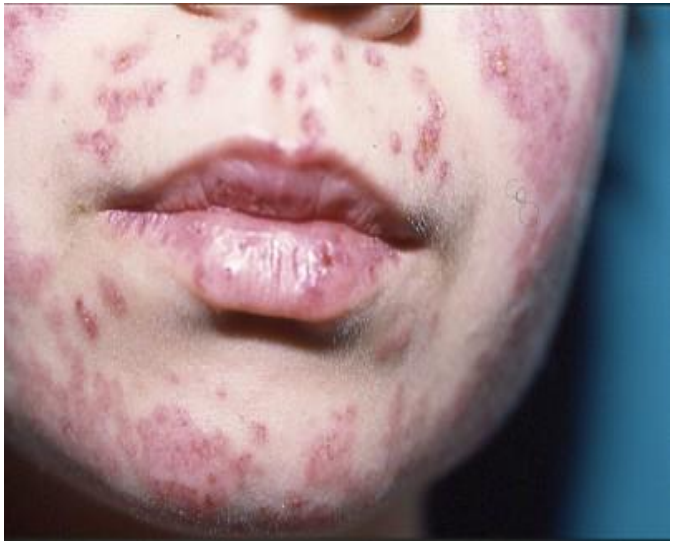
5-10% of SLE patients

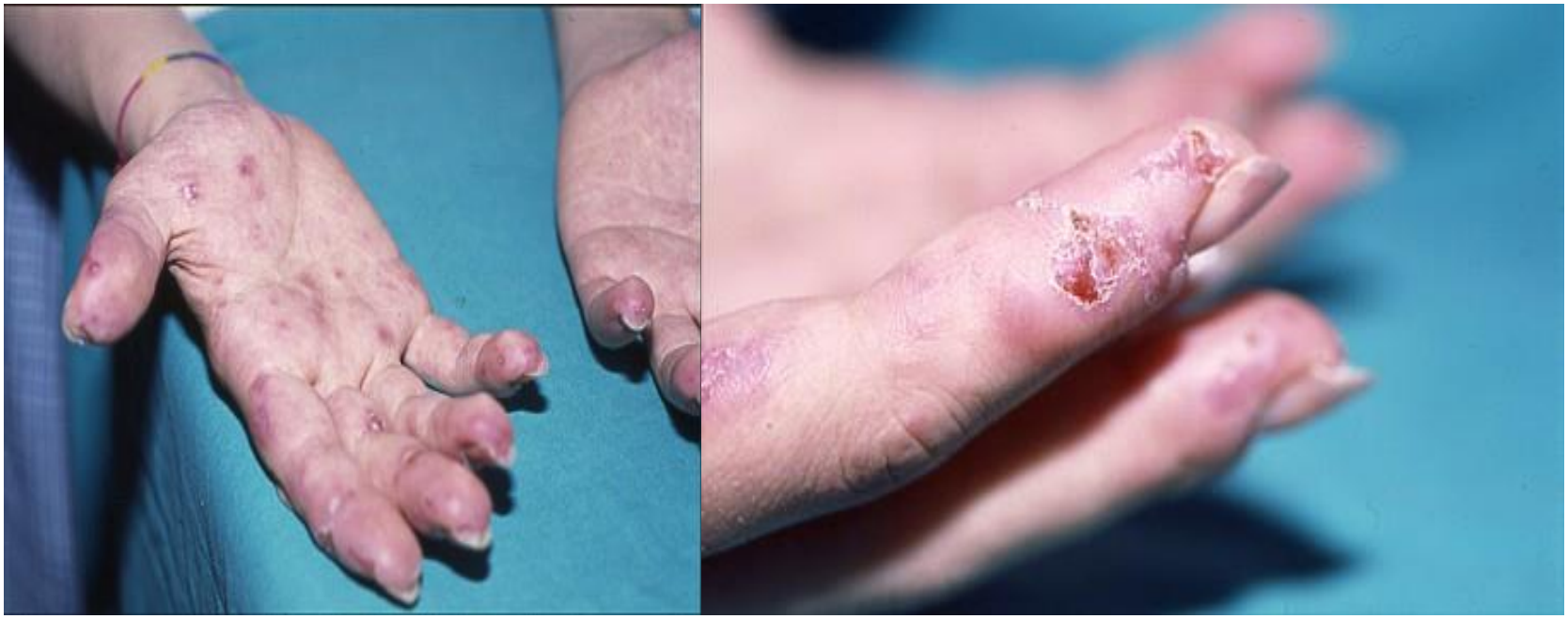
Multiple erythematous, infiltrated and purpuric lesions

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

Oral involvement with erosions/ulcerations

Quick resolution after DDS





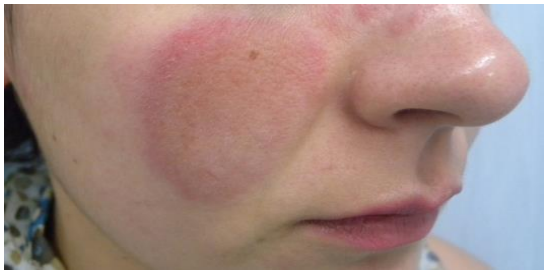
Differential diagnosis : Acute cutaneous lupus erythematosus (ACLE)

• Localized form: rosacea, seborrheic eczema, perioral dermatitis, tinea faciei, erysipelas

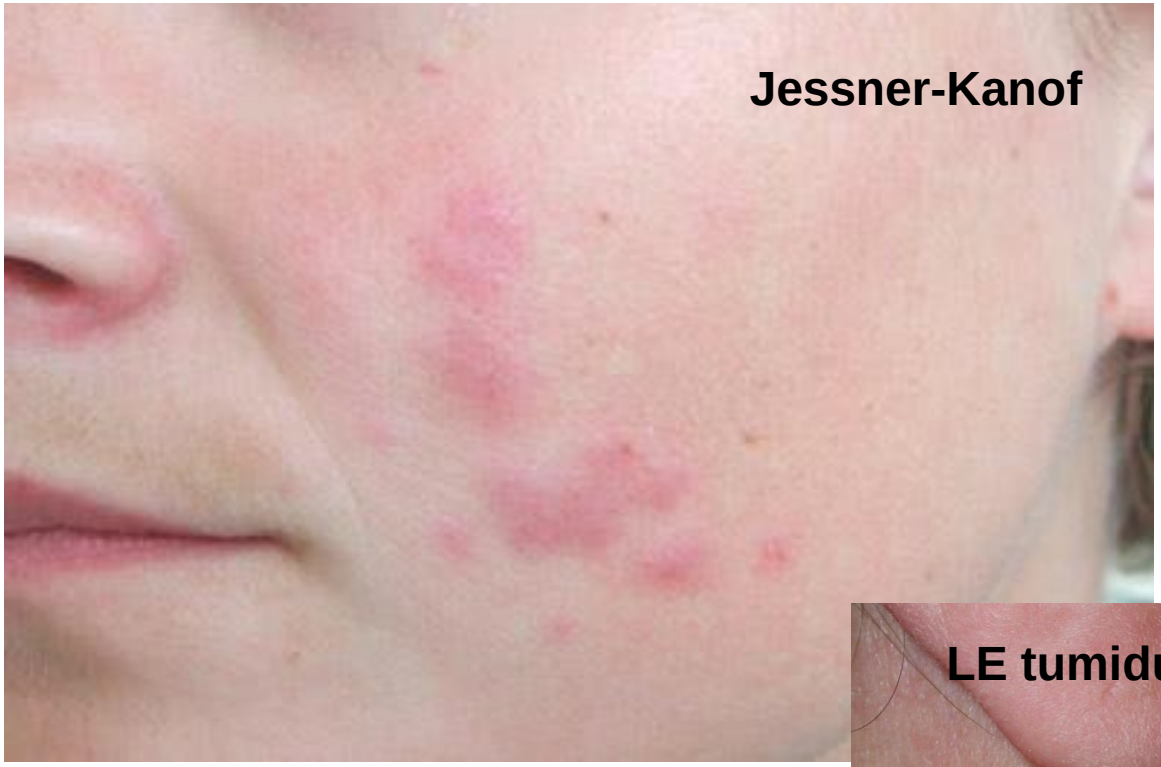
• Generalized form: dermatomyositis, viral and drug-induced rash, erythema multiforme, TEN

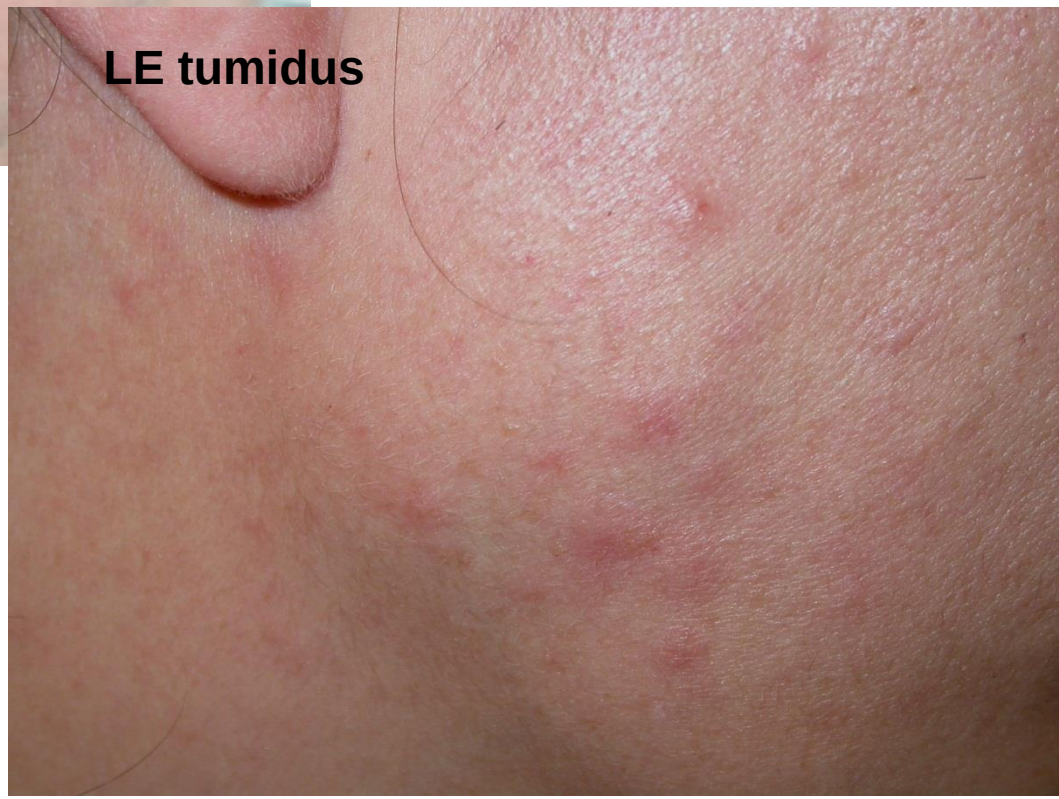
Intermittent LE

- “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.


Jessner-Kanof

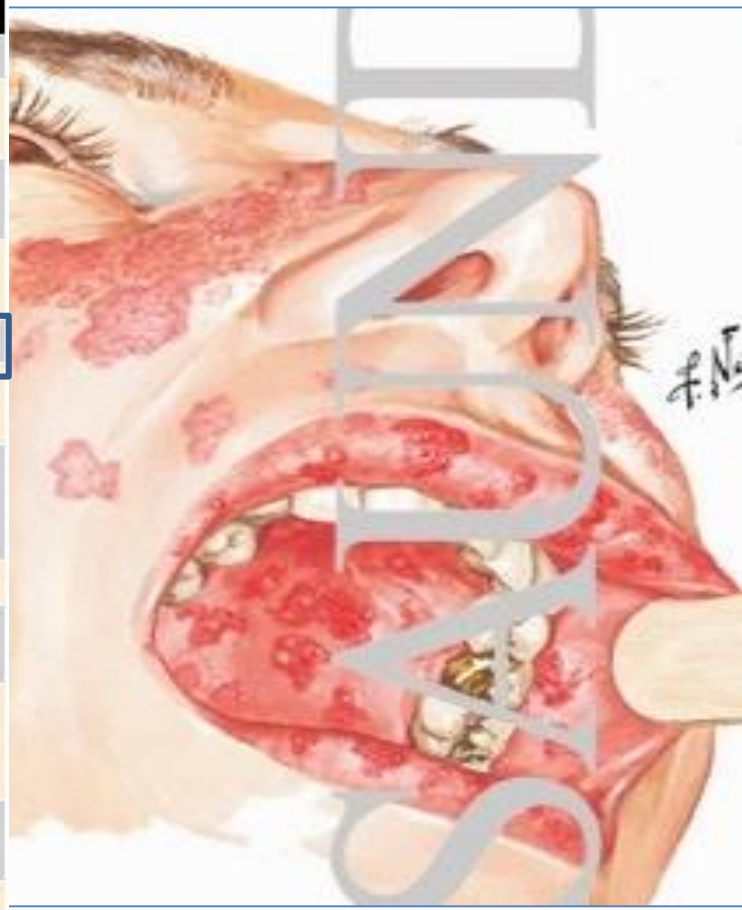

LE tumidus

LUPUS ERYTHEMATOSUS

ACR CRITERIA FOR DIAGNOSIS OF SLE

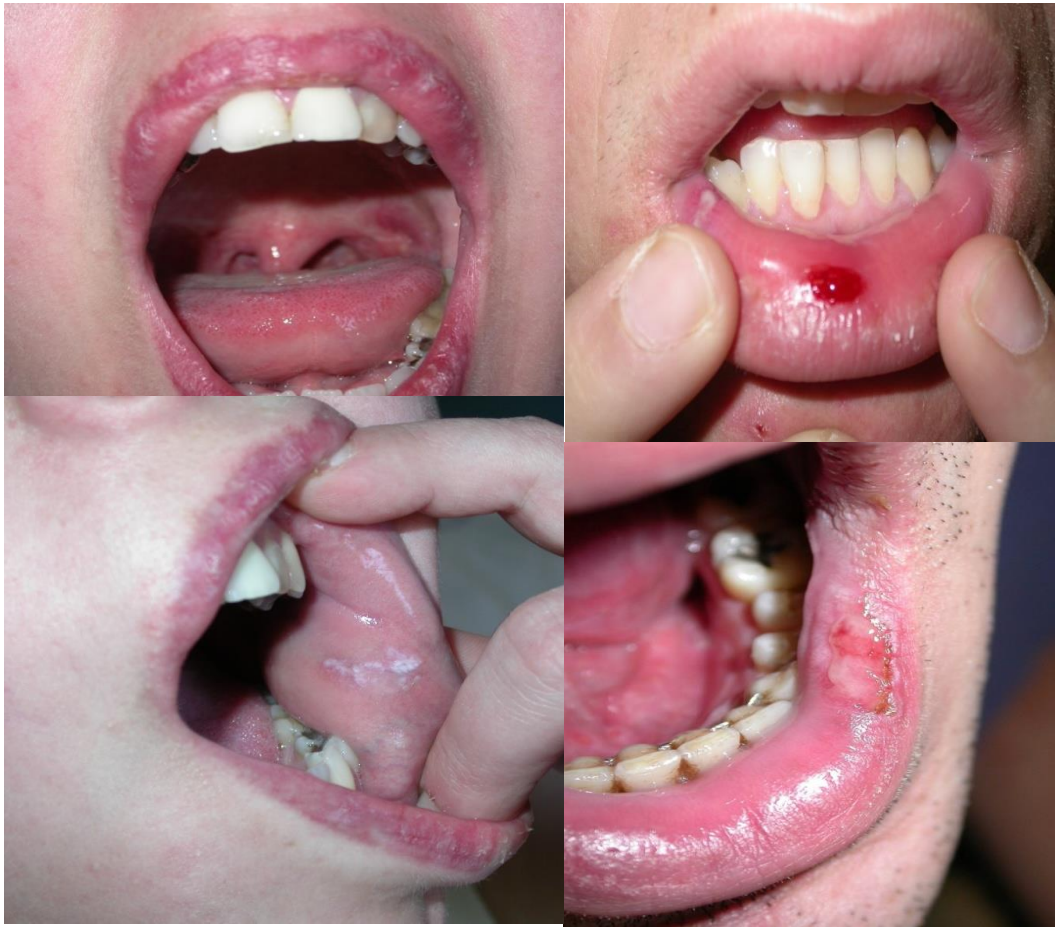
Condition	Description
Malar rash	A "butterfly rash" of flat or raised fixed erythema tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging associated with scarring
Photosensitivity	A reaction to sunlight causing rash that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

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

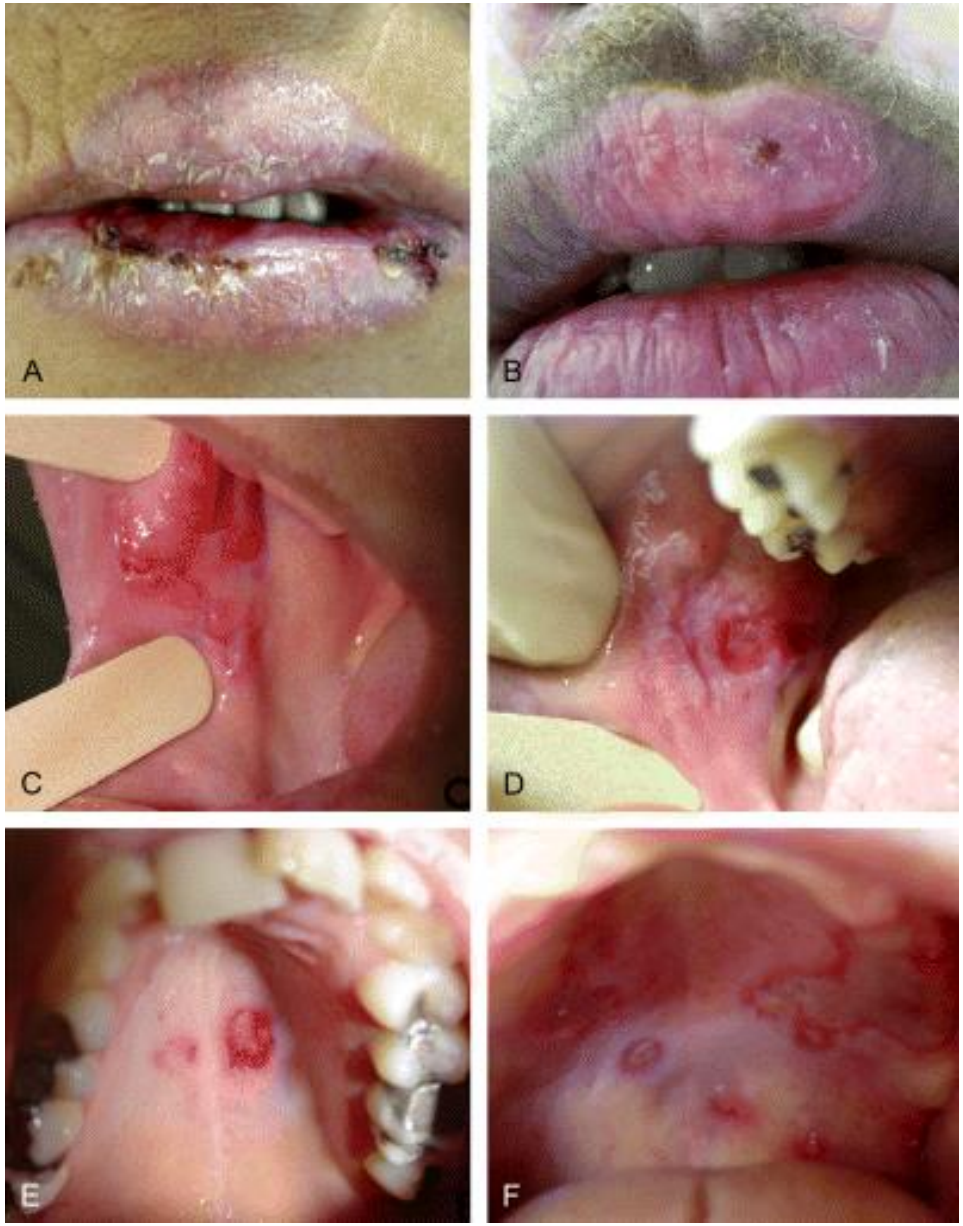


Mucosal Membrane Involvement

- 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.



Ranginwala AM 2012 S **Oral discoid lupus erythematosus: A study of twenty-one cases.** J Oral Maxillofac Pathol.



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 %) Erythemato-purpuric lesion on hard palate present in SLE. (F) Bullous lesions and erosions on palate and alveolar border.

J Cutan Pathol. 2007 Jul;34(7):558-64

Table 12
Clinical manifestations of cutaneous lupus erythematosus.

Cutaneous lupus erythematosus (CLE)	Skin lesions	Oral lesions
Acute Cutaneous Lupus Erythematosus (ACLE)	Localized: Classic butterfly rash in the centre of the face Generalized : maculopapular rash	Circumscribed red macules Diffuse palatal erythema Purpuric macules Symmetrically/ asymmetrically distributed ulcers and erosions
Subacute Cutaneous Lupus Erythematosus (SCLE)	Localized lesions on sun-exposed areas	Intra-oral lesions are rare well-demarcated round red patches Diffuse erythematous labial plaques
Chronic Cutaneous Lupus Erythematosus (CCLE)	Classic discoid lesions (well-demarcated scaly macules), develop into painful indurated plaques. Verrucous lupus erythematosus, intensely keratotic discoid lesions.	Oral discoid lesions: well-demarcated, round, irregular atrophic or ulcerated areas, with radiating keratotic striae Honeycomb plaques: intensely keratotic white lesions and linear fissured ulcerated lesions.

It has been suggested that oral lesions may represent the mucosal counterpart to the cutaneous lesions and should be similarly classified

NicoMM, et al. Oral lesions in lupus erythematosus: correlation with cutaneous lesions. Eur J Dermatol 2008;18:376–81.

