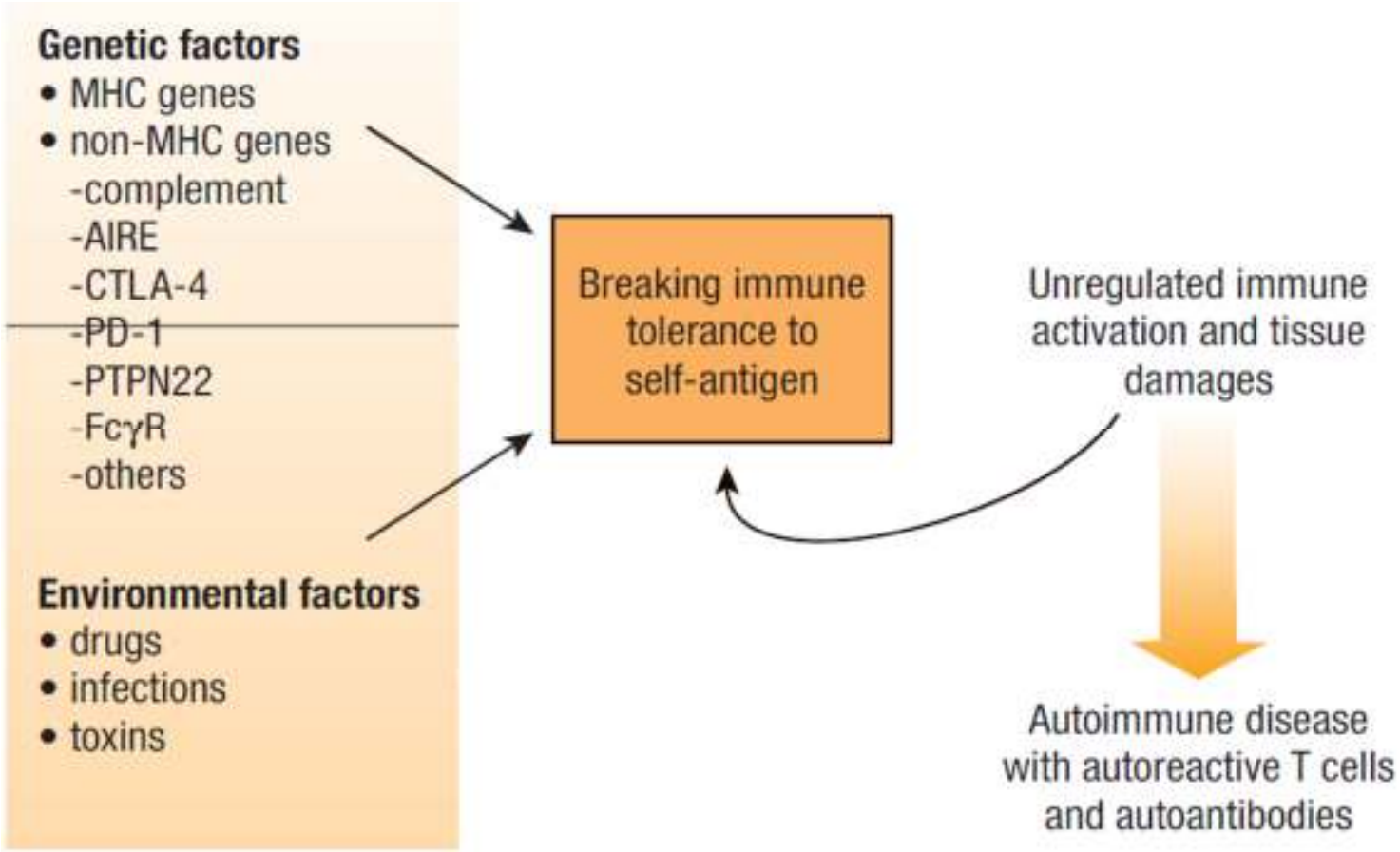
Cutaneous Lupus Erythematosus

M.Betiu

LE in general

- A group of heterogeneous illnesses that have in common the development of immunity to particles of self-DNA, with skin-only disease at one end of the spectrum and severe visceral involvement at the other.
- Skin lesions may be specific to lupus or non-specific and are be seen in other conditions as well.
  - Acute cutaneous lupus erythematosus (malar rash) is almost always associated with underlying visceral involvement, subacute cutaneous lupus patients meet systemic lupus erythematosus criteria about 50 percent of the time, and chronic cutaneous lupus (discoid lupus erythematosus, lupus panniculitis, chilblain lupus, and tumid lupus erythematosus) patients most often have skin-only or skin-predominant disease.
- Discoid lupus erythematosus causes scarring and can be permanently disfiguring. Subacute cutaneous lupus and acute cutaneous lupus erythematosus are highly photosensitive and are characteristically non-scarring.
- Lupus erythematosus–non-specific skin lesions include non-scarring alopecia, mouth ulcers, photosensitivity, Raynaud phenomenon, and vasculitis/vasculopathy, among others. They often herald a systemic lupus erythematosus flare.
- Lupus erythematosus occurs much more commonly in women (9:1 female-male ratio).
  - Treatment consists of sunscreens, local and systemic (short-term) glucocorticoids, antimalarials, retinoids, immunosuppressives, thalidomide, and biologic therapies.

Mechanism of development of systemic autoimmune disease



Definition

- Lupus erythematosus (LE) is an autoimmune disease of unknown cause involving the skin and/or other organs.
- LE is the designation of a spectrum of diseases that are linked by distinct clinical findings and distinct pattern of polyclonal B cell immunity.
- It ranges from life-threatening manifestations of systemic LE (SLE) to the limited and exclusive skin involvement in chronic cutaneous LE (CCLE).
- Lupus erythematosus is a complex and highly variable disease in which a combination of genetic, immunologic and environmental factors acts in concert with the production of the disorder.

LE immunologic factors

- A wide range of immune abnormalities may contribute to autoantibody production:

- polyclonal B-cell activation,
- molecular mimicry and antibody cross reactivity,
- loss of T-cell tolerance,
- abnormal T-cell help,
- cytokine abnormalities (increased production of IL-1, IL-4, IL-6 and IFN gamma), etc.

LE immunologic factors

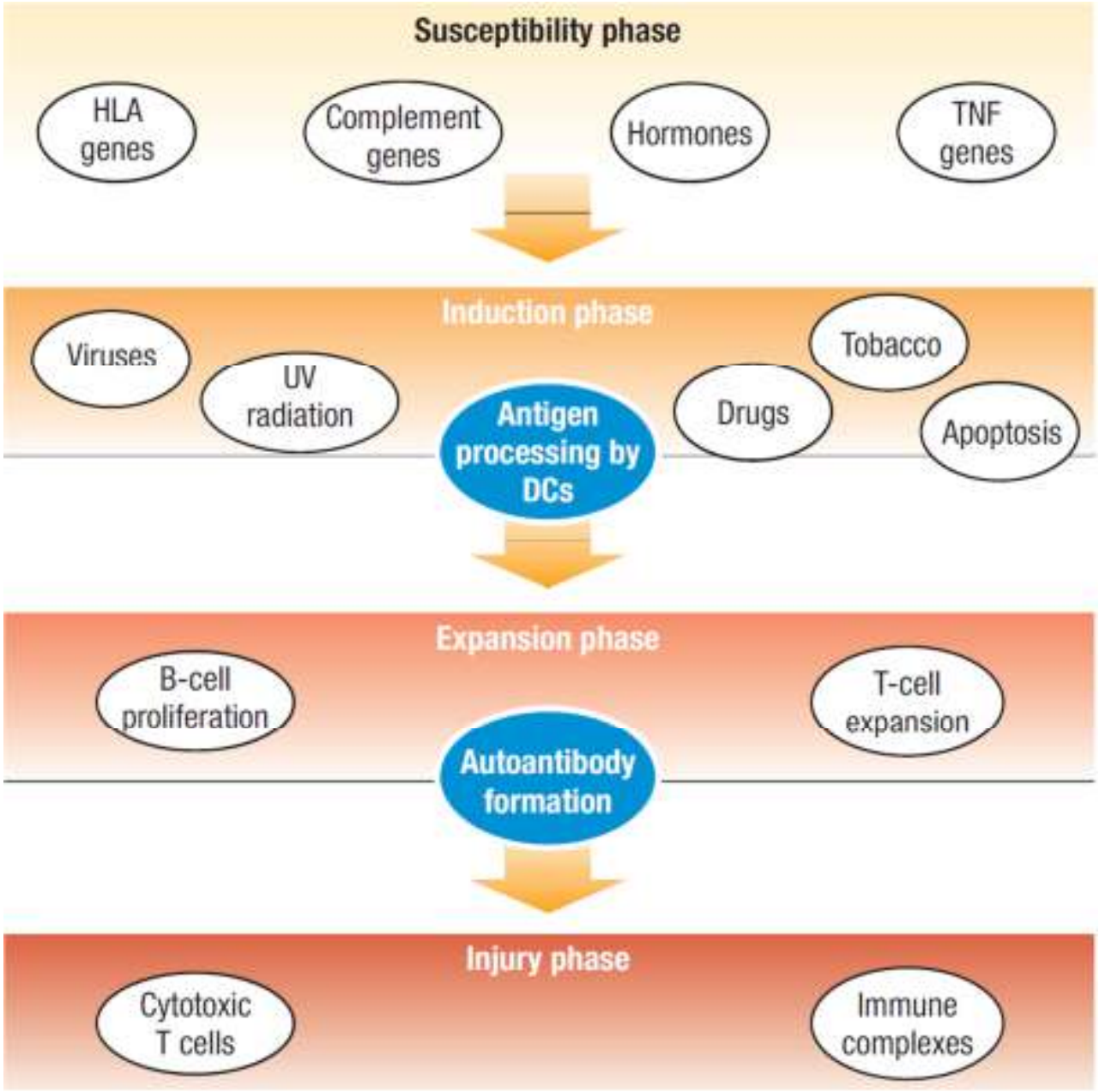
- Auto antibodies can induce tissue damage in LE by two mechanisms:

1. they can bind directly to cells, resulting in type II immunologycally mediated tissue damage;
2. they can bind to circulating antigens with formation of immune complexes; leading to type III immunologically mediated tissue damage.

LE auto-antibodies

- Antinuclear antibodies (ANA);
- Antibodies to double-stranded DNA (anti ds DNA);
- Antibodies to single-stranded DNA (anti ss DNA);
- Anti-SM antibody;
- Anti-Ro antibodies (anti SS-A);
- Anti-La antibodies (anti SS-B);
- Anti-ribonucleoproteins (anti RNP)

LE pathogenesis



Type	Clinical forms	Clinical and laboratory features	Histologic features
DLE, 15%-20%*	Localized Generalized (lesions above and below neck) Hypertrophic	Usually localized, chronic, scarring lesions of head or neck region or both lasting months to years Usually no extracutaneous disease (5% of patients develop SLE) Antinuclear antibodies occasionally present in low titer; anticytoplasmic antibodies not present Anti-dsDNA antibodies rarely present Subepidermal immunoglobulin deposits commonly found in lesions (75%) but rarely present in uninvolved skin Simultaneous occurrence of severe systemic lupus erythematosus with nephritis is rare	Hydropic degeneration of epidermal basal cell layer with focal epidermal atrophy Heavy mononuclear cell infiltrate in upper dermis, periappendiceal, and perivascular regions, extending into deep dermis
SCLE, 10%-15%*	Papulosquamous (psoriasiform), 8% Annular-polycyclic, 5%*	Usually widespread, nonscarring lesions with associated scaling, depigmentation, and telangiectasias on face, neck, upper and extensor arms (photosensitive distribution) lasting weeks to months; lesions often exacerbated by exposure to sun Usually associated with extracutaneous disease, but severe renal or central nervous system disease uncommon Antinuclear and anticytoplasmic antibodies frequently present (60% of patients) Anti-dsDNA antibodies present in low serum concentrations in 30% of patients; hypocomplementemia rare HLA-A1, HLA-B8, and HLA-DR3 significantly increased Subepidermal immunoglobulin deposits present in only 50% of lesions and 30% of uninvolved skin	Marked hydropic changes along epidermal basal cell layer Moderate mononuclear cell infiltrate in superficial dermis only Pilosebaceous atrophy, hyperkeratosis; direct IF staining reveals discrete, speckled IgG deposits in basal cell cytoplasm associated with Ro/SS-A antibodies
Acute cutaneous LE, 30%-50%*	Localized, indurated erythematous lesions (malar areas of face—butterfly rash) Widespread indurated erythema (face, scalp, neck, upper chest, shoulders, extensor arms, backs of hands)	Transient (hours to days) Multisystem disease usually present; renal disease common Antinuclear antibodies usually present Anti-dsDNA antibodies present in 60%-80% of patients, often in high concentration; hypocomplementemia common Subepidermal immunoglobulin deposits commonly found in lesional (>95%) and exposed nonlesional (75%) skin	Hydropic changes along epidermal basal layer Sparse mononuclear cell infiltrate and upper dermal edema

LE Classification

- **Systemic LE (SLE)**
- acute cutaneous LE (ACLE): malar rash, discoid rash, photosensitivity, oral ulcers
- arthritis: nonerosive involving two or more peripheral joints
- serositis: pleuritis; pericarditis
- renal disorder: persistent proteinuria; cellular casts
- neurologic disorder: seizures; psychosis
- hematologic disorder: hemolytic anemia; leukopenia; lymphopenia; thrombocytopenia
- immunologic disorder: anti-DNA, anti-SM and antiphospholipid antibodies
- antinuclear antibody: abnormal titer of antinuclear antibodies
- **Cutaneous LE (CLE)**
- subacute cutaneous LE (SCLE)
- chronic cutaneous LE (CCLE)

Classification of LE skin lesions (Gilliam, 1997)

- **I. LE-specific skin disease (CLE)**

  A. Acute cutaneous LE (ACLE)

  1.Localized ACLE (malar rash, butterfly rash)

  2.Generalized ACLE (maculopapular lupus rash, malar rash, photosensitive lupus dermatitis)

  B. Subacute cutaneous LE (SCLE)

  1. Annular SCLE

  2. Papulosquamous SCLE

  C. Chronic cutaneous LE (CCLE)

  1. Classic discoid LE (DLE)

  2. Disseminated DLE

  3. Superficial LE (Besnier's centrifugal erythema)

  4. LE profundus (chronic lupus panniculitis)

  5. Mucosal DLE (oral DLE, conjunctival DLE)

  6. Lupus tumidus (urticarial plaque of LE)

  7. Chilblains LE

  8. Lichenoid DLE (LE / lichen planus overlap).

- **II. LE-nespecific skin disease**

  These range from necrotizing and urticarial vasculitis to livedo reticularis, Raynaud's phenomenon, dermal mucinosis, and bullous lesions in LE.

OVERVIEW OF LUPUS SYNDROMES: AUTOANTIBODY PROFILES AND CUTANEOUS MANIFESTATIONS

CHRONIC CUTANEOUS (DISCOID) LE

ANA negative

- Photosensitive
- Head and neck
- Plaques
  - Atrophic or Hypertrophic
  - Hypopigmentation
- Scarring
- Follicular plugs
- Scarring alopecia

SUBACUTE CUTANEOUS LE

ANA negative
Ro (SS-A)
La (SS-B)

- Photo distribution
  - Trunk
- Patterns
  - Papulosquamous
  - Annular
- Chronic, recurrent
- No scarring

ACUTE CUTANEOUS (SYSTEMIC) LE

ANA
dsDNA
Ro (SS-A)
La (SS-B)
Sm

- Red plaques
  - Photo distribution
  - No atrophy
  - Butterfly rash–face
- Palmar erythema

- Telangiectasia (palms)
- Nailfold capillaries
  - Meandering loops
- Alopecia

- Urticarial vasculitis
- Palpable purpura (necrosing angiitis)
- Raynaud's

Joints

NEONATAL LE

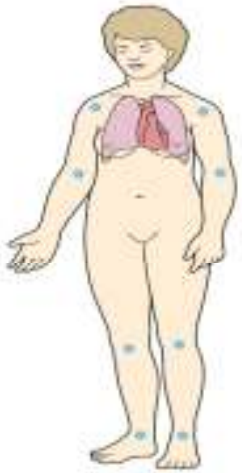
Maternal passge of
Ro (SS-A) and/or La (SS-B)
or U 1-RNP
Antiphospholipids (in infants with heart block)

- Appear in first month
- Photosensitive distribution
- Patterns
  - Papulosquamous
  - Annular

- Congenital heart block
  - 50% of cases
  - Permanent defect
  - Antiphospholipid Abs

