Cutaneous manifestations of Connective Tissue Diseases

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Objectives

1) Differentiate between the various types of **Lupus** (clinical presentation, investigations and management)

2) Learn about **Dermatomyositis** (clinical presentation, investigations and management)

3) Learn about the clinical presentations of **Morphea, Systemic sclerosis** and their management.

4) This lecture is not meant to be inclusive of all the information about these diseases but to highlight important aspects in their diagnosis and management.

Connective Tissue Diseases

- **Lupus Erythematosus**
  - Acute Cutaneous Lupus Erythematosus (ACLE)
  - Subacute Cutaneous Lupus Erythematosus (SCLE)
  - Discoid Lupus Erythematosus (DLE)
  - Lupus Erythematosus Tumidus
  - Lupus Panniculitis
  - Neonatal Lupus Erythematosus
- **Dermatomyositis**
- **Scleroderma (systemic sclerosis)**
- **Morphea & Lichen Sclerosus**
- **Other Rheumatologic Disease**
  - Still's disease
  - Relapsing Polychondritis
  - Sjogren's syndrome
  - Mixed connective tissue disease

LUPUS ERYTHEMATOSUS

Lupus Erythematosus

- A multisystem disorder that prominently affects the skin.
- It ranges from life threatening manifestations of SLE to the limited and exclusive skin involvement in Chronic cutaneous lupus.
- A common classification of cutaneous LE: Specific vs non-specific.

Specific:

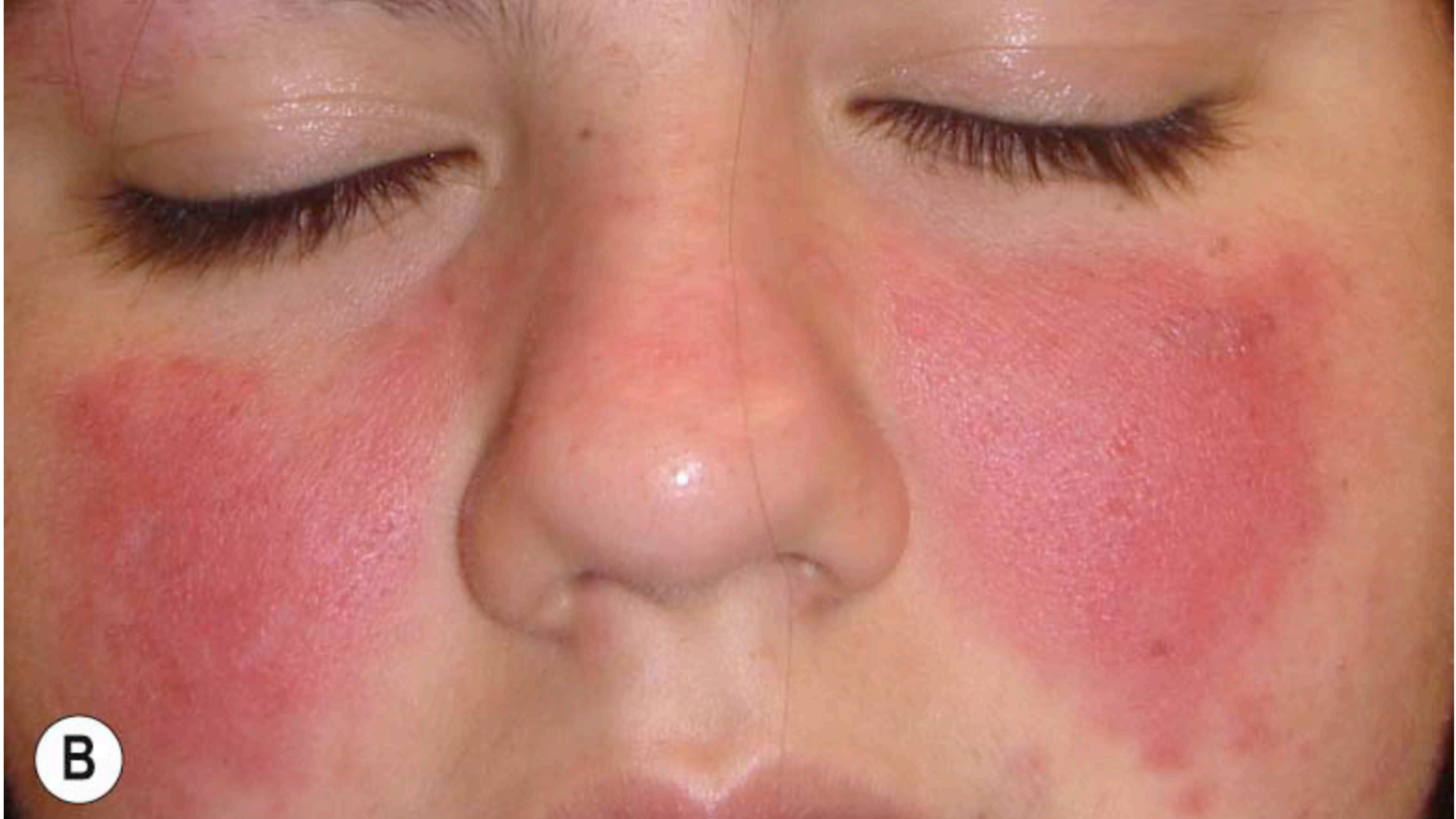
- Acute (ACLE)
- Subacute (SCLE)
- Chronic (DLE, Tumid lupus, Lupus panniculitis)

Non-specific:

- Raynaud's, Livedo Reticularis, Palmar Erythema, Periungual Telangiectasias.

Acute Cutaneous Lupus Erythematosus (ACLE)

- These Patients must be evaluated carefully for evidence of internal disease.
- The lesions tend to be transient, follow sun exposure, and resolve without scarring.
- **Bilateral Malar erythema** (Butterfly rash)
- The morphology ranges from mild erythema to intense edema.
- Telangiectasias, erosions, dyspigmentation and epidermal atrophy help distinguish the malar erythema from other facial rashes.
- The duration may range from a few hours to several weeks.
- Sometimes may be more widespread in distribution.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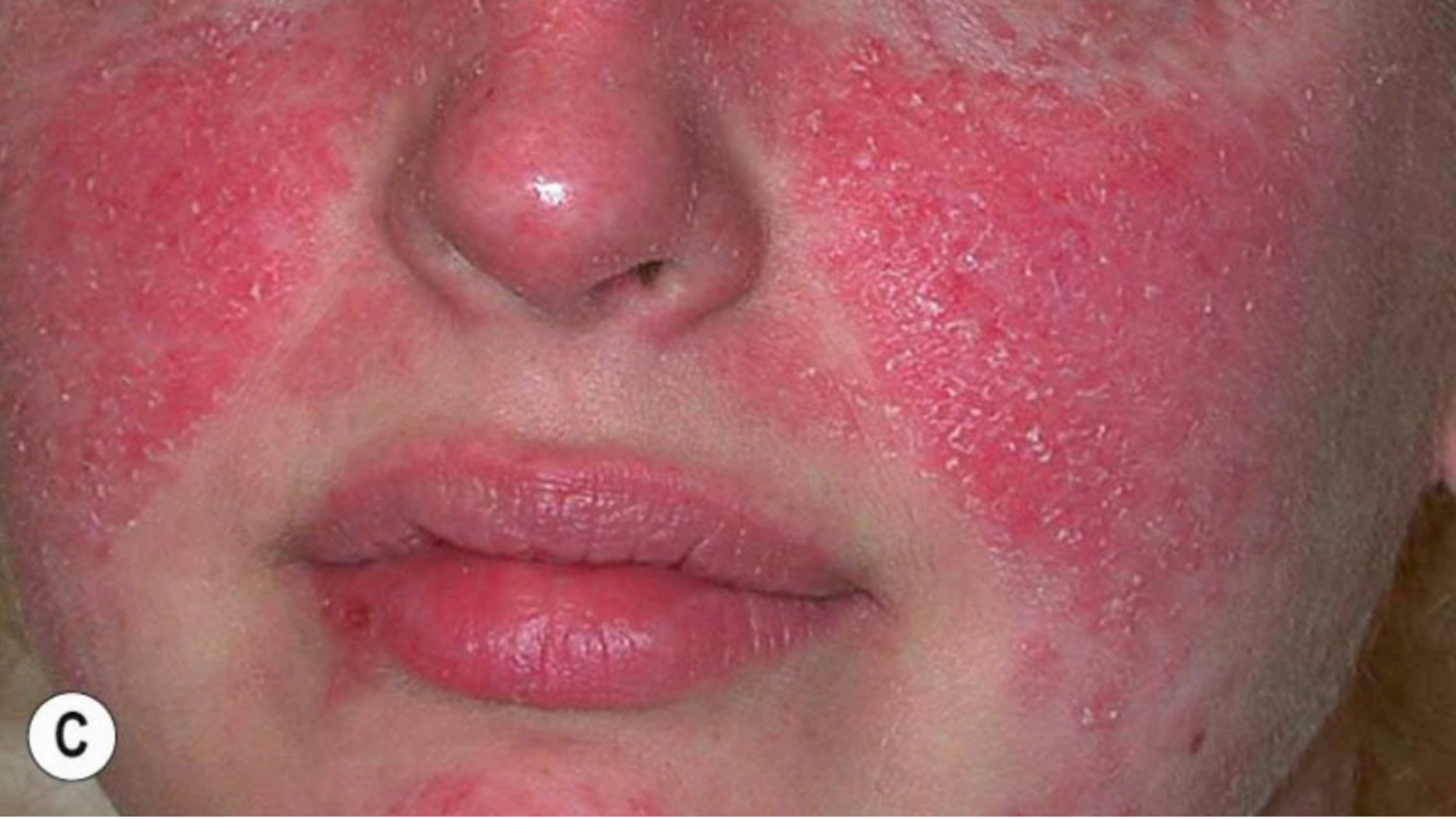
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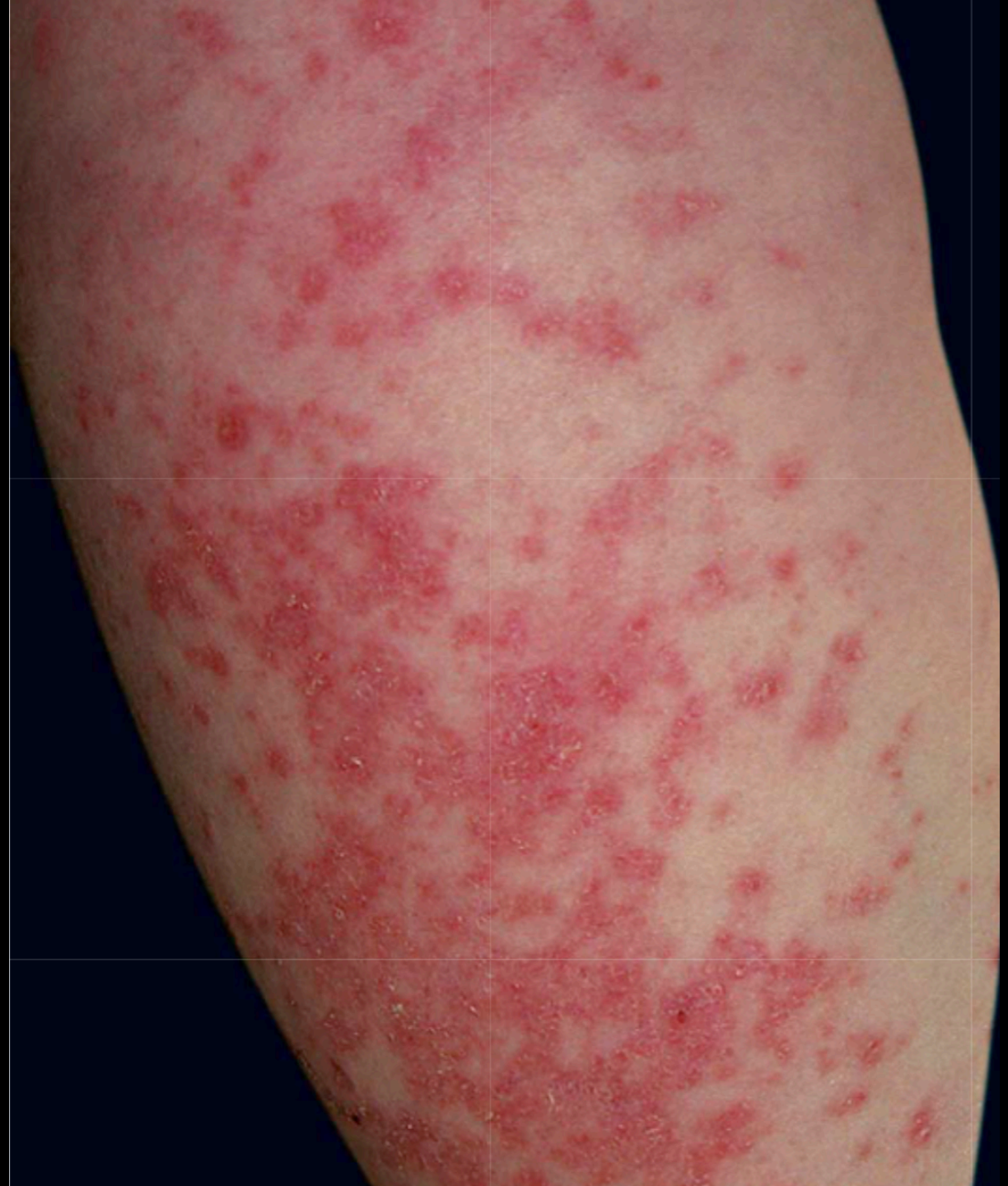
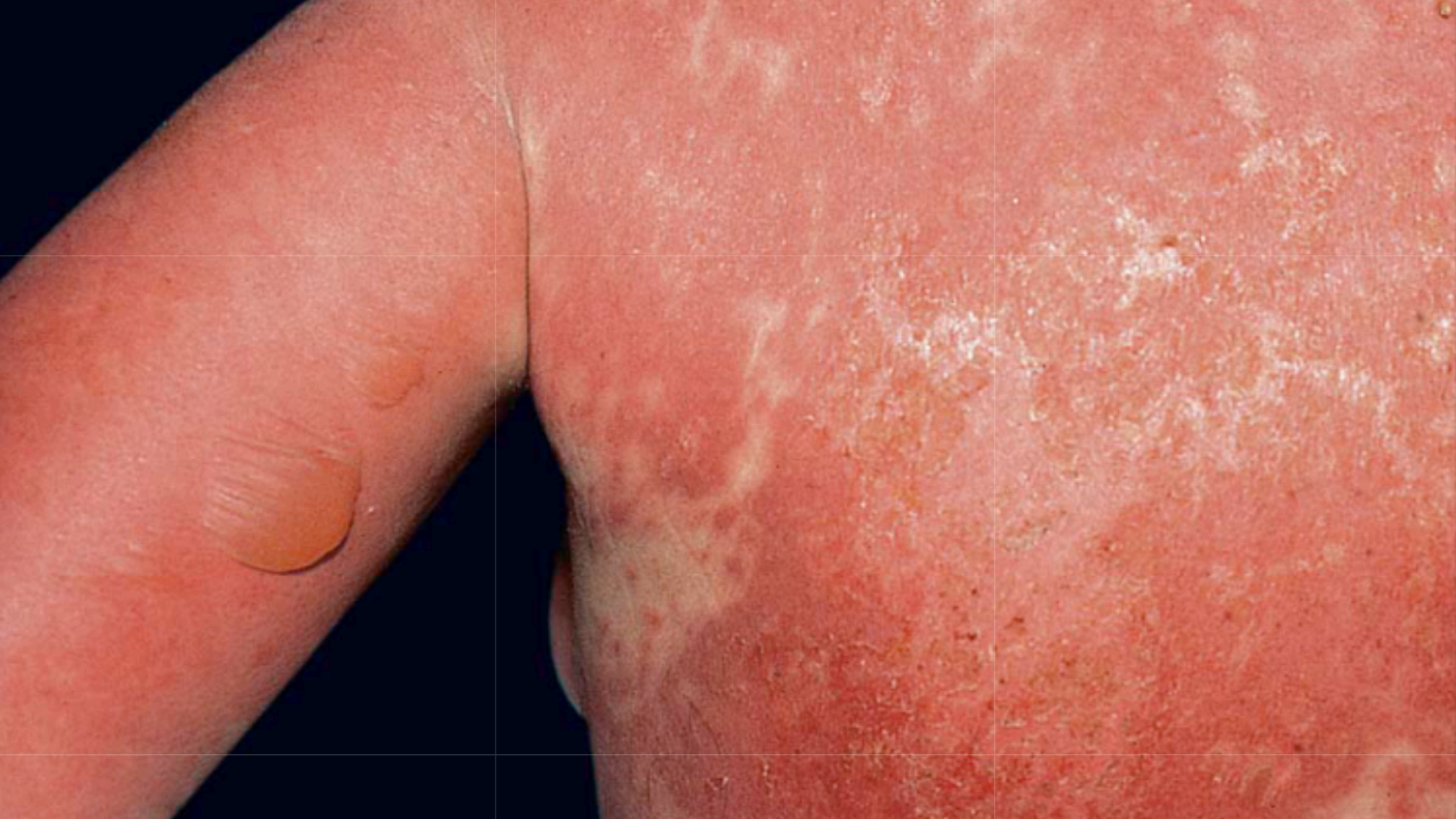