LE-nonspecific manifestations

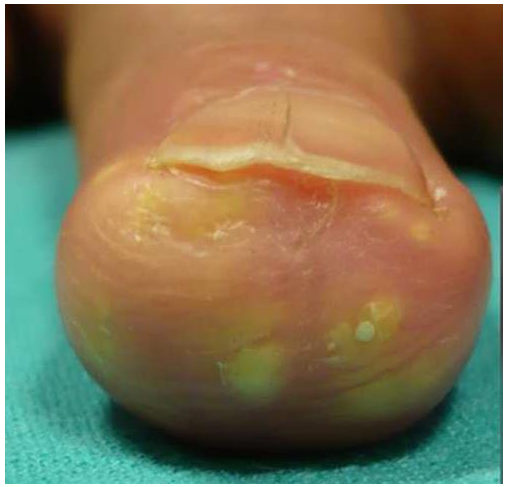
❖**CUTANEOUS VASCULAR DISEASE**
- Urticaria vasculitis
- Palpable purpora
- Periungual teleangiectasia
- Cutaneous micro-infarctions
- Periarteritis nodosa-like
- Ulcerations
- Livedo reticularis
- Peripheral gangrena
- Raynaud's phenomenon

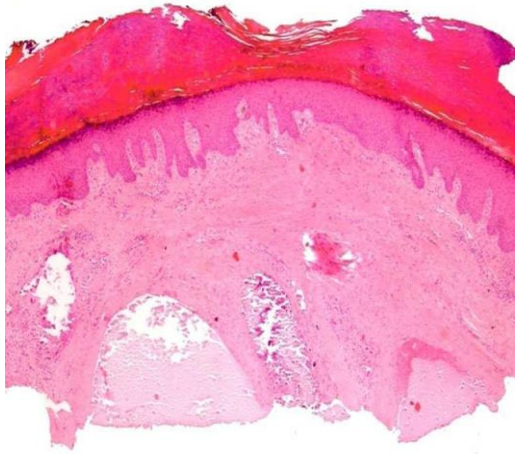
❖**ALOPECIA**
- Non scarring (lupus hair, telogen efluvium, alopecia areata)

❖**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 (erythemalgia)
2. Alopecia (non-scarring)
   - 'Lupus hair'
   - Telogen effluvium
   - Alopecia areata
3. Sclerodacytly
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

Jenette JC et al. Arthritis & Rheumatism 2012

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)

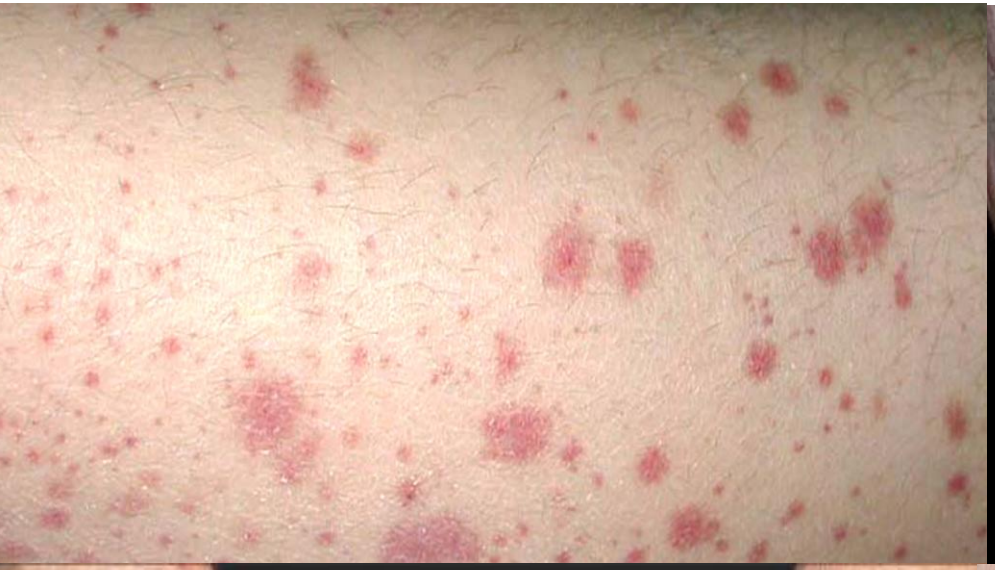
Variable vessel vasculitis (VVV)
- Behçet's disease (BD)
- Cogan's syndrome (CS)

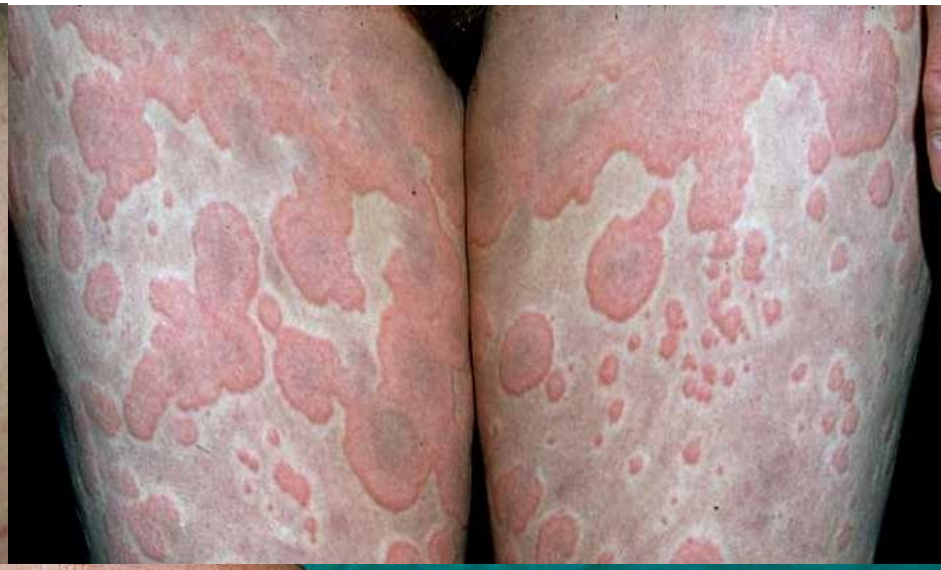
Single-organ vasculitis (SOV)
- Cutaneous leukocytoclastic angiitis
- Cutaneous arteritis
- Primary central nervous system vasculitis
- Isolated aortitis
- Others

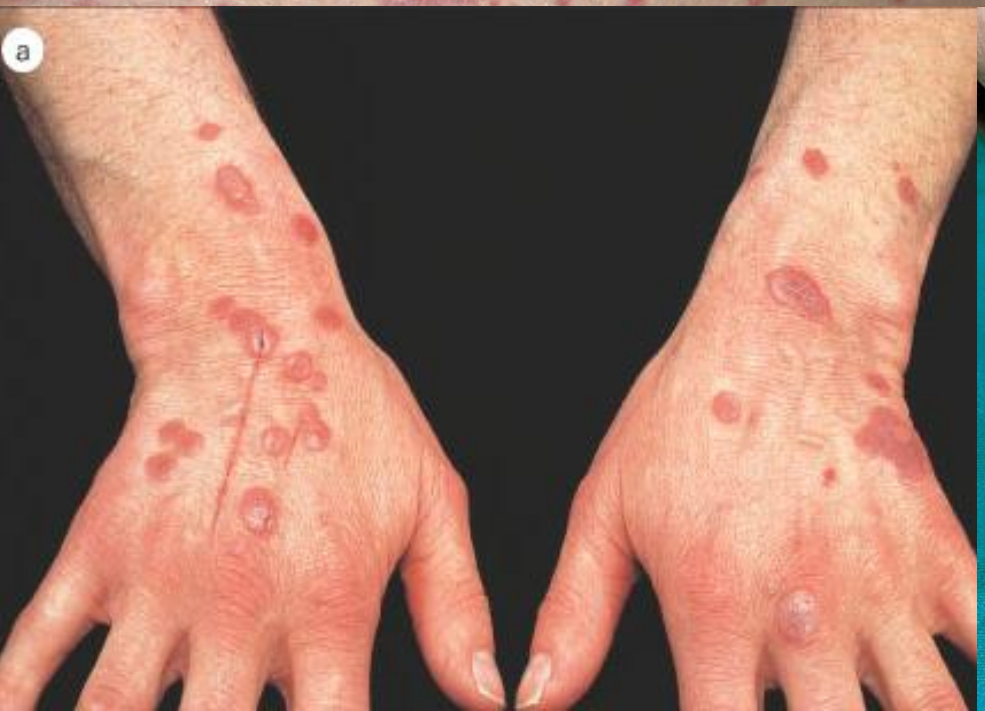
Vasculitis associated with systemic disease
- Lupus vasculitis
- Rheumatoid vasculitis
- Sarcoid vasculitis
- Others

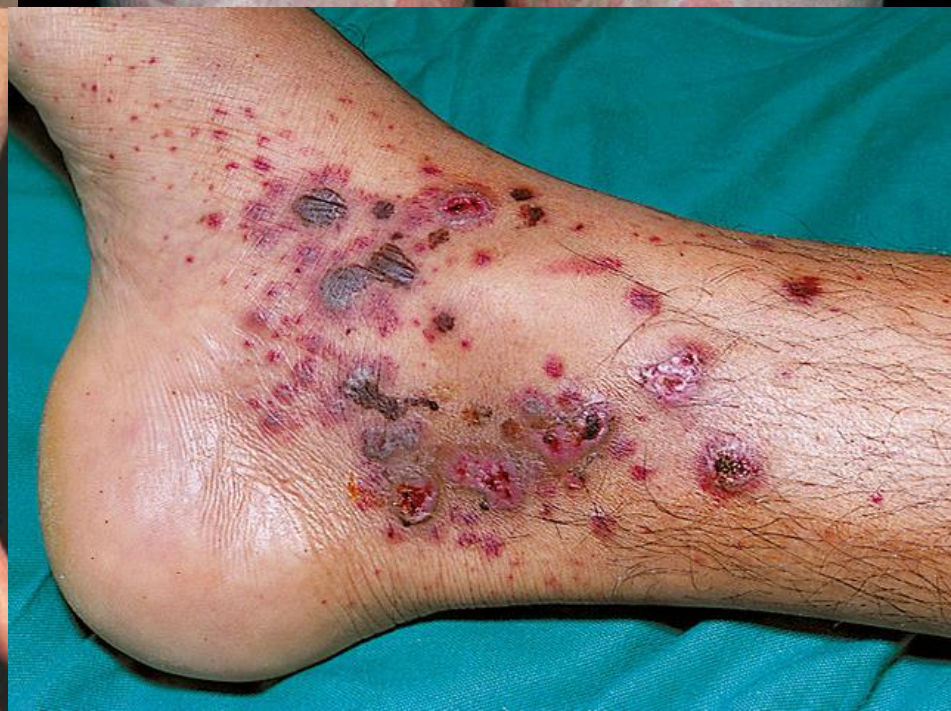
Vasculitis associated with probable etiology
- Hepatitis C virus–associated cryoglobulinemic vasculitis
- Hepatitis B virus–associated vasculitis
- Syphilis-associated aortitis
- Drug-associated immune complex vasculitis
- Drug-associated ANCA-associated vasculitis
- Cancer-associated vasculitis
- Others

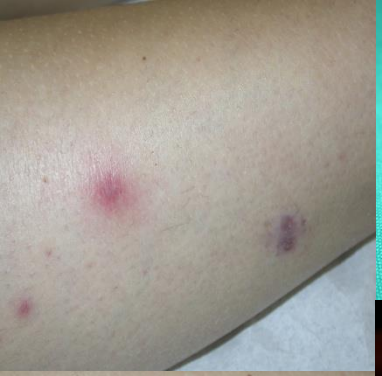
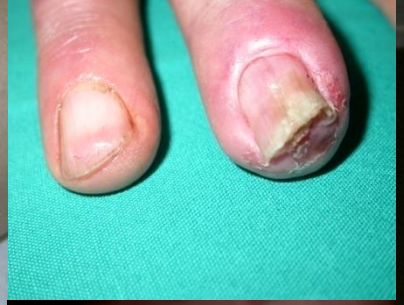
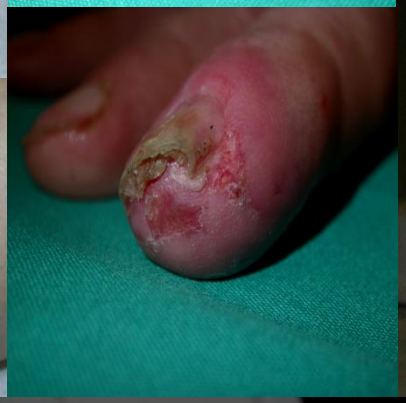
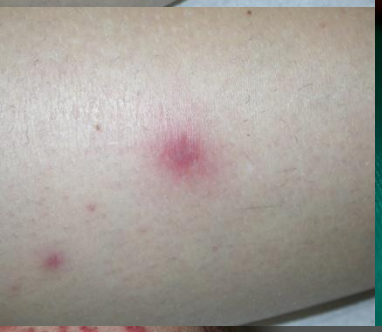
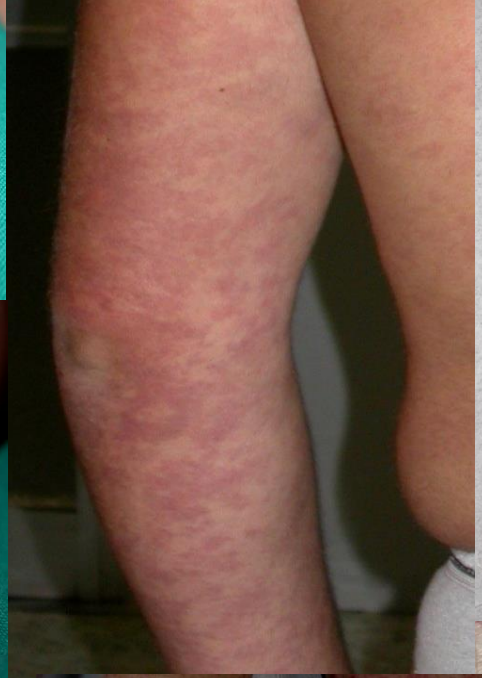
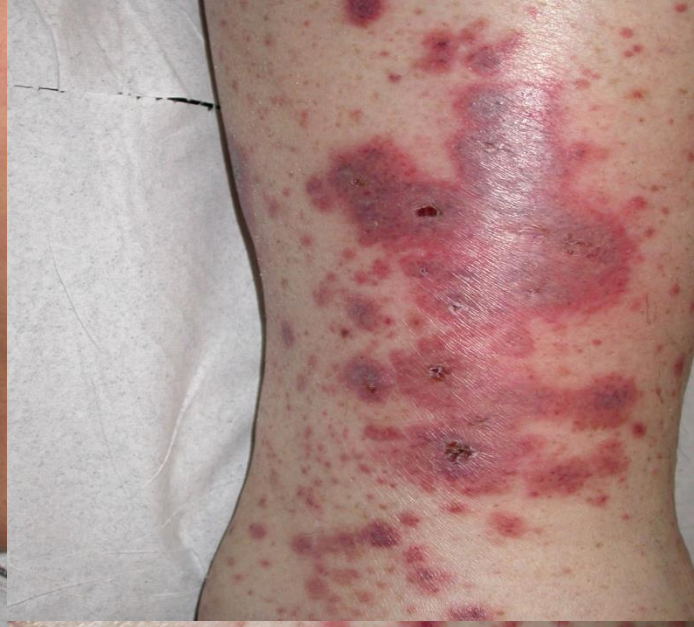
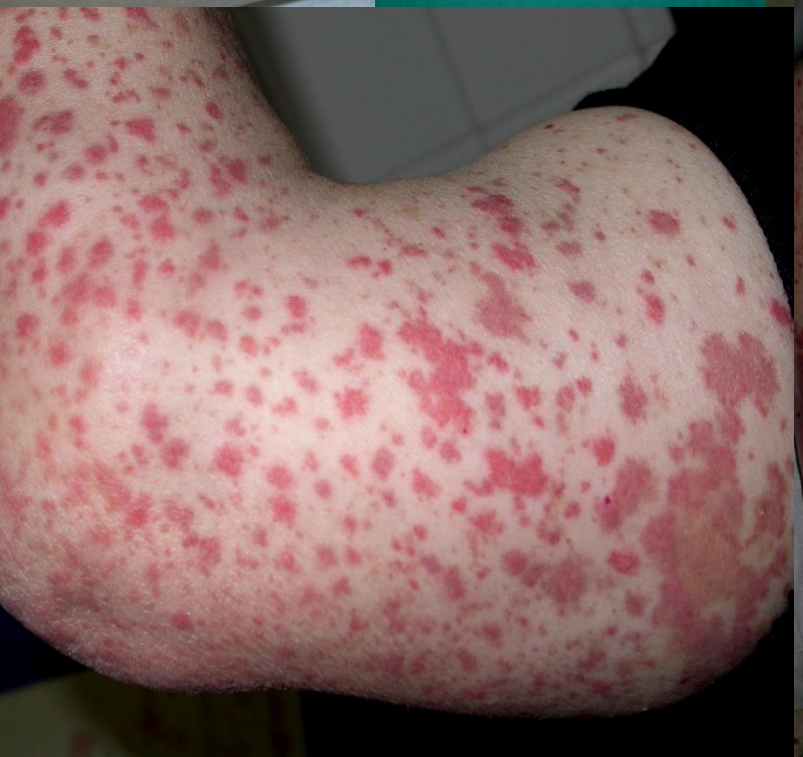
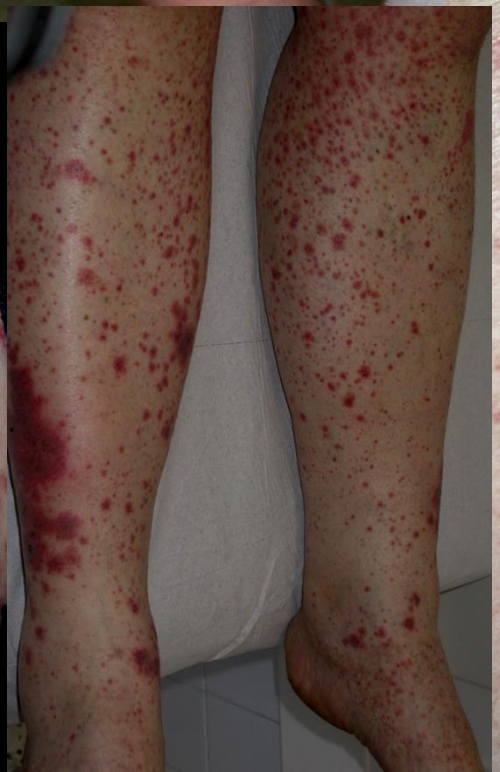
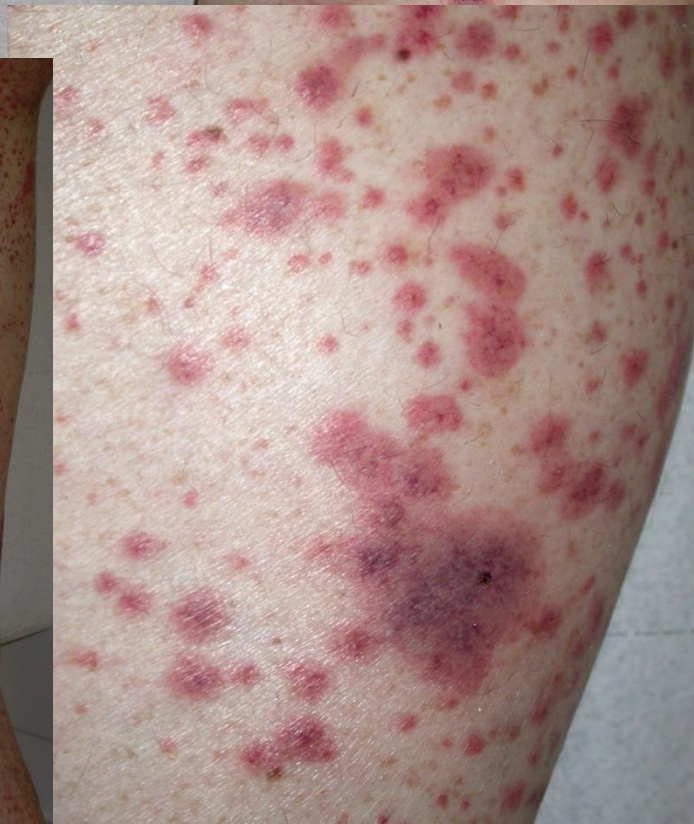
VASCULITIS : PALPABLE PURPURA and URTICARIAL VASCULITIS