DRUG-INDUCED LE

ANA
ssDNA
Antihistone



- Rash—uncommon

- Drugs
  - Procainamide
  - Hydralazine
  - Isoniazid
- Others reported

- Symptoms
  - Fever, arthralgia, myalgias, pleurisy, pericarditis

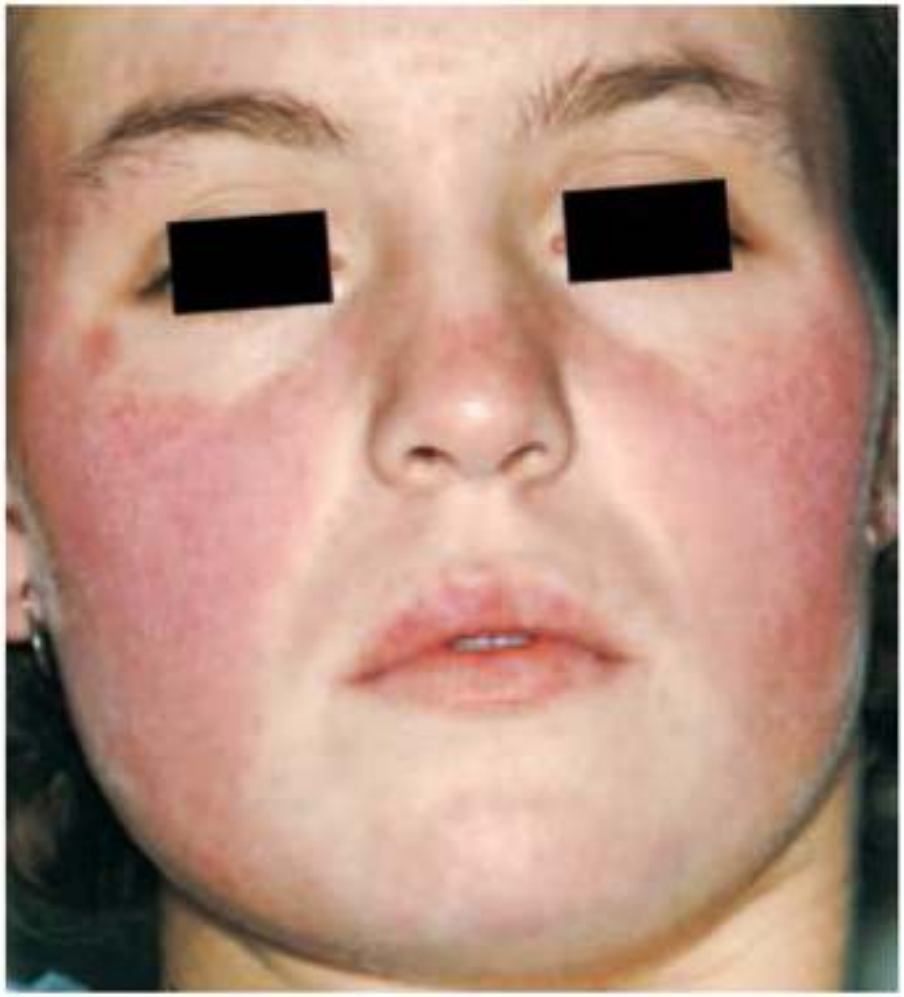
- Drug is stopped
  - Symptoms clear
  - ANA disappears

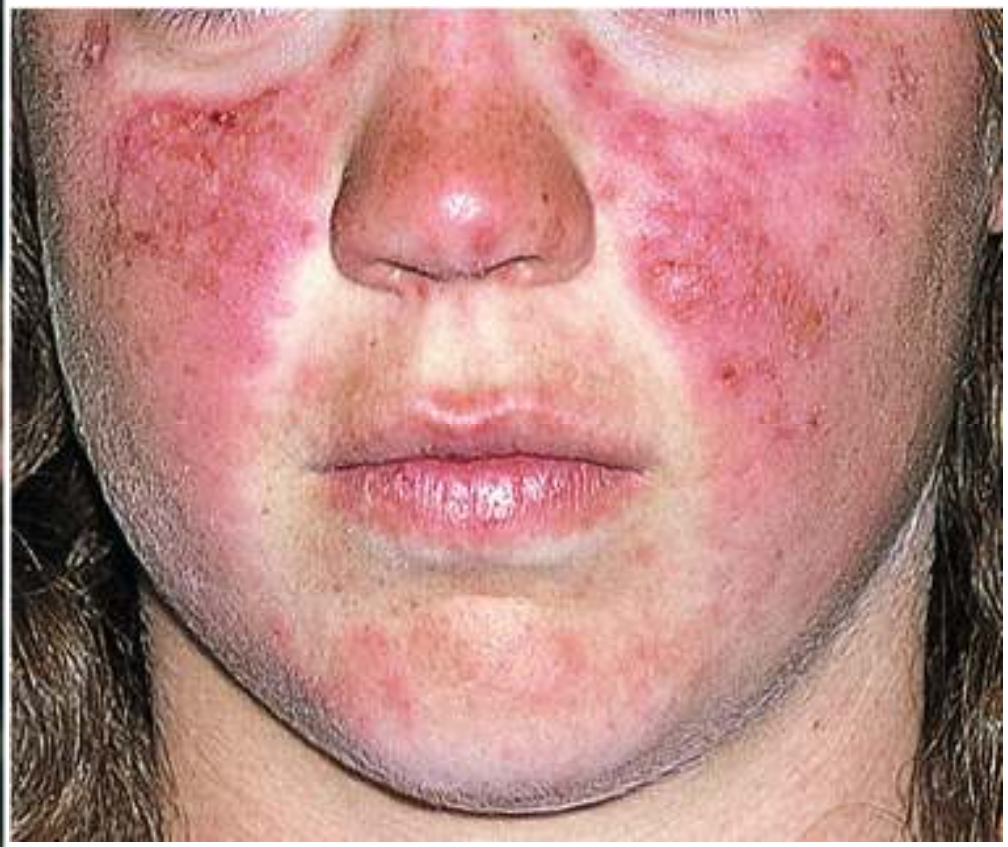
Comparison of the Major Types of Lupus Erythematosus–Specific Skin Disease

Disease Features	ACLE	SCLE	Classic DLE
Clinical features of skin lesions			
Induration	0	0	+++
Dermal atrophy	0	0	+++
Pigment changes	+	++	+++
Follicular plugging	0	0	+++
Hyperkeratosis	+	++	+++
Histopathology			
Thickened basement membrane	0	+	+++
Lichenoid infiltrate	+	++	+++
Periappendageal inflammation	0	+	+++
Lupus band			
Lesional	++	++	+++
Non-lesional	++	+	0
Anti-nuclear antibodies	+++	++	+
Ro/SS-A antibodies			
By immunodiffusion	+	+++	0
By ELISA	++	+++	+
Anti–double-stranded DNA antibodies	+++	+	0
Hypocomplementemia	+++	+	+
Risk for developing systemic lupus erythematosus	+++	++	+

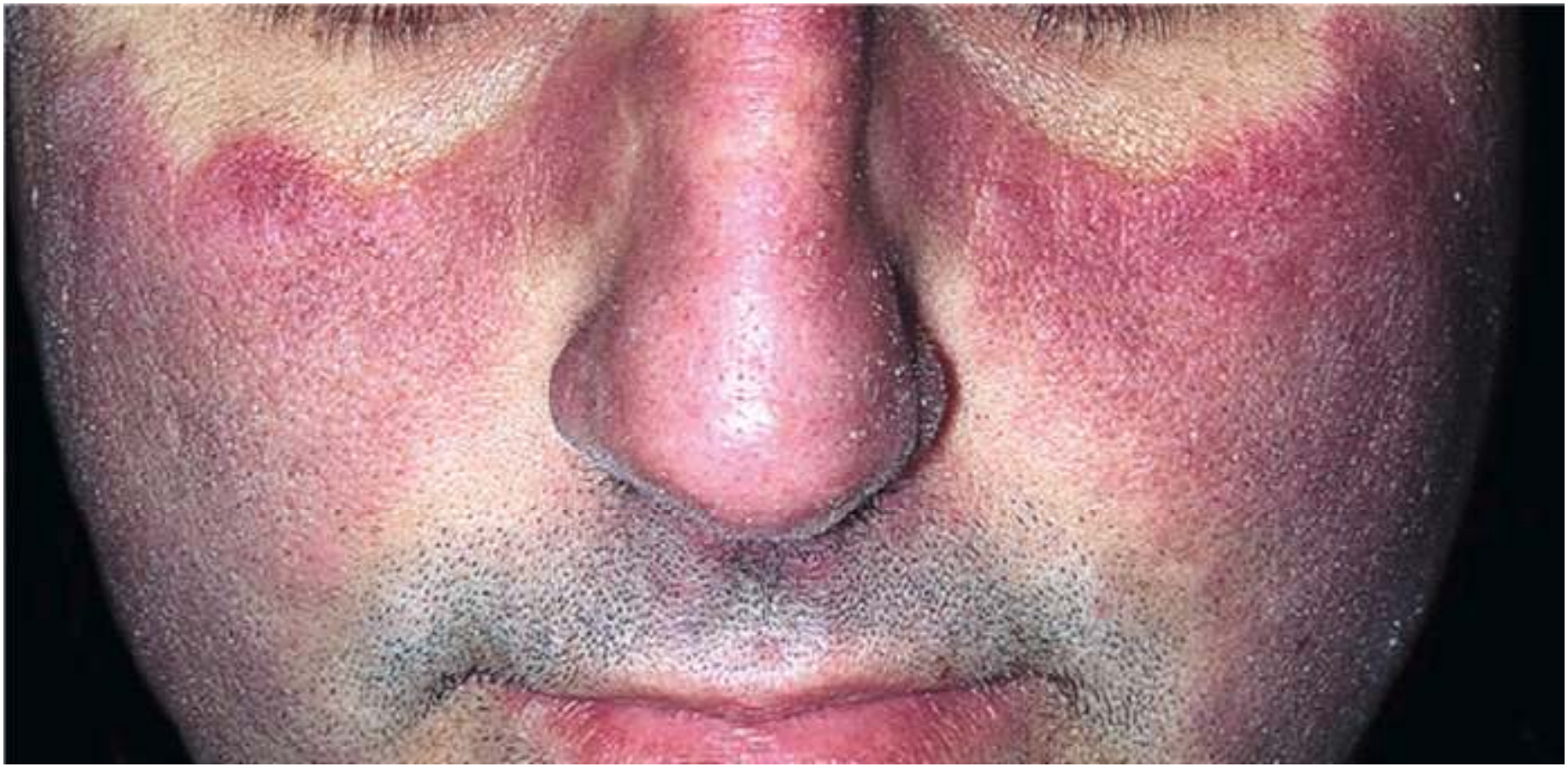
ACLE = acute cutaneous lupus erythematosus; DLE = discoid lupus erythematosus; ELISA = enzyme-linked immunosorbent assay; SCLE = subacute cutaneous lupus erythematosus; +++ = strong association; ++ = moderate association; + = weak association; 0 = negative, no association.