Subacute Cutaneous Lupus Erythematosus (SCLE)

- Typically Photosensitive, lesions confined to sun-exposed skin.
- The midfacial skin is usually spared, while the sides of the face, upper trunk and extensor aspects of the upper extremities are commonly involved.
- Can be mild, with only a few small scaly patches appearing after sun exposure.
- Lesions may have an **annular** configuration or a **papulosquamous** presentation.
- Lesions often result in dyspigmentation (mainly hypopigmentation) but **do not scar.**

Subacute Cutaneous Lupus Erythematosus (SCLE)

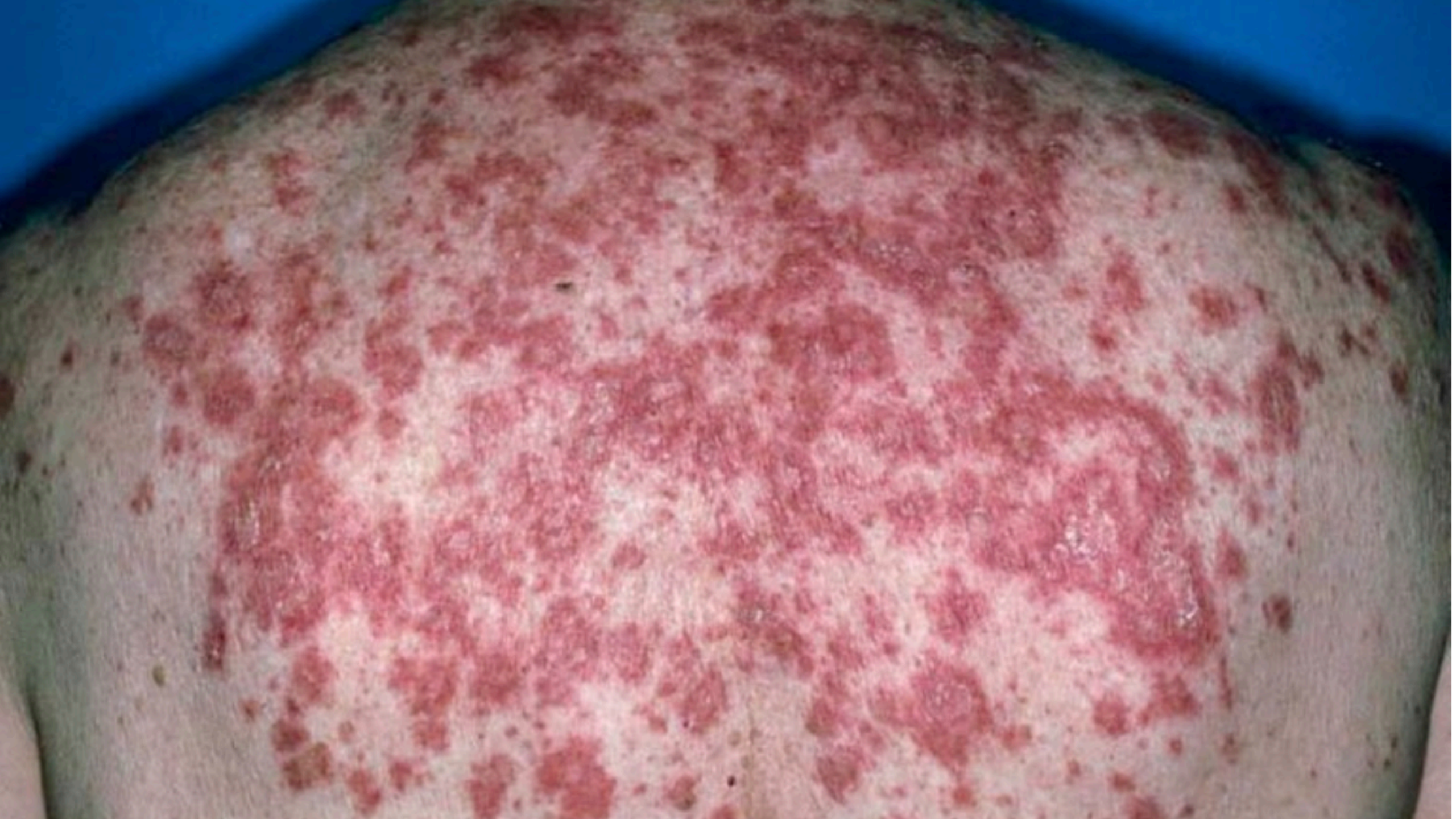
- The long-term prognosis of patients who have SCLE is not completely known.
- 10-15% of SCLE patients will over time develop internal disease, including nephritis.
- SCLE is associated with the anti-Ro autoantibody (Approximately 70%)

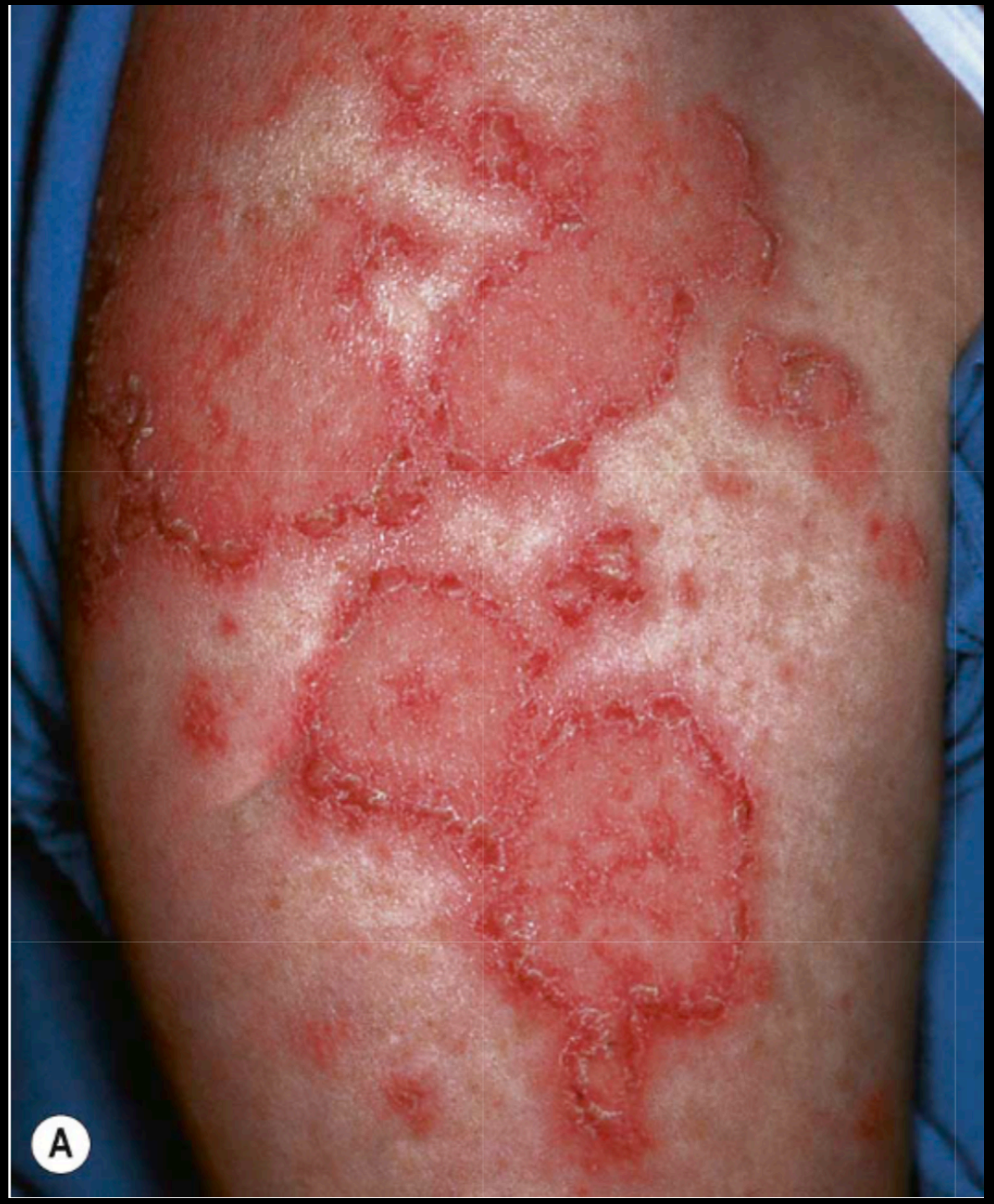
Drug-induced SCLE

- SCLE lesions can appear after receiving certain medications including:

- **Hydrochlorothiazide and Terbinafine**.
- Calcium channel blockers
- NSAID's (Naproxen)
- Griseofulvin
- Antihistamines.

- The lesions may or may not clear once the medication is discontinued.

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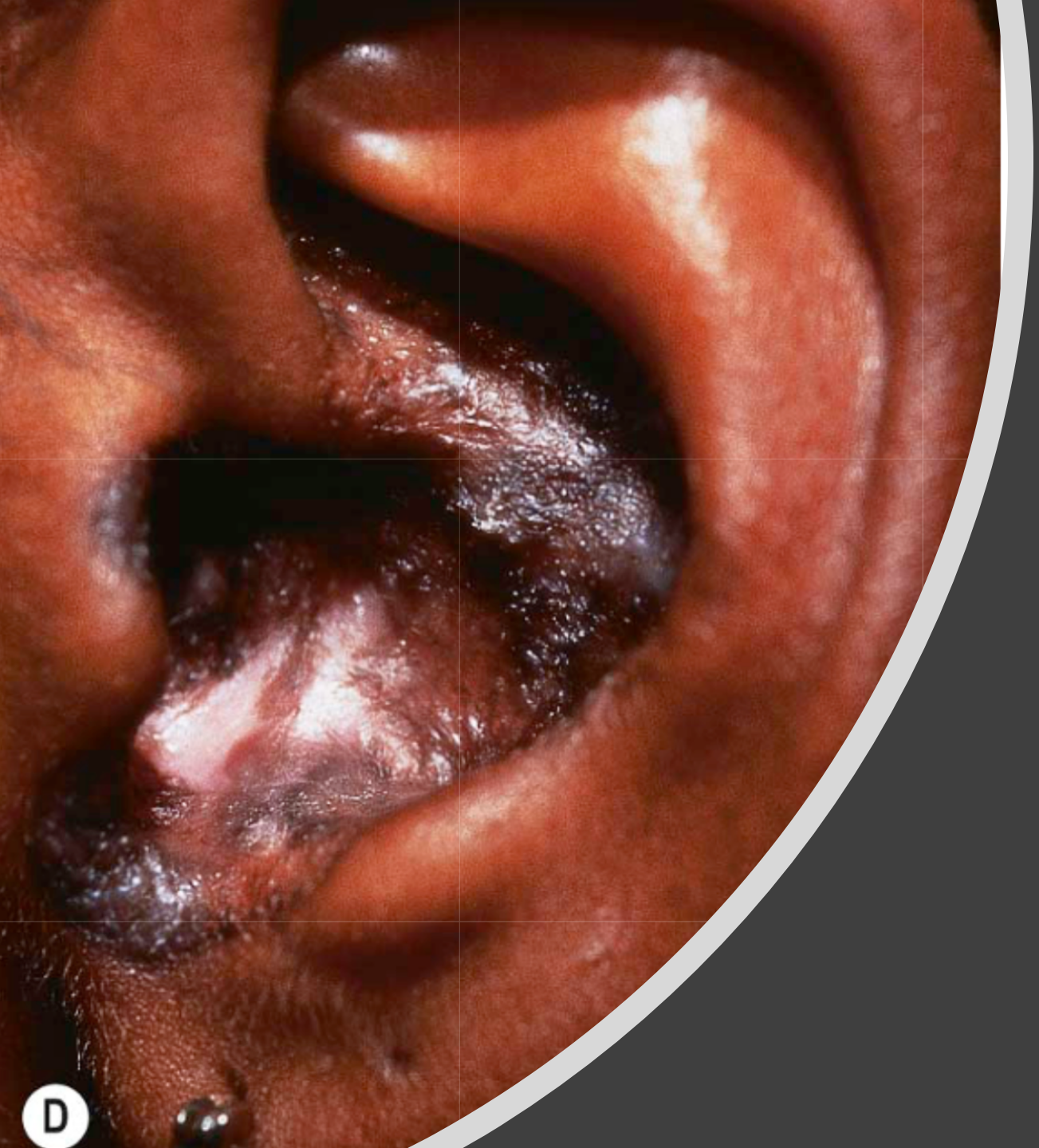
Discoid Lupus Erythematosus (DLE)

- One of the most common skin manifestations of Lupus.
- Most often involves the face, scalp and ears.
- Unusual to present below the neck without lesions present above the neck.
- No clear association between sun exposure and developing DLE lesions.
- DLE lesions have the potential for **scarring.**
- Active lesions tend to feel indurated on palpation.
- Follicular plugging and scarring alopecia.
- Dyspigmentation (Hypo in the central area and hyper at the periphery).