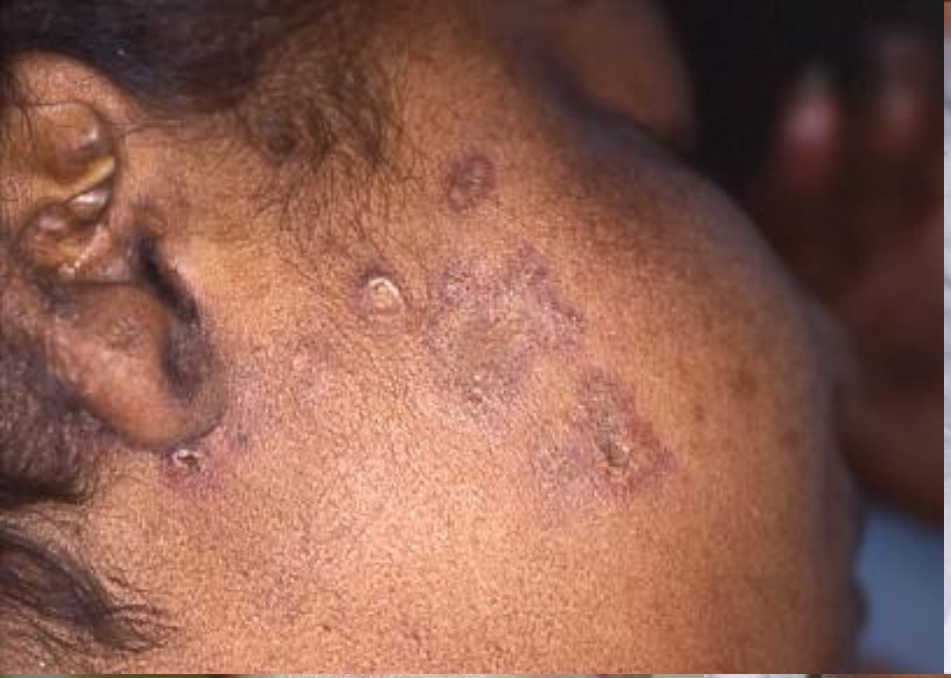


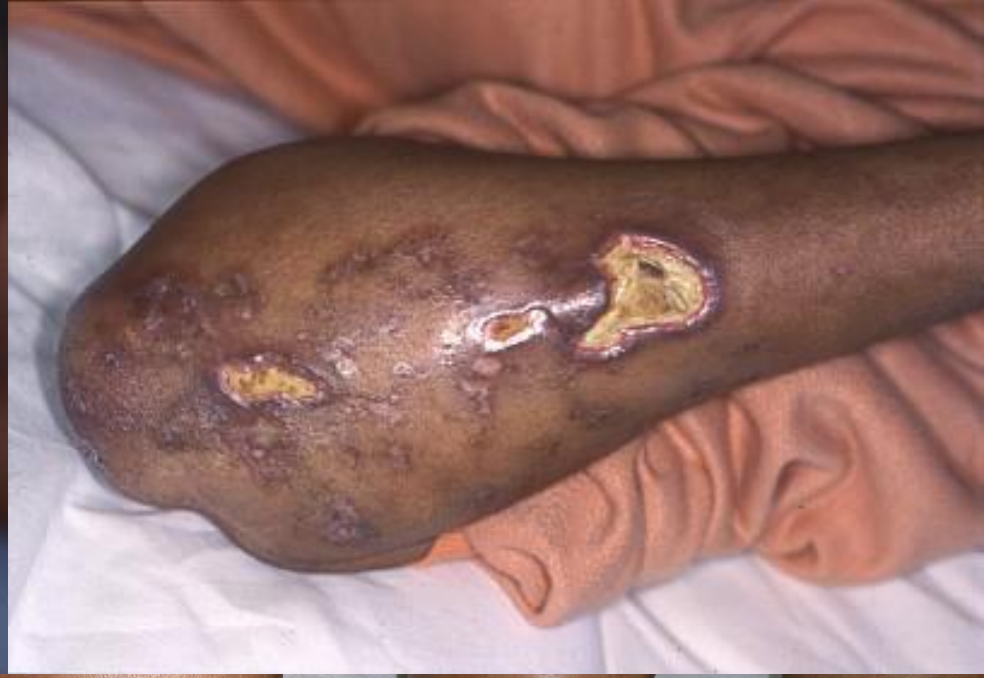


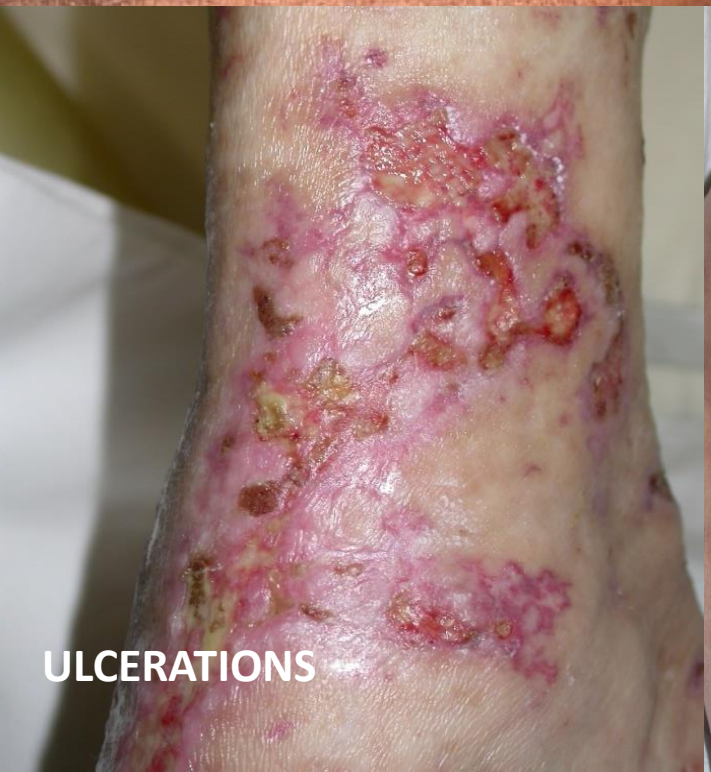


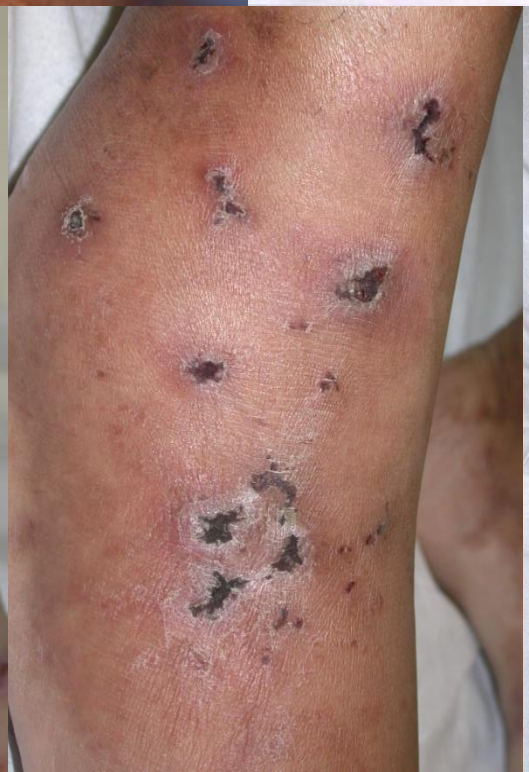


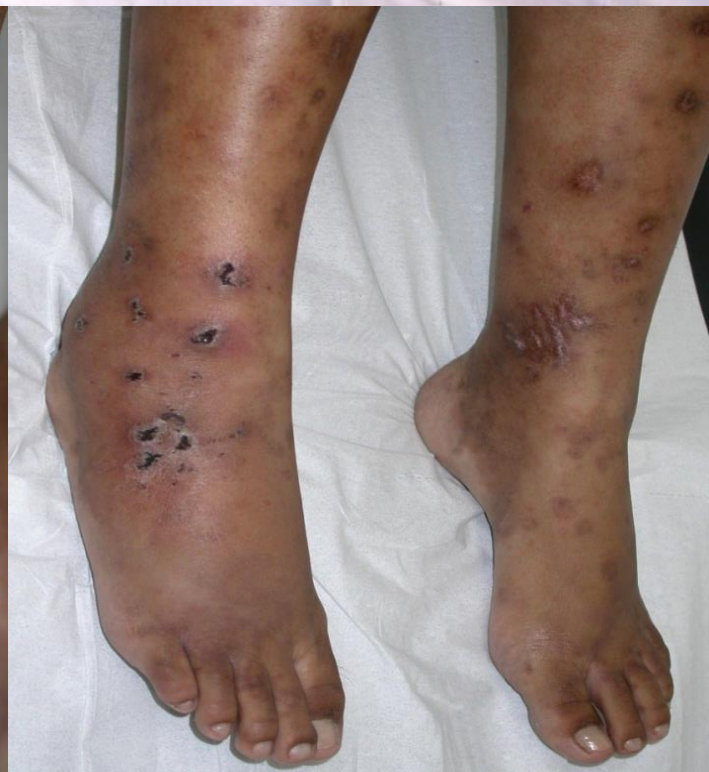












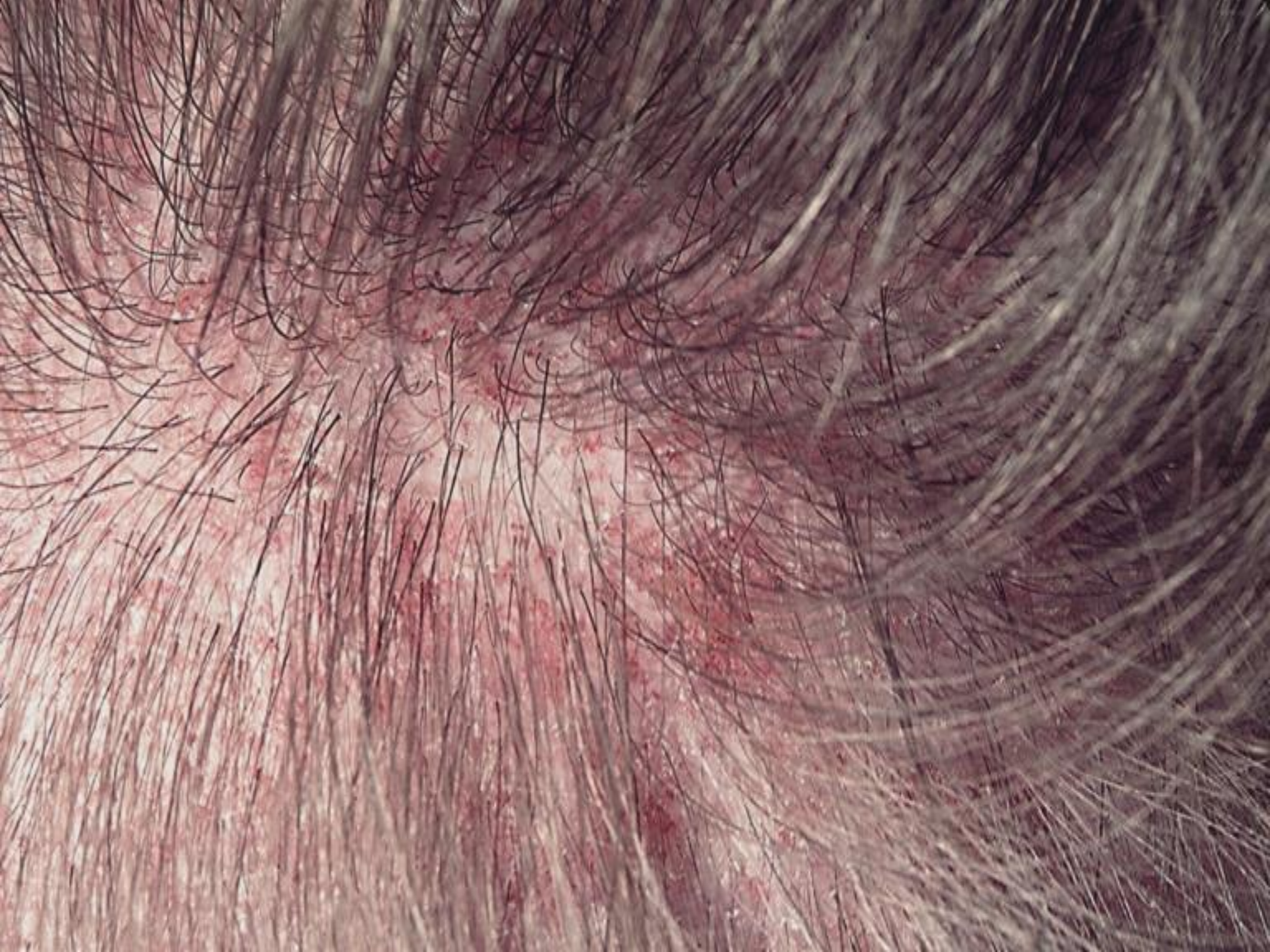


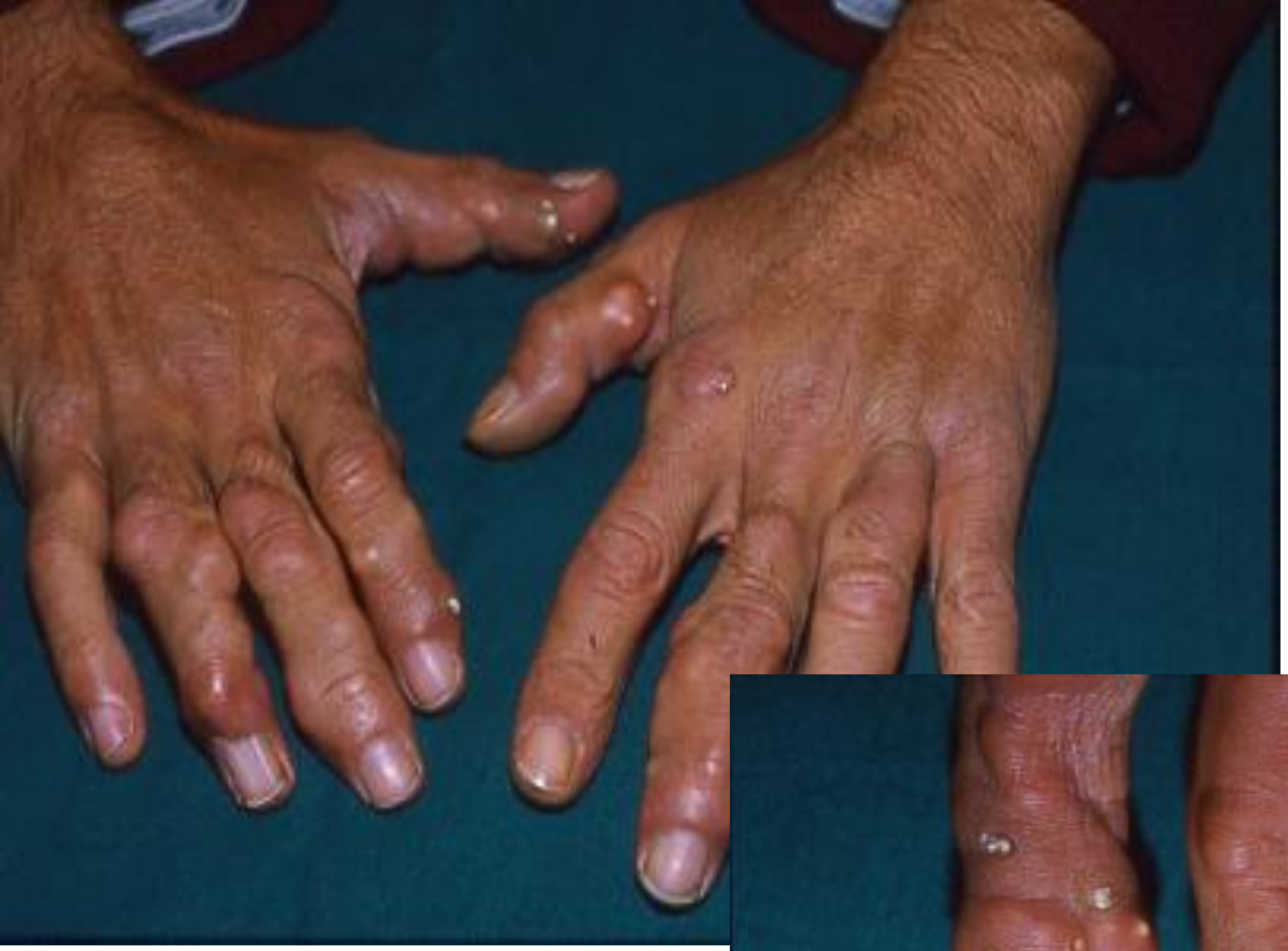


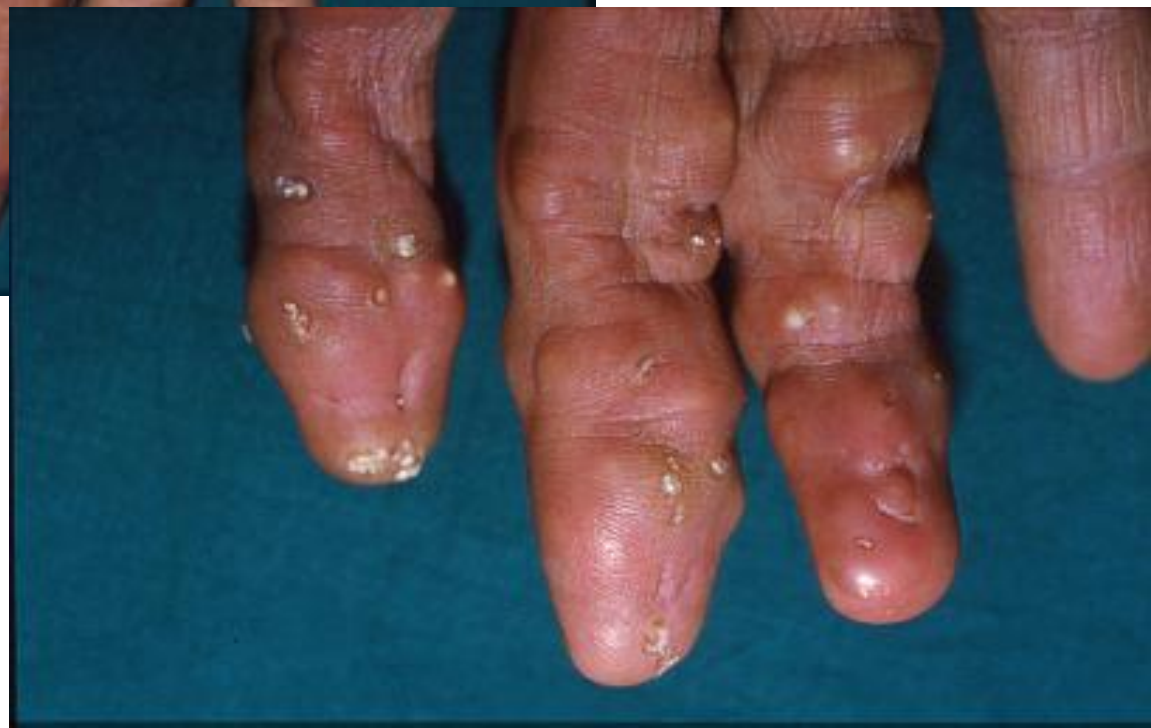




ULCERATIONS





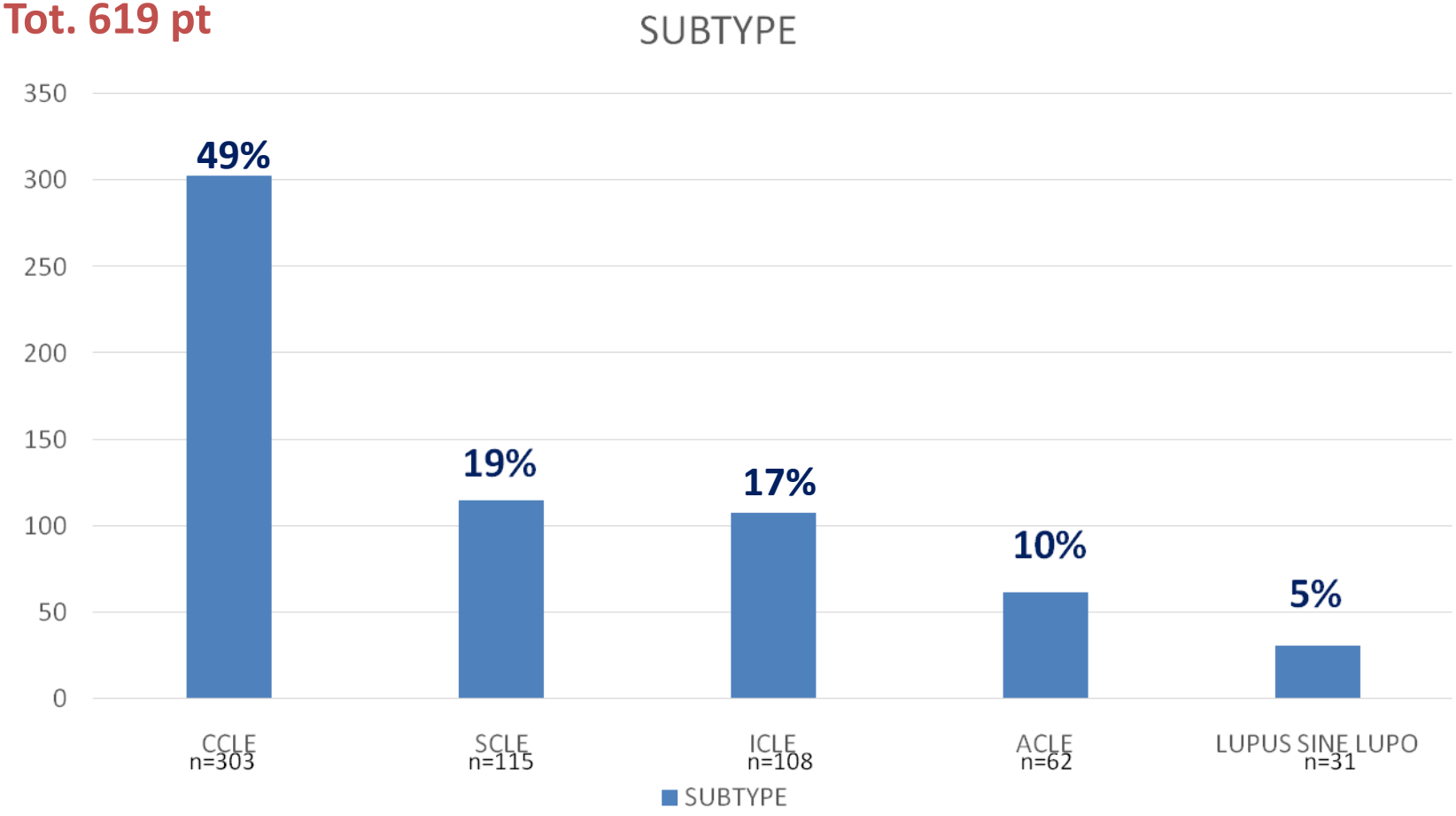


Our Experience

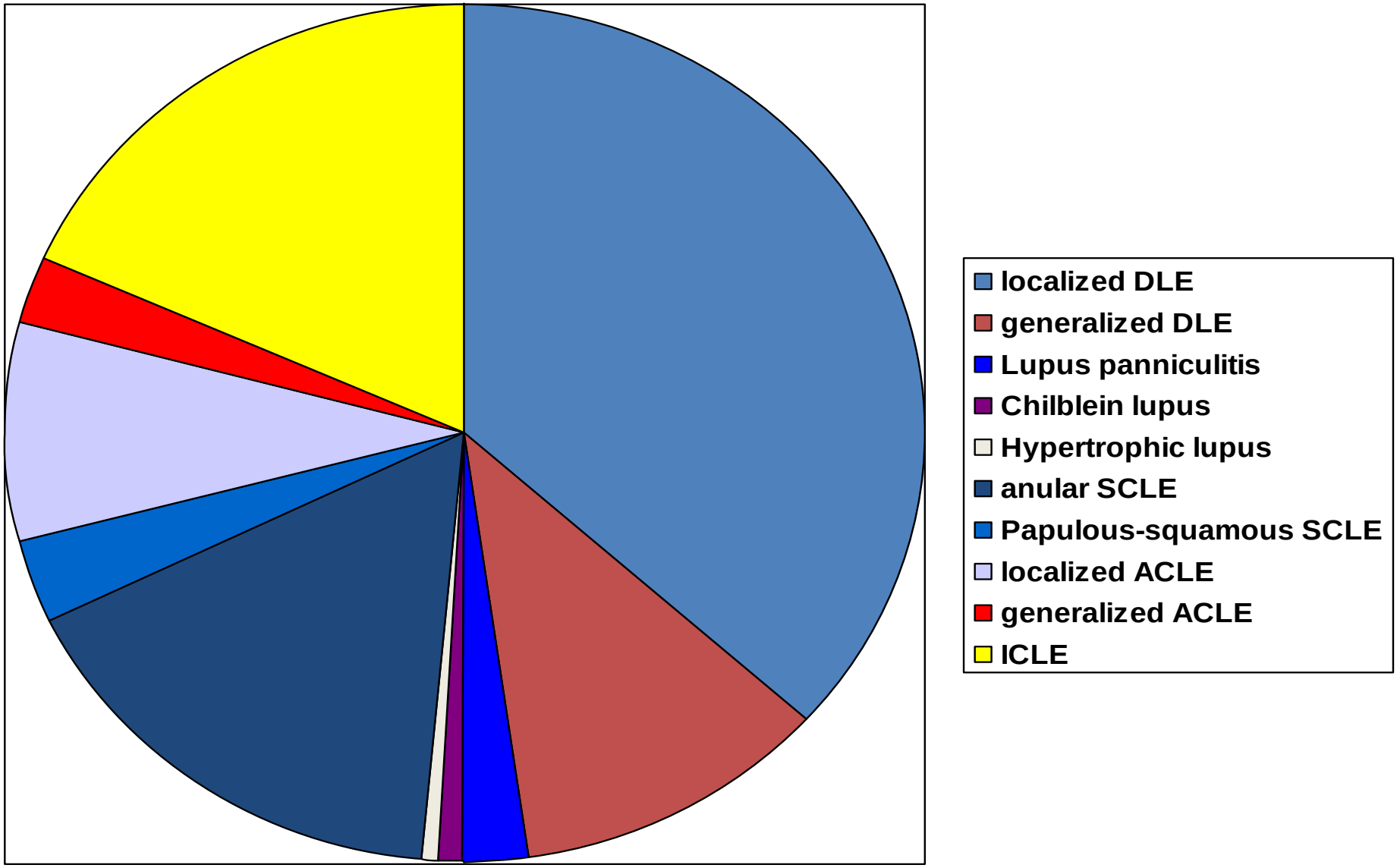
"AUTOANTIBODY PROFILE AND SPECIFIC CLINICAL PATTERNS IN 619 ITALIAN PATIENTS WITH CUTANEOUS LUPUS ERYTHEMATOSUS"