Localized Acute Cutaneous LE

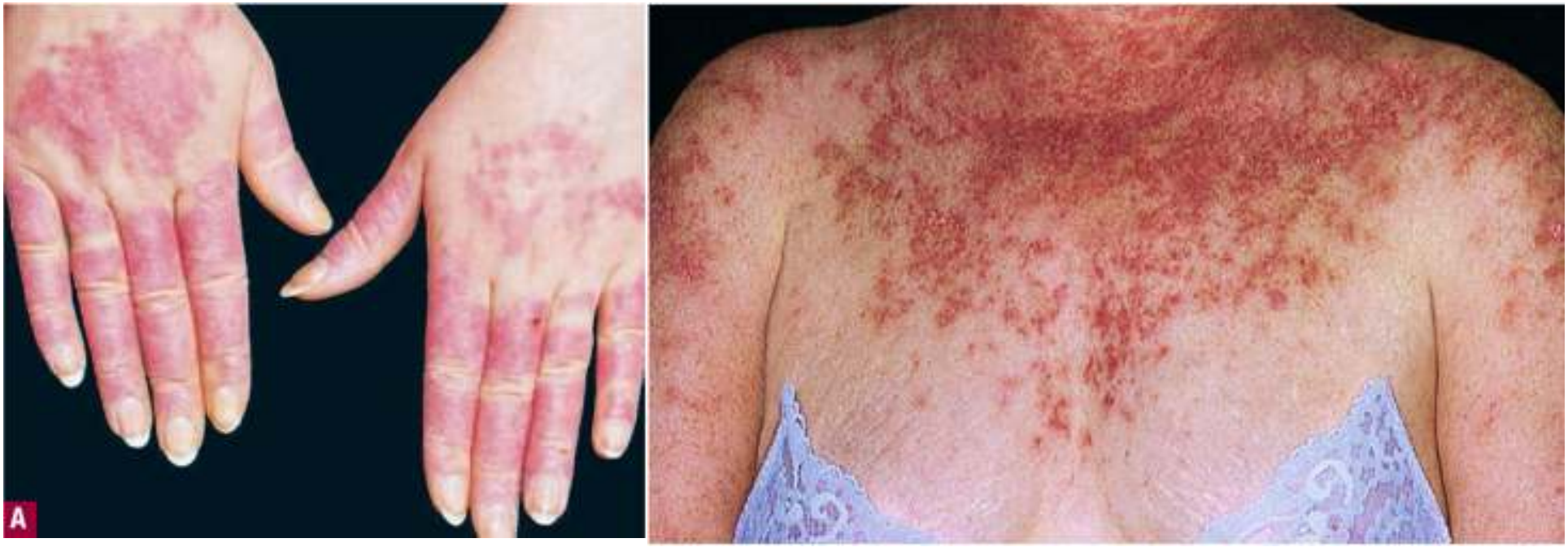




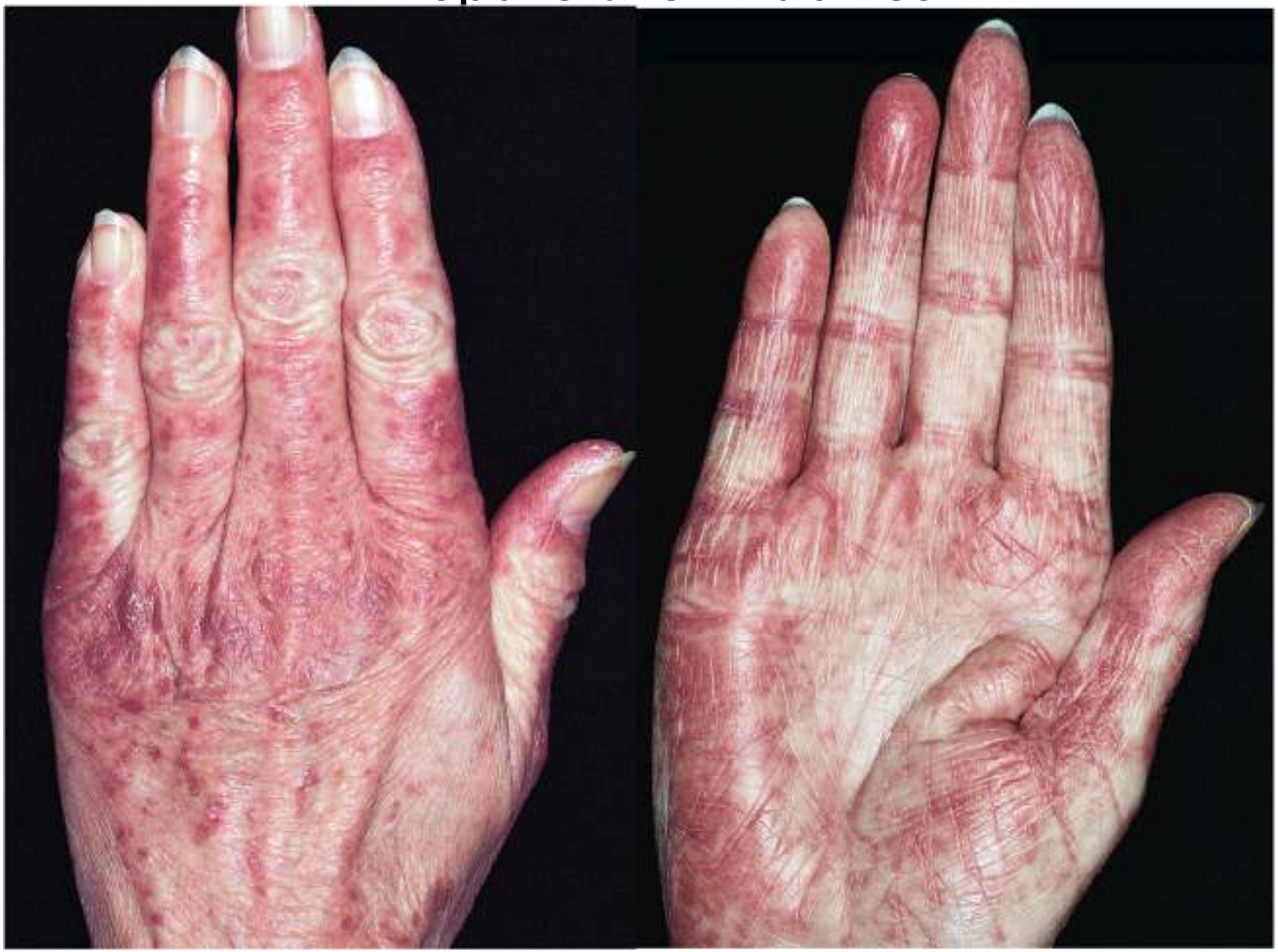
Localized Acute Cutaneous LE



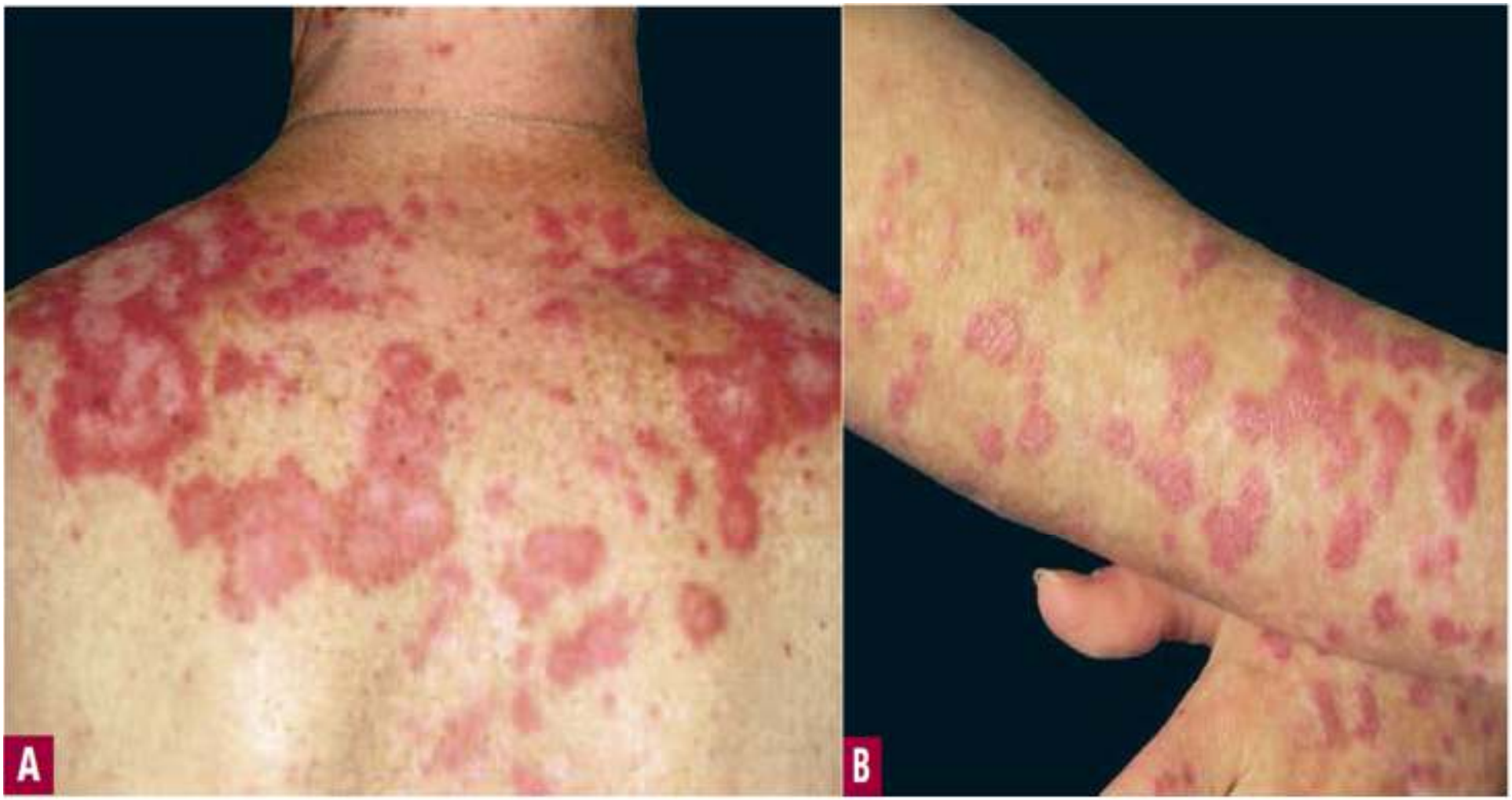
Generalized acute cutaneous LE



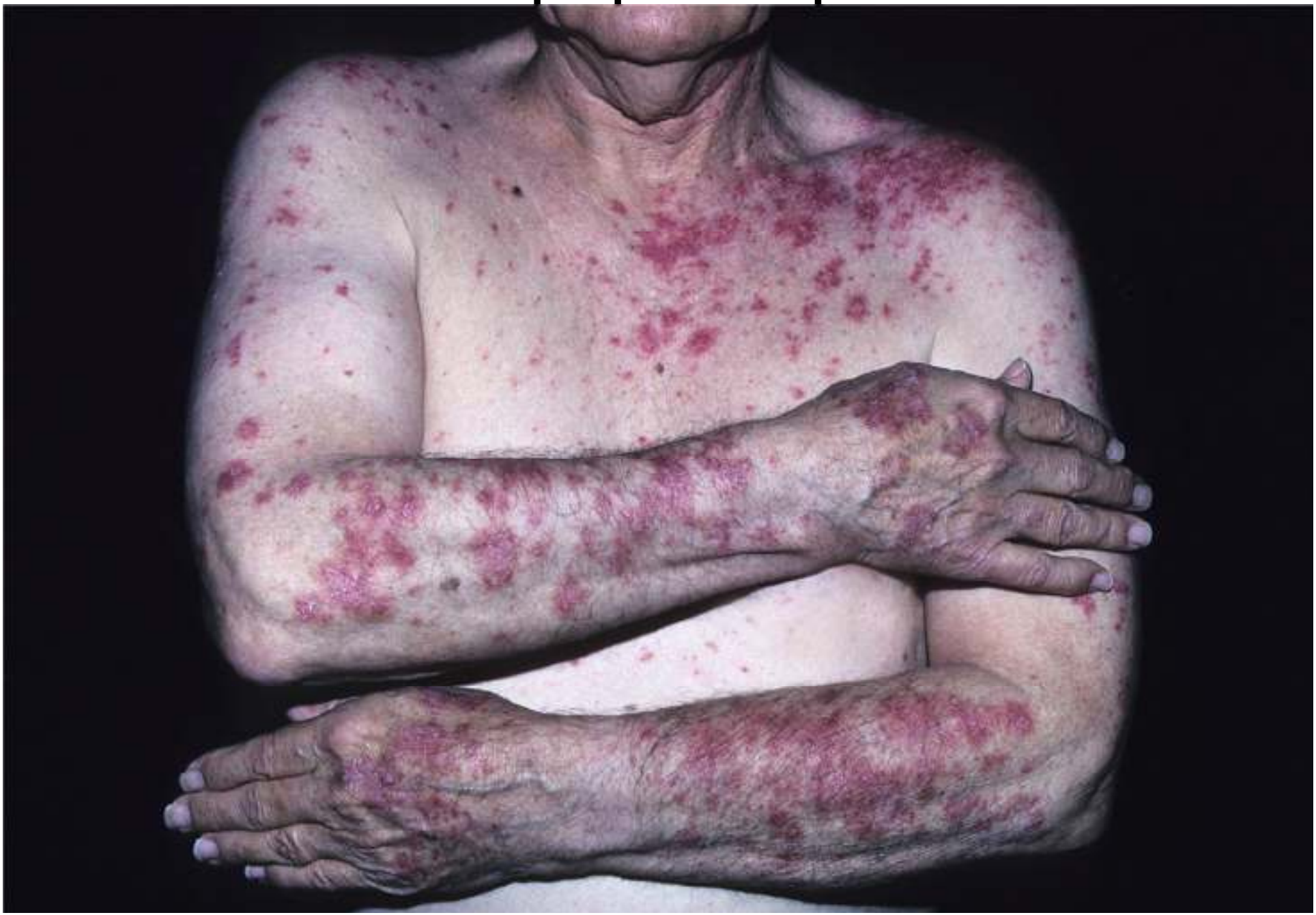
Systemic LE: erythema and telangiectasias spare the knuckles

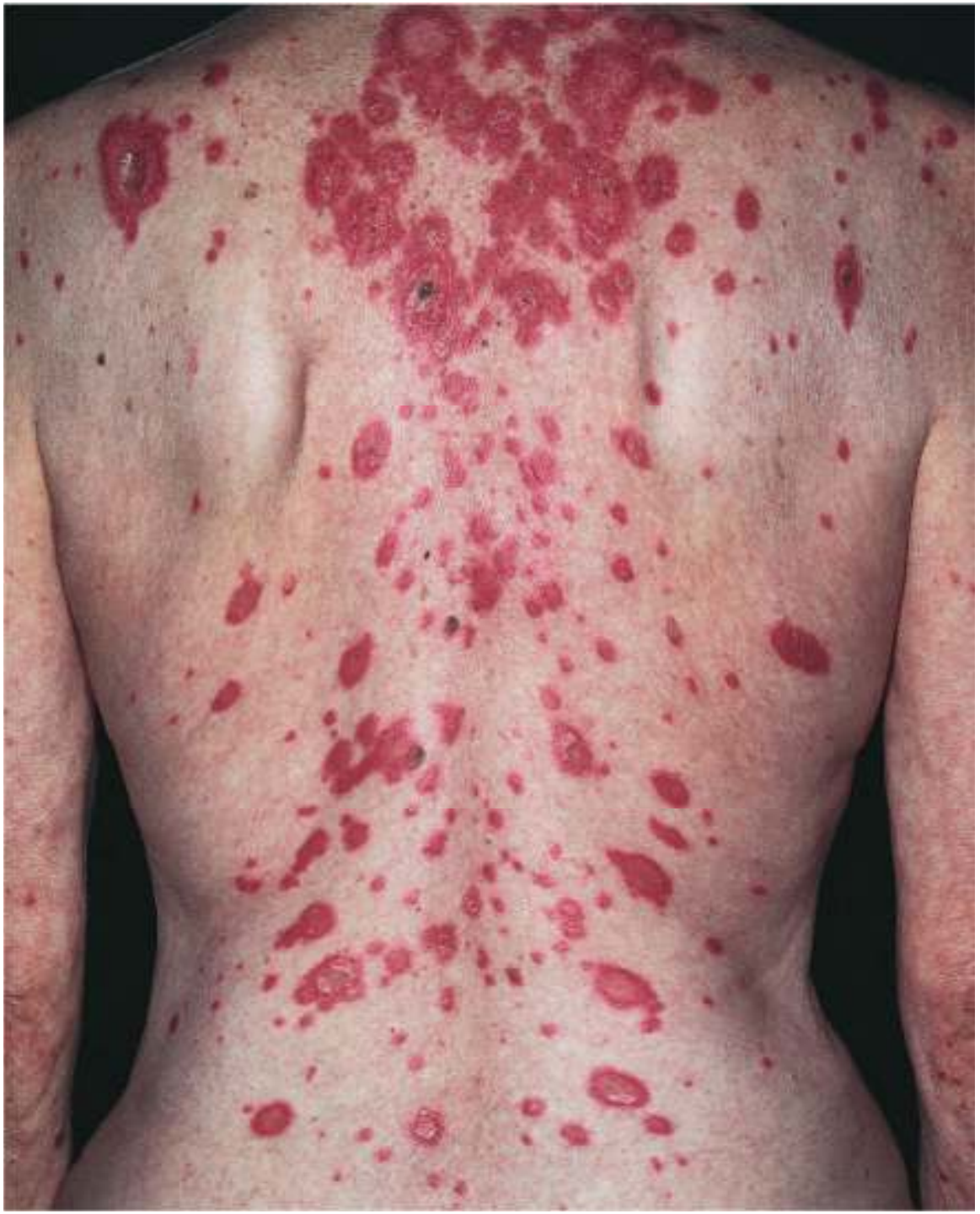


Subacute cutaneous lupus erythematosus – annular (A) and papulosquamos forms (B)



Subacute CLE: papulosquamous form





Subacute CLE: annular-polycyclic form

Discoid Chronic Cutaneous LE

- **The basic symptoms: erythematic plaques, hyperkeratotic plaques and atrophy.**

➢ Early lesions are usually confined to head and neck and appearing as **inflammatory, erythematous, edematous and scaling macules** or papules, with few mm in d, which spread centrifugally into larger plaques. The scales are adherent, with horny plugs in dilated pilosebaceous canals.

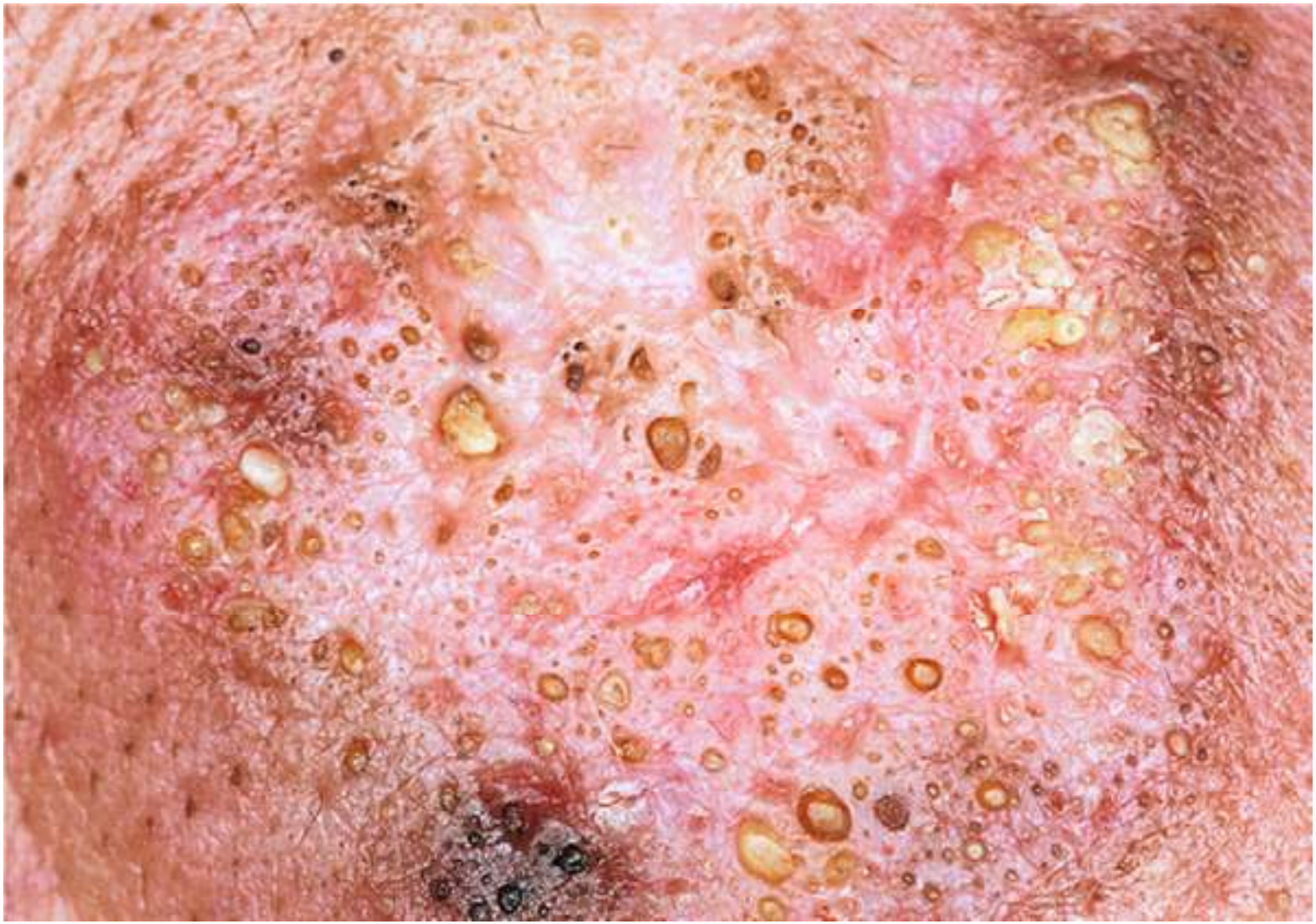
➢ The removal of the scale (Besnier-Mescerski sign) demonstrates a characteristic **„carpet tack”** appearance corresponding to patulous and plugged follicular orifices.

➢ The face is most commonly affected. Other sites are: scalp, neck, ears, hands, rarely arms, legs and trunk. Permanent scarring alopecia occurs in the scalp lesions.