Discoid Lupus Erythematosus (DLE)

- Only **5-15%** of DLE patients eventually develop clear-cut SLE.
- The risk is higher in patients with widespread discoid lesions.
- Remember: Discoid lesions represent 1 of the 11 ARA criteria for SLE.
- Hypertrophic DLE is an unusual variant (Thick, scaly) mostly on the arms.

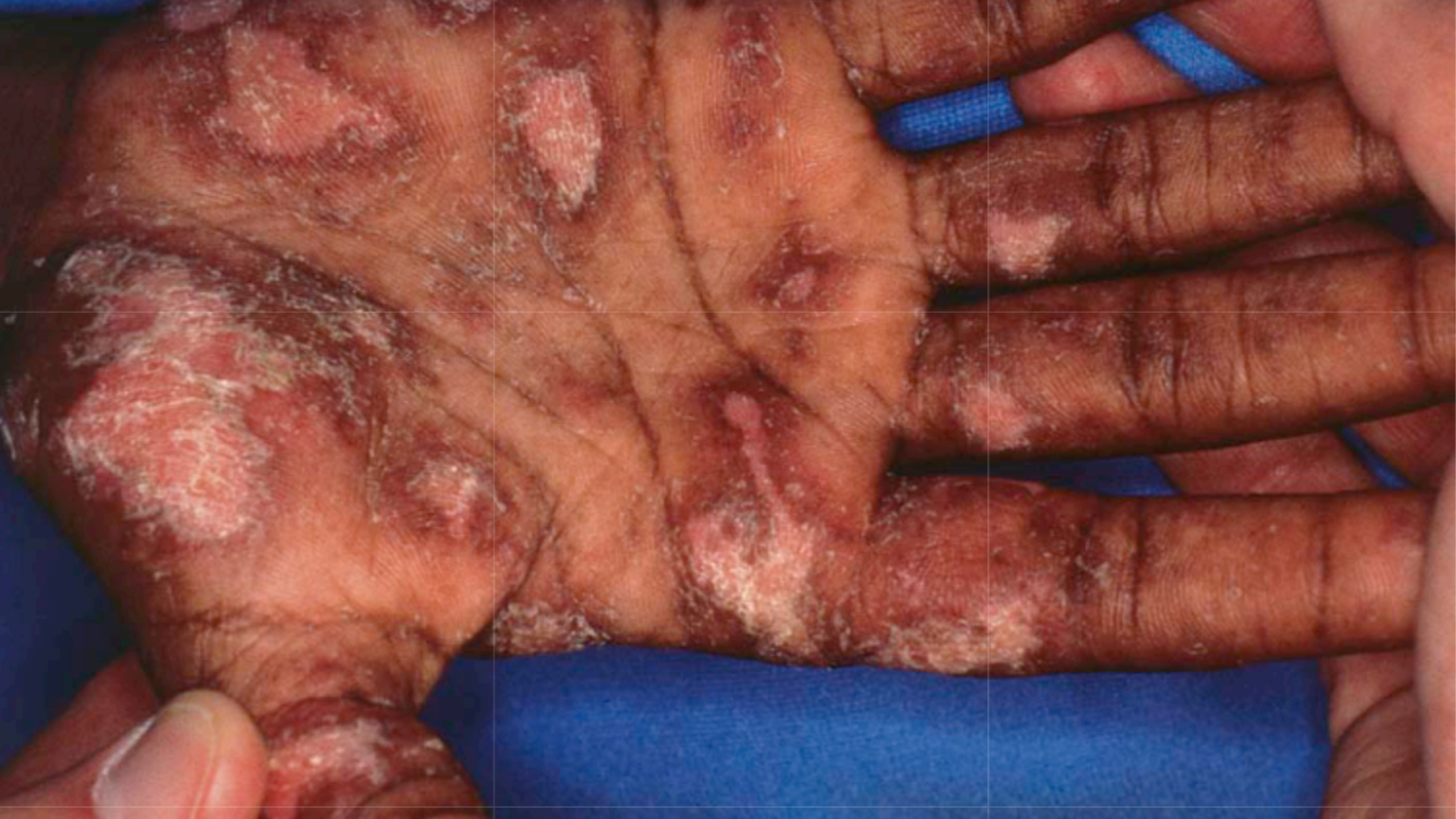


Erythema

Scaling

Hyperpigmentation

Atrophy

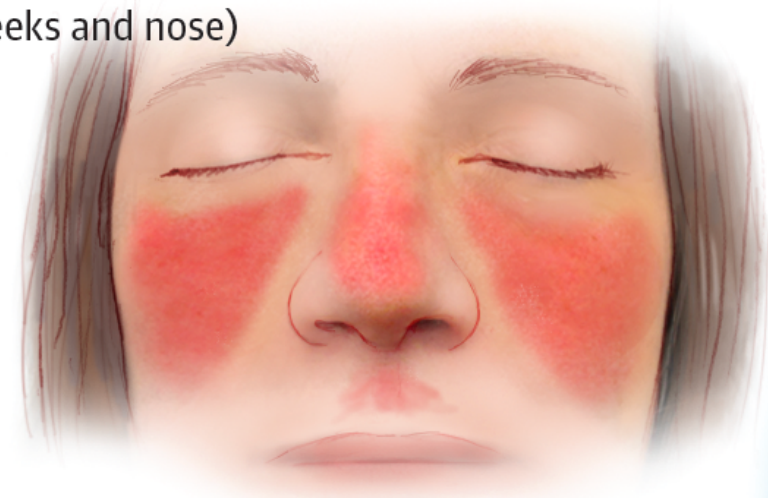



Scarring
Alopecia
(DLE)

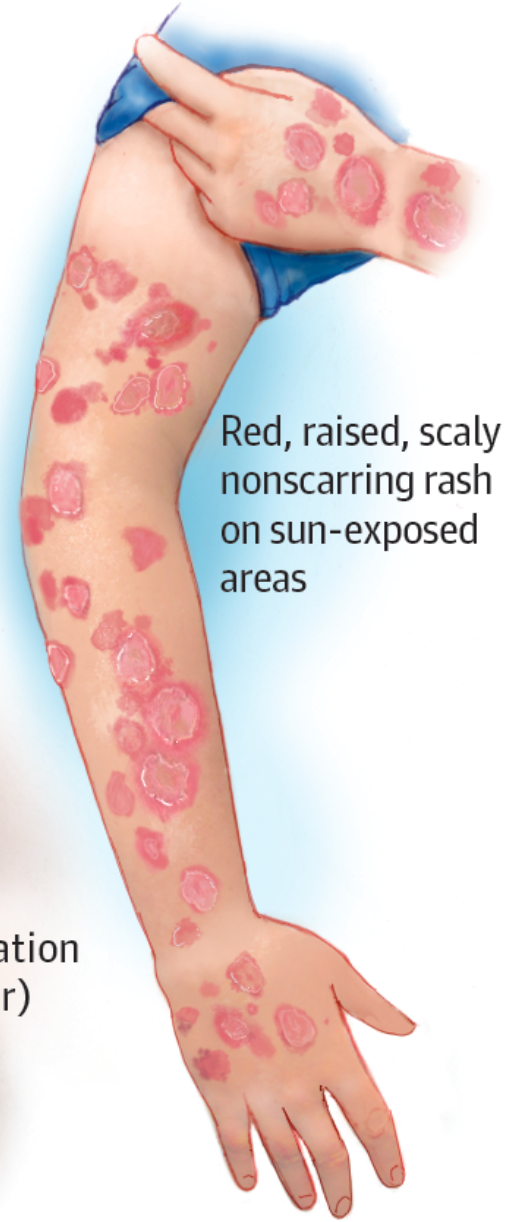
Types of cutaneous lupus erythematosus

Acute cutaneous lupus ("acute skin lupus")

"Butterfly rash" (redness across cheeks and nose)

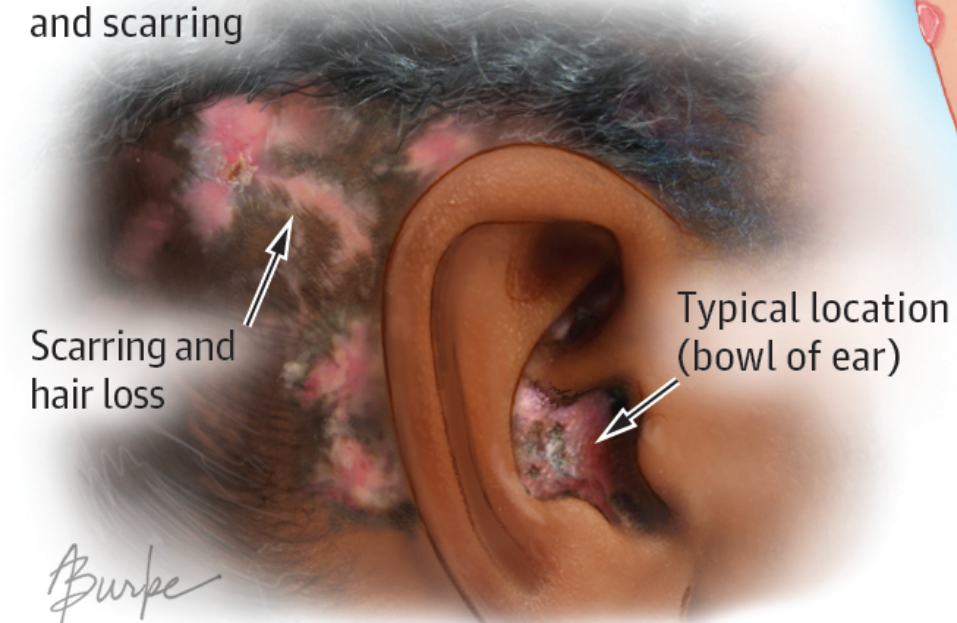


Subacute cutaneous lupus ("subacute lupus")



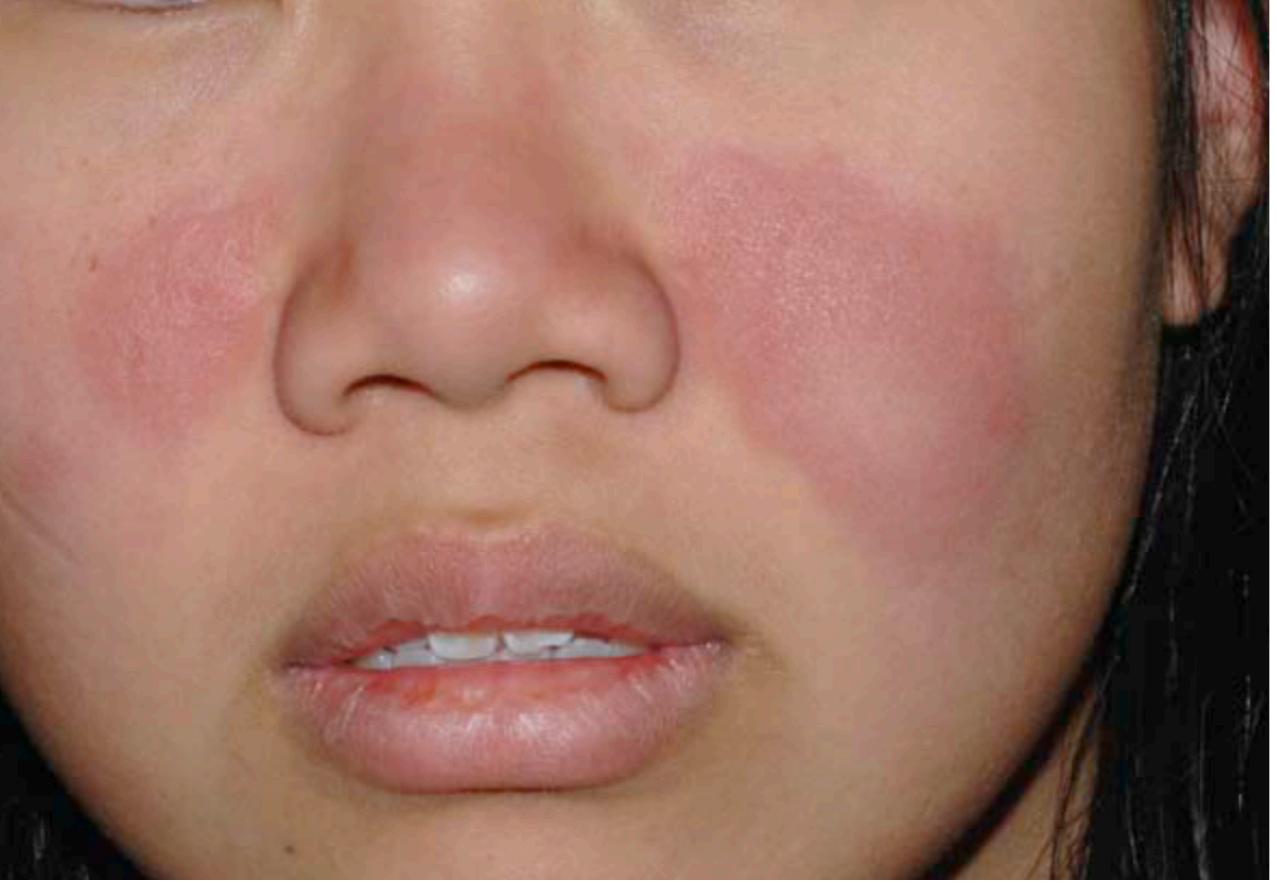
Chronic cutaneous lupus ("discoid lupus")