ITALIAN EXPERIENCE
GIIP 2009-2014

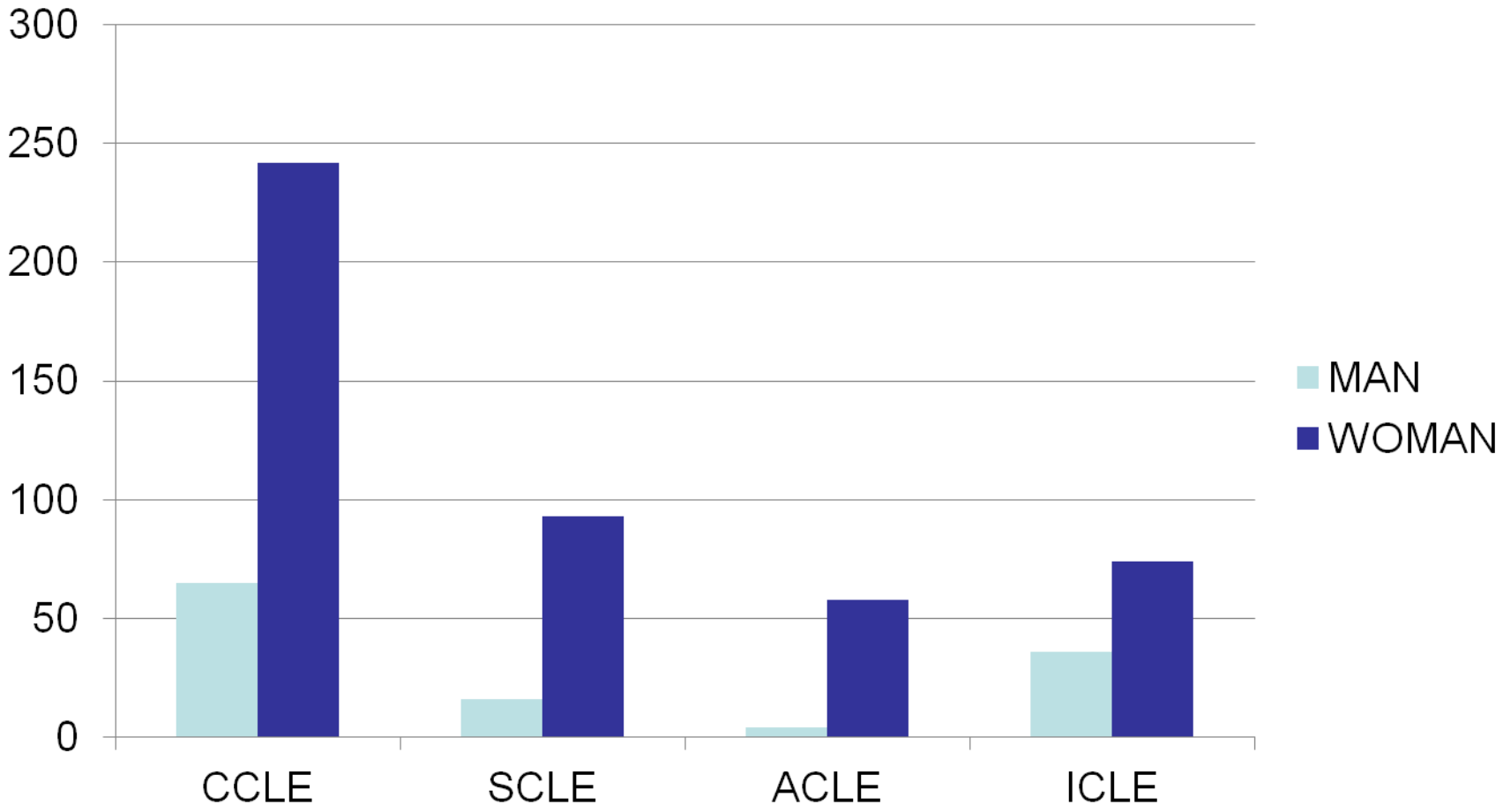
Tot. 619 pt



Subtypes

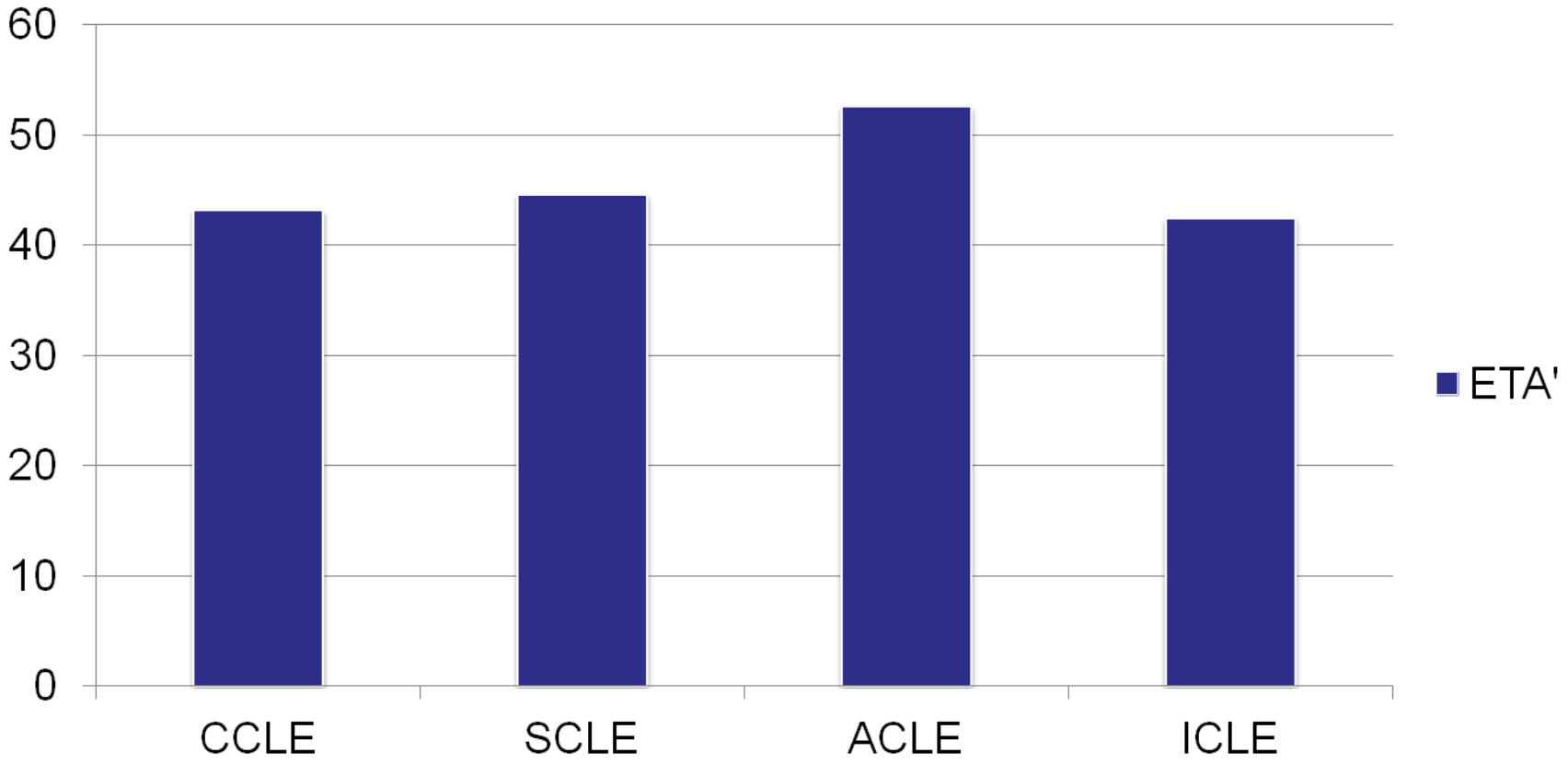

localized DLE
generalized DLE
Lupus panniculitis
Chilblein lupus
Hypertrophic lupus
anular SCLE
Papulous-squamous SCLE
localized ACLE
generalized ACLE
ICLE

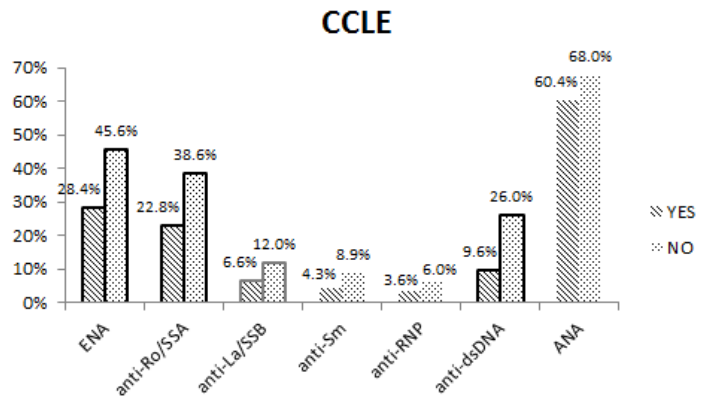
Men vs Woman

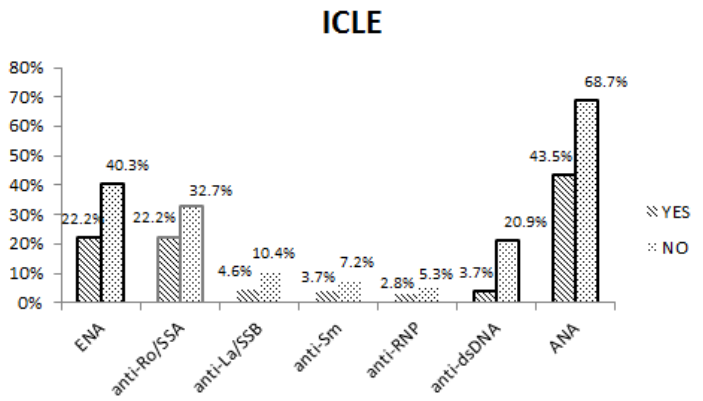


Age at Diagnosis

Età media: 45.2 ± 1.2 anni




CCLE
70%
60%
50%
40%
30%
20%
10%
0%
28.4%
45.6%
22.8%
38.6%
6.6%
12.0%
4.3%
8.9%
3.6%
6.0%
9.6%
26.0%
60.4%
68.0%
ENA
anti-Ro/SSA
anti-La/SSB
anti-Sm
anti-RNP
anti-dsDNA
ANA
YES
NO


ICLE
80%
70%
60%
50%
40%
30%
20%
10%
0%
22.2%
40.3%
22.2%
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4.6%
10.4%
3.7%
7.2%
2.8%
5.3%
3.7%
20.9%
43.5%
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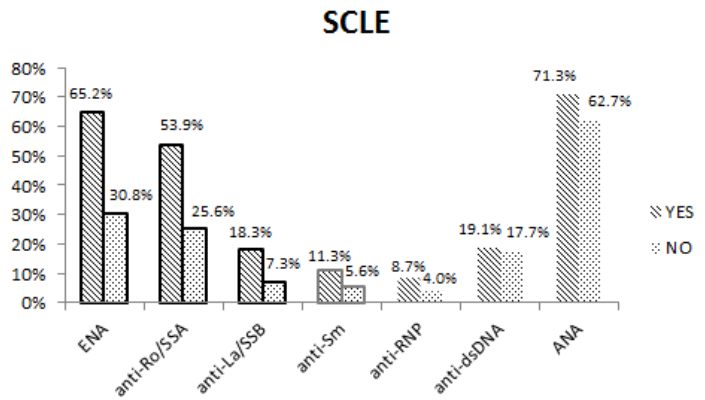
ENA
anti-Ro/SSA
anti-La/SSB
anti-Sm
anti-RNP
anti-dsDNA
ANA
YES
NO


SCLE
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4.0%
19.1%
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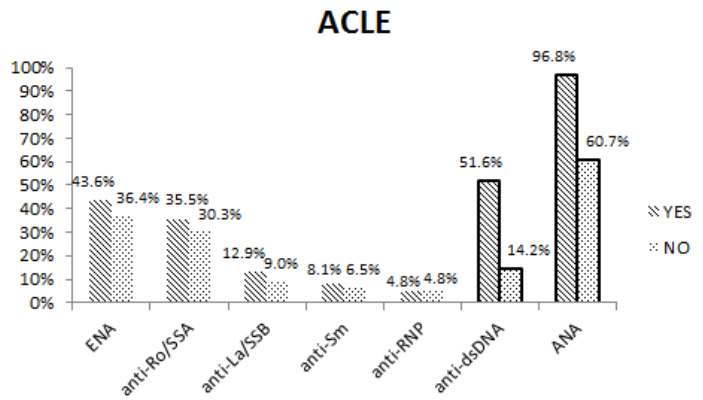
anti-La/SSB
anti-Sm
anti-RNP
anti-dsDNA
ANA
YES
NO


ACLE
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36.4%
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30.3%
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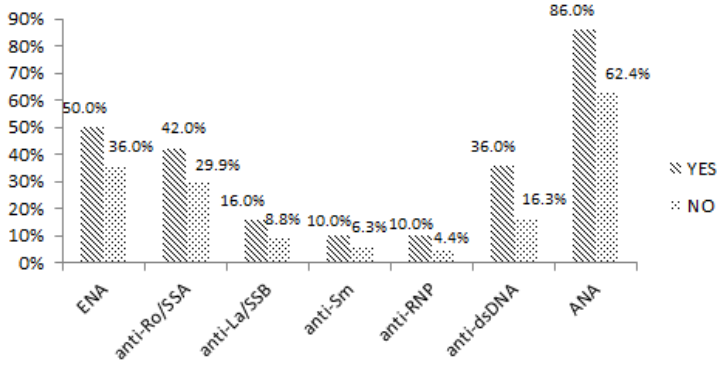
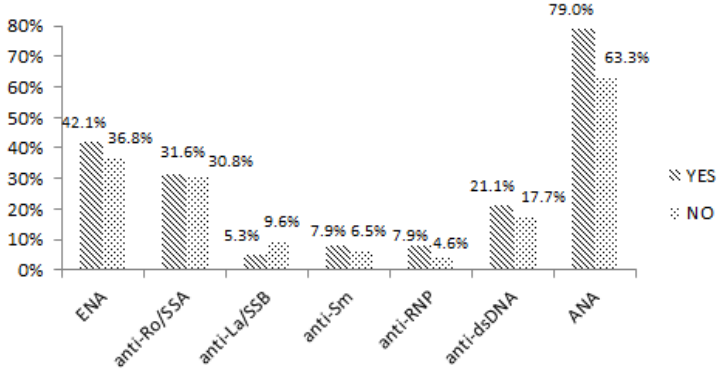
9.0%
8.1%
6.5%
4.8%
4.8%
51.6%
14.2%
96.8%
60.7%
ENA
anti-Ro/SSA
anti-La/SSB
anti-Sm
anti-RNP
anti-dsDNA
ANA
YES
NO

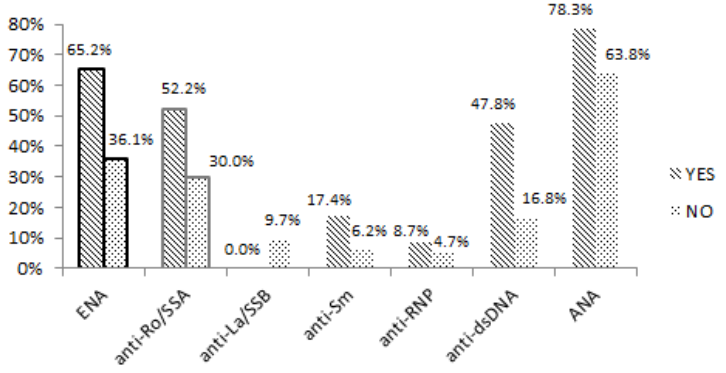
Raynaud's Phenomenon



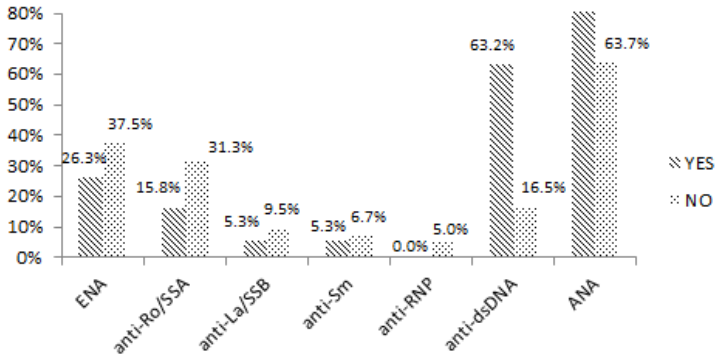
Diffuse alopecia



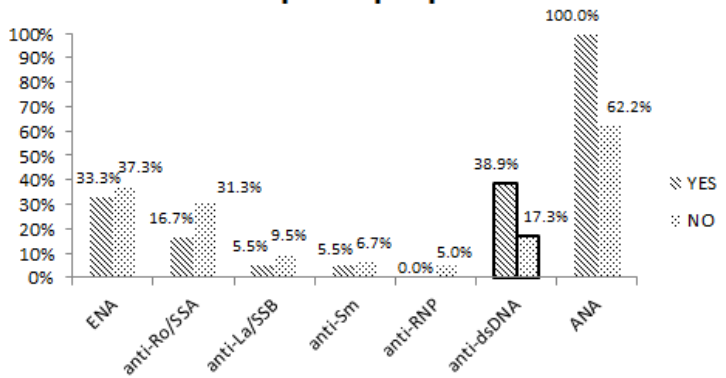
Livedo reticularis



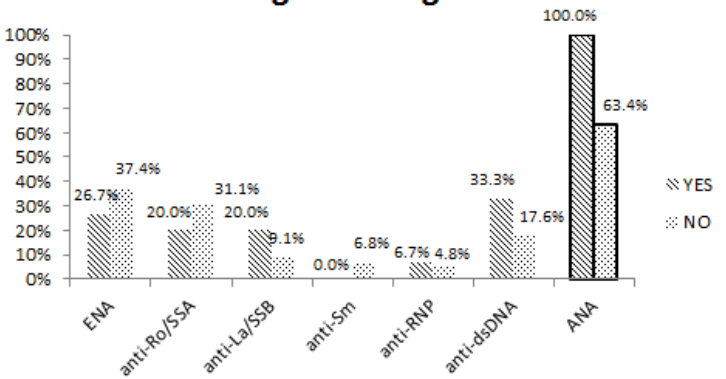
Urticarial leukocytoclastic vasculitis



Palpable purpura



Periungual telangiectasia



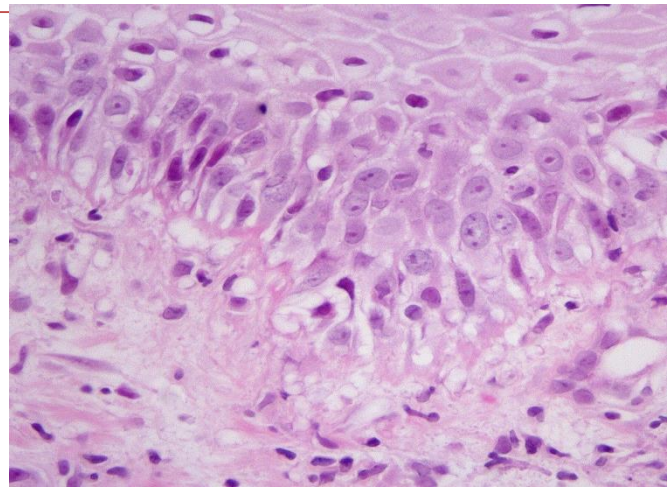
Patient Management

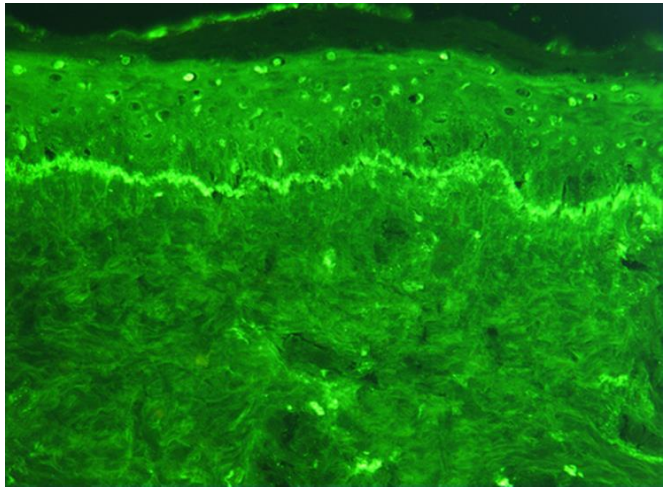
Diagnosis Cutaneous form

- 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

Revised Cutaneous Lupus Erythematosus Disease Area and Severity Index (RCLASI)*

[*CLASI modified after Albrecht et al. J Invest Dermatol 125:889–94, 2005]

Center No. | Date (DAY / MONTH / YEAR) | Name of Physician (FIRST NAME (INITIAL) SURNAME)

PATIENT

Patient No. | Date of birth (YEAR) | Sex: ☐ male ☐ female | Initials [second letter of first name and surname] (INITIALS)

SKIN LESIONS

Select the score in each site of involvement that describes the most severely affected LE-specific lesion.