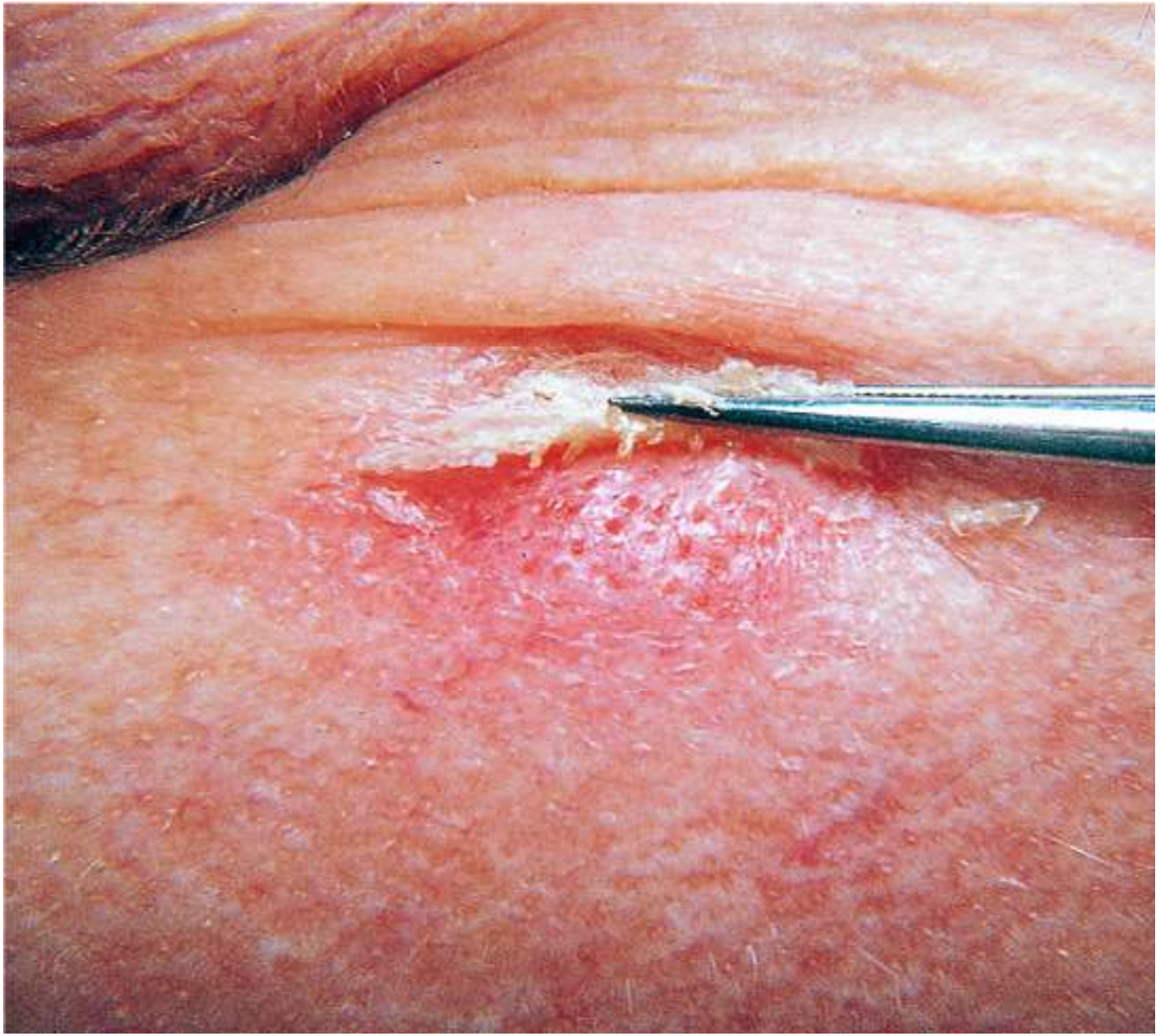
➢ Nail changes are subungual hyperkeratosis, longitudinal striae, and red-blue colorings of the nail plate.

➢ Mucous membrane lesions are erythematous patches, hyperkeratotic plaques, leucoplakia and ulcerations, commonly located on the inner cheeks, tongue, lips and palate.

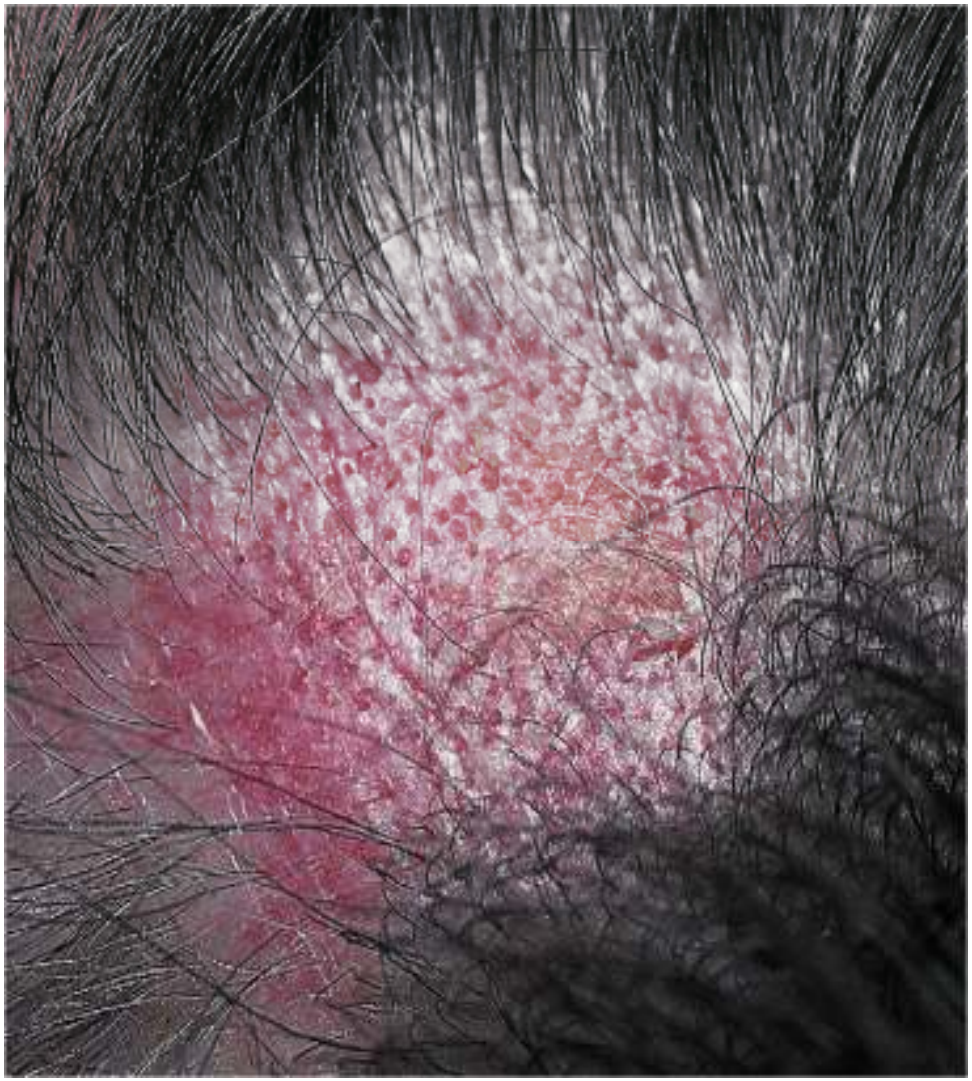
DCLE: follicular plugging

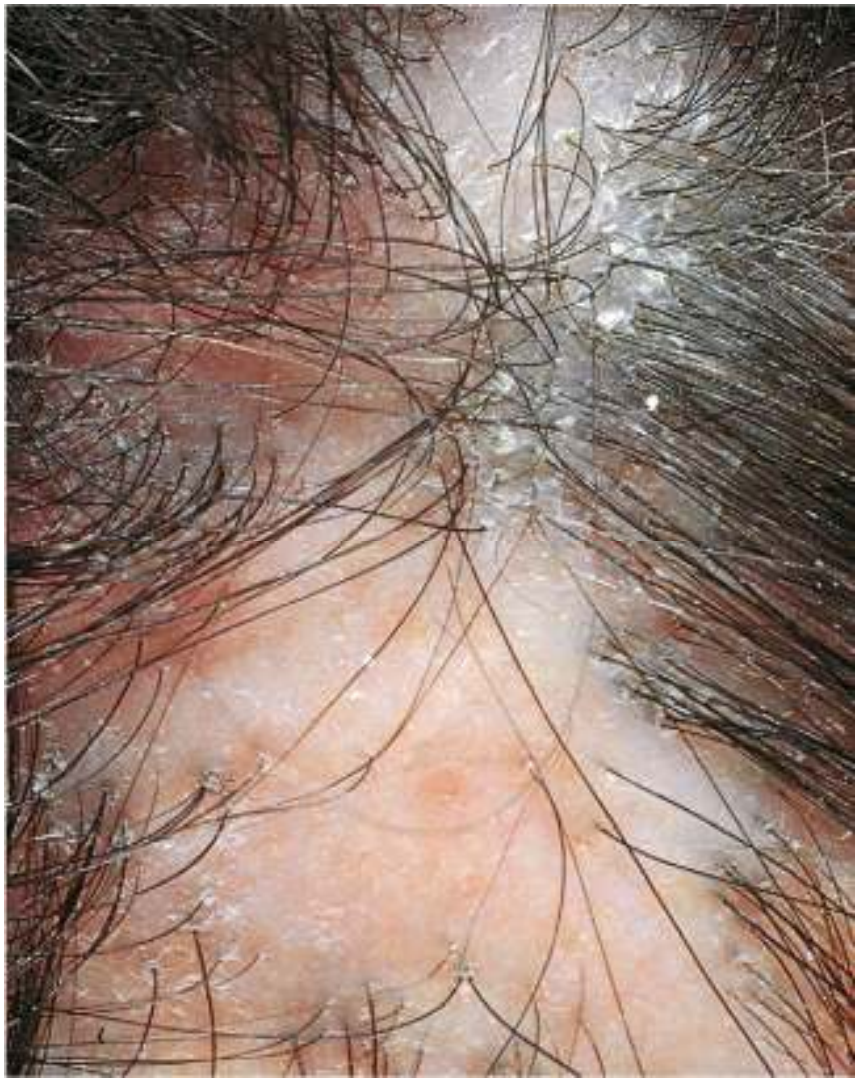


DCLE signs: carpet tack; orange peel

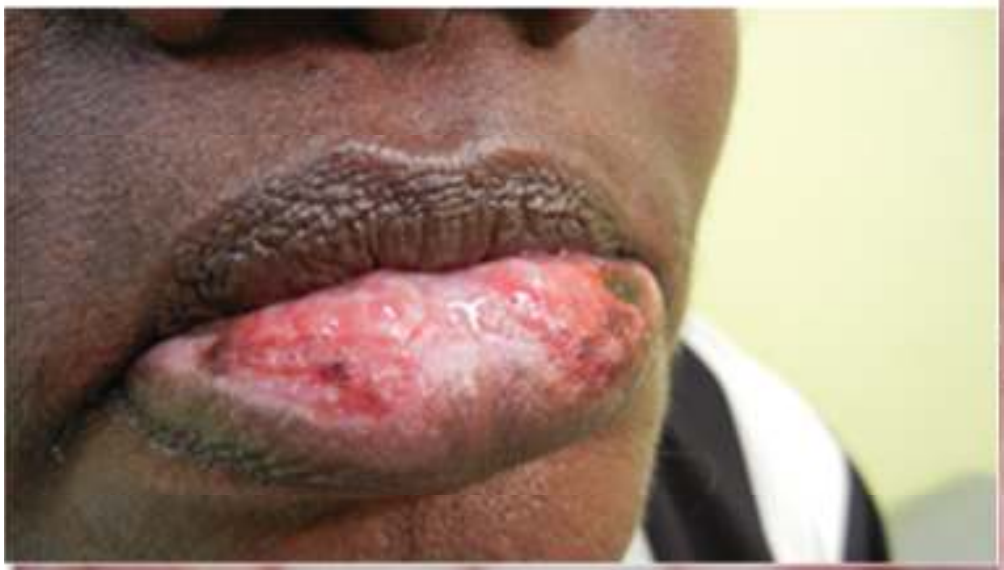


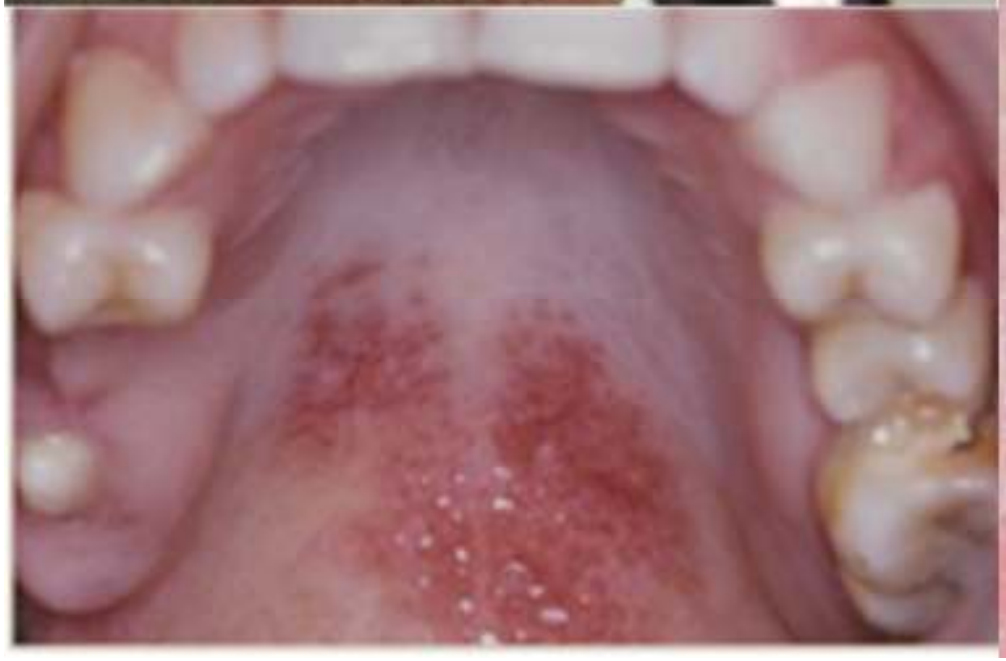
LE alopecia:
follicular plugging; end-stage scarring