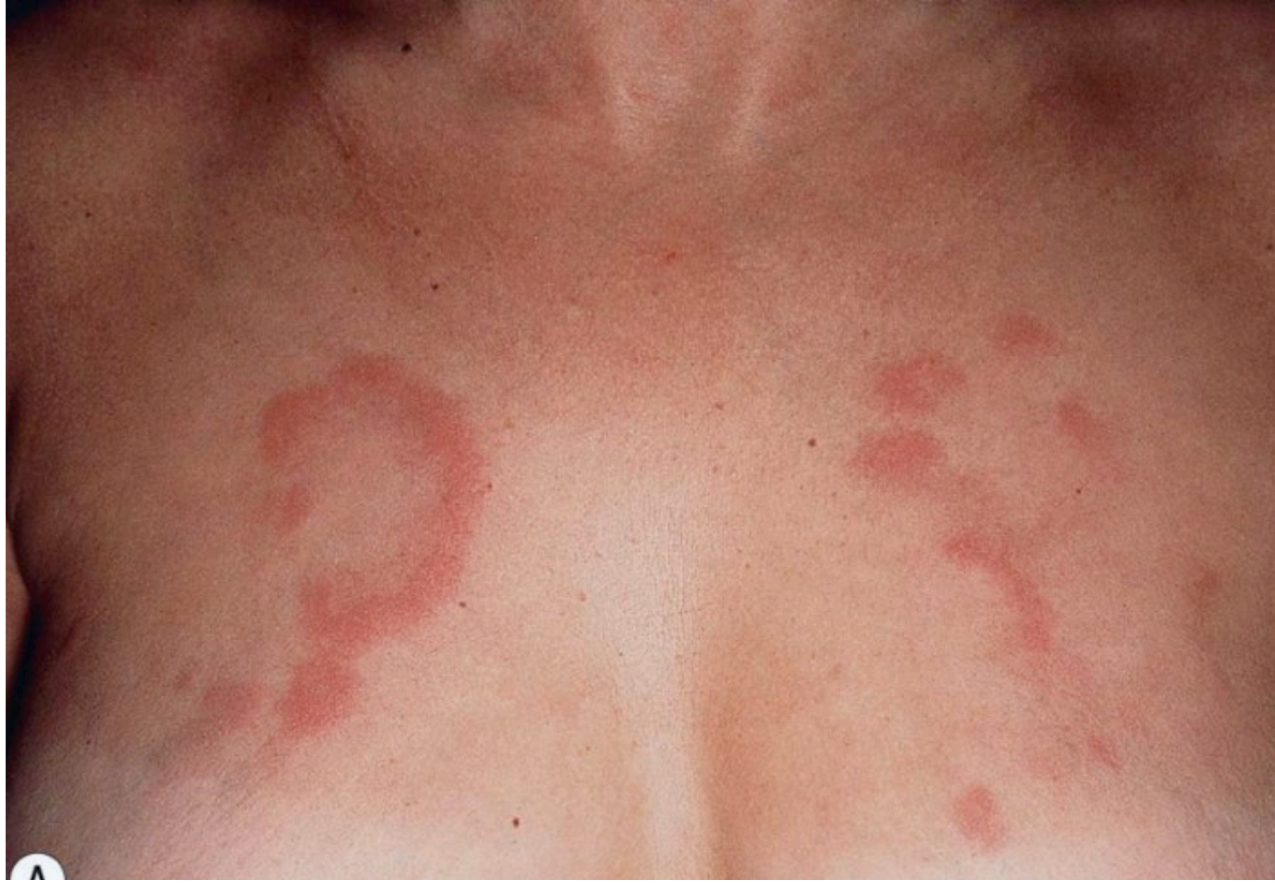
Red to purple rash with discoloration and scarring



Lupus Erythematosus Tumidus

- Induration and erythema without scaling and follicular plugging.
- The epidermis is uninvolved but has intense dermal inflammatory infiltrate.
- Appears on the face and Trunk.
- Negative serology, does not lead to systemic disease.

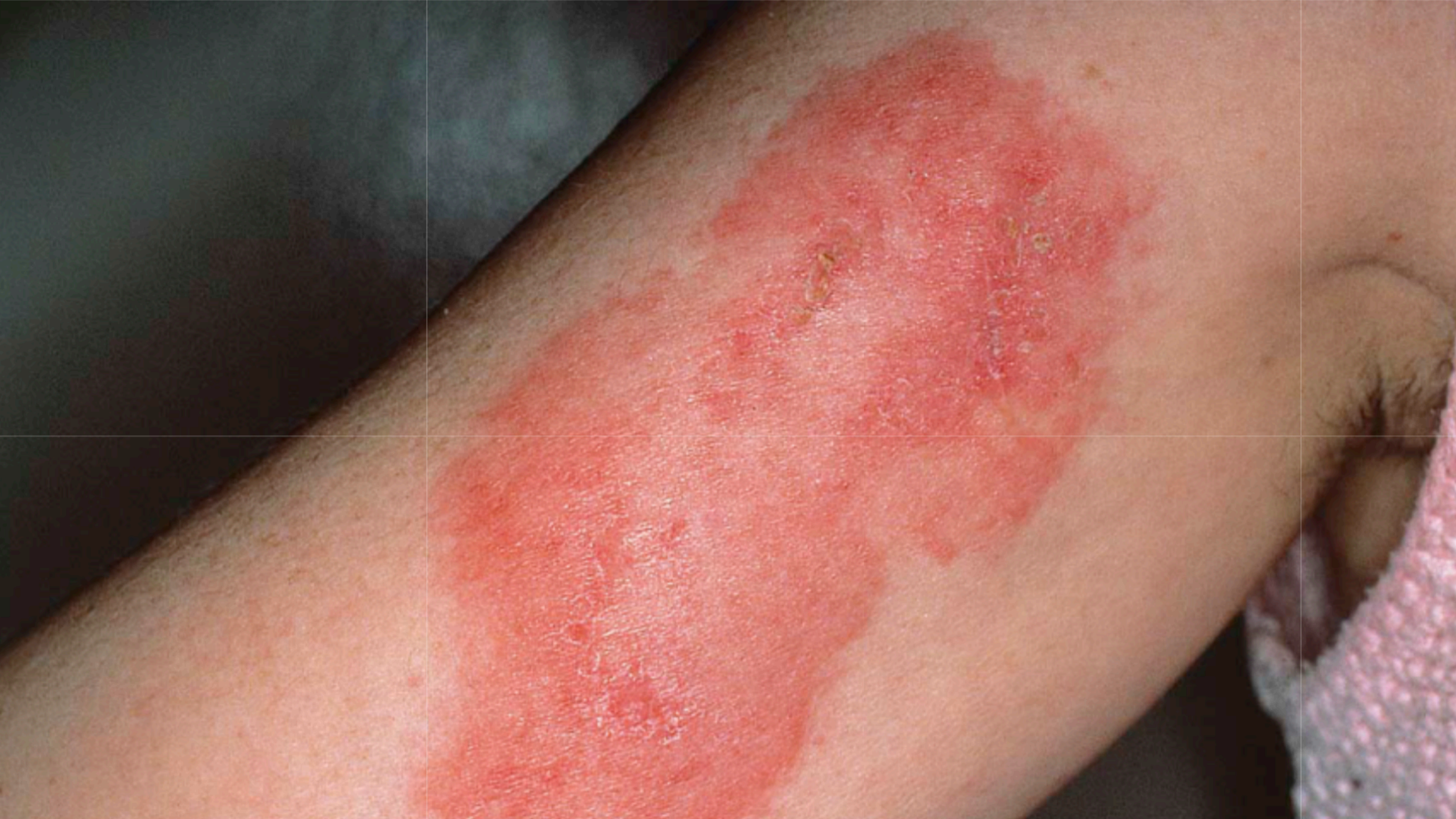




Tumid lupus

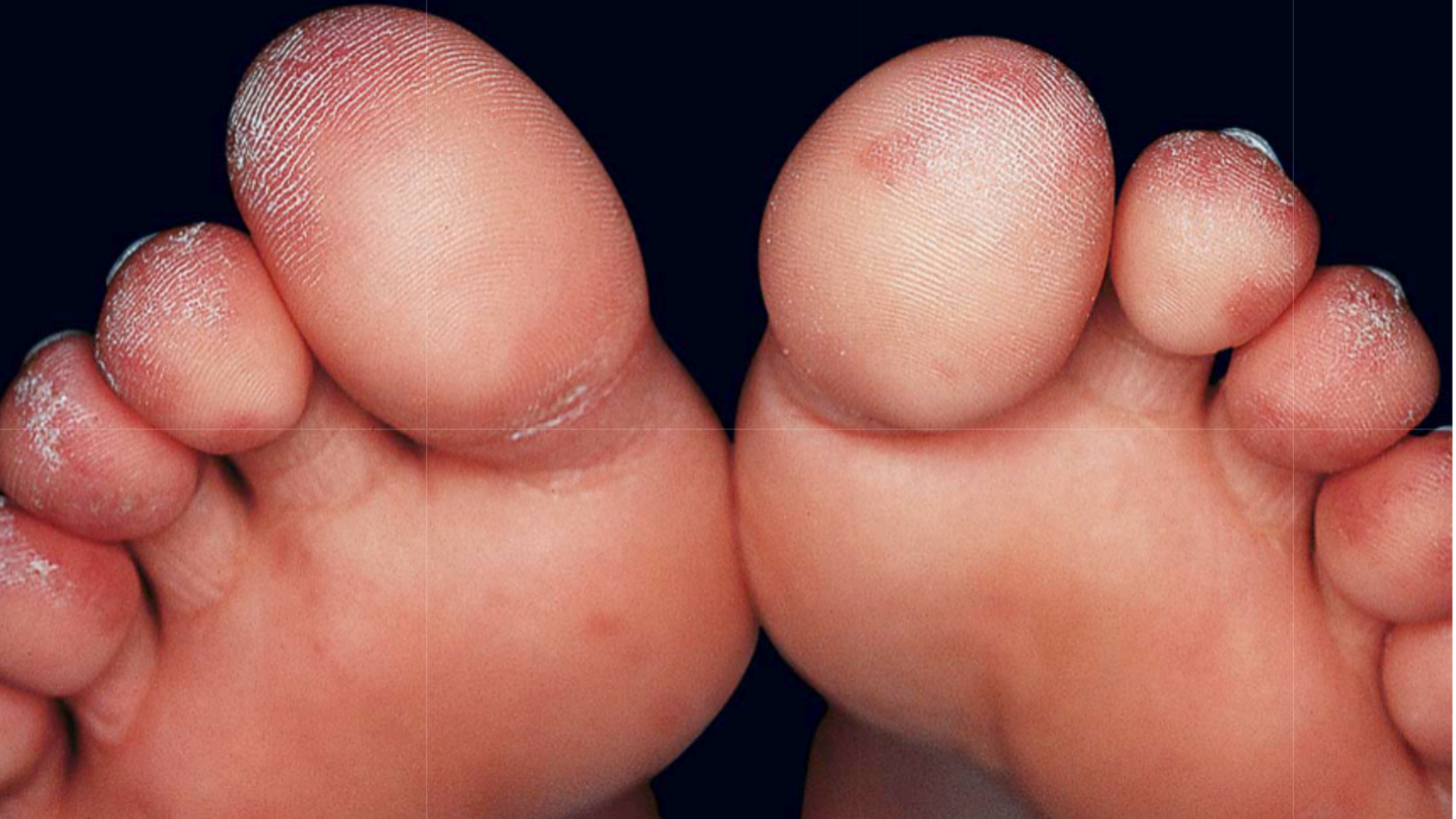
Lupus Panniculitis

- Indurated plaques that can evolve into disfiguring, depressed areas.
- Occur on the face, upper arms, upper trunk, breasts, buttocks and thighs.
- Some patients have discoid lesions overlying the panniculitis (Lupus Profundus)



Chilblain Lupus

- Red or dusky purple papules and plaques on the toes, fingers, and sometimes the nose, elbows, knees and lower legs.
- The lesions are brought on or exacerbated by cold.
- The lesions may represent the concurrence of ordinary chilblains with LE, although, with time, the lesions may develop a discoid lesion.