LESION

ACTIVITY

- **Erythema**: 0 absent; 1 pink, faint; 2 red; 3 dark red, purple/violaceous/crusted/hemorrhagic
- **Scaling / Hyperkeratosis**: 0 absent; 1a circumscribed annular/papulosquamous-psoriasiform scaling; 1b circumscribed adherent scaling/follicular plugging; 2 verrucous hyperkeratosis
- **Edema / Infiltration**: 0 absent; 1 slight, just palpable; 2 palpable & visible
- **Subcutaneous Nodule / Plaque**: 0 absent; 1 subcutaneous induration; 2 ulceration of subcutaneous nodule/plaque

DAMAGE

- **Dyspigmentation**: 0 absent; 1a hypo-pigmentation; 1b hyper-pigmentation; 2 hypo- & hyper-pigmentation
- **Scarring / Atrophy**: 0 absent; 1 initial scarring; 2a severe firm/atrophic/vermicular scarring; 2b lipatrophy

SITE OF INVOLVEMENT

Scalp | Ears | Nose &/or malar area | Lips | Rest of face | V-area of the neck (frontal) | Post neck &/or shoulders | Chest | Abdomen | Back, buttocks | Arms | Hands | Legs | Feet

SUM OF EACH LESION → | SUM OF EACH LESION →

ACTIVITY SCORE | DAMAGE SCORE

MUCOUS MEMBRANE LESIONS

Select the score in each mucous membrane location that describes the most severely affected LE-specific lesion.

LESION

ACTIVITY

- **Erythematous Lesion**: 0 absent; 1 erythematous lesion
- **Keratotic Lesion**: 0 absent; 1 white, lichen planus-like keratotic lesion
- **Erosion/Ulceration**: 0 absent; 1 erosion; 2 ulceration

SITE OF INVOLVEMENT

Buccal mucosa | Hard and soft palate | Other mucous membranes

SUM OF EACH LESION →

ACTIVITY SCORE

ALOPECIA

ACTIVITY

Diffuse Alopecia (clinically not scarred)

- 0 absent
- 1 slight diffuse effluvium
- 2 marked diffuse effluvium with partly visible scalp
- 3 severe diffuse effluvium affecting the whole scalp

'Lupus Hair' = 'Wooly Hair' (clinically not scarred)

- 0 absent
- 3 thin, weakened hairs that easily fragment above the surface of the scalp (especially at the anterior hairline &/or at the periphery of the scalp)

ACTIVITY SCORE

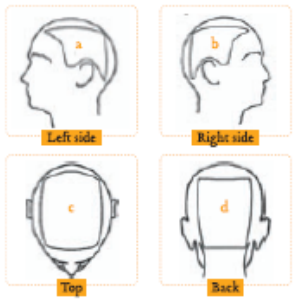
TOTAL ACTIVITY SCORE

For the total Activity Score please add up the scores of the left side i.e. for Skin lesions, Mucous membrane lesions, and Alopecia (non-scarring).

ALOPECIA

[**Alopecia Score modified after Olsen et al. J Am Acad Dermatol 51:440–447, 2004]

DAMAGE



Scarring Alopecia Please estimate the percentage (0–100%) of scarring alopecia in each of the four areas (a, b, c, d) using the above diagram**:

a) Left side: ____ %
b) Right side: ____ %
c) Top: ____ %
d) Back: ____ %

Calculate the scarring alopecia score (using the estimated percentages from above)**:

a) Left side: 'estimated percentage' x .18 = ____ %
b) Right side: 'estimated percentage' x .18 = ____ %
c) Top: 'estimated percentage' x .40 = ____ %
d) Back: 'estimated percentage' x .24 = ____ %
Please add a + b + c + d: ____ %

Choose the adequate category for the total sum of a, b, c, & d:

- 0 absent
- 1 < 5%
- 2 5–9%
- 3 10–24%
- 4 25–49%
- 5 50–74%
- 6 75–100%

DAMAGE SCORE

TOTAL DAMAGE SCORE

For the total Damage Score please add up the scores of the right side i.e. for Skin lesions and Alopecia (scarring).

SLICC† Classification Criteria for Systemic Lupus Erythematosus

RheumTutor.com

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)
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/mm^3)

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

Petri M, et al. Arthritis and Rheumatism. Aug 2012

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 Kuhn[1], Elisabeth Aberer[2*], Zsuzsanna Bata-Csörgő[3*], Marzia Caproni[4*], Andreas Dreher[5], Camille Frances[6*], Regine Gläser[7*], Hans-Wilhelm Klötgen[8*], Aysche Landmann[9], Branka Marinovic[10*], Filippa Nyberg[11*], Rodica Olteanu[12*], Annamari Ranki[13*], Jacek C. Szepietowski[14*], Beatrix Volc-Platzer[15*]

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.

DOI: 10.1111/jdv.14053 JEADV

GUIDELINES

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-Platzer[15,†]

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.

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GUIDELINES

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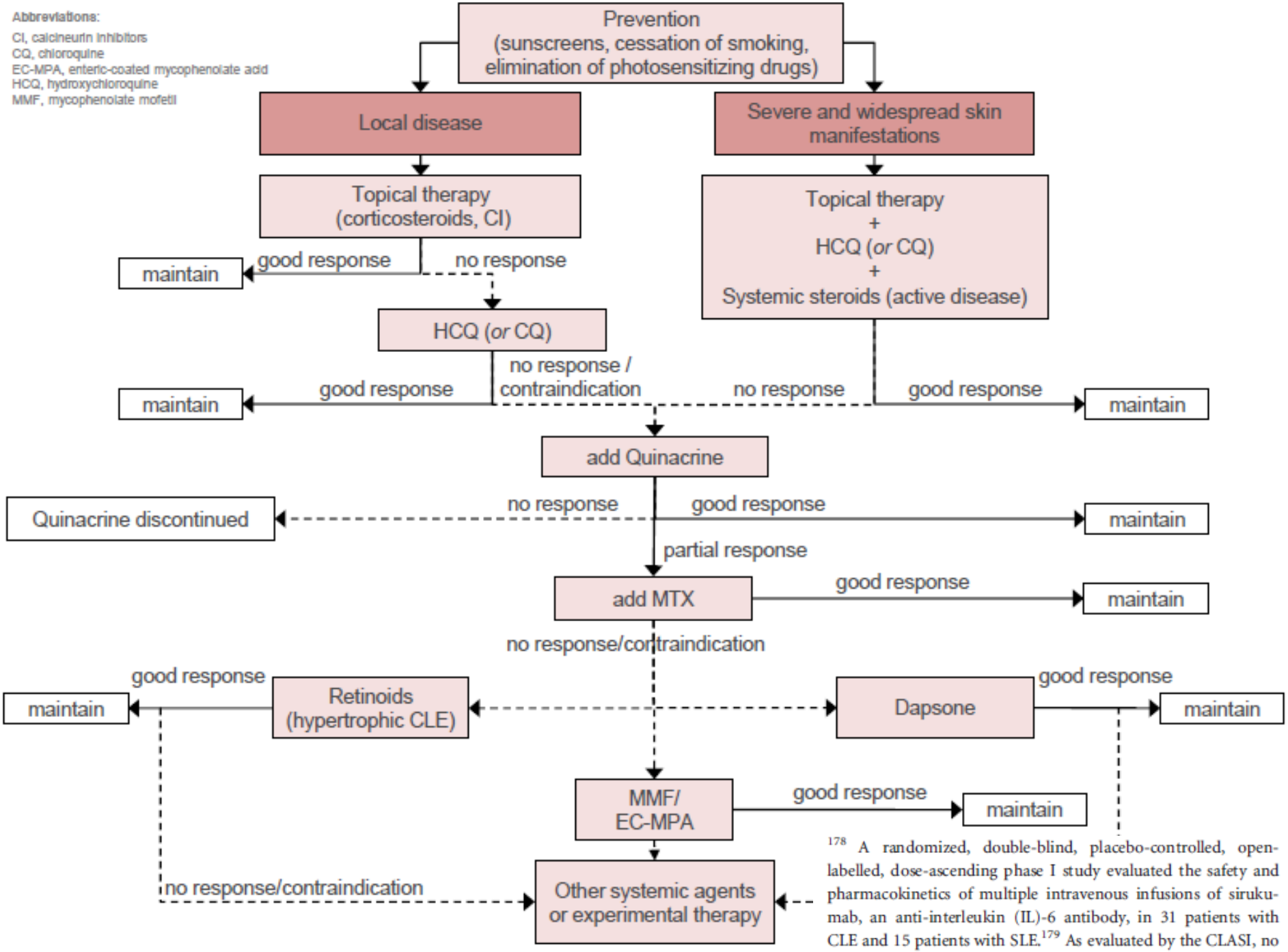
Table 1 Drugs inducing cutaneous lupus erythematosus*

Drug Class	Low Risk (<5%)	High Risk (>5%)
Antifungal agents		Griseofulvin, terbinafine
Antihypertensives	Angiotensin-converting enzyme inhibitors: cilazapril, captopril	Calcium channel blockers: diltiazem, verapamil, nifedipine, nitrendipine, Betablockers: oxprenolol, acebutolol; Diuretics: hydrochlorothiazide, spironolactone
Chemotherapeutic agents	5-Fluorouracil, capecitabine	Docetaxel
Antacids	Omeprazole, lansoprazole, ranitidine	
Antiepileptics	Phenytoin, oxcarbazepine	
Immunomodulators	Etanercept, infliximab, efalizumab, IFN-α, leflunomide	
Lipid-lowering agents	Pravastatin, simvastatin	
Anti-inflammatory drugs	Naproxen, piroxicam	
Antidepressants	Bupropion	
Antidiabetic drugs	Sulphonylurea (glyburide)	
Antiarrhythmia agents	Procainamide	
Benzodiazepines	Tetrazepam, lormetazepam	
Platelet aggregation inhibitors	Ticlopidine	



modified after *Kuhn A et al. J Am Acad Dermatol (2011): Part I: 65: e179–193, Part II: 65: e195–213*

[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.

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GUIDELINES

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- 'Recommended' → strong (positive) recommendation
- 'Suggested' → moderate (positive) recommendation
- 'Not recommended' → strong (negative) recommendation
- 'Not suggested' → moderate (negative) recommendation.

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**.

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GUIDELINES

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Name of Drug/Intervention	Type	Study Design	Condition	Enrolment	ClinicalTrials.gov Identifier	Status
Etanercept (intradermal)	anti-TNF-α antibody	Phase II, open-label study	DLE	25 patients	NCT02656082	Ongoing
Ex vivo expanded human autologous polyclonal regulatory T cells	–	Phase I, open-label, dose escalation study	SLE (ACLE, SCLE, DLE, LET)	18 patients	NCT02428309	Ongoing
RSLV-132	monospecific nuclease Fc-fusion protein	Phase IIa, randomized, placebo-controlled, double-blind study	SLE (CLE)	50 patients	NCT02660944	Ongoing
ALX-0061	anti-IL-6 receptor nanobody	Phase II, randomized, placebo-controlled, double-blind study	SLE	300 patients	NCT02437890	Ongoing
BMS-931699 (lulizumab pegol)	anti-CD28 antibody	Phase II, randomized, placebo-controlled, double-blind study	SLE	350 patients	NCT02265744	Ongoing
CC-220	small molecule	Phase II, randomized, placebo-controlled, double-blind study	SLE	140 patients	NCT02185040	Ongoing
Abatacept	fusion protein	Phase II, randomized, placebo-controlled, double-blind study	SLE	60 patients	NCT02270957	Ongoing
Anifrolumab	type I IFN receptor antagonist	Phase III, randomized, placebo-controlled, double-blind study	SLE	450 patients	NCT02446912	Ongoing
TAB08	CD28 superagonist	Phase II, randomized, placebo-controlled, double-blind study	SLE	60 patients	NCT02711813	Not yet ongoing
CC-11050	small molecule	Phase II, randomized, placebo-controlled, double-blind study	DLE, SCLE	48 patients	NCT01300208	Completed, not yet published
KRP203	S1P1/4/5 agonist	Phase II, randomized, placebo-controlled, double-blind study	SCLE	10 patients	NCT01294774	Completed, not yet published
Apremilast (CC10004)	phosphodiesterase 4 (PDE-4) inhibitor	Phase I/II, open-label study	DLE	10 patients	NCT00708916	Published[182]
Fumaric Acid Esters	Fumaric acid esters	Phase II, open-label pilot study	CLE (DLE, SCLE)	11 patients	NCT01352988	Published[183]
Paquinimod (ABR-215757)	small molecule	Phase II, open-label study	SLE	13 patients	NCT00997100	Published[184]
AMG 811	anti-IFN-γ IgG1 antibody	Phase I, randomized, placebo-controlled, double-blind study	DLE	16 patients	NCT01164917	Published[185]
PD-0360324	IgG1 antibody	Phase I, randomized, placebo-controlled, double-blind study	DLE, SCLE	28 patients	NCT01470313	Published[186]

*Only studies are listed, in which a skin score is applied to evaluate cutaneous manifestations, modified after.[187]

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**

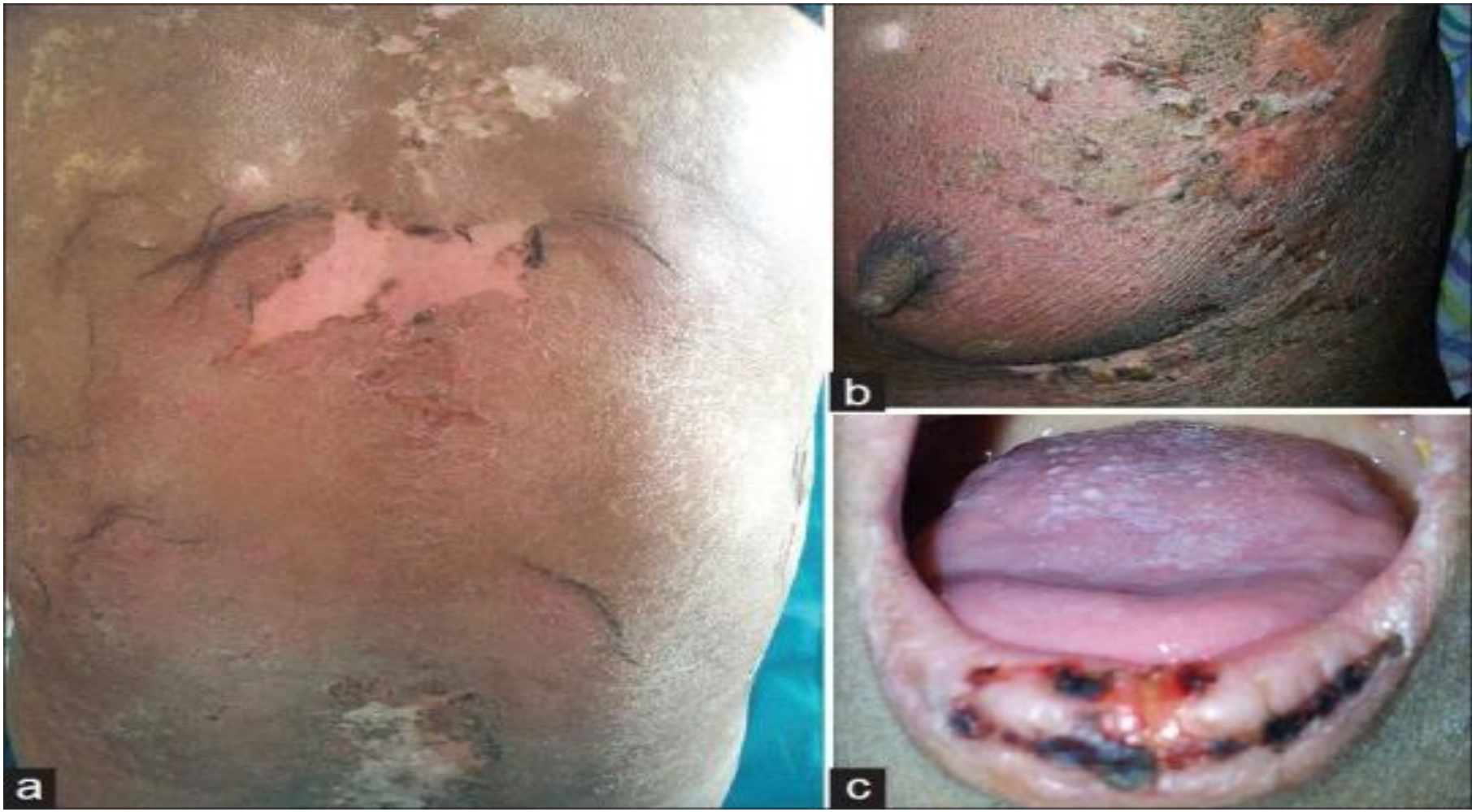
CONCLUSION

- **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**

Serpula vermicula
Capraia Isola

Toxic Epidermal Necrolysis-like Rash of Lupus: A Dermatologist's Dilemma

Brahmita Monga, Sangita Ghosh, VK Jain



Acta Derm Venereol 2010; 90: 175–178

CLINICAL REPORT

Toxic Epidermal Necrolysis-like Cutaneous Lupus Erythematosus: A Series of Three Patients

Claudia G. C. CISNEROS, Ricardo ROMITI, Cláudia G. SANTI, Valéria AOKI, Neusa Y. S. VALENTE and Marcello M. S. NICO
Department of Dermatology, University of São Paulo, São Paulo, Brazil

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

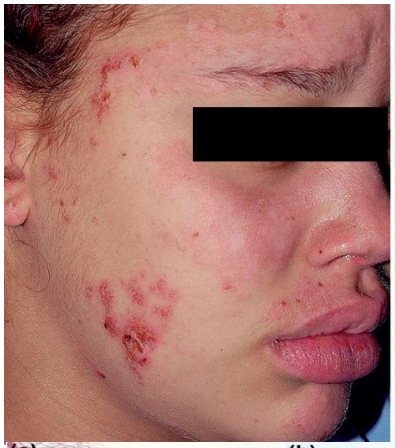
Patient/ age/sex	Initial presentation	Serological abnormalities	Haematological abnormalities	Previous treatment	Mucosal lesions	Time	Treatment	Outcome
1/23/F	SCLE	ANA-1:320 nucleolar anti-RO + anti-LA +	rbc 3920 wbc 2400	Chlor. 250 mg/day Pred. 40 mg BID pulse Pred. 40 mg BID pulse	No	45 days	Chlor. 250 mg/day Pred. 60 mg/day Aza. 150 mg/day	Improved
2/19/F	ACLE	ANA-1:1280 homogenous anti-DNA +	rbc 3900 wbc 3770	Chlor. 250 mg/day Pred. 40 mg/day	No	3 months	Chlor. 250 mg/day Pred. 60 mg/day	Improved
3/17/F	SCLE	ANA- 1:1280 speckeled anti-DNA + anti-Sm + anti-RNP +	rbc 3600 wbc 3460	Chlor. 250 mg/day Pred. 40 mg/day	Yes	1 year	Chlor. 250 mg/day Pred. 60 mg/day	Death from sepsis

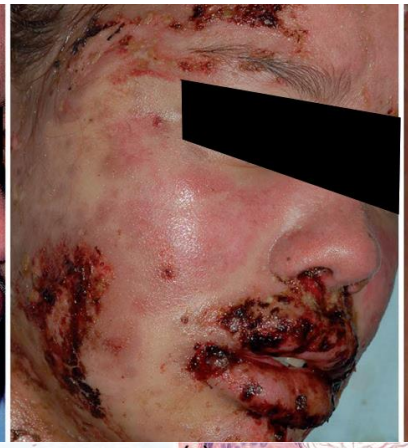
Acta Derm Venereol 2010; 90: 175–178

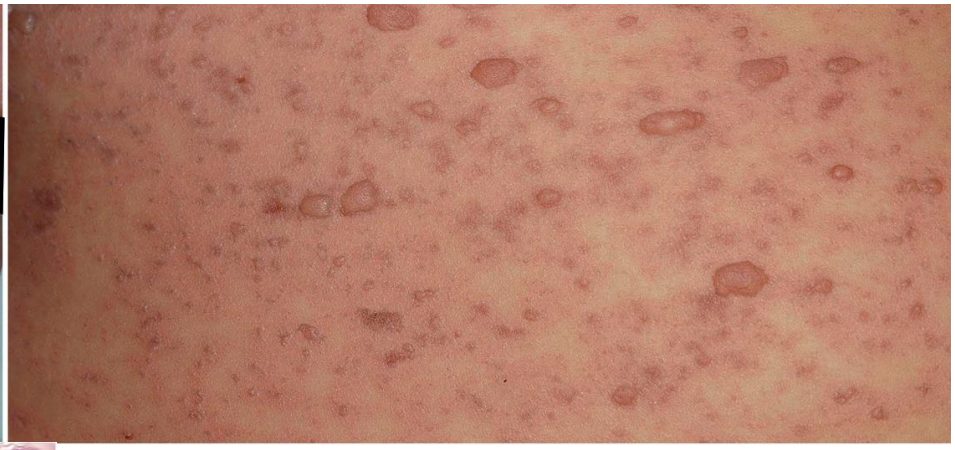
CLINICAL REPORT

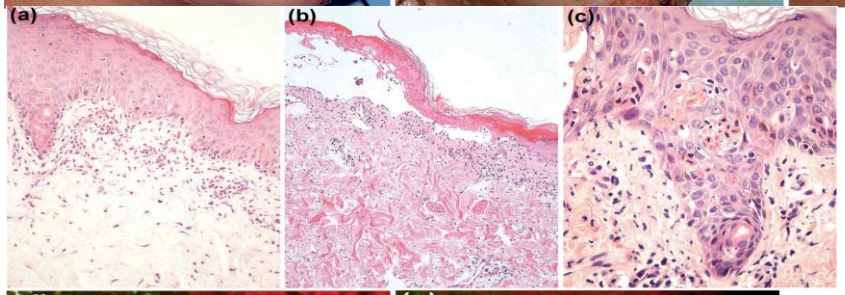
Toxic Epidermal Necrolysis-like Cutaneous Lupus Erythematosus: A Series of Three Patients

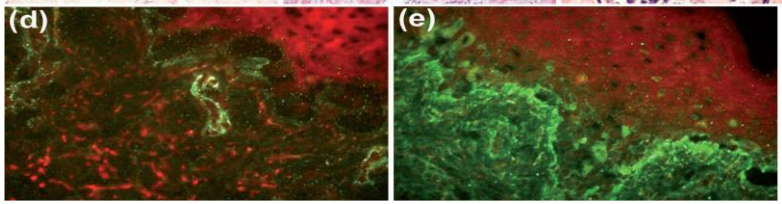
Claudia G. C. CISNEROS, Ricardo ROMITI, Cláudia G. SANTI, Valéria AOKI, Neusa Y. S. VALENTE and Marcello M. S. NICO
Department of Dermatology, University of São Paulo, São Paulo, Brazil











Definitive differential diagnosis may be impossible, since histopathological, serological, and immunofluorescence markers were almost identical in all cases.