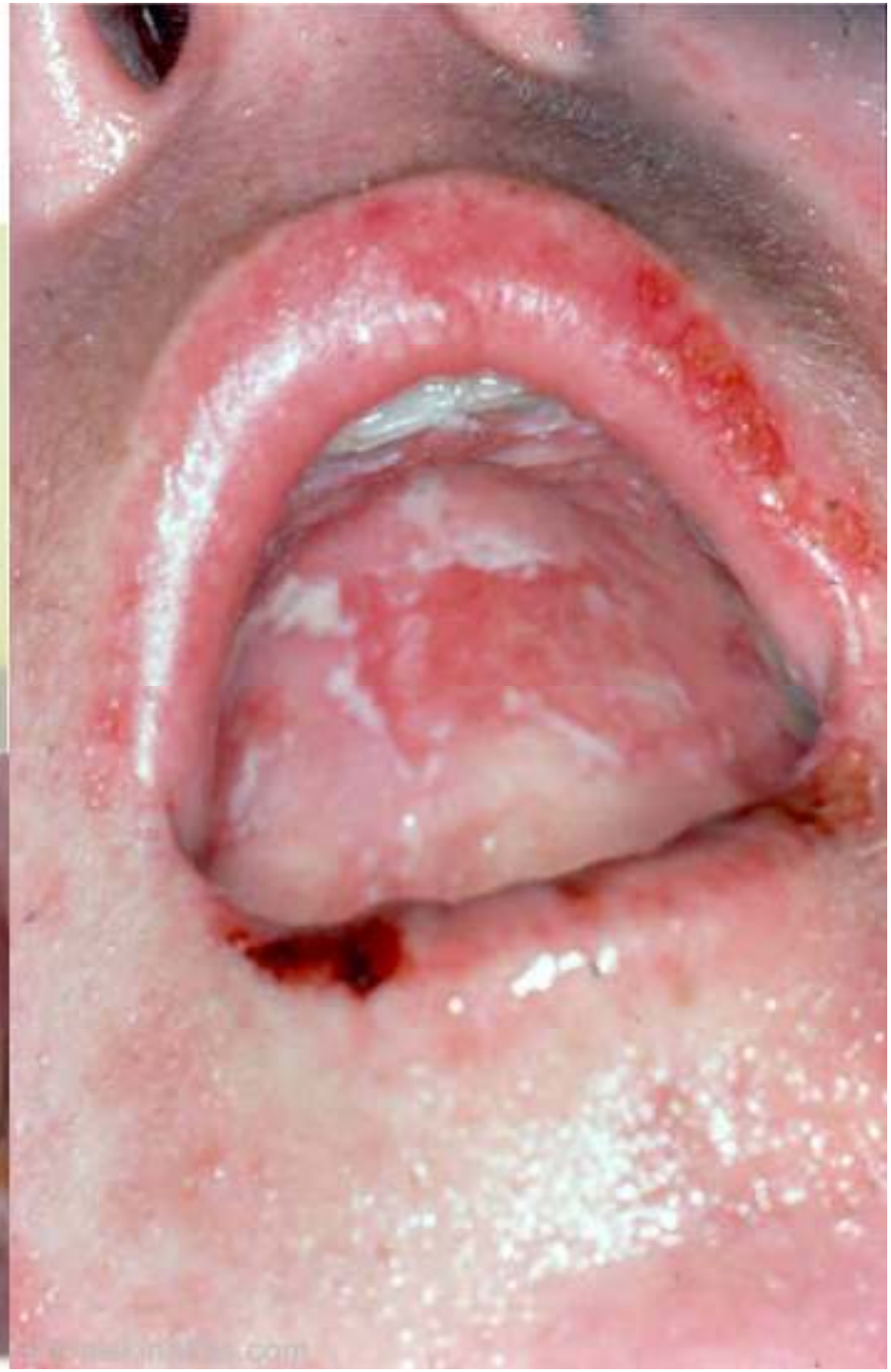




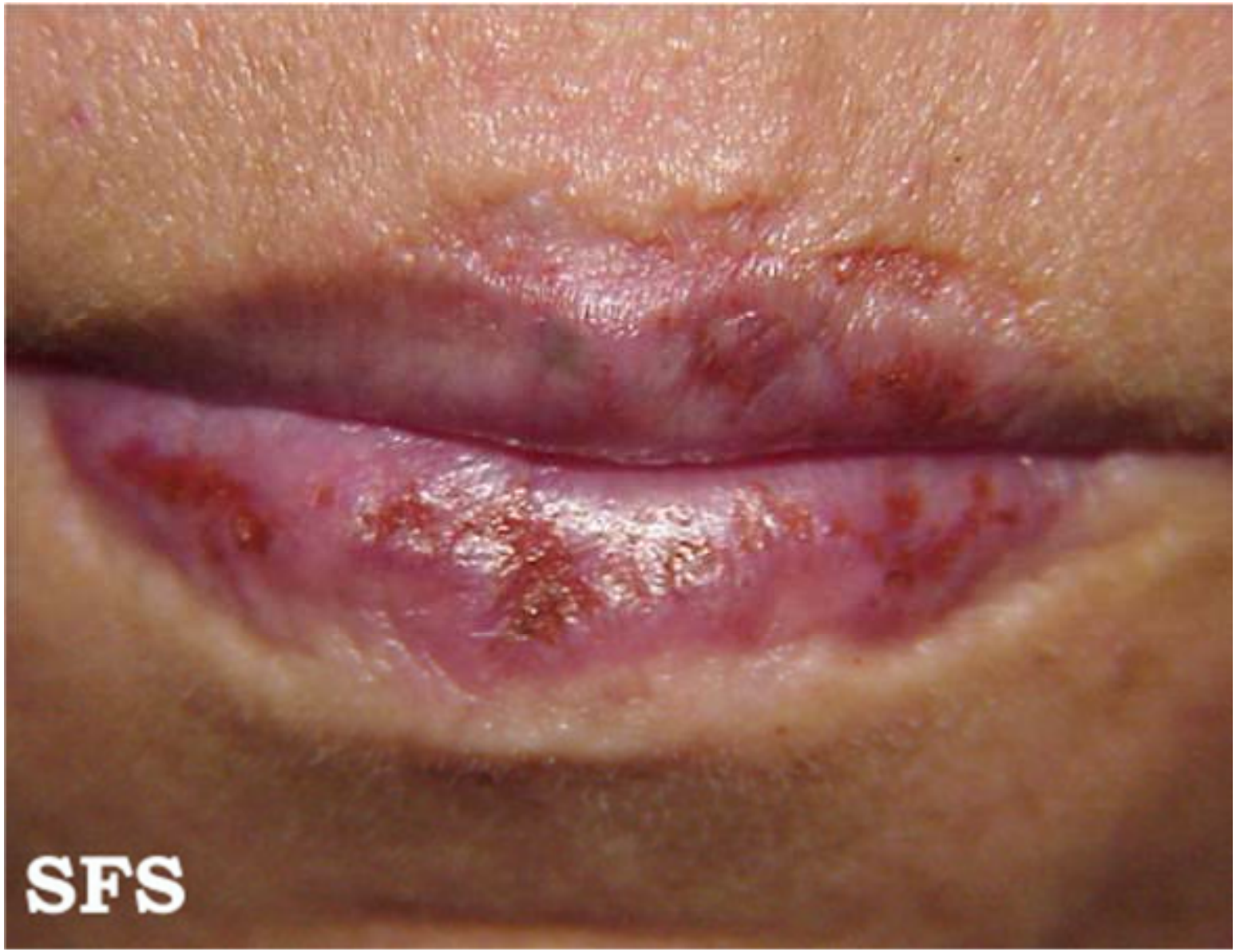
LE lip and mucosal involvement







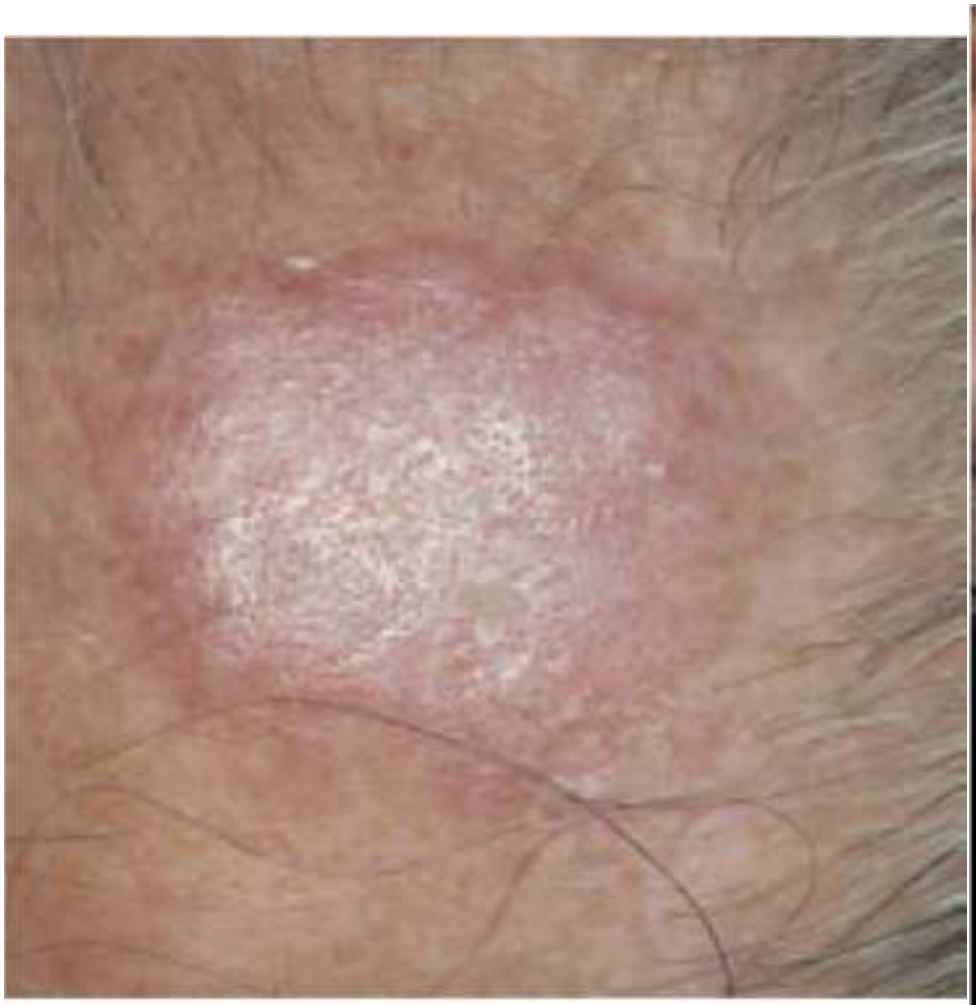
DCLE on the lips

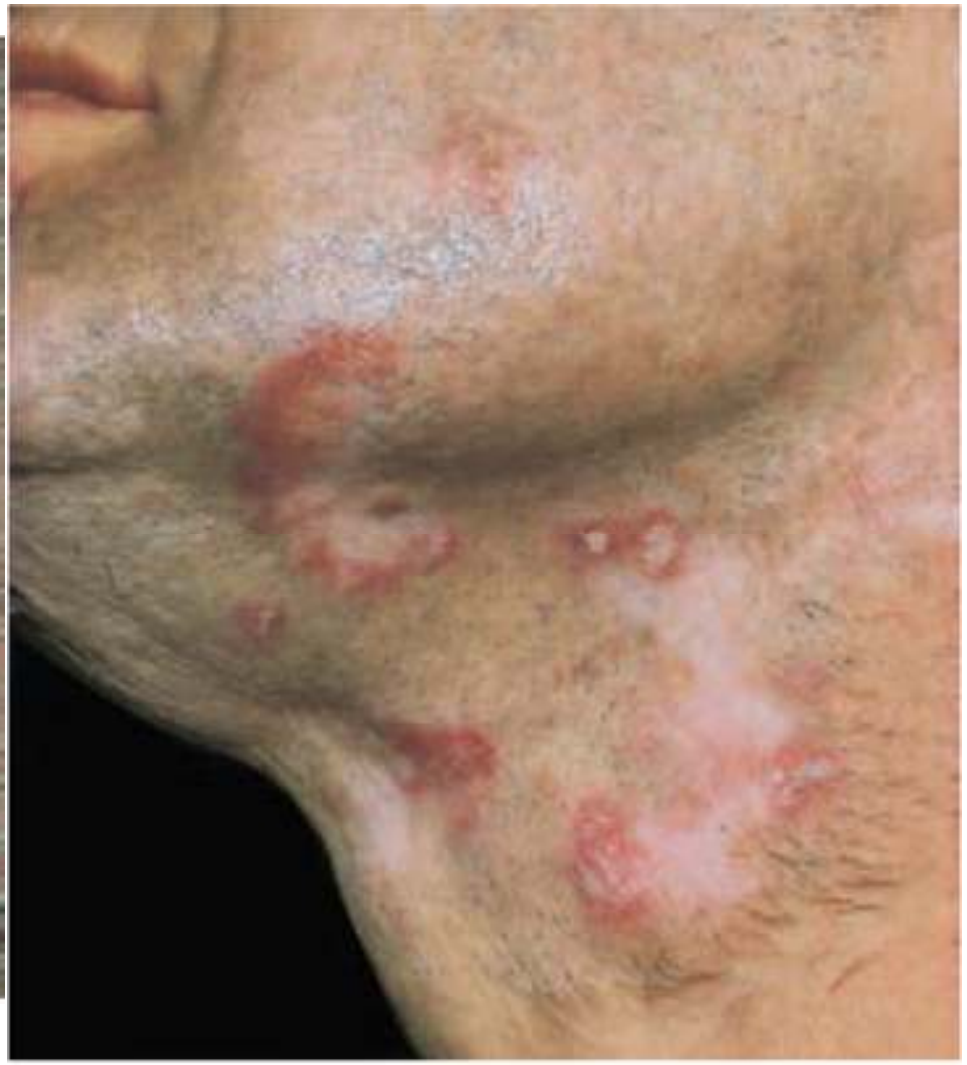


Discoid Chronic Cutaneous LE

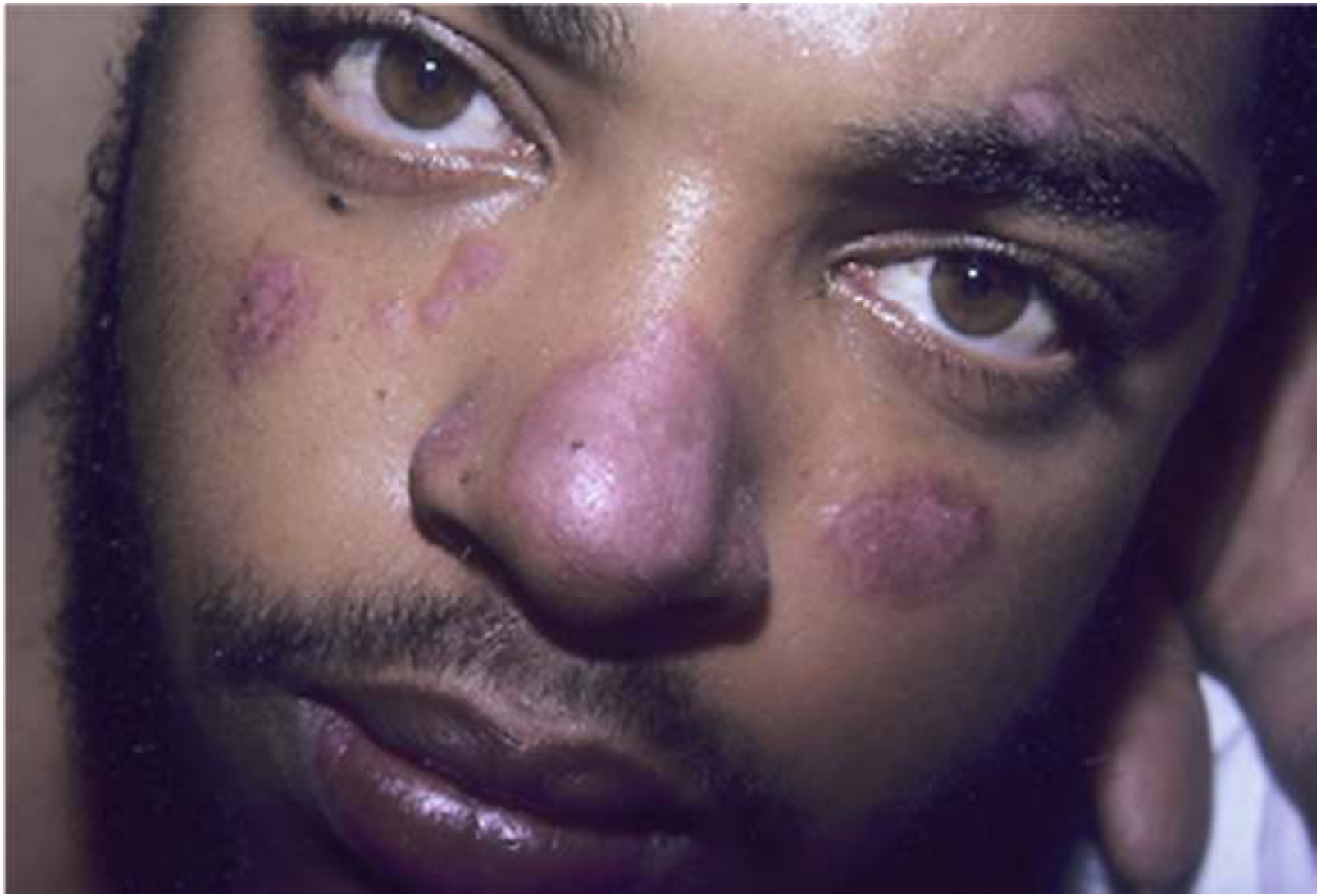
- **The secondary symptoms:**
- pigmentary disturbances: hyperpigmentation and hypopigmentation
- telangiectases
- infiltration are frequently associated.
- The evolution with scarring is common.