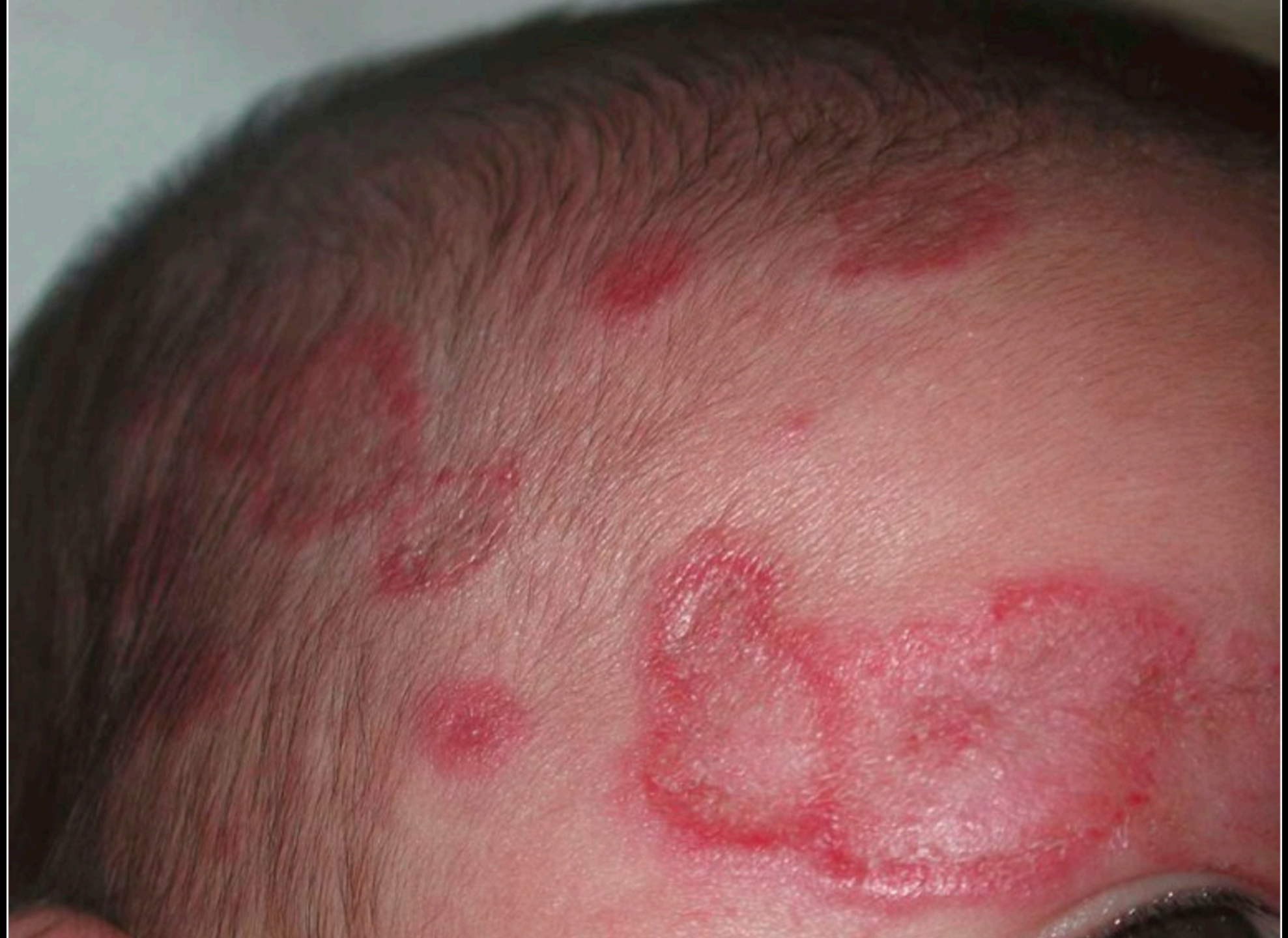


Neonatal Lupus Erythematosus (NLE)

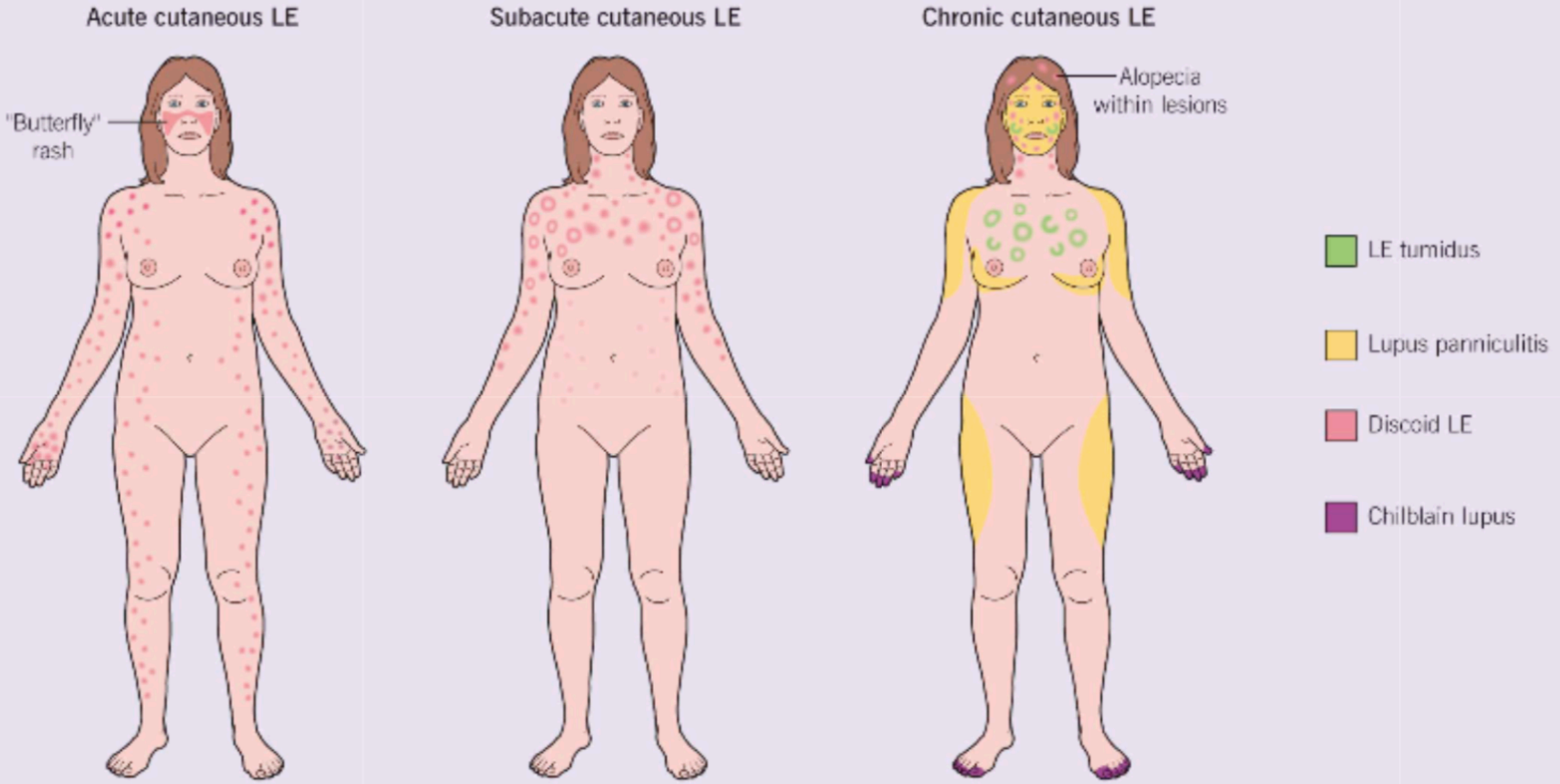
- May occur in infants whose mothers have anti-Ro autoantibodies.
- In Babies who have NLE, the SCLE-like lesions are histologically identical to those of SCLE in adults.
- Almost 100% of babies with NLE have **anti-Ro antibodies.**
- Unlike SCLE in adults, lesions have a predilection for the face (**Periorbital region**).
- Photosensitivity is very common in NLE, but sun exposure is not required for lesions to form. (lesions can be present at birth).
- Lesions typically resolve **without scarring**, although dyspigmentation and residual telangiectasias may develop.

Neonatal Lupus Erythematosus (NLE)

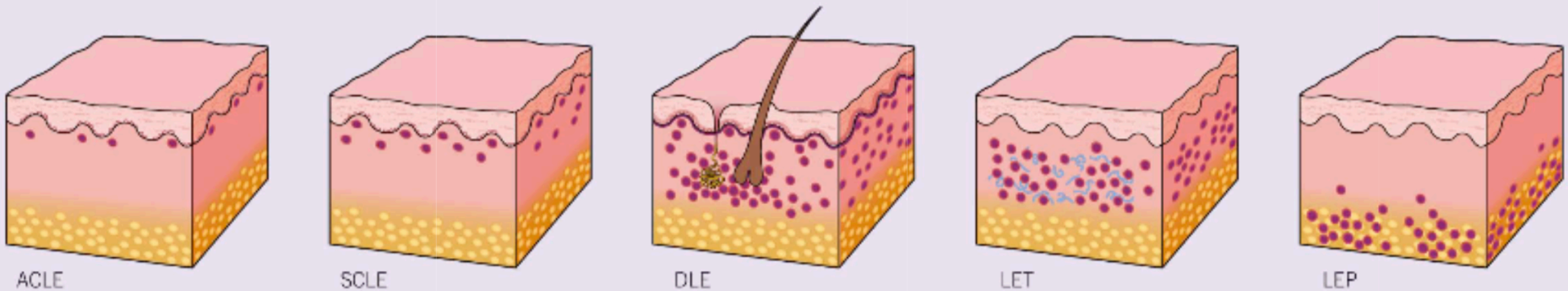
- The major extracutaneous findings are: Congenital **heart** block, **hepatobiliary** disease and **thrombocytopenia**.
- Heart block is almost always present at birth. Cardiomyopathy can occur in a small percentage of patients (neonatal period).
- Cardiac NLE has a mortality of 20% and two-thirds will require pacemakers.
- Hepatobiliary disease and thrombocytopenia, may present at birth or within the first few months of life.
- Hepatobiliary disease ranges from mild elevation of liver enzymes to liver failure.
- All NLE children should be evaluated for internal manifestations with a **physical exam** in addition to an **ECG, CBC and LFT**.



CHARACTERISTIC SITES OF INVOLVEMENT FOR THE THREE MAJOR SUBTYPES OF CUTANEOUS LUPUS ERYTHEMATOSUS



PREDOMINANT LOCATIONS OF INFLAMMATORY INFILTRATES IN SUBSETS OF CUTANEOUS LUPUS ERYTHEMATOSUS



Drug-Induced Lupus Erythematosus

Drug-induced lupus differs from SLE by the following features:

- Sex ratios are nearly equal.
- Nephritis and central nervous system features are not commonly present.
- **Anti-DsDNA –ve, Anti-Histone AB +ve**.
- When the drug is discontinued, the patient has resolution of clinical & laboratory abnormalities.
- Procainamide, Hydralazine, Penicillamine, Isoniazid, Quinidine, Anti-TNF, IFN…

Diagnosis

- History and Physical examination.
- Skin Biopsy (+/- DIF).
- Autoantibodies (ANA, Anti-DsDNA, Anti-Sm)
- CBC with differential.
- Urinalysis, BUN, Creatinine.
- ESR, CRP.
- Complement levels (C3, C4)

Skin Biopsy

- **Skin Biopsy (Lesional)**

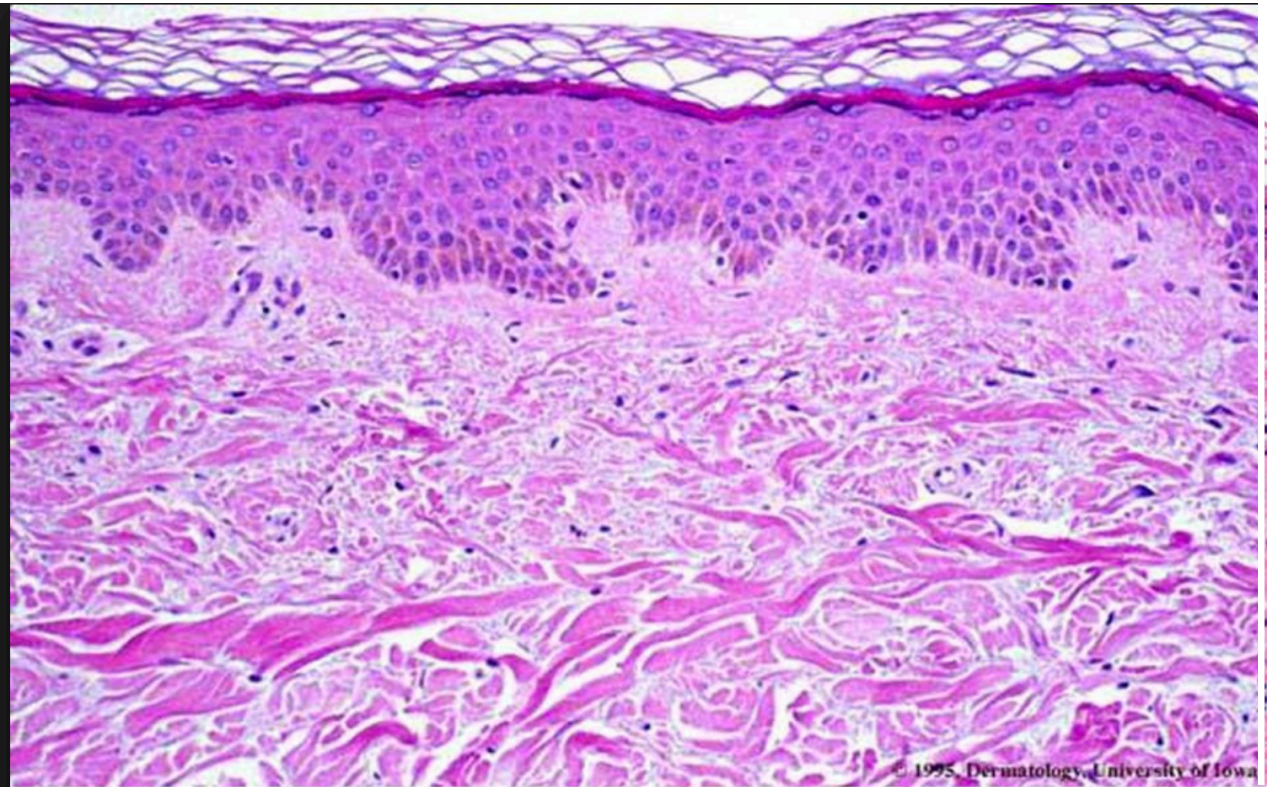
- The most valuable diagnostic test.