Autoimmunity Reviews 12 (2013) 444–454

Contents lis

Auto

journal homepa

Review

Cutaneous lupus erythematosus: Fi from the European Society of Cuta

Cyrus Biazar [a], Johanna Sigges [a], Nikolaos Pa
Gisela Bonsmann [a], Annegret Kuhn [a,*]
and the EUSCLE co-authors [1]

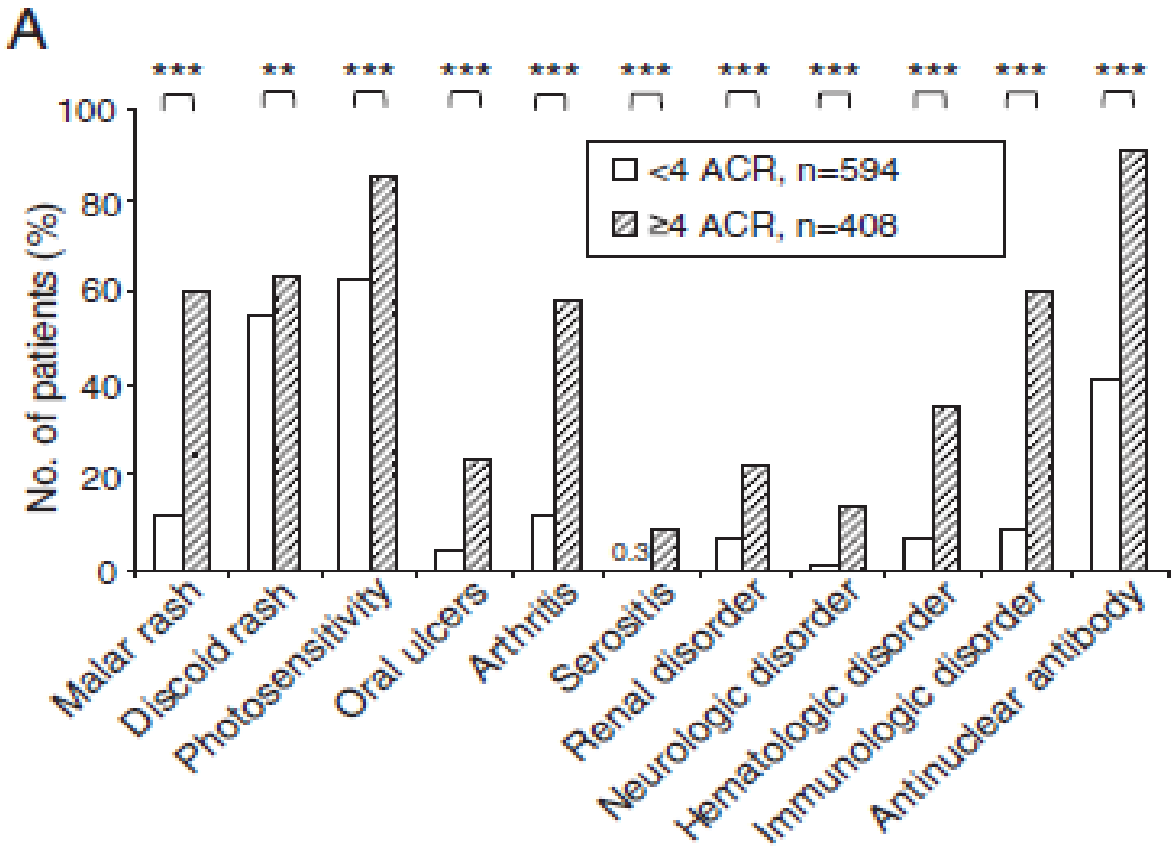


Fig. 3. A) Percentages of patients fulfilling the ACR criteria. The 11 ACR criteria are listed with respect to the percentages of patients who fulfilled each criterion in the subgroup of patients who fulfilled four or more or fewer than four ACR criteria, respectively. **B) Percentages of CLE patients 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

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

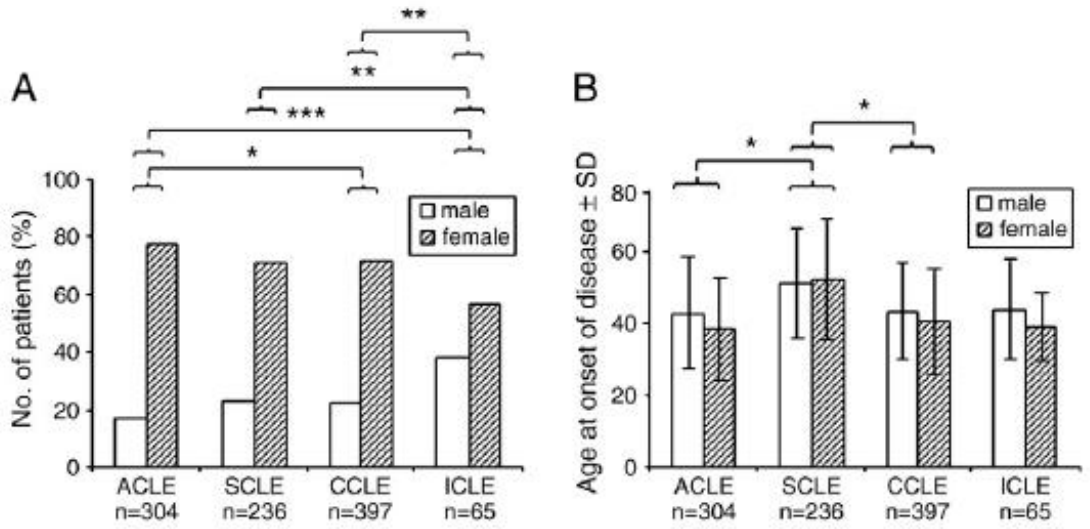
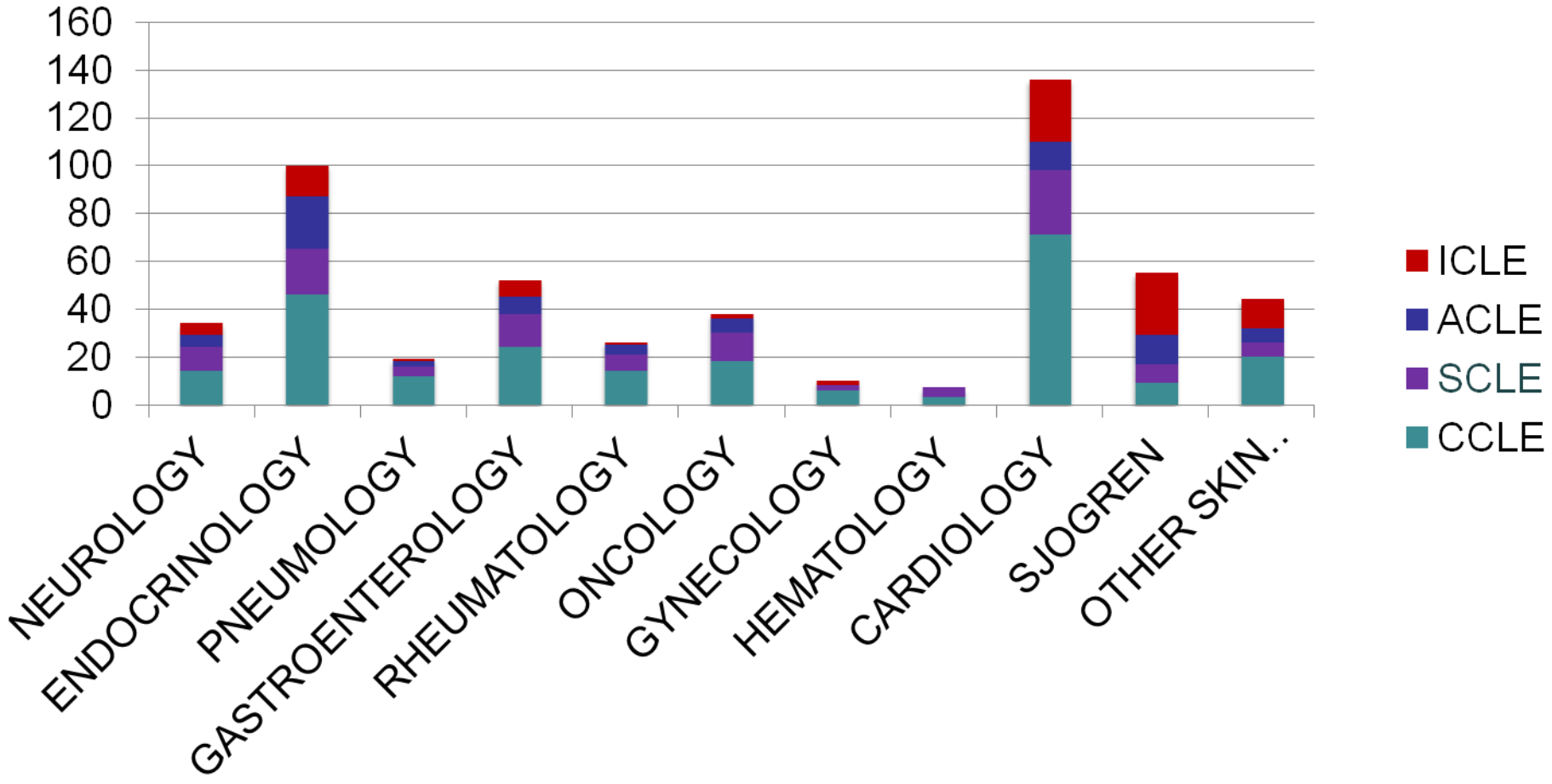


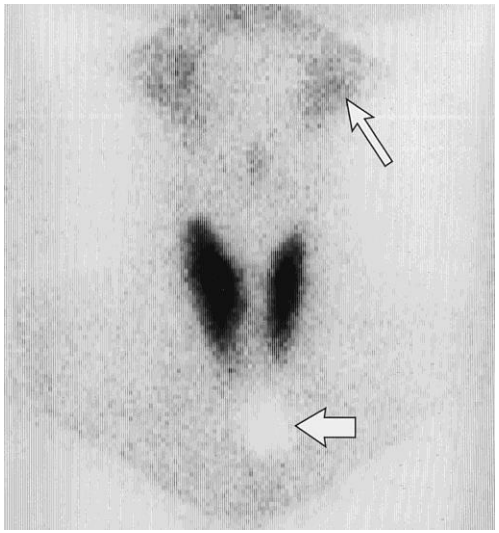
Fig. 1. A) Male and female patients with different CLE subtypes. The percentage of males (n=234, 23.4%) and females (n=768, 76.6%) is itemized by the four subtypes of the disease. **B) Mean age at onset of disease in CLE subtypes (main diagnosis).** The data present the mean age at onset of disease ±SD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

ASSOCIATED DISORDERS



Malattie associate

160 pazienti con malattie associate (53%)

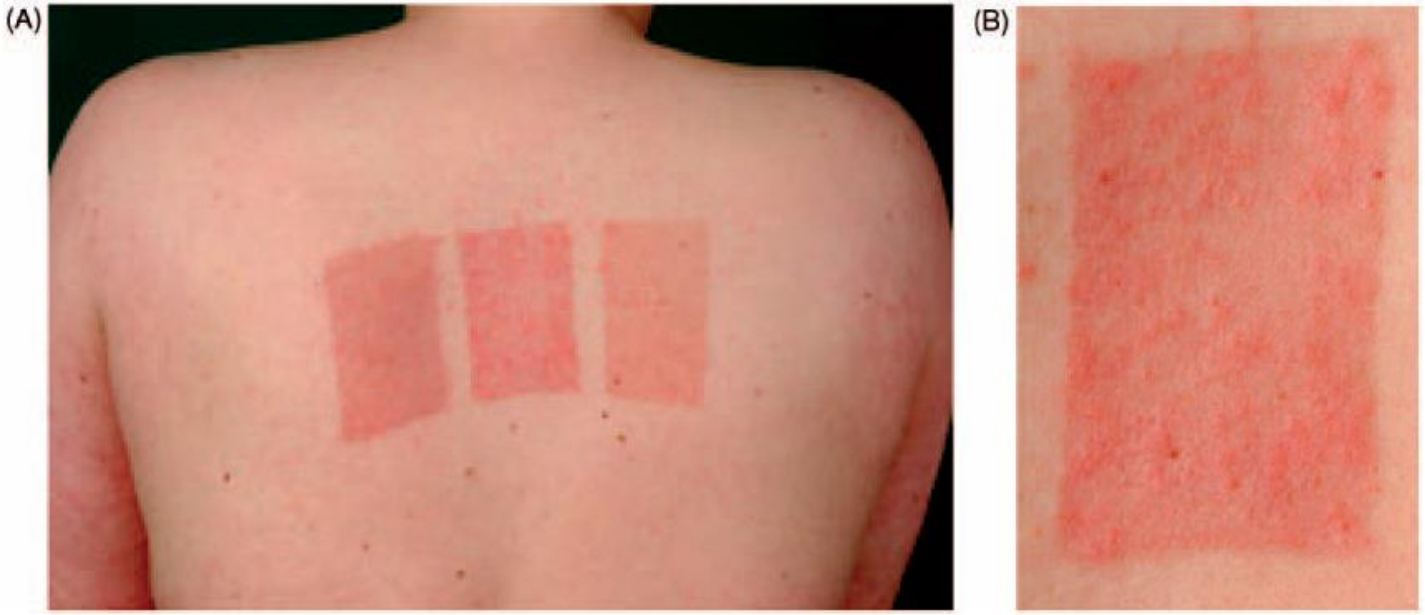


Malattie autoimmuni	81 (27%)
- Tiroidite	38 (12,5%)
- Sindrome di Sjogren	21 (7%)
Ipertensione, ipercolesterolemia, DM II	48 (16%)
Malattie cutanee (psoriasi, vitiligine, LP, DA)	23 (7,5%)
Infezioni	17 (5,5%)
Neoplasie	11 (3,5%)
S. Ansioso-depressiva	6 (2%)

Koskenmies et al, Lupus 2008

Phototest

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



Photoprotection

Display Settings: Abstract Send to:

Lupus. 2010 Aug;19(9):1036-46. doi: 10.1177/0961203310370344.

Photosensitivity, phototesting, and photoprotection in cutaneous lupus erythematosus.

Kuhn A[1], Ruland V, Bonsmann G.

- Key role in preventing exacerbations (also systemic) disease
- Most photosensitive forms:
  - Subacute cutaneous lupus erythematosus
  - Lupus erythematosus

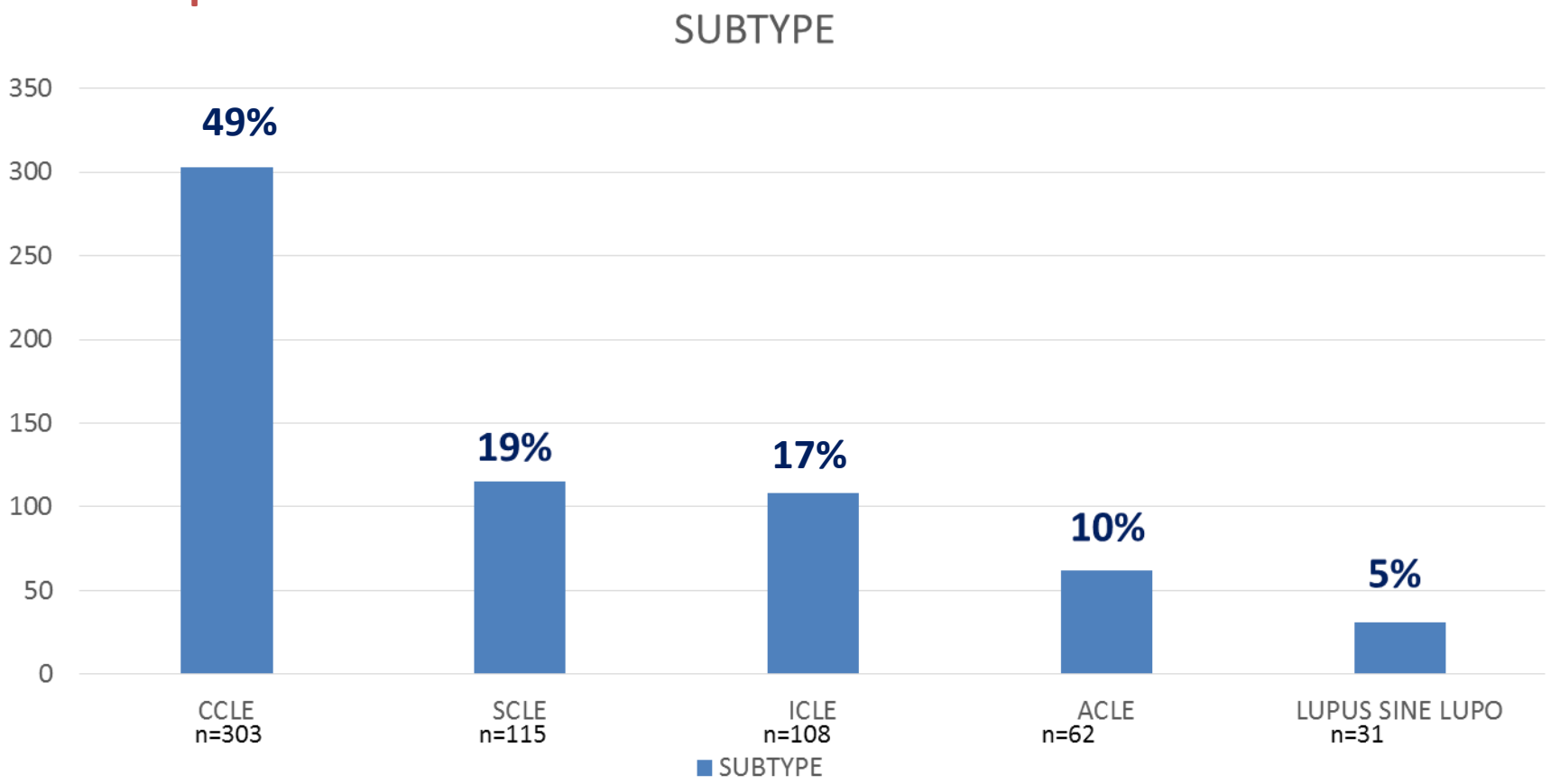
Photosensitivity in CLE

- 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

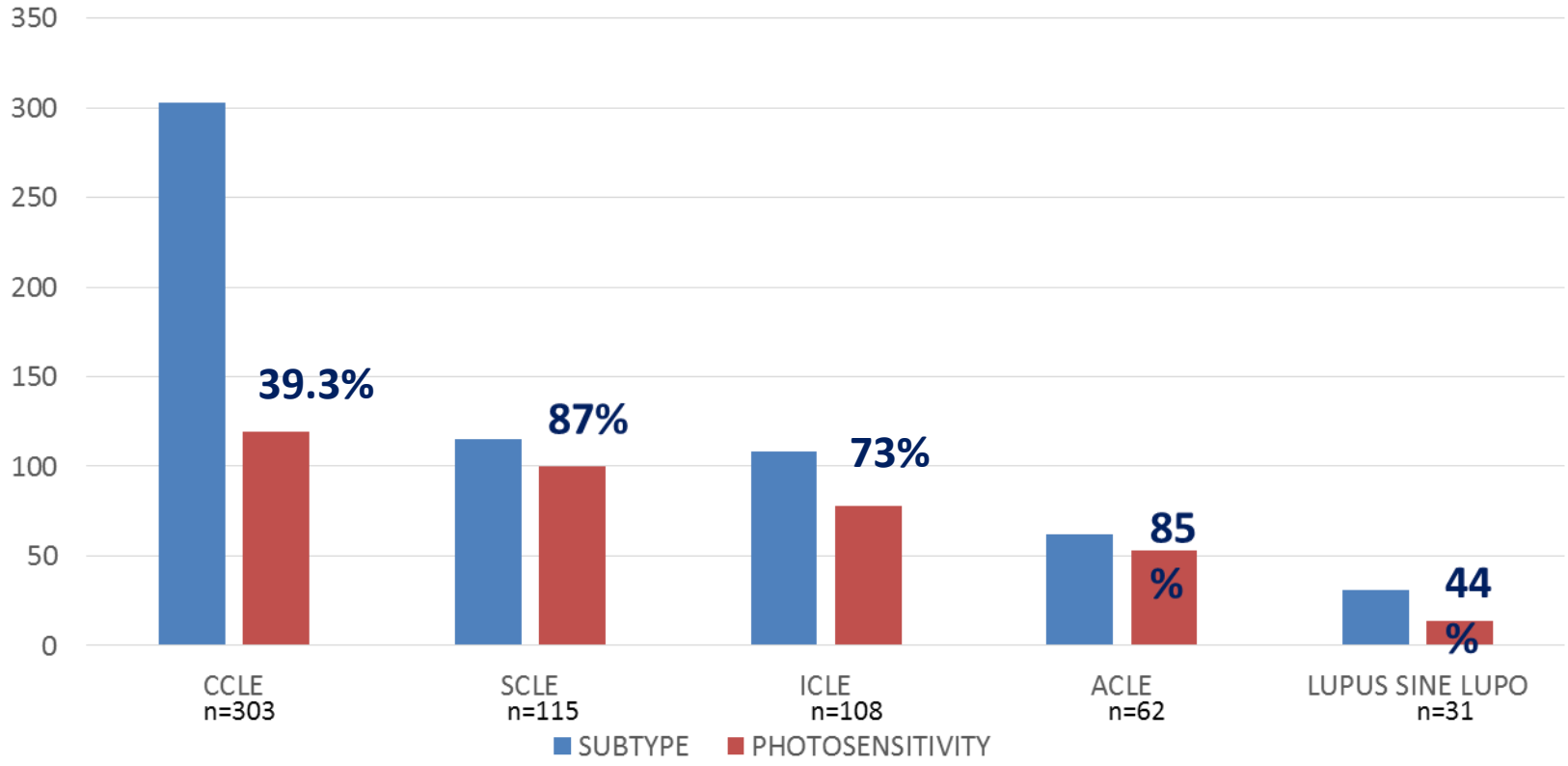
ITALIAN EXPERIENCE
GIIP 2009-2014

Tot. 619 pt



PHOTOSENSITIVITY

Tot. 619 pt



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

ACR Criteria

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

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
- …

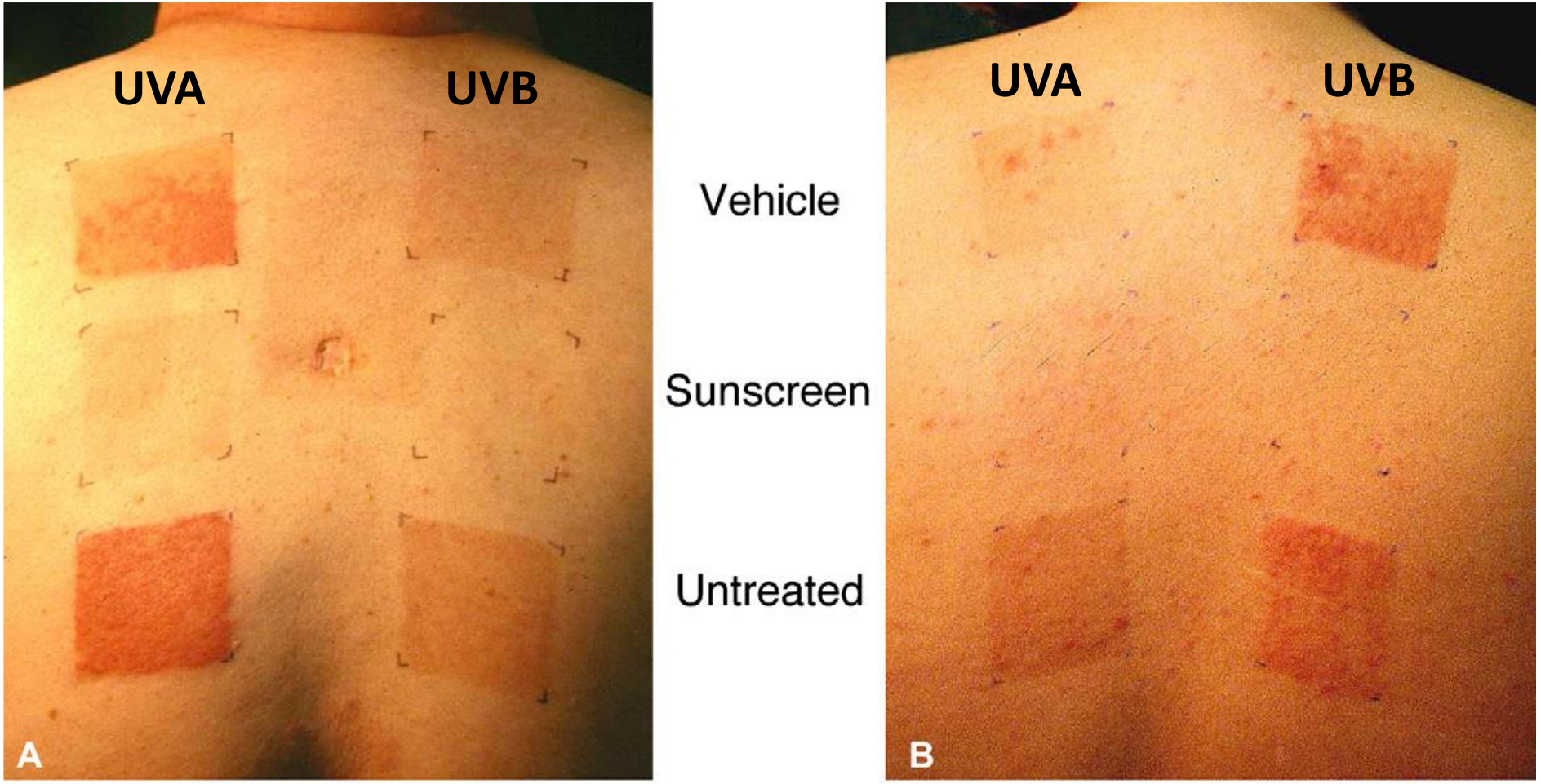
Photoprovocation test

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,[a] Kristina Gensch, MD,[b] Merle Haust, MD,[b] Anna-Maria Meuth, MA,[a] France Boyer, MD,[c] Patrick Dupuy, MD,[c] Percy Lehmann, MD,[d] Dieter Metze, MD,[a] and Thomas Ruzicka, MD[e]
Muenster, Duesseldorf, Wuppertal, and Munich, Germany; and Toulouse, France