Chronic discoid lupus erythematosus

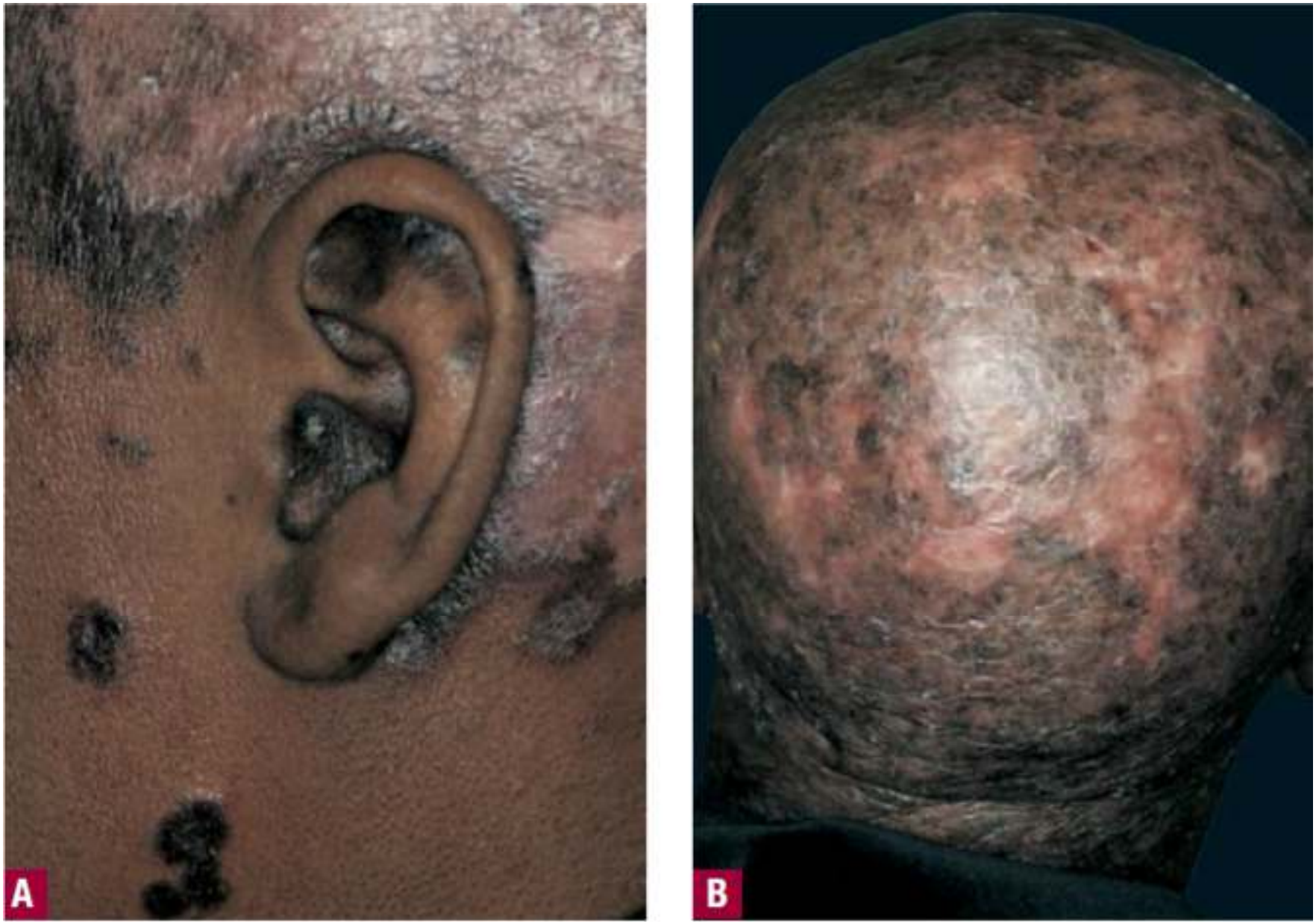




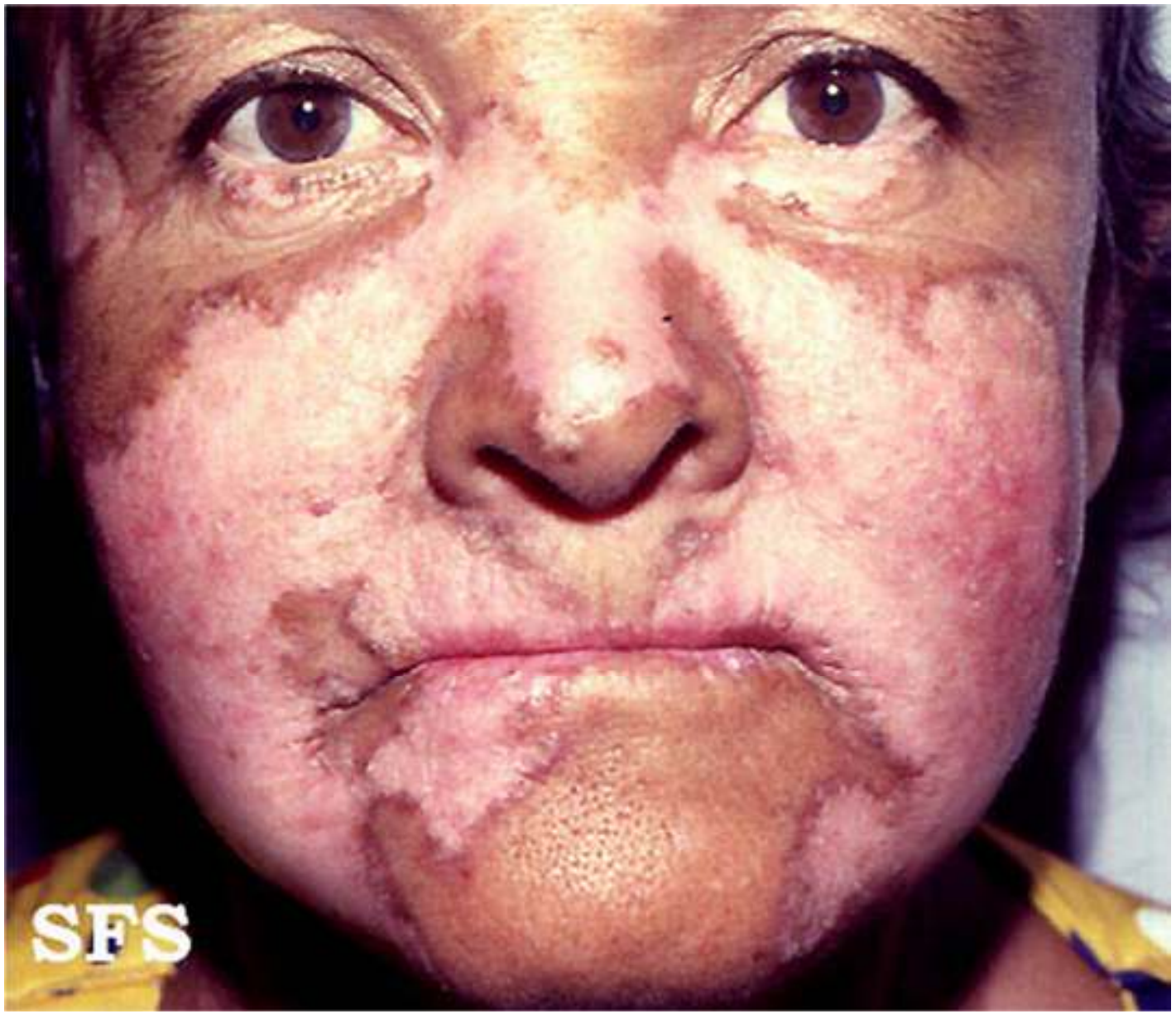
Chronic discoid LE



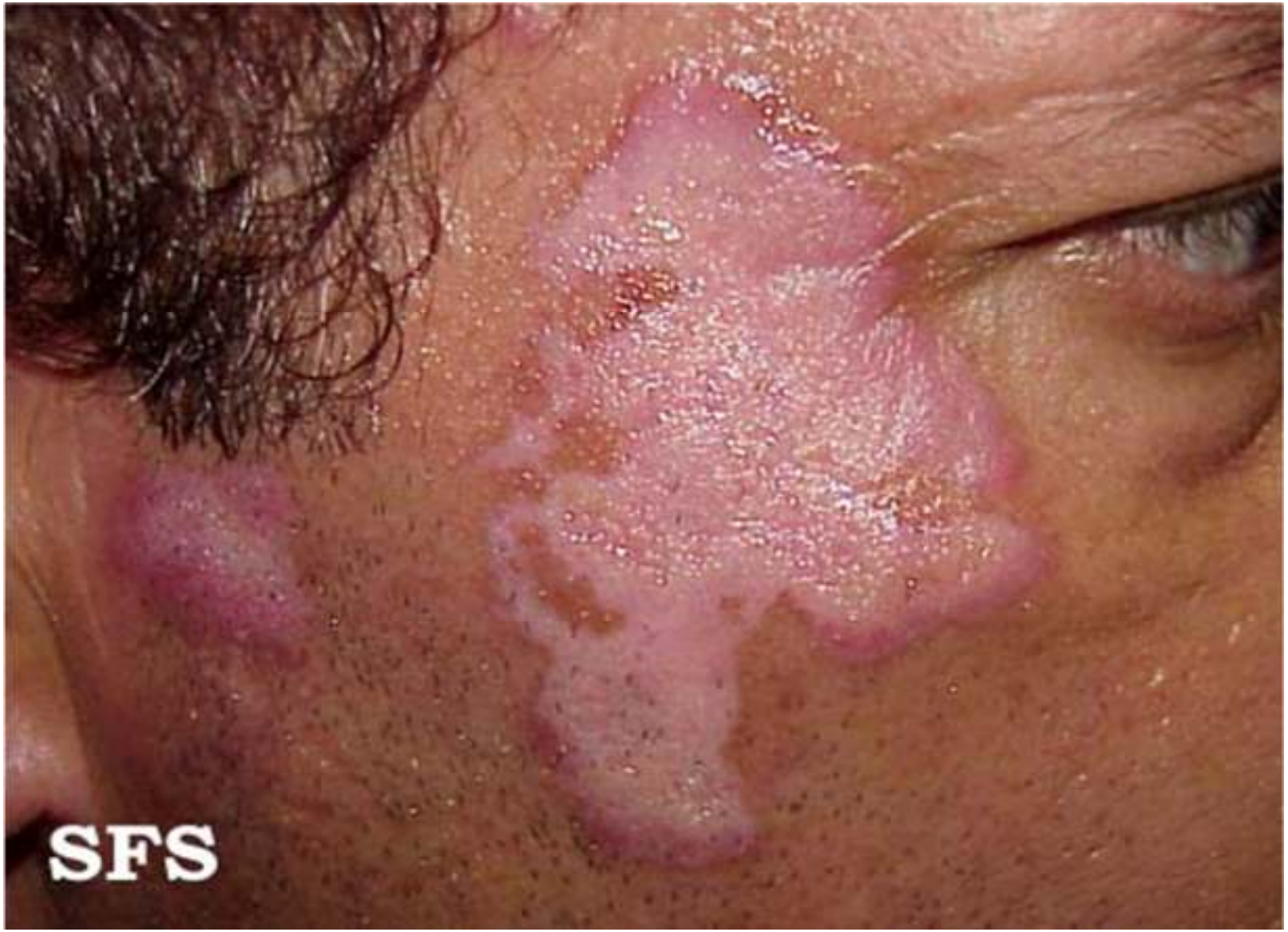
DCLE: A – atrophy, hyper/hypo-pigmentation
B – Scarring alopecia