- **Direct Immunofluorescence (DIF)**

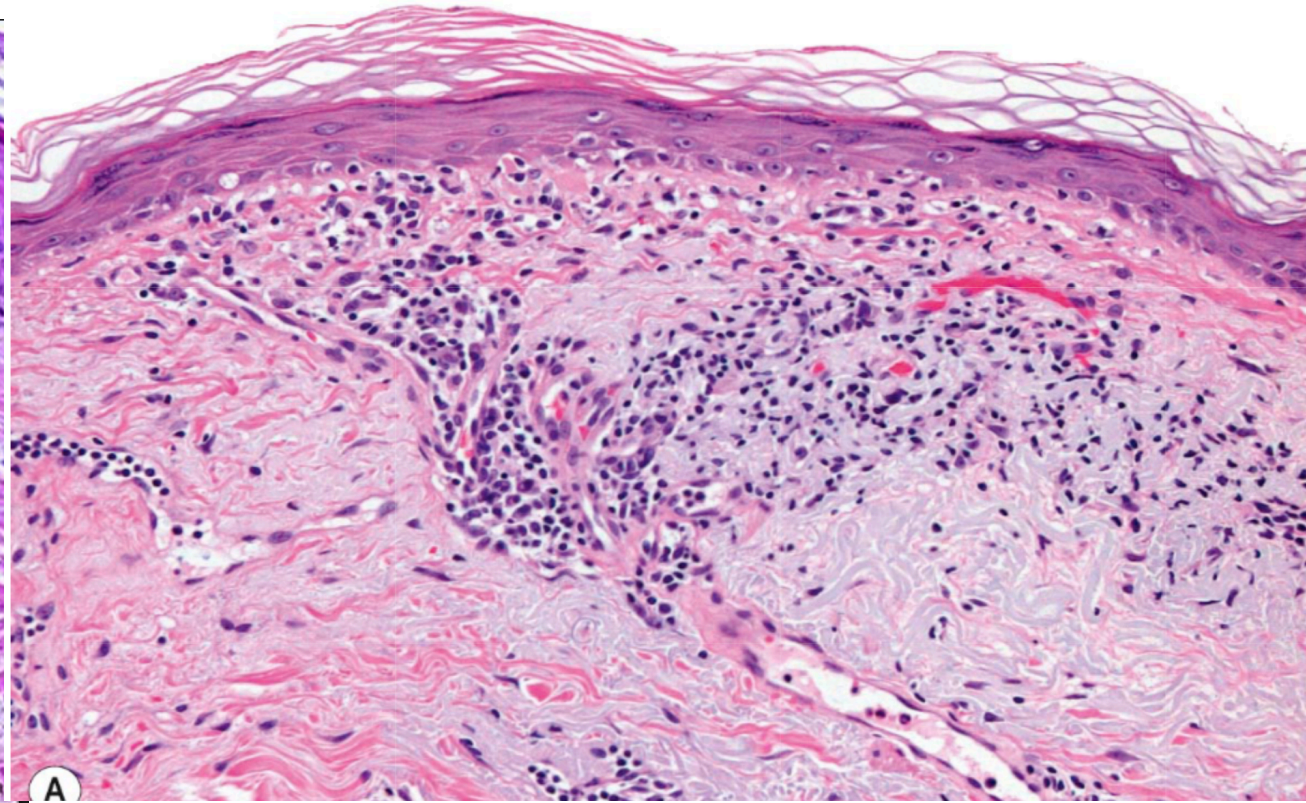
- Done to support the diagnosis, negative results does not exclude dx.
- Lesional DIF: Granular deposition of IgG/IgM in the DEJ and around hair follicles.
- Non-lesional DIF (Normal skin) is referred to as ''Lupus band'' test. Positive reaction usually indicates systemic SLE.

Skin Biopsy

Normal Skin

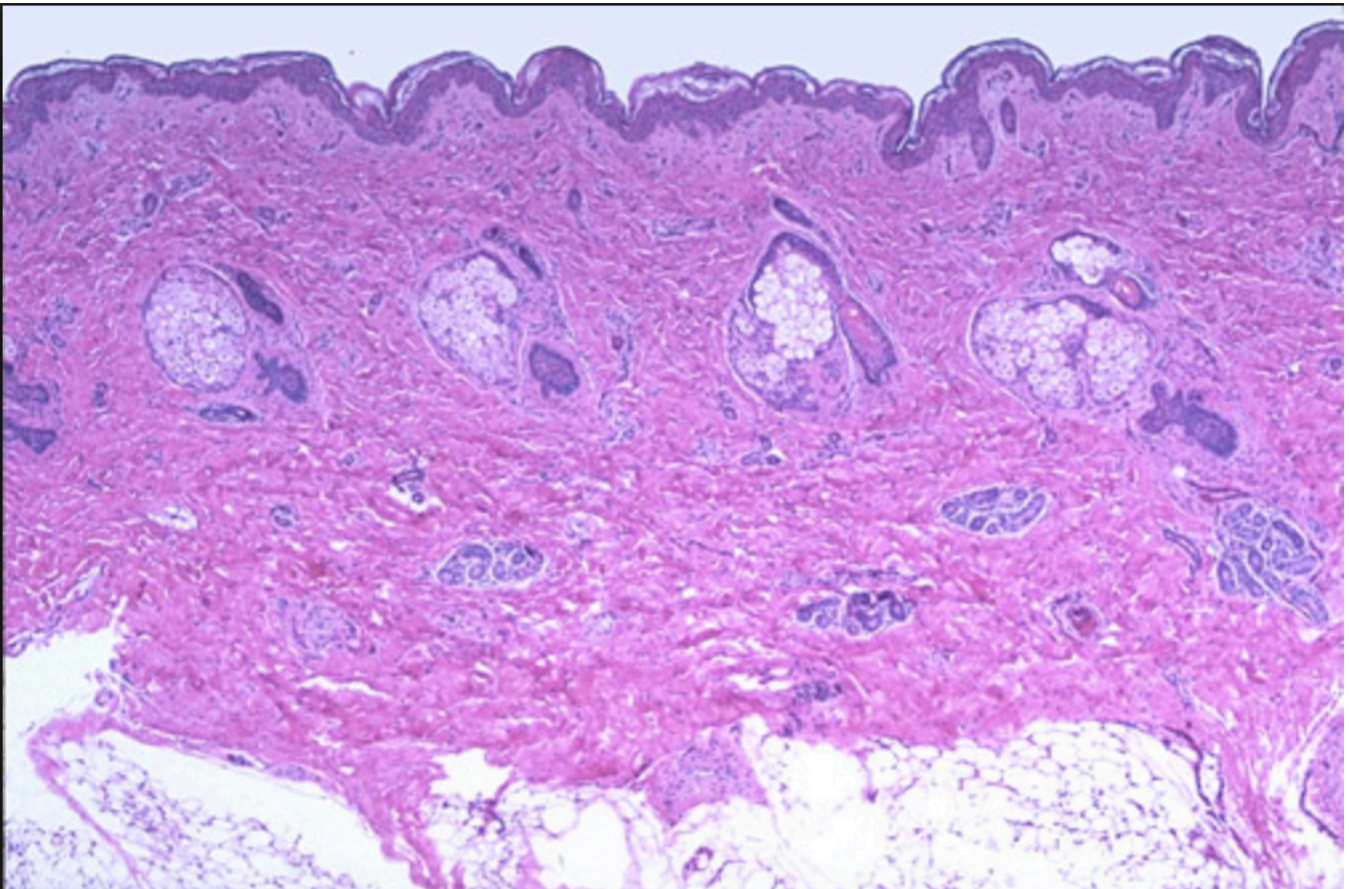


ACLE

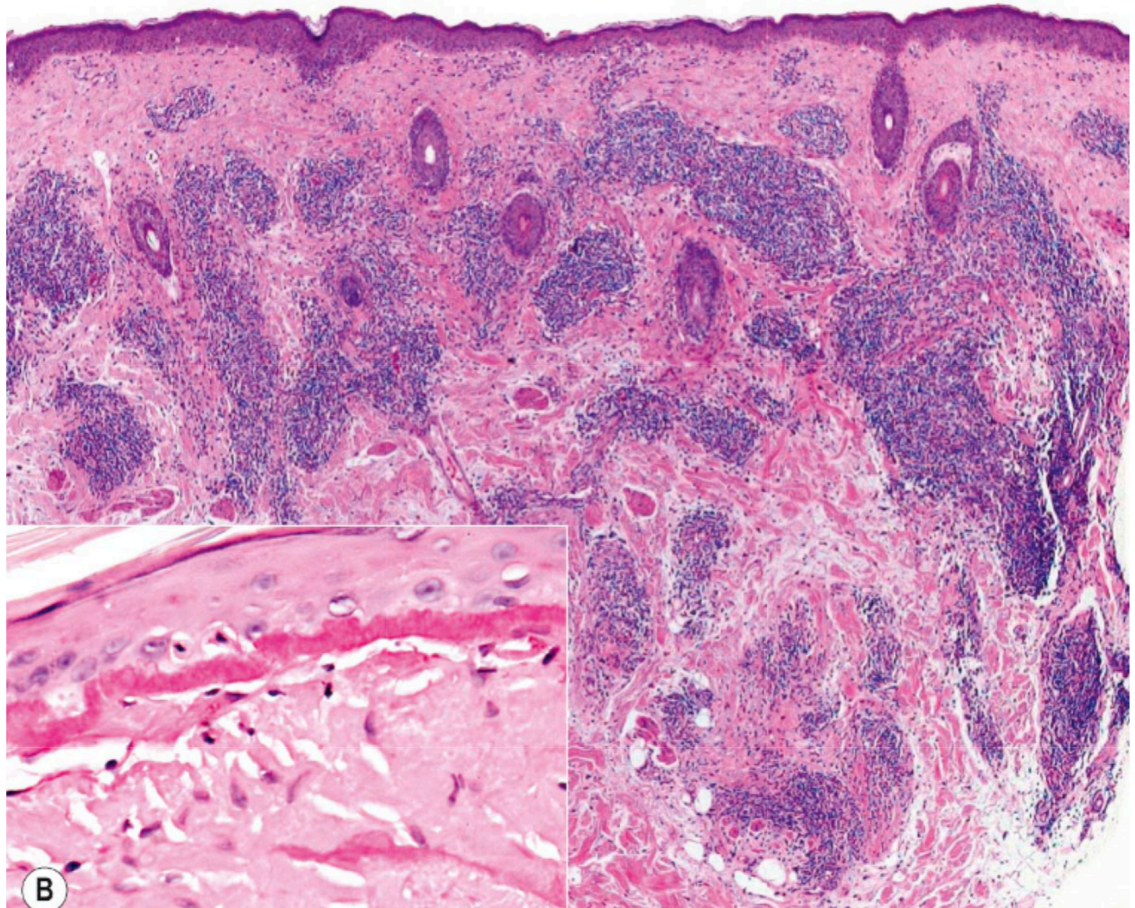


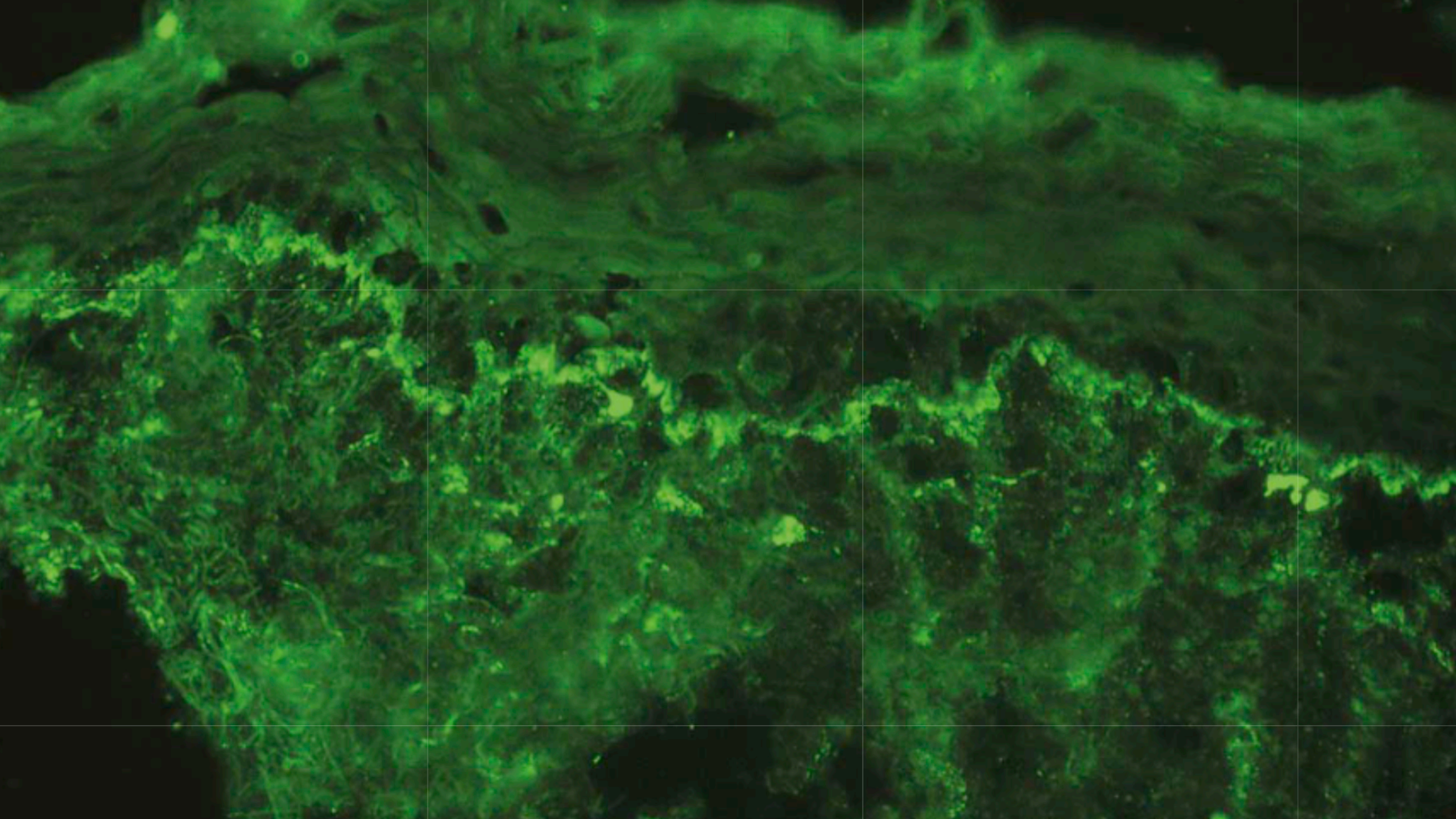
Skin biopsy

Normal skin



DLE





Autoantibodies

- **Specific** but not Sensitive:
- Anti-dsDNA (lupus nephritis)
- Anti-Sm

- **Sensitive** but not specific:
- ANA (>95%)
- ssDNA (70%)

- Drug-induced lupus:
- Anti-Histone Ab

Diagnosis

- **<u>ACR criteria for diagnosis of SLE (4 out of 11):</u>**

1) Malar Rash
2) Discoid Rash
3) Photosensitivity
4) Oral ulcers
5) Arthritis
6) Serositis (Pleuritis OR Pericarditis)
7) Renal disorder (Proteinuria OR Cellular casts)
8) Neurologic disorder (Seizures OR Psychosis)
9) Hematologic disorder (Anemia OR leukopenia OR lymphopenia OR thrombocytopenia)
10) Immunologic disorder (Anti-DNA OR Anti-Sm OR antiphospholipid AB's)
11) Antinuclear antibody (ANA)

Treatment

1) Sun protection
2) Topical therapy

- Topical steroids
- Topical Calcineurin inhibitors
- ILK injections

3) Systemic Therapy

- Antimalarials (Hydroxychloroquine, Chloroquine, Quinacrine)
- Others (Retinoids, Thalidomide, Mycophenolate, azathioprine, systemic steroids….)