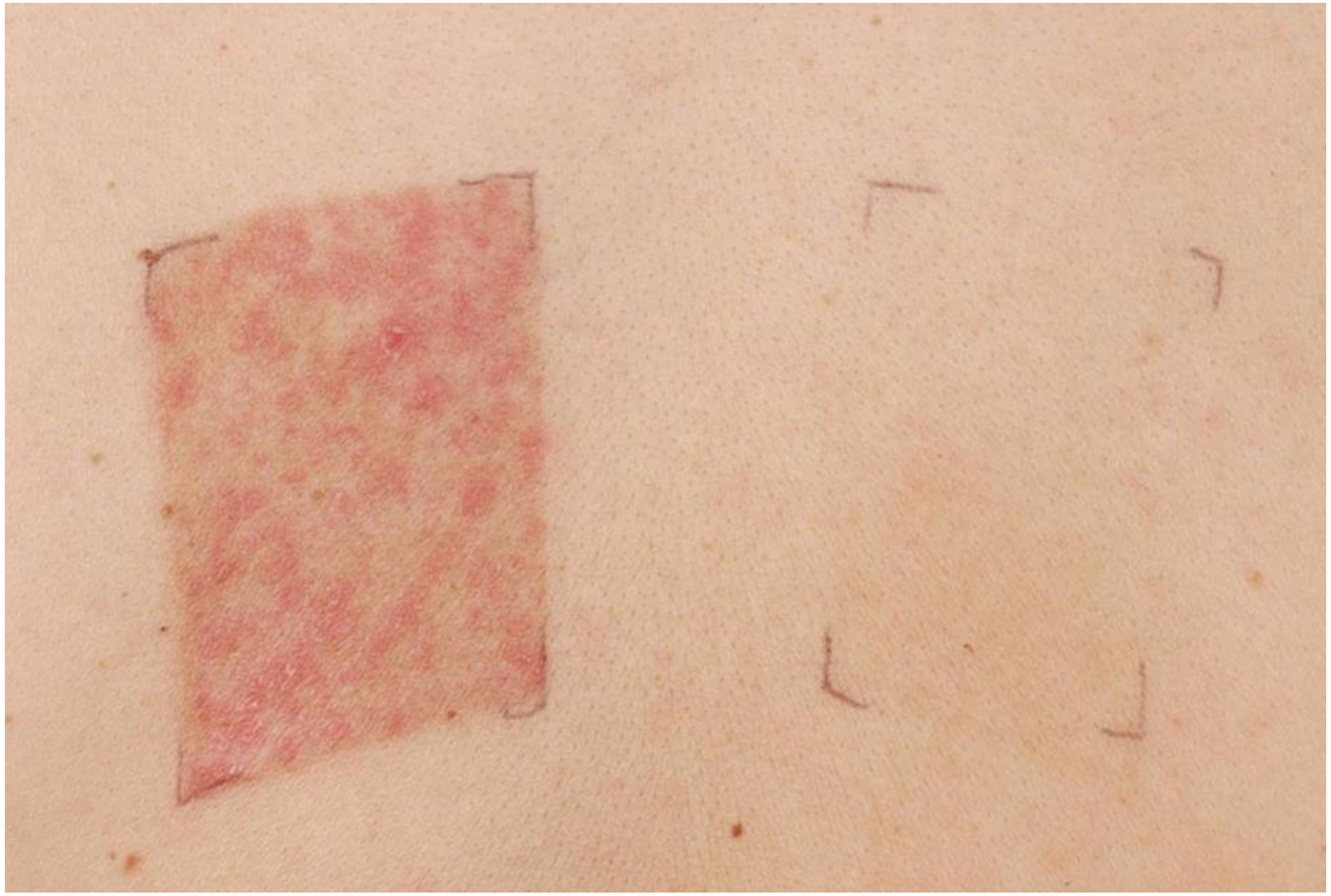


Table 1 Photoprovocation in lupus erythematosus: review of the literature since 1986 (modified after [9])

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

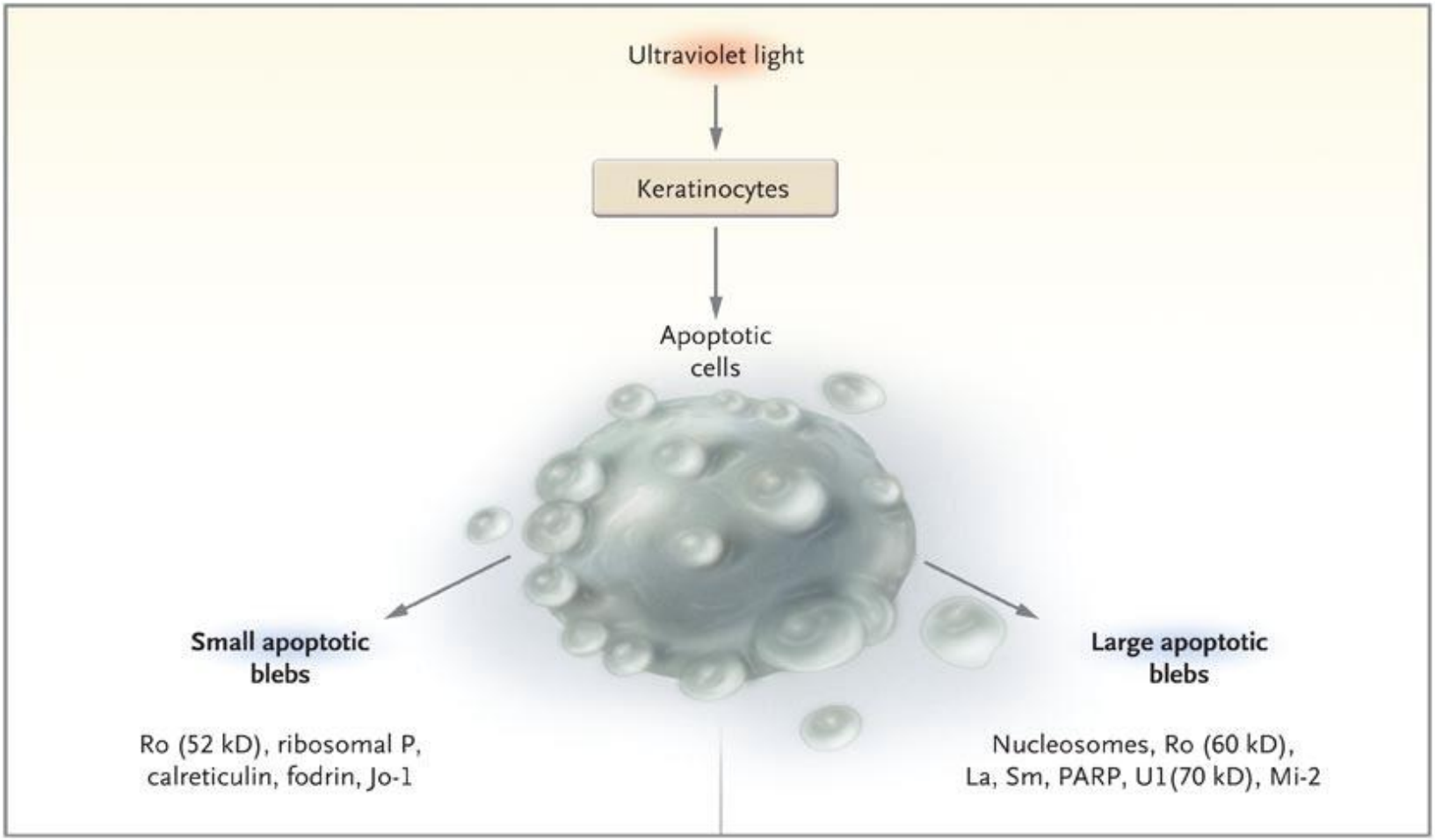
Photoprovocation test: summary

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.

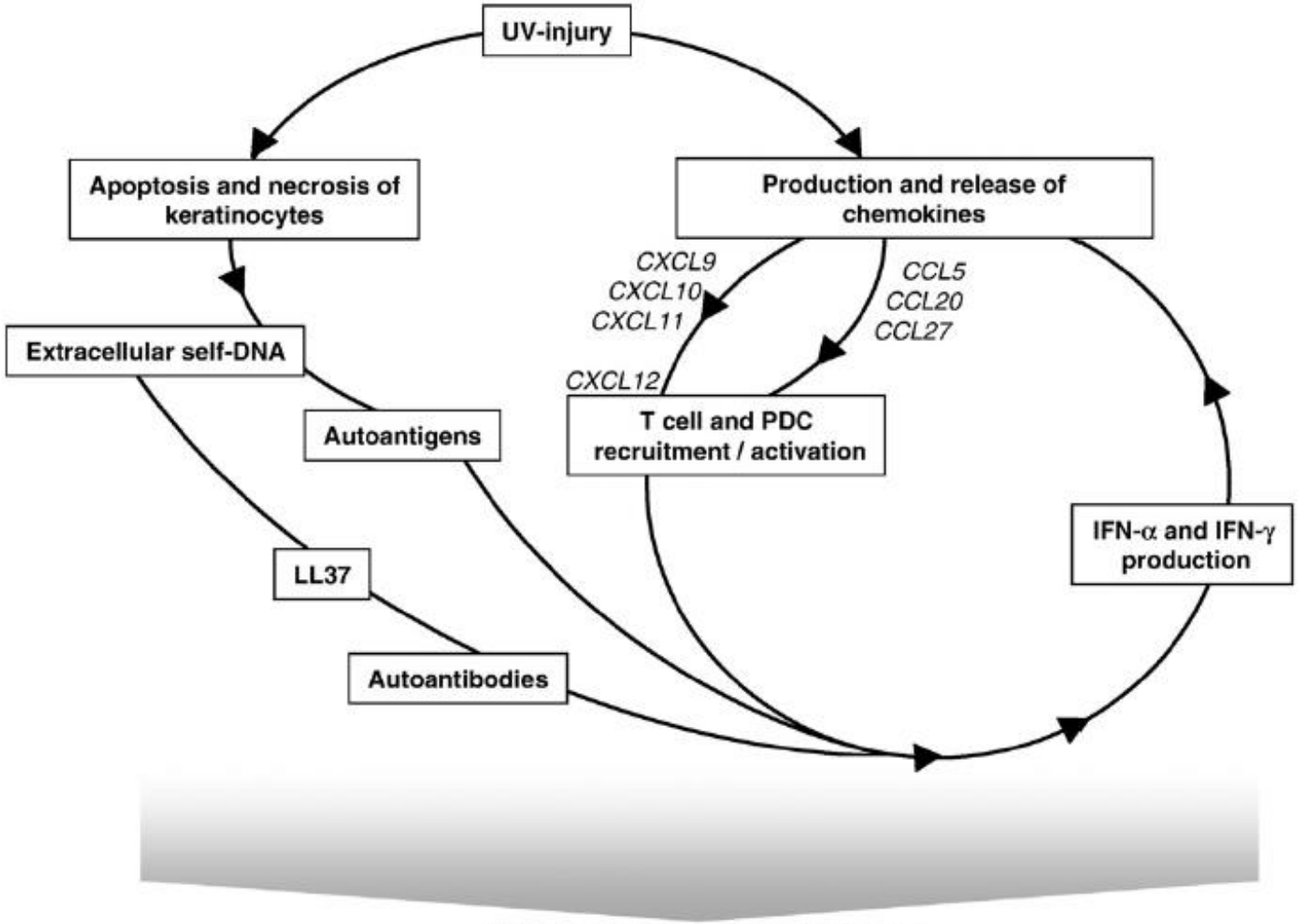
Lehmann et al, Autoimmun Rev 2009

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 or antigen



Rahman A, Isenberg DA. N Engl J Med 2008;358:929-939.


UV-injury
Apoptosis and necrosis of keratinocytes
Production and release of chemokines
CXCL9
CXCL10
CXCL11
CCL5
CCL20
CCL27
CXCL12
Extracellular self-DNA
Autoantigens
T cell and PDC recruitment / activation
IFN-α and IFN-γ production
LL37
Autoantibodies
UV-induced cutaneous LE phenotype

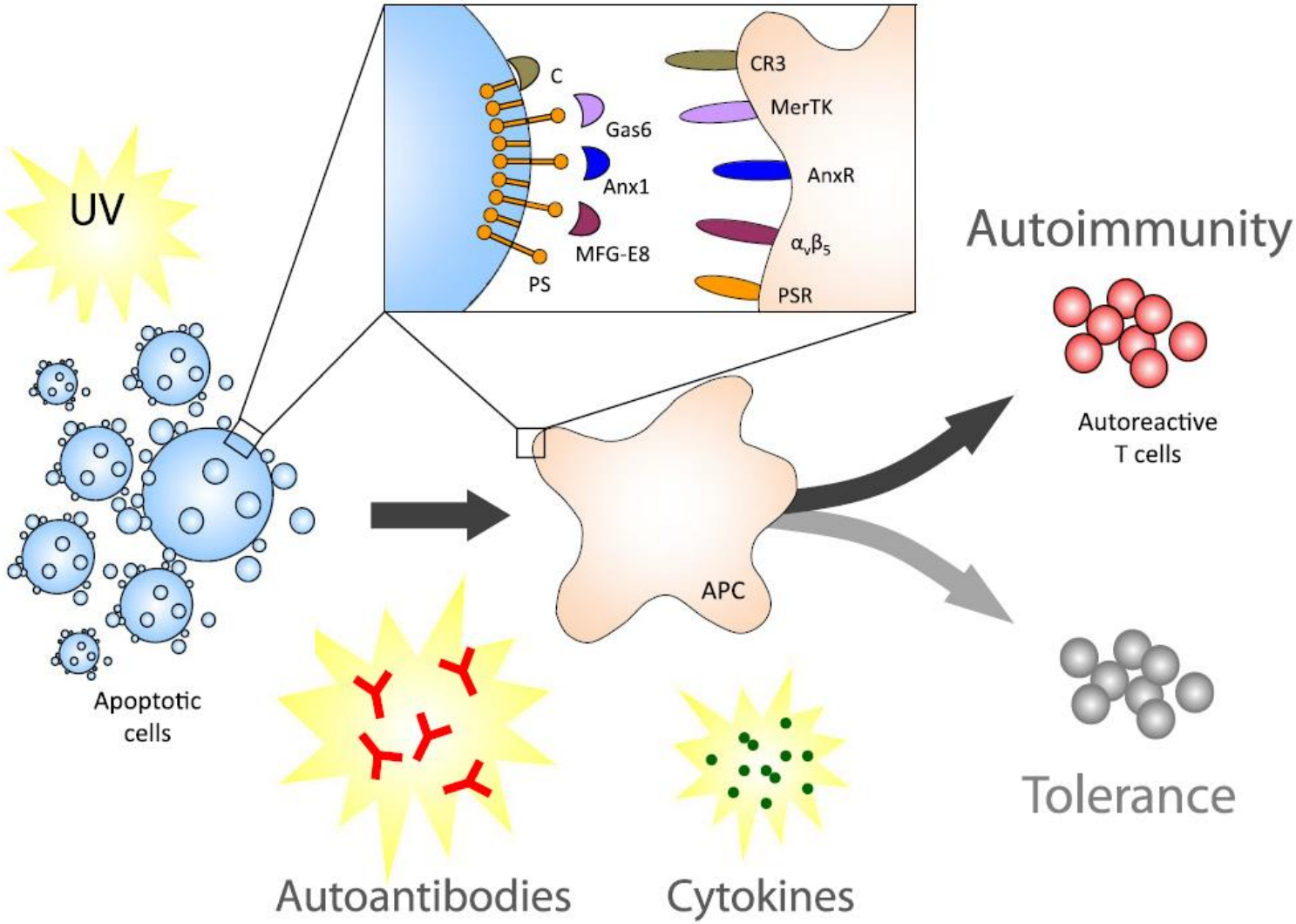


Fig. 1 Clearance of UV-induced apoptotic cells in autoimmunity. Under physiological conditions, apoptotic cells are efficiently cleared by phagocytes such as antigen presenting cells (APC). Various molecules on the surface of apoptotic cells and corresponding receptors on the APC mediate phagocytosis 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; $\alpha_v\beta_5$, $\alpha_v\beta_5$ integrin; *PS*, phosphatidylserine; *PSR*, phosphatidylserine receptors)

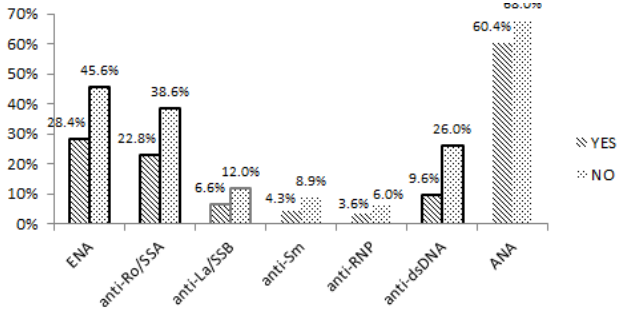
Unanswered question

- 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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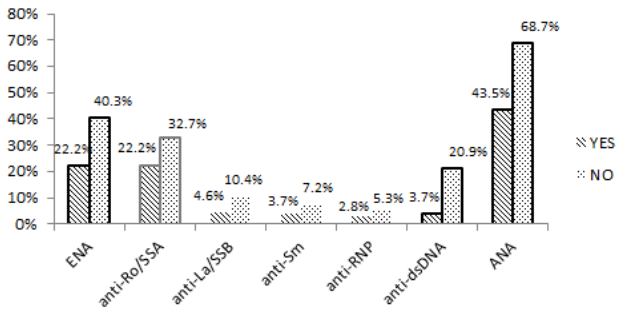
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anti-La/SSB
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anti-RNP
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ANA
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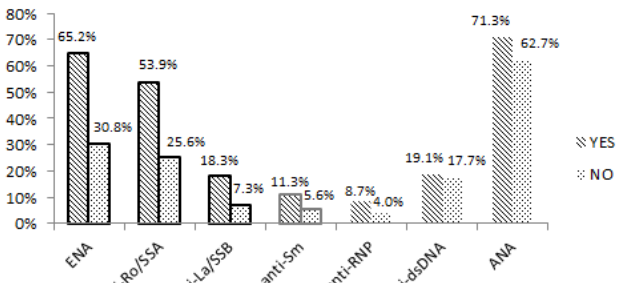
SCLE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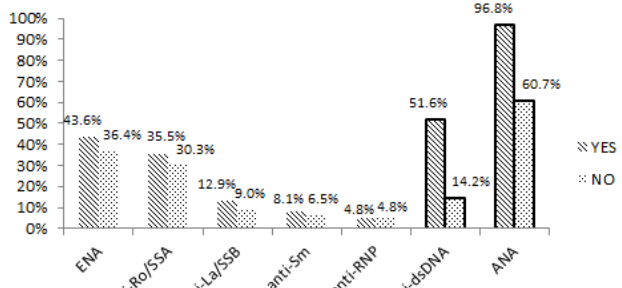
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4.8%
51.6%
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96.8%
60.7%
ENA
anti-Ro/SSA
anti-La/SSB
anti-Sm
anti-RNP
anti-dsDNA
ANA
YES
NO

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

Disease	Treatment modality	Level of evidence[a]
Lupus erythematosus	Phototherapy	
	UVA1	Ib
	Photodynamic therapy	IV
	Photopheresis	IIIb