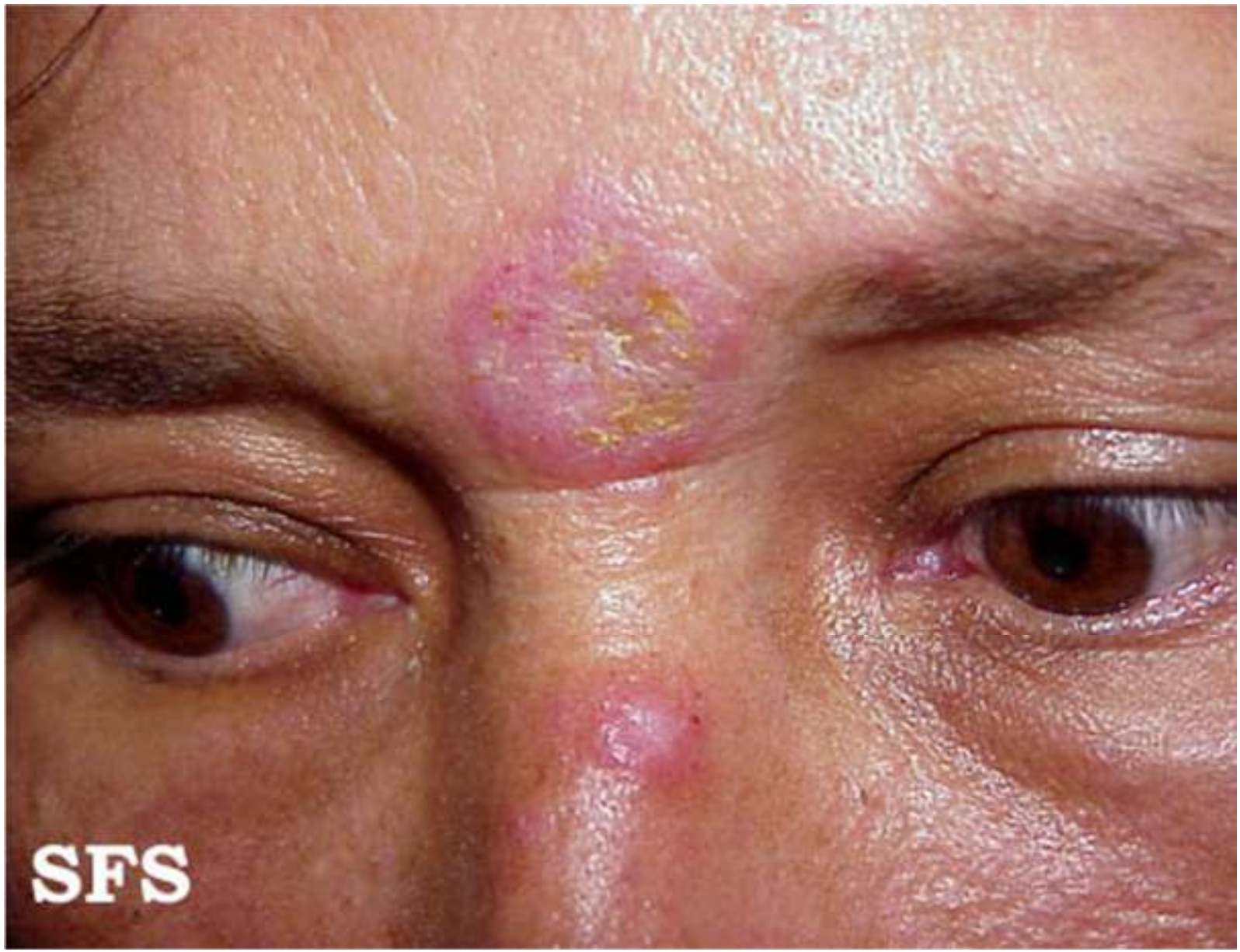
Chronic discoid LE



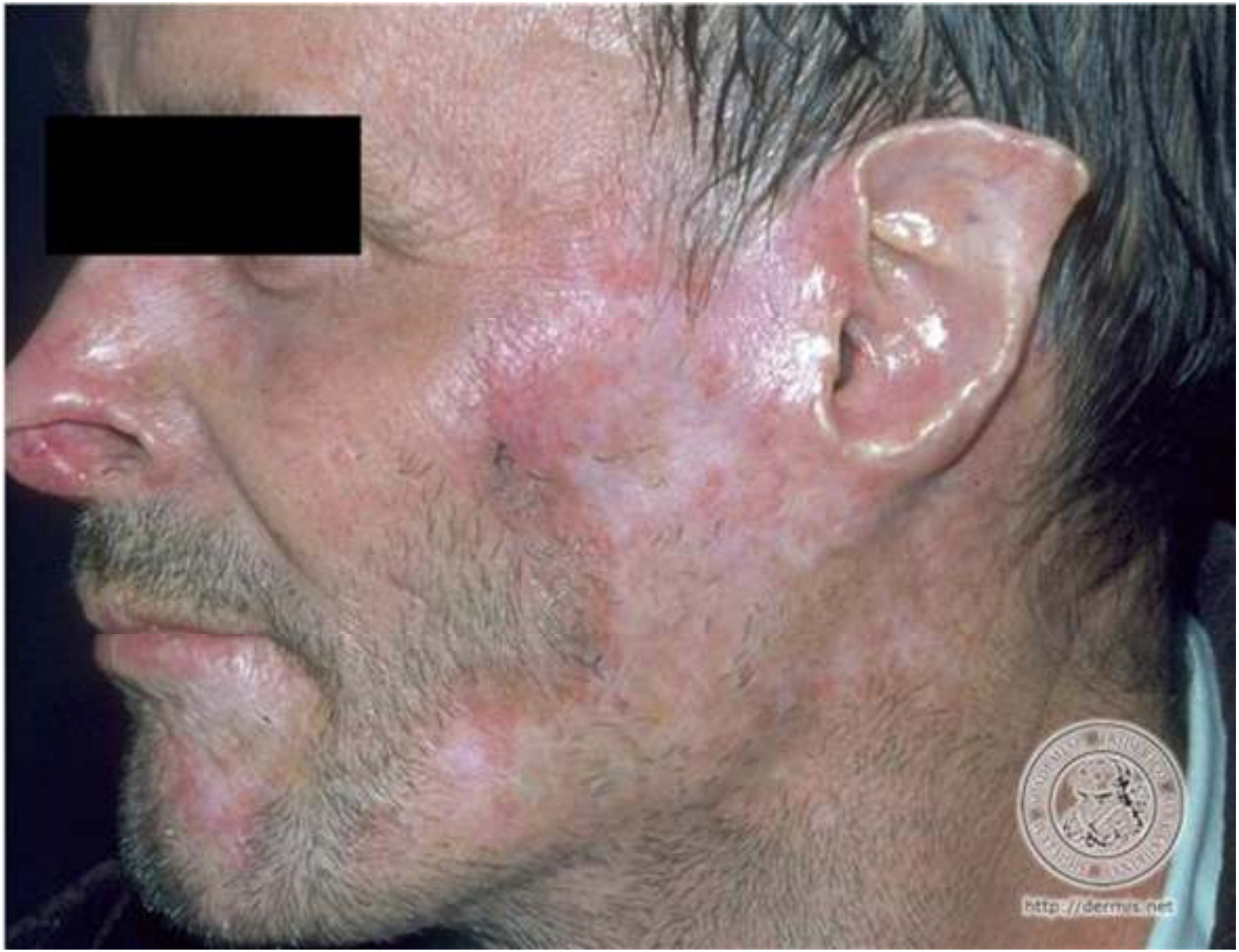
DCLE: atrophy, hypopigmentation



Discoid Chronic Cutaneous LE



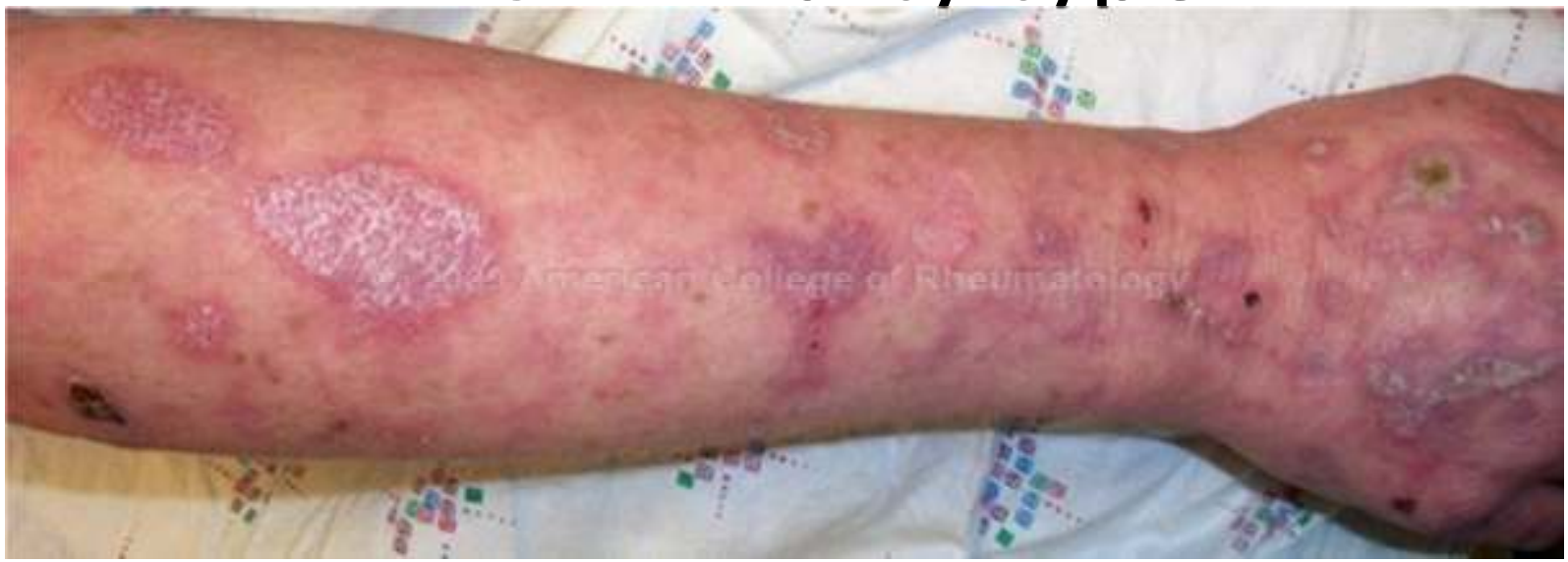
DCLE: atrophic mutilations

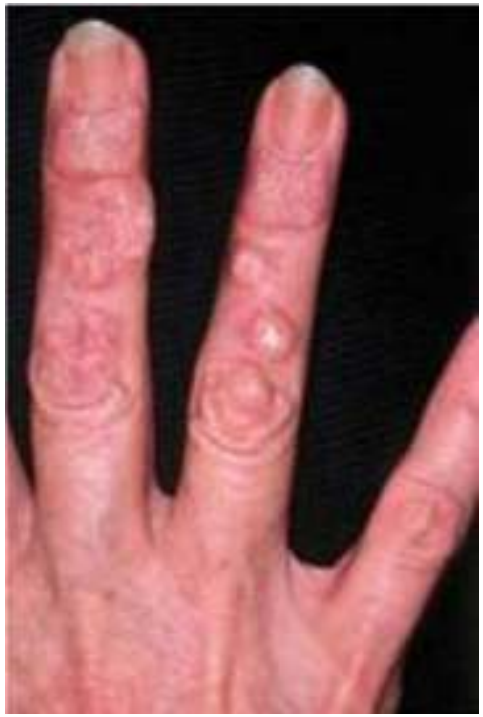


Discoid Chronic Cutaneous LE Atypical forms

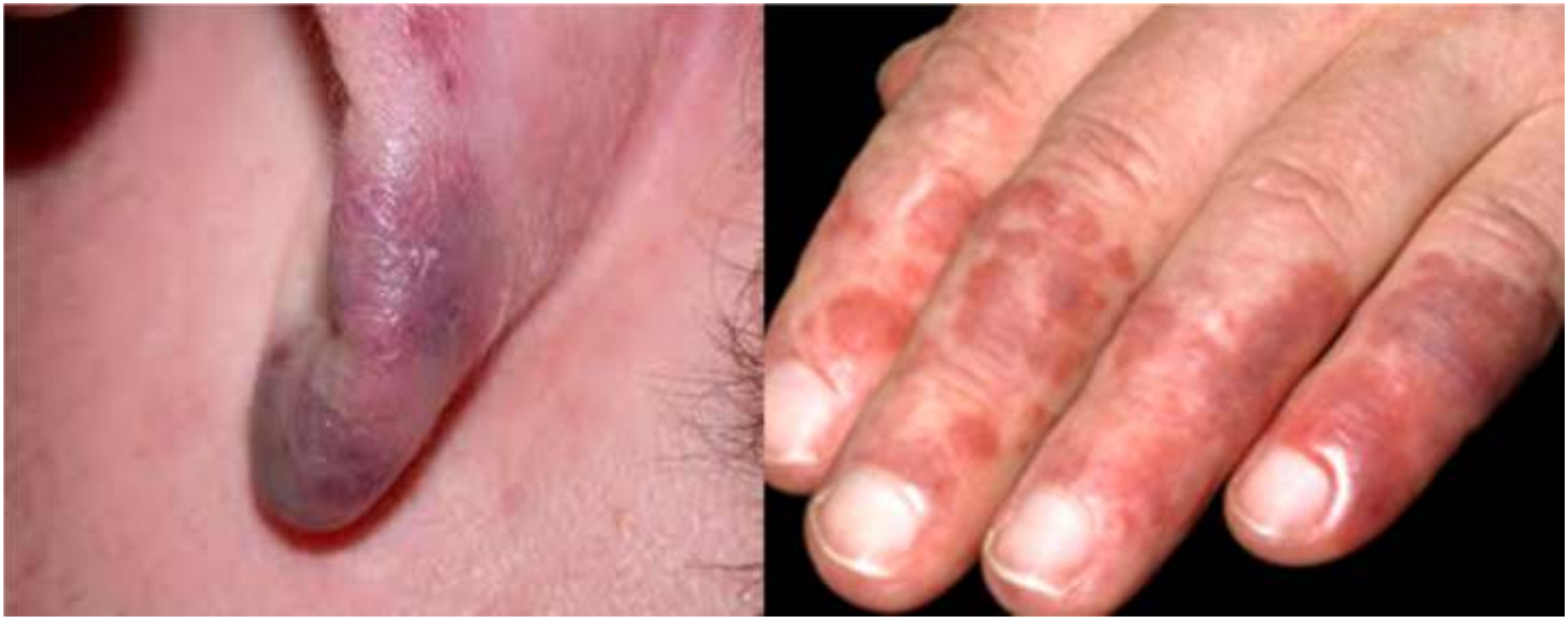
1. **Warty type,** with marked hyperkeratosis and the formation of a warty plaque or nodule. Common sites are nose, temples, ears, scalp, dorsal hands, but also palms and soles;
2. **Tumidus form,** with swollen, warm and tense plaques on the check, on a limb;
3. **Chilblain lupus,** with perniotic lesions on the toes and fingers, but also on the heels, calves, knees, elbows, nose and ears.
4. **Lupus panniculitis (profundus):** movable subcutaneous nodule on the arms, forehead, cheecks, chin, back, buttocks, thighs, scalp, breasts, eyelids etc.
5. **LE centrifugal erythema of Besnier –** superficial form.

DCLE: warty type

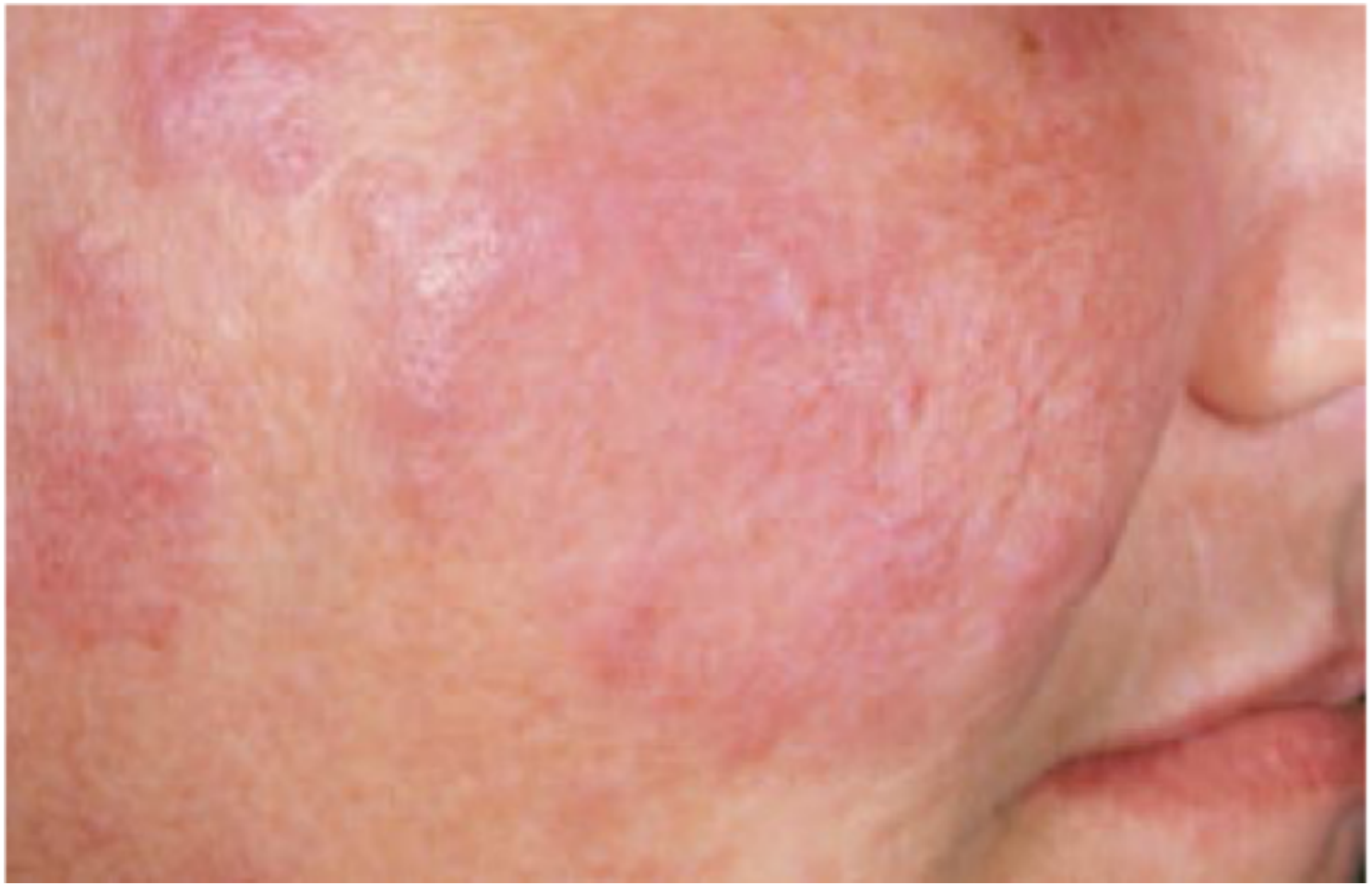




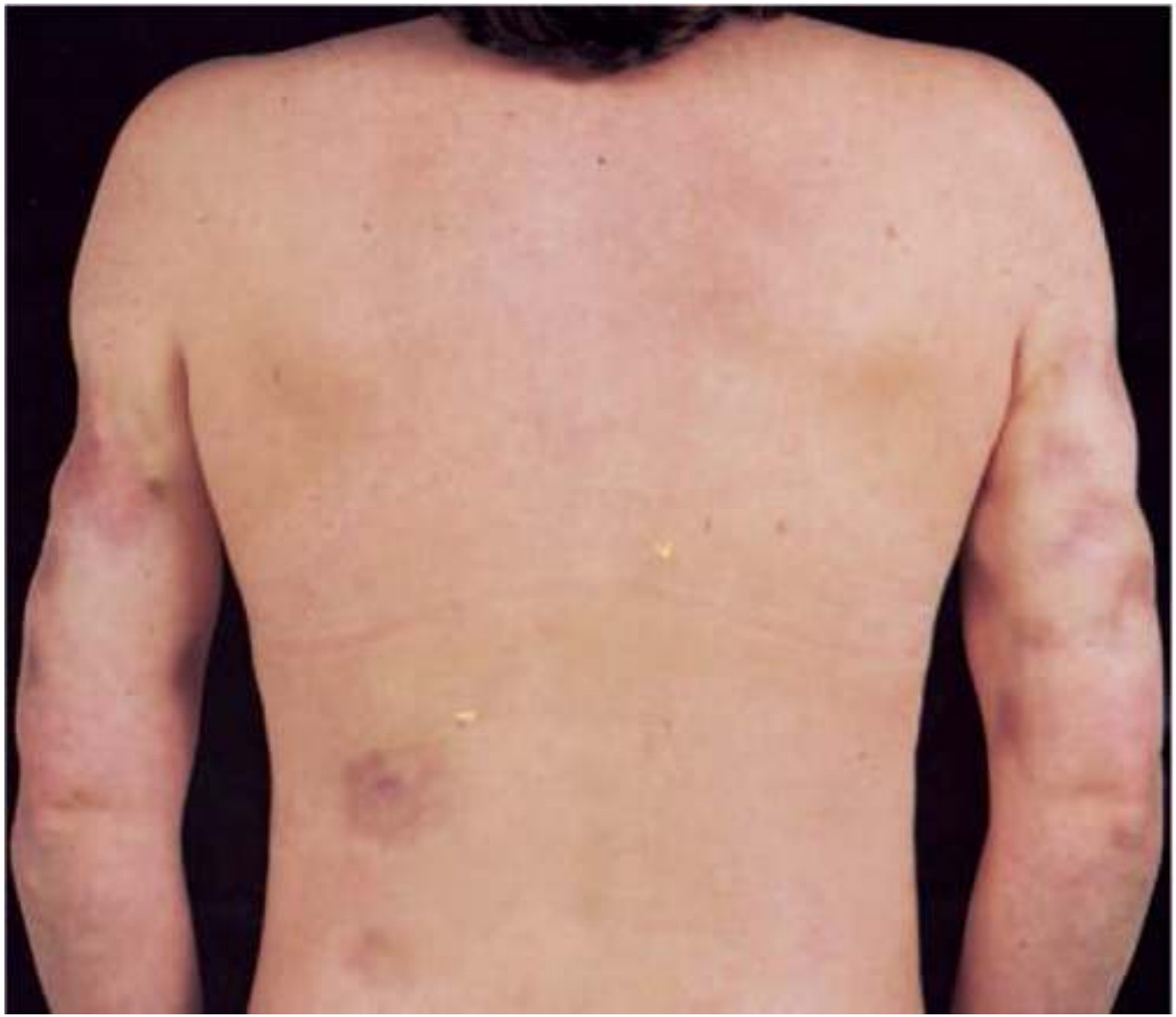
DCLE: chilblain lupus



DCLE: lupus tumidus



Lupus panniculitis

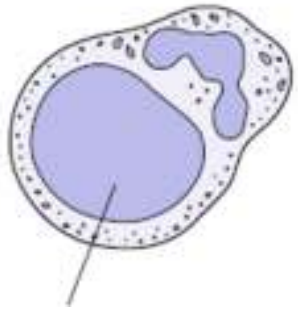


Complications

- ACLE/SCLE
- Associated flaring SLE with potentially organ-threatening involvement
- Ulceration with risk for superinfection
- Progression to TEN-like ACLE/SCLE
- Post-inflammatory hyperpigmentation
- DLE
- Associated flaring SLE with potentially organ-threatening involvement (especially if disseminated)
- Scarring/disfigurement, including scarring alopecia
- Ulceration with risk for superinfection
- Post-inflammatory hyperpigmentation
- LE panniculitis
- Dystrophic calcification
- Depressed atrophic disfigurement
- Lupus mastitis
- LE–non-specific skin disease
- Vasculitis/vasculopathy
  - Associated systemic involvement with life- or organ-threatening involvement
  - Cutaneous necrosis/ulceration
- Raynaud phenomenon
  - Digital ulceration/dry gangrene/loss of digits

ACLE = acute cutaneous lupus erythematosus; DLE = discoid lupus erythematosus; LE = lupus erythematosus; SCLE = subacute cutaneous lupus erythematosus ; SLE = systemic lupus erythematosus; TEN = toxic epidermal necrolysis.

LE Laboratory Investigations

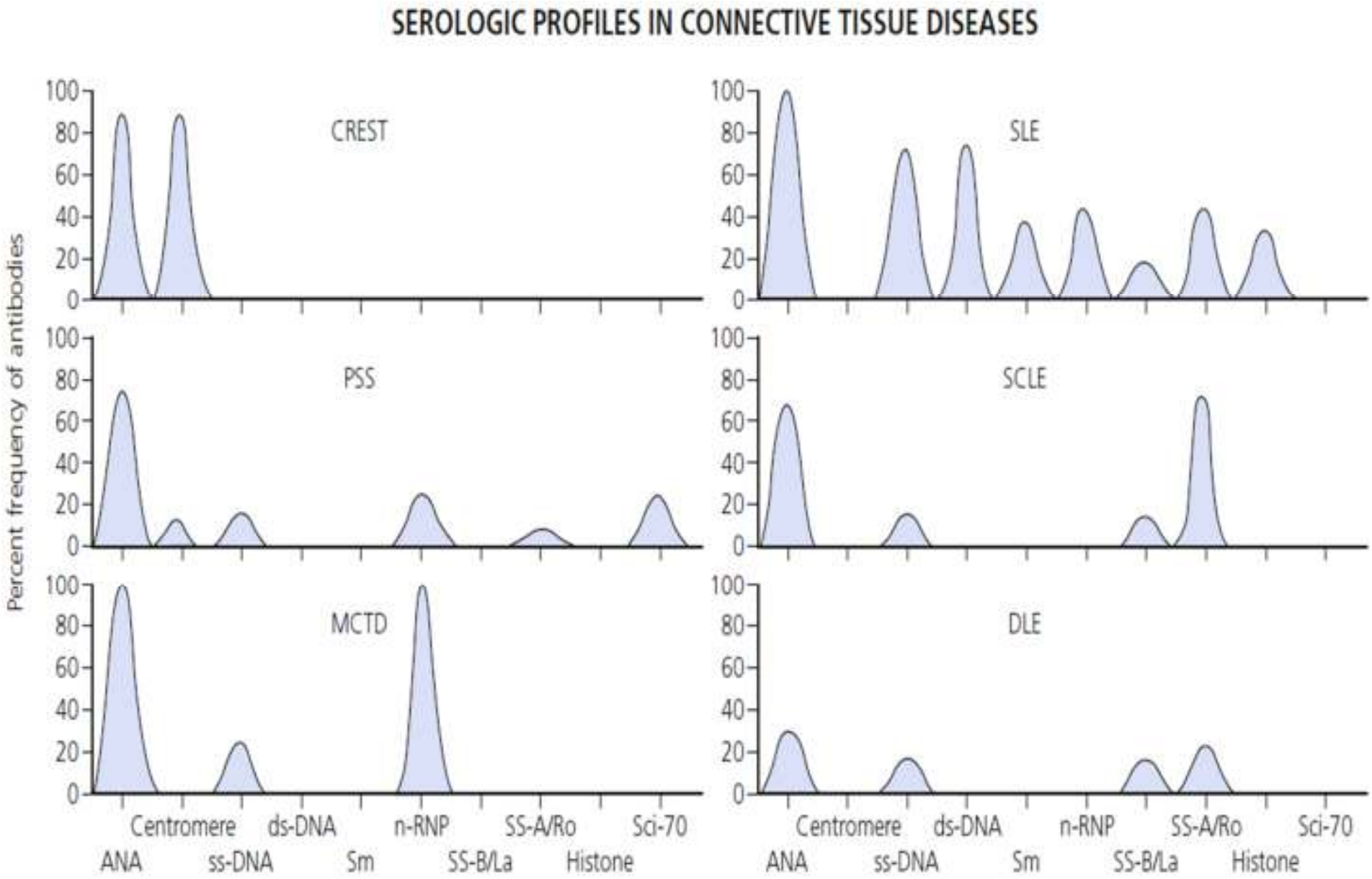


- LE cell test is positive in over 80% of patients with SLE;
- Antinuclear antibodies test (ANA test) – 95-100% in SLE;
- Antibodies to double-stranded DNA (anti ds DNA);
- Antibodies to single-stranded DNA (anti ss DNA)
- Anti-SM antibody;
- Anti-Ro antibodies (anti SS-A);
- Anti-La antibodies (anti SS-B);
- Serum complement level is low.