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DERMATOMYOSITIS

Dermatomyositis

- A relatively rare disease of presumed autoimmune pathogenesis that mainly affects the skin and muscles.
- Bimodal age distribution.
- Affects women two to three times more than men.
- ¼ of adults with DM have an associated **occult malignancy**.
- Skin manifestations often precede the onset of symptoms related to malignancy.
- Some pts do not have evidence of muscle inflammation (Amyopathic dermatomyositis)

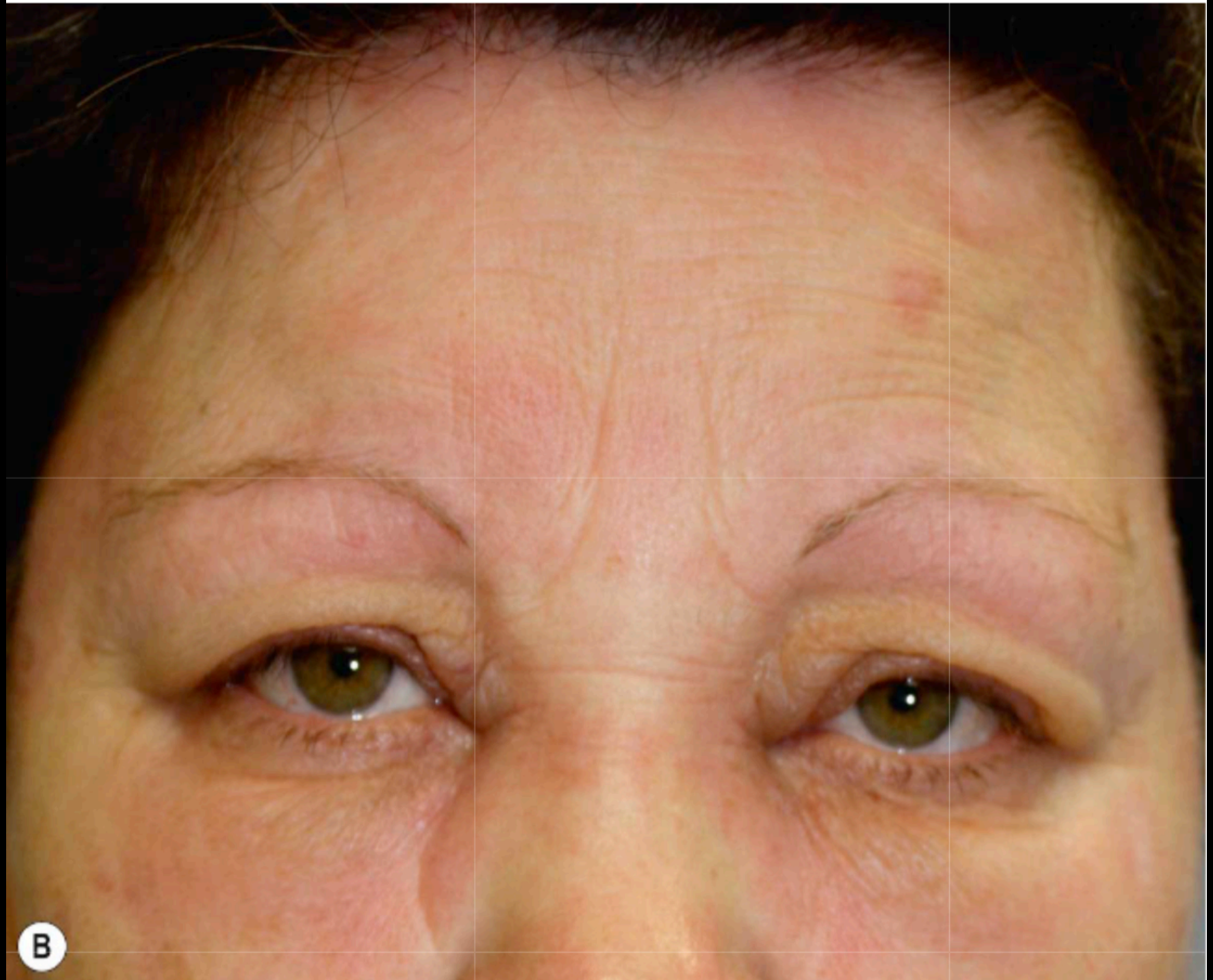
Cutaneous Manifestations of Dermatomyositis

- **<u>Common:</u>**

- Heliotrope sign.
- Eyelid edema.
- Gottron's papules.
- Gottron's sign.
- Photo-distributed Poikiloderma (V-sign, Shawl sign, Facial erythema).
- Psoriasiform scalp rash.
- Nailfold changes (Ragged cuticles Nailfold telangiectasia).
- Calcinosis Cutis (Juvenile DM).
- Pruritis.