Gordon Spratt et al, Br J Dermatol 2015

Table 2. UVA-1 radiation trials for lupus patients

Year	Author	N	Study type	UVA-1 regimen	Comments
1993	Sönnichsen *et al.* (46)	1	Case report	186.1 J/cm^2 over 9 weeks	Clinical improvement in a 71-year-old female with SCLE having contraindications to corticosteroid and immunosuppressive therapy
1994	McGrath *et al.* (47)	15	Open-label	6.5 J/cm^2/day: 5 days/wk × 3 weeks	Disease activity scores decreased
1994	McGrath (48)	10	Open-label	6 J/cm^2/day: 5 days/wk × 3 weeks	Disease activity scores decreased, and one SCLE patient's skin lesions improved
1996	McGrath *et al.* (37)	26	DB-RCT (crossover)	6 J/cm^2/day: 5 days/wk × 3 weeks (or visible light)	SLAM scores and dsDNA autoantibodies significantly decreased with UVA-1 radiation group
2001	Polderman *et al.* (40)	11	DB-RCT (crossover)	6 J/cm^2/day: 5 days/wk × 3 weeks (or visible light)	SLAM and SLEDAI scores decreased in both groups, but no significant difference between groups
2003	Menon *et al.* (38)	1	open-label (case report)	16 J/cm^2/day: 3 days/wk × 24 weeks (minus 12–14)	Clinically significant improvement seen by week 2–3 of UVA-1 treatment, brain function improvement on PET paralleled reversal of cognitive dysfunction
2004	Polderman *et al.* (41)	12	DB-RCT (crossover)	12 J/cm^2/day: 5 days/wk × 3 weeks	SLAM and SLEDAI scores significantly decreased in UVA-1 group vs. placebo group, one SCLE patient's skin lesions improved
2005	Szegedi *et al.* (39)	9	Open-label	6 J/cm^2/day: 5 days/wk × 3 weeks, then 3 days/wk × 3 weeks then 4 days/wk × 3 weeks	SLEDAI scores declined significantly, decrease in IFN-γ producing T_H1 and T_H2 cells, decreased ratio of T_H1:T_H2 and T_C1:T_C2
2005	McGrath (49)	1	Case report	10 J/cm^2/day: 2 days/wk × 30 weeks	Elimination of anticardiolipin antibodies and termination of cognitive decline in SLE patients
2010	Jabara *et al.* (50)	1	Case report	8 J/cm^2/day: 2 days/wk × 5 years	Incidental improvement of interstitial lung disease and pulmonary hypertension

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

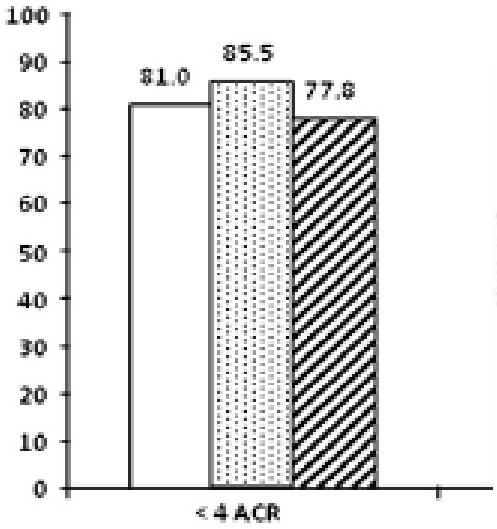
Annegret Kuhn [a,*], Johanna Sigges [a], Cyrus Biazar [a], Aysche Landmann [b], Vincent Ruland [a], Nikolaos Patsinakidis [a], Susanne Amler [c], Gisela Bonsmann [a] and the EUSCLE Co-Authors [1]

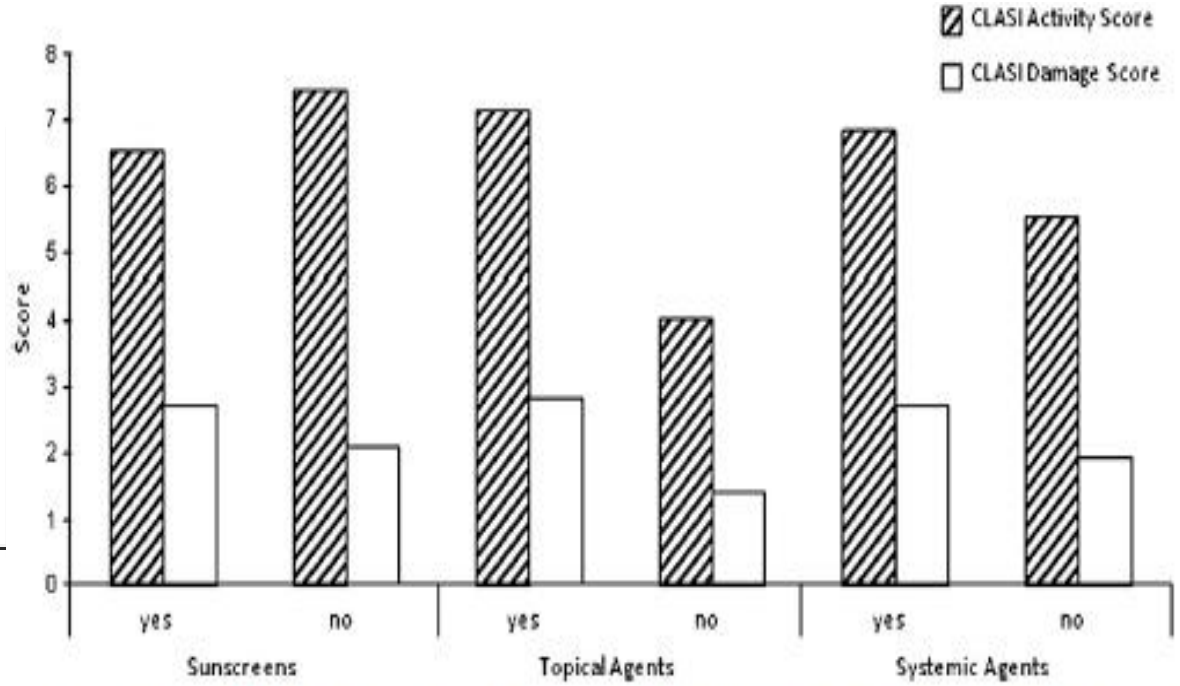
[a] Department of Dermatology, University of Muenster, 48149 Muenster, Germany
[b] Division of Immunogenetics, Tumorimmunology Program, German Cancer Research Center, 69120 Heidelberg, Germany

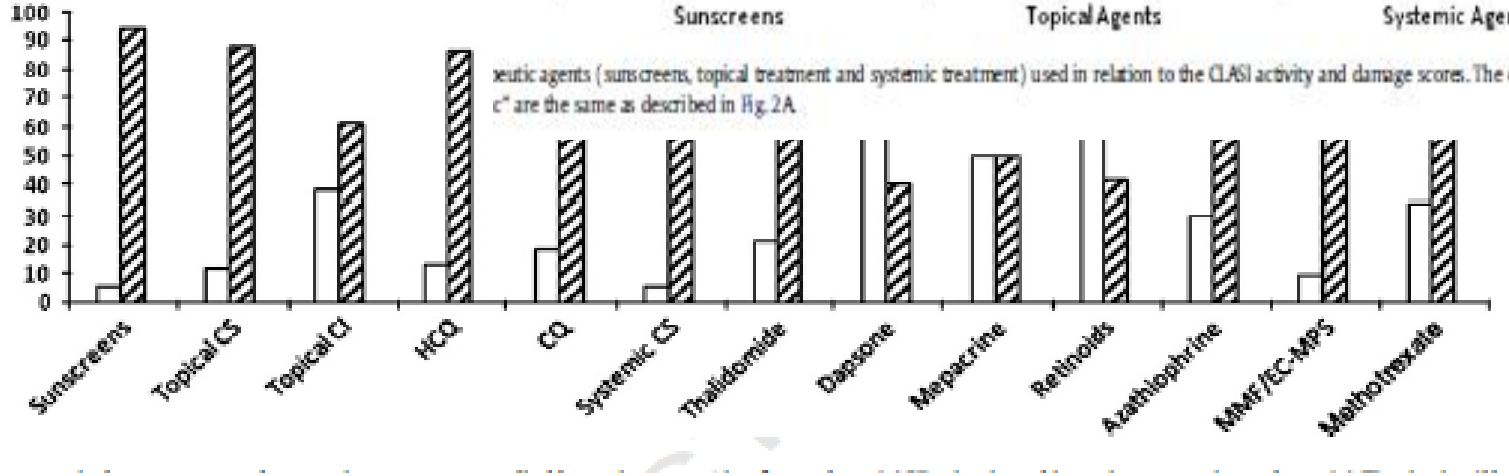
* Corresponding author at: Department of Dermatology, University of Muenster, Von-Esmarch-Strasse 58, D-48149 Muenster, Germany. Tel.: +49 251 8352210, +49 6221 423773; fax: +49 251 8358947, +49 6221 423749.

E-mail addresses: kuhnan@uni-muenster.de (A. Kuhn), johanna.sigges@gmx.de (J. Sigges), cyrusbiazar@googlemail.com (C. Biazar), a.landmann@dkfz.de (A. Landmann), vruland@gmail.com (V. Ruland), nikos.patsi@uni-muenster.de (N. Patsinakidis), Susanne.Amler@ukmuenster.de (S. Amler), 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. Olteanu, Colentia Hospital, Dermatology, Bucharest, Romania; R. M. Pujol, J. M. Sánchez-Schmidt, Department of Dermatology, Parc de Salut Mar-IMAS, Barcelona, Spain; L. Medenica, D. Skiljevic, Department of Dermatovenereology, School of Medicine, University of Belgrade, Clinic of Dermatovenereology, Clinical Centre of Serbia, Belgrade, Serbia; A. Reich, J. C. Szepietowski, Department of Dermatology, Venerology and Allergology, Wroclaw Medical University, Wroclaw, Poland; C. Dalle Vedove, G. Girolomoni, Department of Dermatology, University of Verona, Verona, Italy; T. Hawro, A. Zalewska-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. Huegel, Department of Dermatology of the University Hospital of Schleswig-Holstein, Campus Kiel, Kiel, Germany; H. Jedličková, Department of Dermatology, St. Anna University Hospital, Brno, Czech Republic; A. Bygum, R. Laurinaviciene, Department of Dermatology and Allergy Centre, Odensee University Hospital, Odensee 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 and Venerology, 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, Universitaetsmedizin Berlin, Berlin, Germany; A. Gruschke, N. Hunzelmann, Department of Dermatology and Venerology, University Hospital Cologne, Cologne, Germany; K. Steinbrink, 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. Avgerinou, D. Papafragkaki, 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, Donauspital 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.



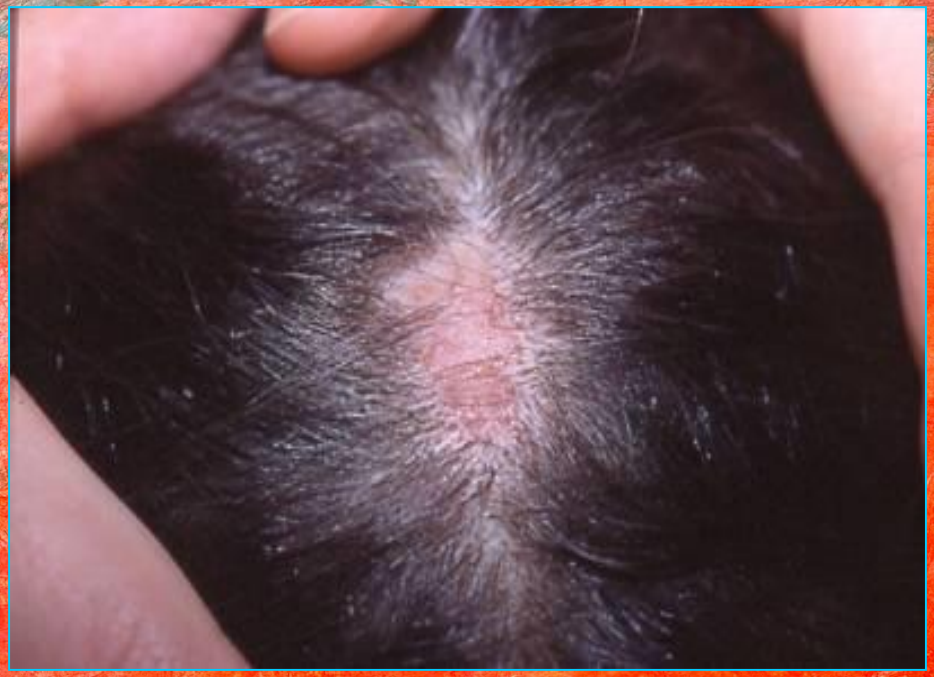
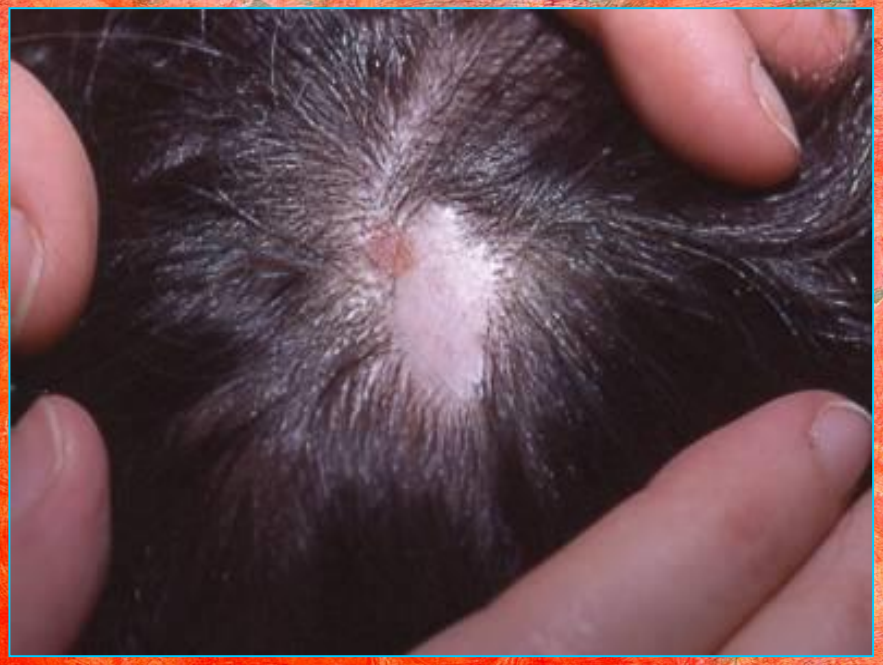
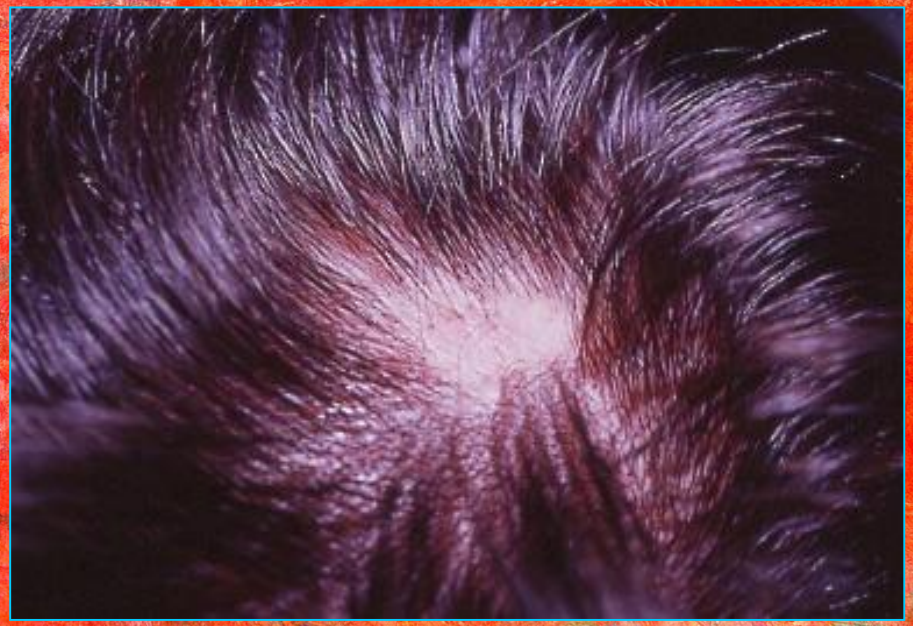
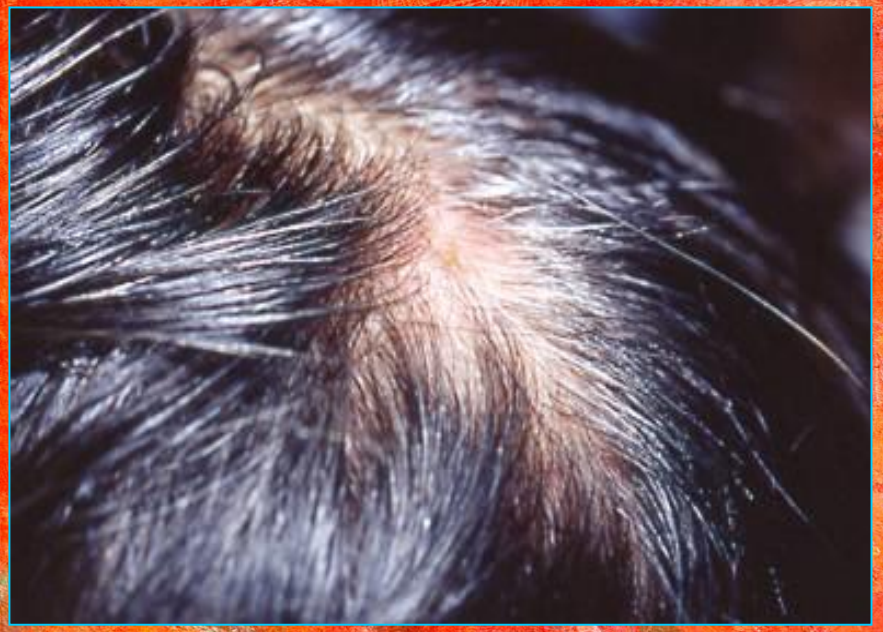




xeutic agents (sunscreens, topical treatment and systemic treatment) used in relation to the CLASI activity and damage scores. The categories "Sunscreens", "Topical c" are the same as described in Fig. 2A.

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.

ACR CRITERIA FOR DIAGNOSIS OF SLE

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

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

Abstract

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.

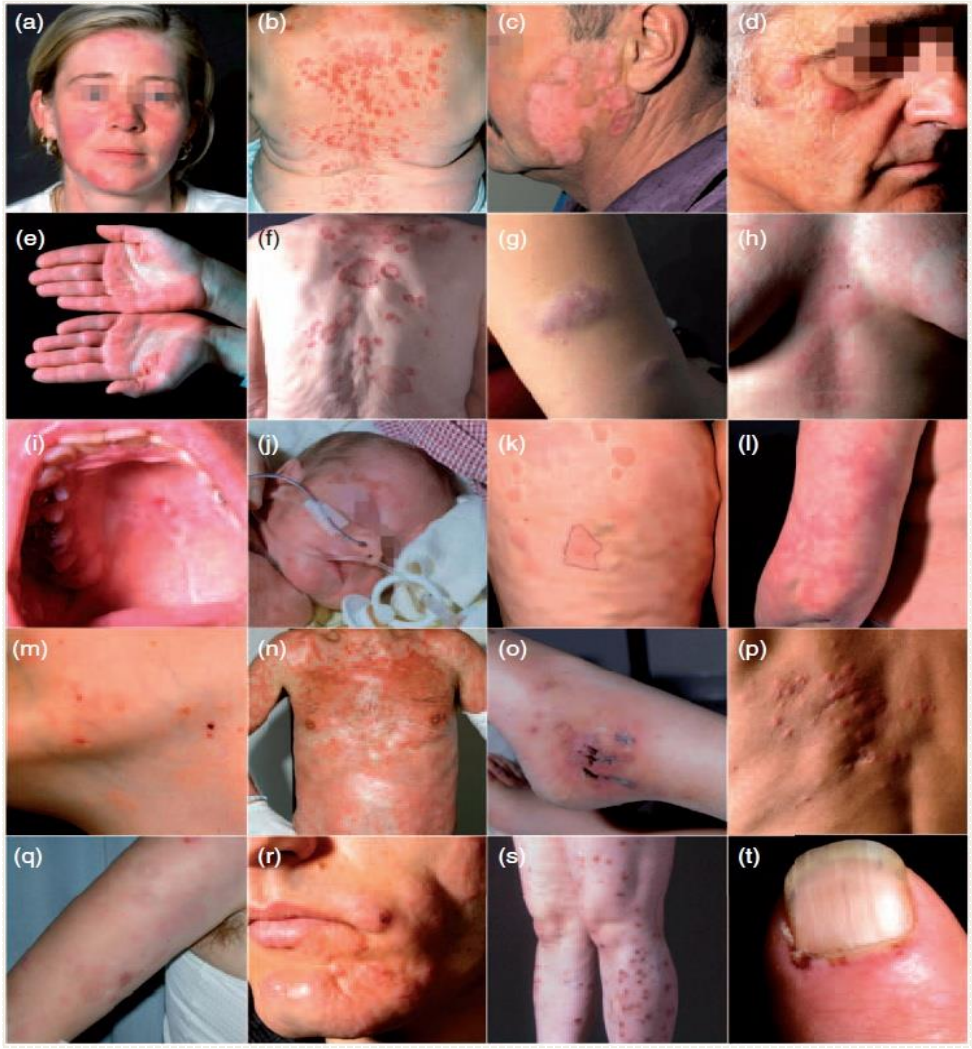
RESULTS:

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.

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

Criteri ACR 1997		Criteri SLICC 2012	
		CRITERI CLINICI	
1	Rash malare	1	Lupus cutaneo acuto o LECS
2	Rash discoide	2	Lupus cutaneo cronico
3	Fotosensibilità		
4	Ulcere orali e nasofaringee	3	Ulcere orali o nasali
		4	Alopecia non cicatriziale
5	Artriti non erosive di 2 o più articolazioni periferiche	5	Sinovite o dolorabilità
6	Sierositi (pleurite o pericardite)	6	Sierositi
7	Disturbi renali (proteinuria >0.5 g/die o 3+ oppure cilindri cellulari)	7	Manifestazioni renali (Proteinuria 500mg/24h oppure cilindri urinari)
8	Disturbi neurologici (crisi convulsive oppure psicosi)	8	Disturbi neurologici (Epilessia, psicosi, mononeurite multipla; mielite periferica o neuropatia nervi cranici; stato confusionale)

9	Disordini ematologici (anemia emolitica con reticolocitosi, oppure leucopenia <4000/μl in due occasioni, oppure linfopenia <1500/μl in due occasioni, oppure trombocitopenia <100000/μl)	9	Anemia emolitica
		10	Leucopenia <4000/μl almeno una volta, oppure linfopenia <1500/μl almeno una volta
		11	Trombocitopenia <100000/μl almeno una volta
		CRITERI IMMUNOLOGICI	
10	Disordini Immunologici (anticorpi anti-dsDNA, oppure anticorpi anti-Sm, oppur positività di anticorpi antifosfolipidi, LAC o falsa positività al test sierologico per la sifilide	1	Anticorpi antinucleo
		2	Anticorpi anti-dsDNA
		3	Anticorpi anti-Sm
11	Anticorpi antinucleo	4	Positività per anticorpi antifosfolipidi
		5	Riduzione del complemento (C3, C4, CH50)
		6	Positività del test di Coombs diretto