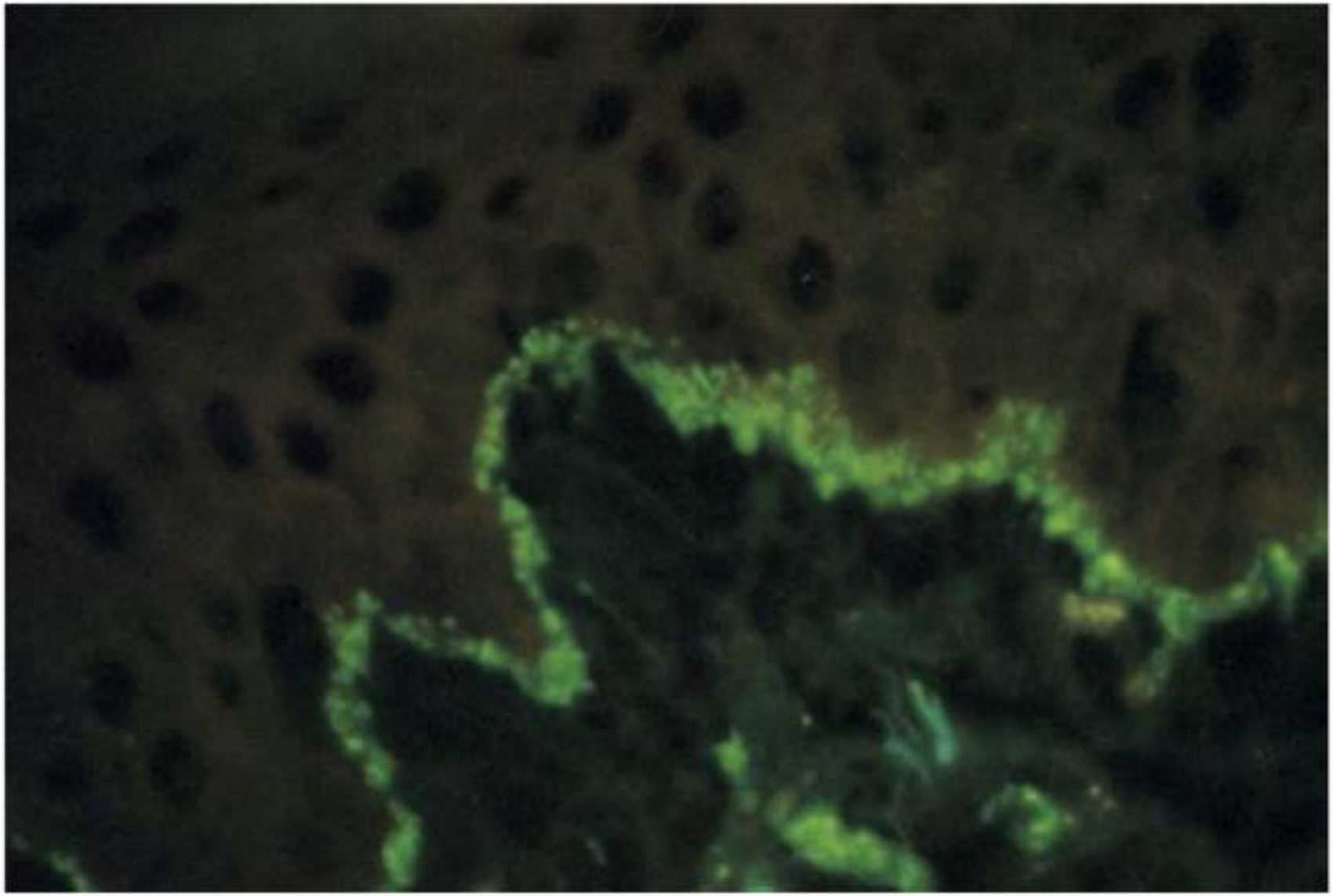
Autoantibodies Associated with Unselected Systemic Lupus Erythematosus

Antigen	Autoantibody Frequency (%) ID	SPA/RIA	Molecular Specificity	Clinical Association
High disease specificity for SLE				
dsDNA		60	Native DNA	LE nephritis
Sm	25		Ribonucleoprotein	—
rRNP	10		Ribosomal P protein	CNS LE
PCNA	3		Cyclin	—
Low disease specificity for SLE				
ssDNA		60	Denatured DNA	Risk for SLE in patients with DLE
Histones		50	Histones	Drug-induced SLE
U1RNP	25		Ribonucleoprotein	Overlap CTD (MCTD)
Ro/SS-A	25	50	Ribonucleoprotein	SLCE, SSj, neonatal LE
La/SS-B	10	20	Ribonucleoprotein	SSj, SCLE
Ku	10		Transcription factor	Overlap CTD

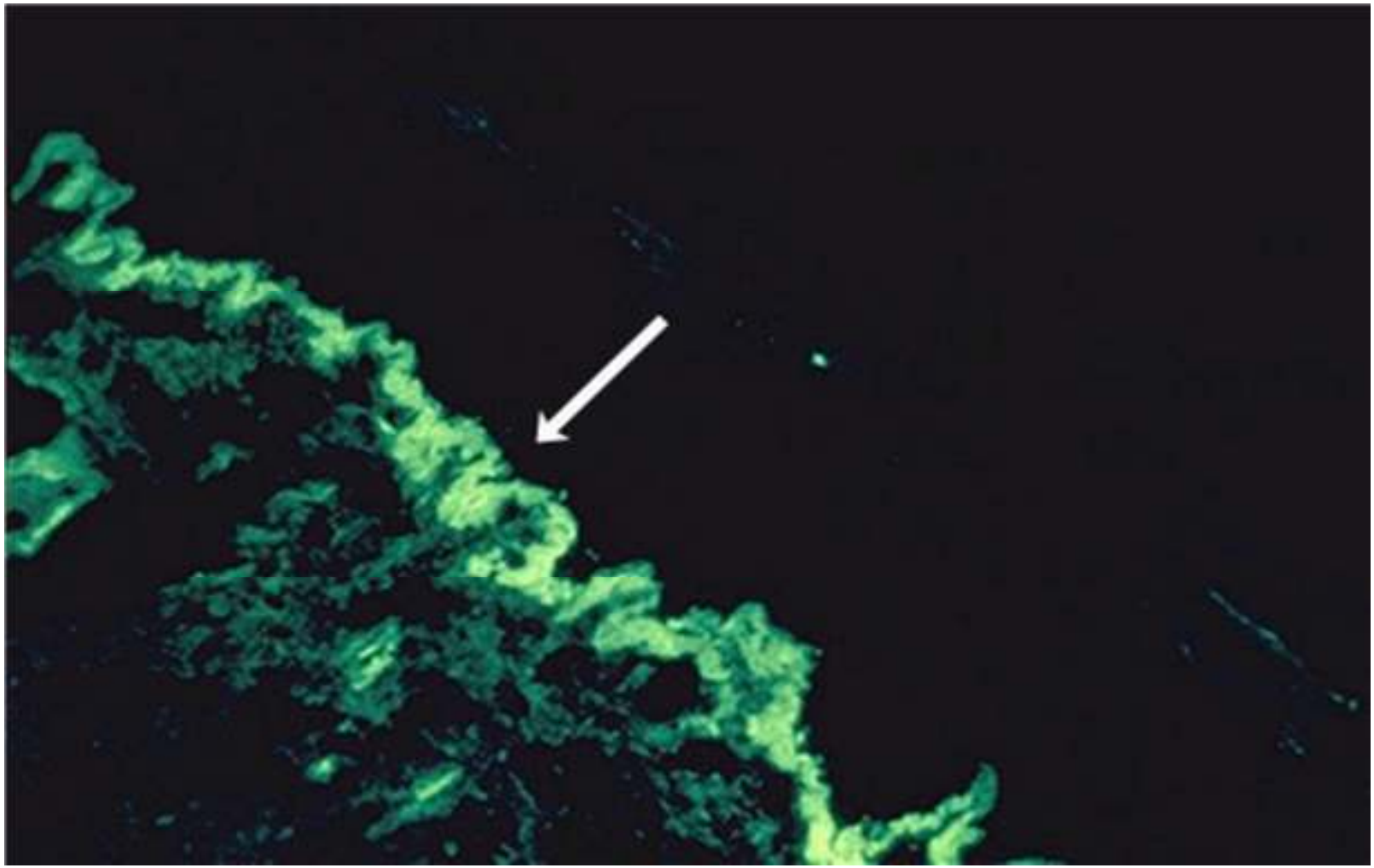
CNS = central nervous system; CTD = connective tissue disease; DLE = discoid lupus erythematosus; dsDNA = doubled-stranded DNA; ID = immunodiffusion; MCTD = mixed CTD; PCNA = proliferating cell nuclear antigen; RIA = radioimmunoassay; RNP = ribonucleoprotein; SCLE = subacute cutaneous lupus erythematosus; SLE = systemic lupus erythematosus; SPA = solid phase immunoassay (i.e., enzyme-linked immunoassay); ssDNA = single-stranded DNA; SSj = Sjögren syndrome.


SEROLOGIC PROFILES IN CONNECTIVE TISSUE DISEASES
Percent frequency of antibodies
100
80
60
40
20
0
CREST
SLE
PSS
SCLE
MCTD
DLE
Centromere
ds-DNA
n-RNP
SS-A/Ro
Sci-70
ANA
ss-DNA
Sm
SS-B/La
Histone

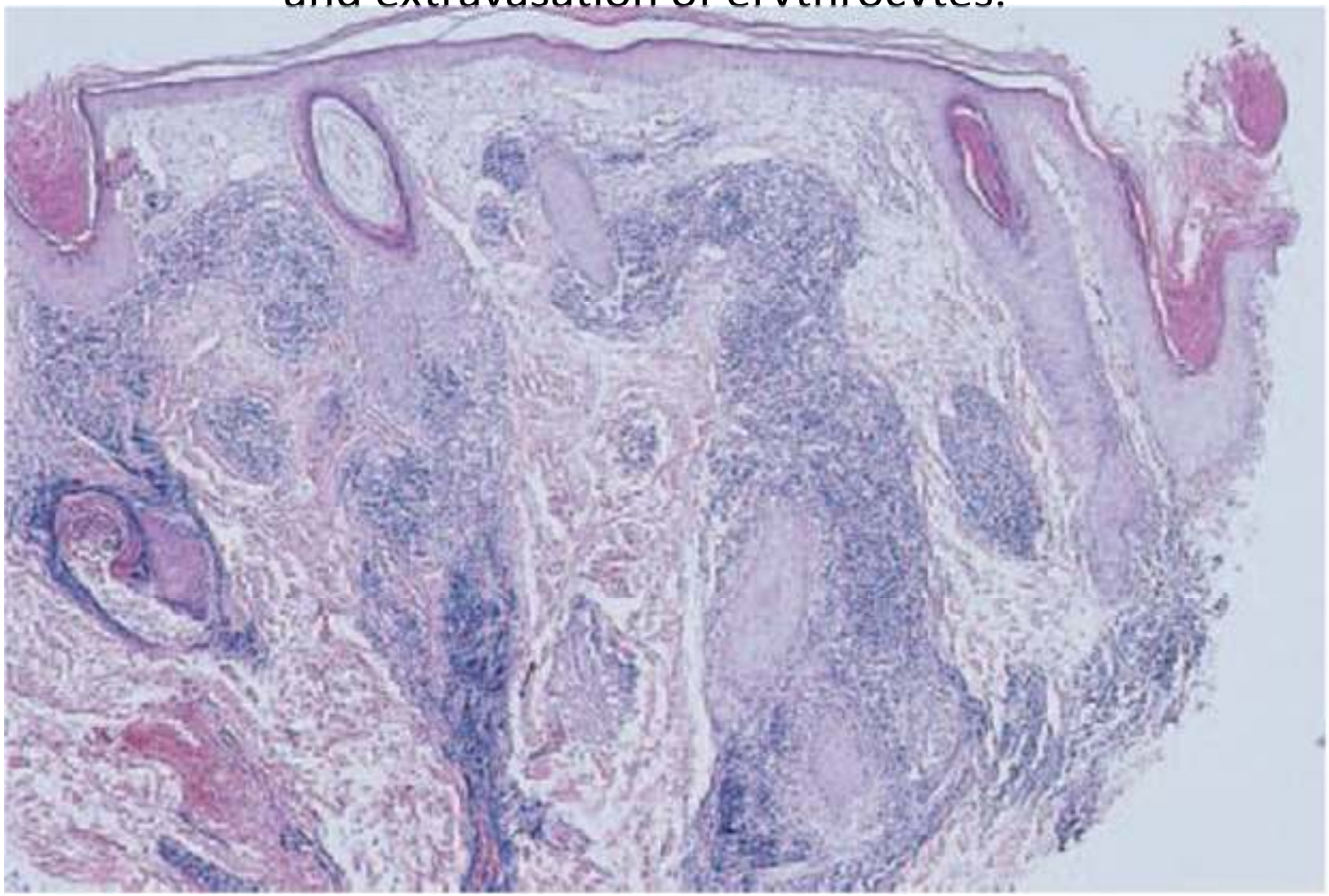
Lupus band test: direct immunofluorecence evidencing IgG and IgM and complement (C3) in a continuous granular line or band along the dermo-epidermal junction – in 90% of active lesions.



LUPUS BAND TEST



Histology: vacuolar degeneration of epidermal basal cells, hyperkeratosis, atrophy of the epidermis, follicular plugging, papillary dermal edema, a perivascular mononuclear infiltrate and extravasation of erythrocytes.



Treatment Cutaneous LE

- **Topical therapy**
  - ✓ **topical corticosteroids:** potent or superpotent are effective (methylprednisolone aceponate, mometasone furoate, hydrocortisone butirate, betamethasone dipropionate, fluticasone propionate, flucinonide, halcinonide, amcinonide, clobetasol dipropionate, halbetasol propionate etc);
  - ✓ **sun-screens (SPF 30);**
- **Systemic treatment**
  - ✓ antimalarials: chloroquine sulphate, hydroxychloroquine;
  - ✓ corticosteroids;
  - ✓ thalidomide;
  - ✓ retinoids;
  - ✓ dapsone;
  - ✓ clofazimine

Therapeutic Options for Lupus Erythematosus–Specific Skin Disease

	Drug	Dose
First line	Topical glucocorticoids Topical calcineurin inhibitor Intralesional: triamcinolone acetonide	Class I steroid qd–bid for 2 wk alternating with class IV pimecrolimus, 1% bid; tacrolimus, 0.1% bid 2.5–10.0 mg/cc
Second line (low threshold for use if scarring, widespread lesions, systemic symptoms)	Hydroxychloroquine Chloroquine Quinacrine (if monotherapy fails, add quinacrine to either hydroxychloroquine or chloroquine)	6.5 mg/kg/day ideal body weight 3.5 mg/kg/day ideal body weight 100 mg daily (available at compounding pharmacies)
Short courses only (2–16 wk) (must have patient on concomitant alternative agent to prevent rebound on discontinuation)	Prednisone Thalidomide	5–60 mg/day 50 mg qd–200 mg/day; taper to 50 mg qod on response
Third line (safer immunosuppressives)	Azathioprine Mycophenolate mofetil Methotrexate	1.5–2.5 mg/kg/day 2.5–3.5 g/day 7.5–25 mg PO or SQ/wk
Worth consideration	Dapsone Accutane or Acitretin Gold	50–200 mg/day 0.5–2 mg/kg/day 10–50 mg/day Work up to 50 mg weekly, taper after 1 g
Fourth line (limited by side effects)	Cyclophosphamide Clofazimine	1.5–2.0 PO mg/kg/day
Investigational (some currently available)	Efalizumab (Raptiva) Leflunomide (Arava) Anti-tumor necrosis factor agents Rituximab (Rituxan) Abatacept Epratuzumab Anti–interferon-α agents	