Cutaneous Manifestations of Dermatomyositis

- **<u>Uncommon:</u>**
- Cutaneous erosions or ulcerations
- Holster sign
- Flagellate Erythema
- Vesicobullous lesions
- Exfoliative erythroderma.
- Panniculitis
- Gingival Telangiectasia
- Pustular eruption of the elbows and knees
- Lipoatrophy
- Small vessel vasculitis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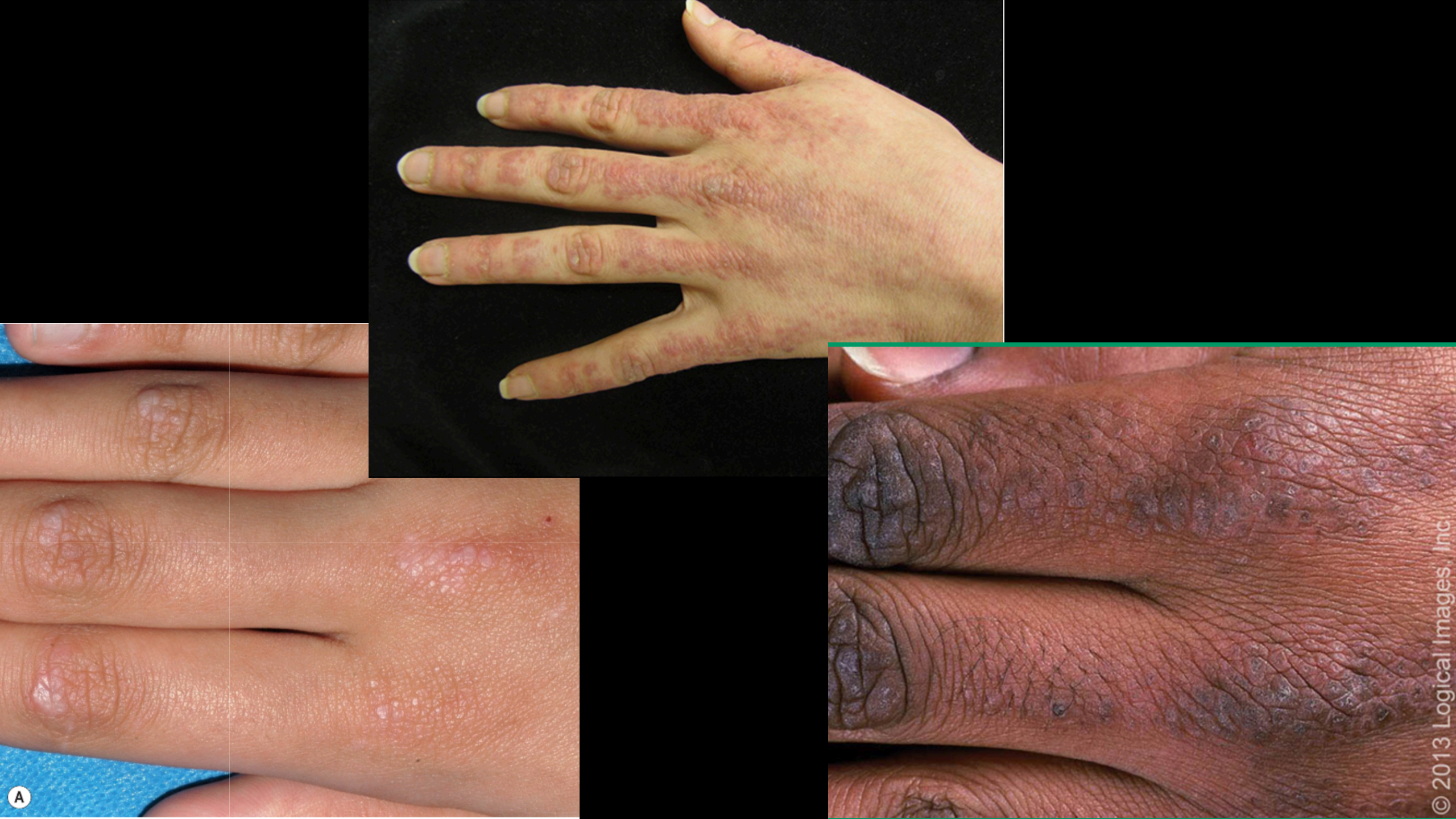
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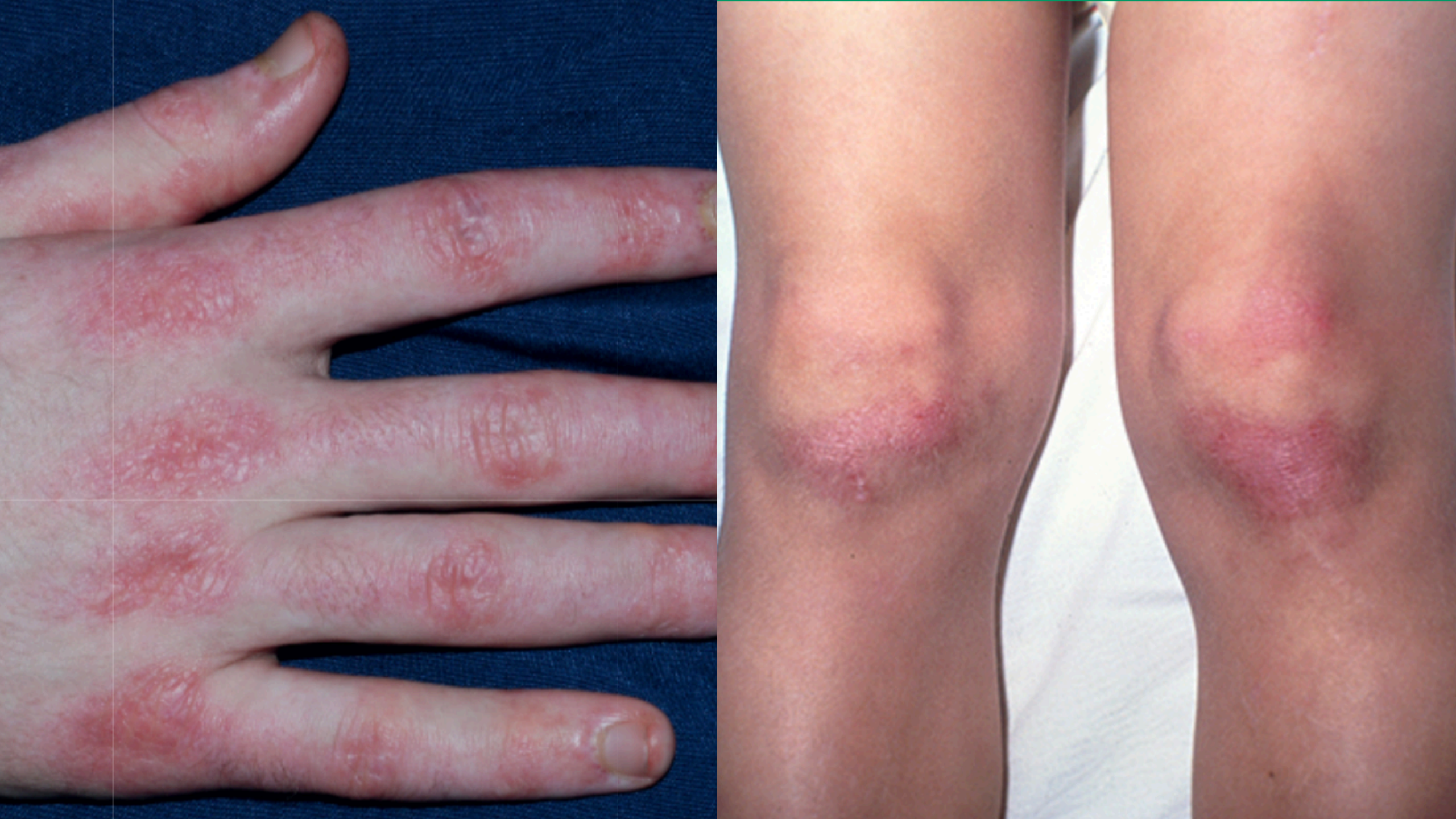
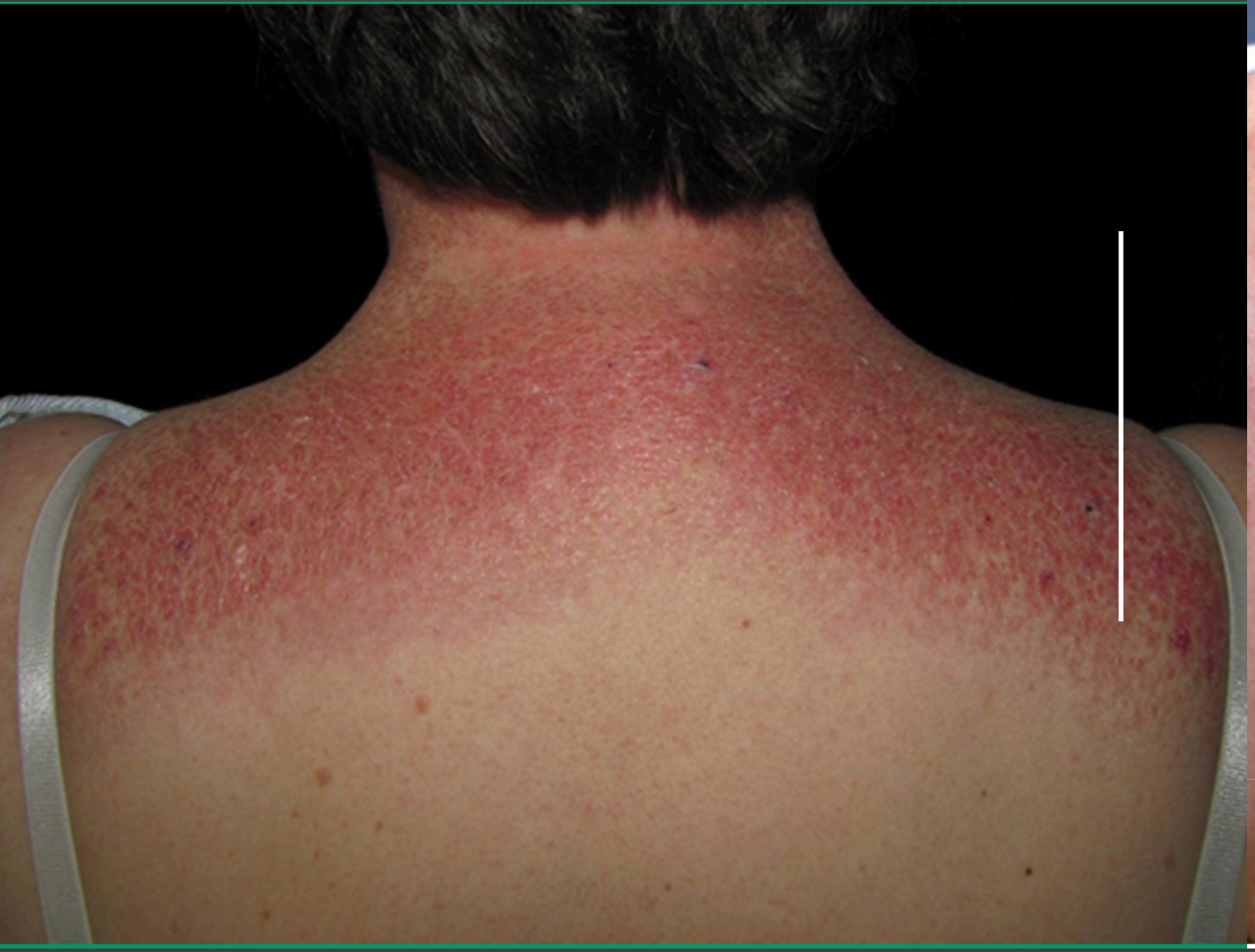
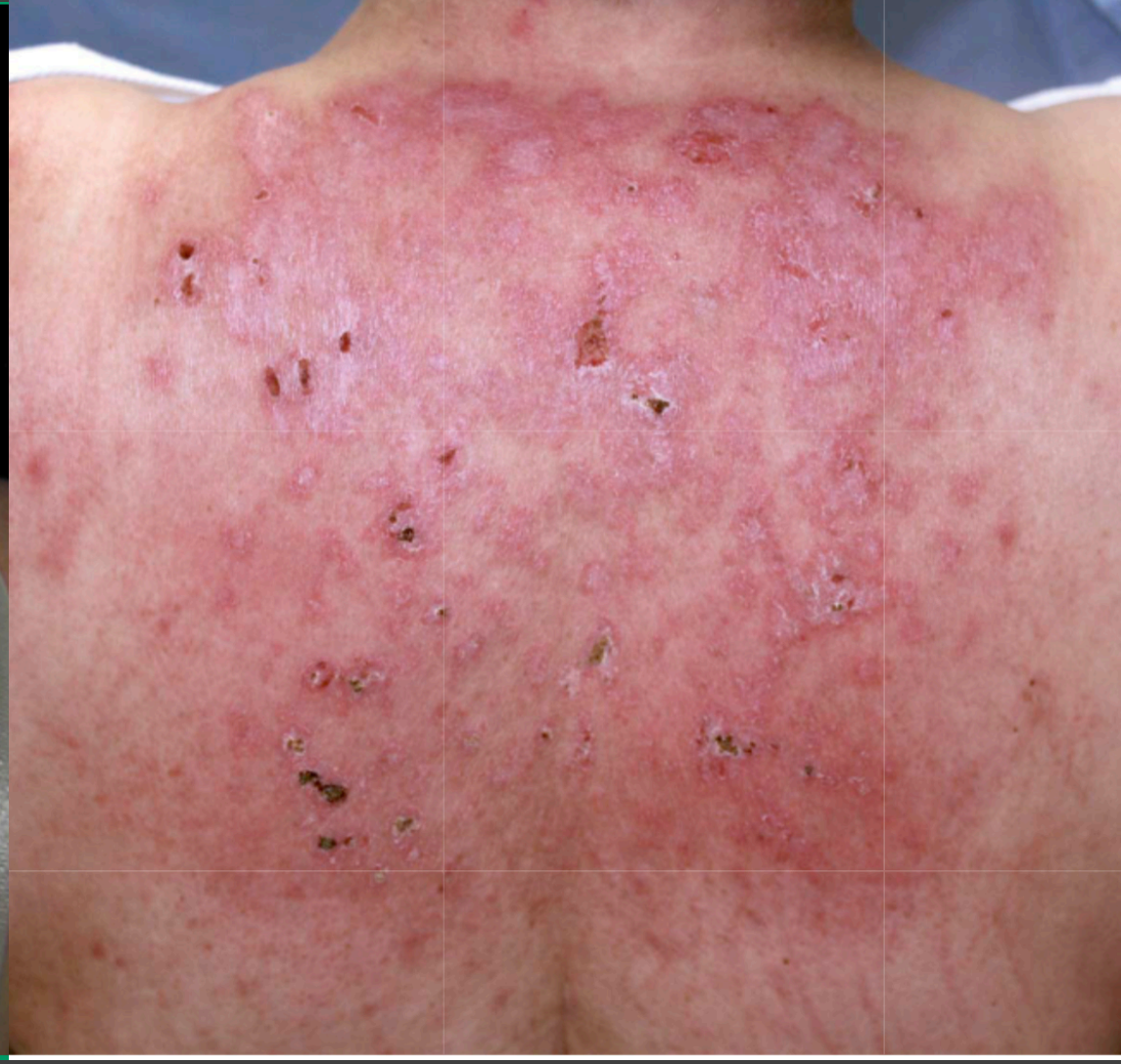
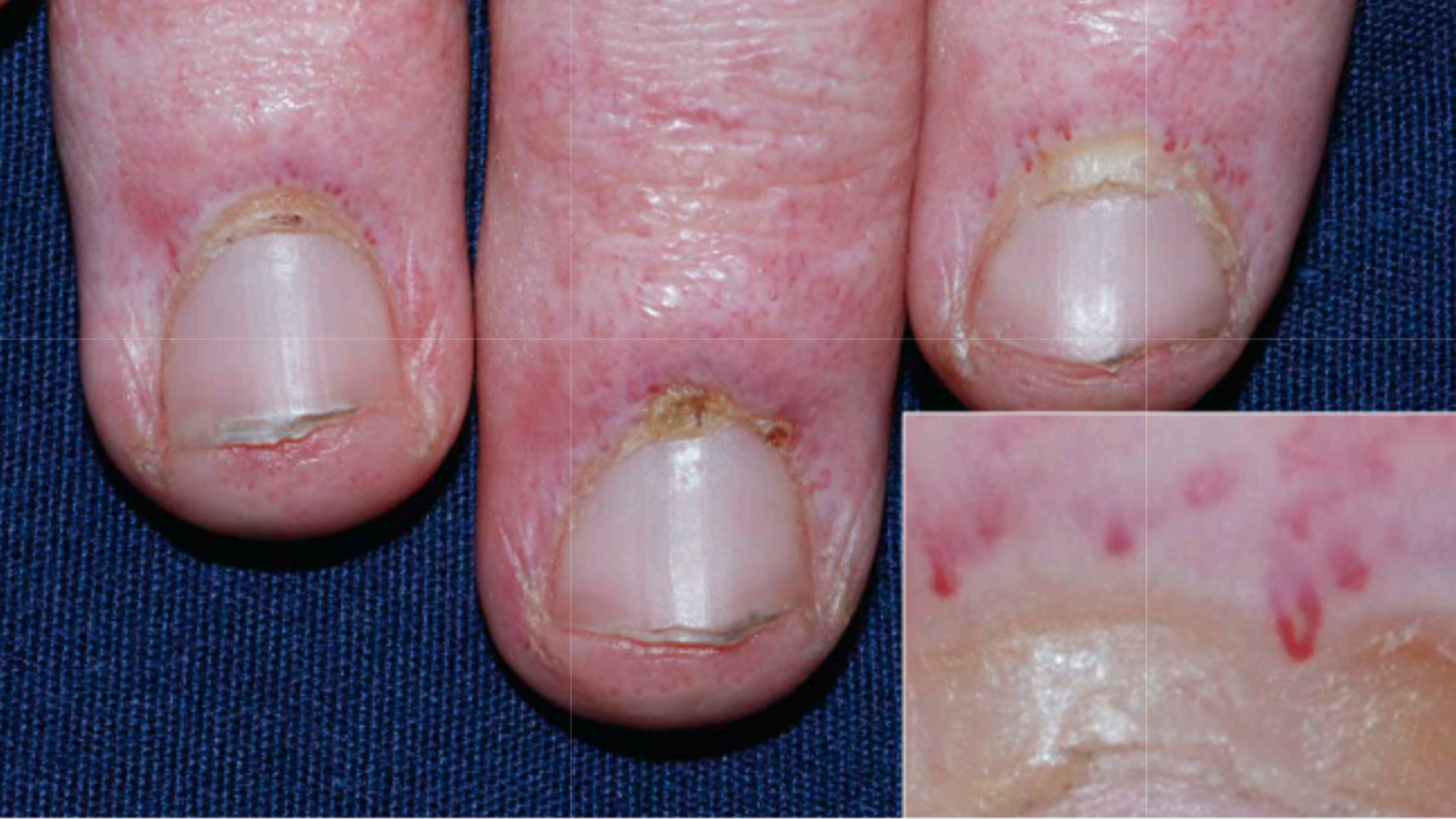
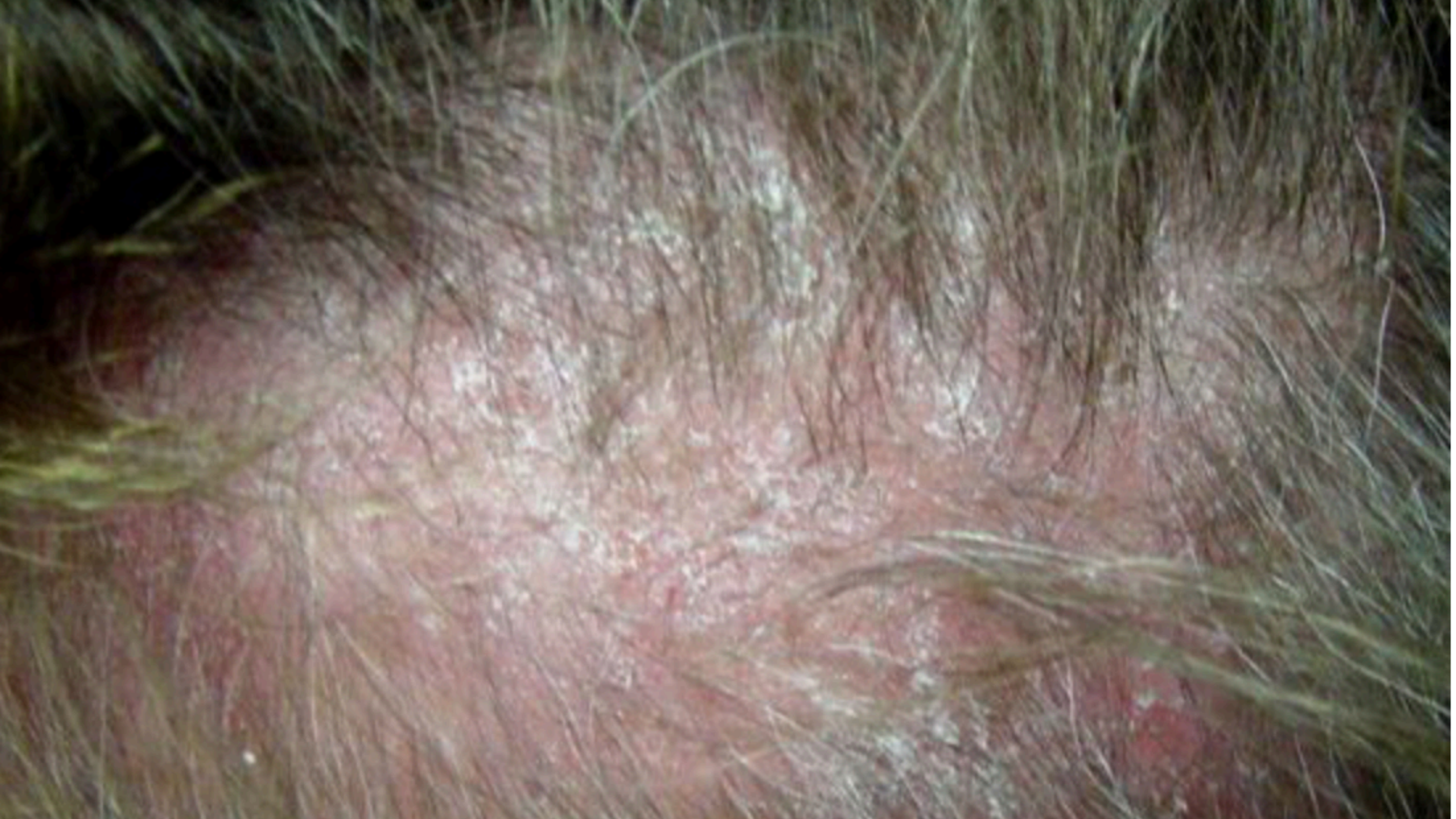


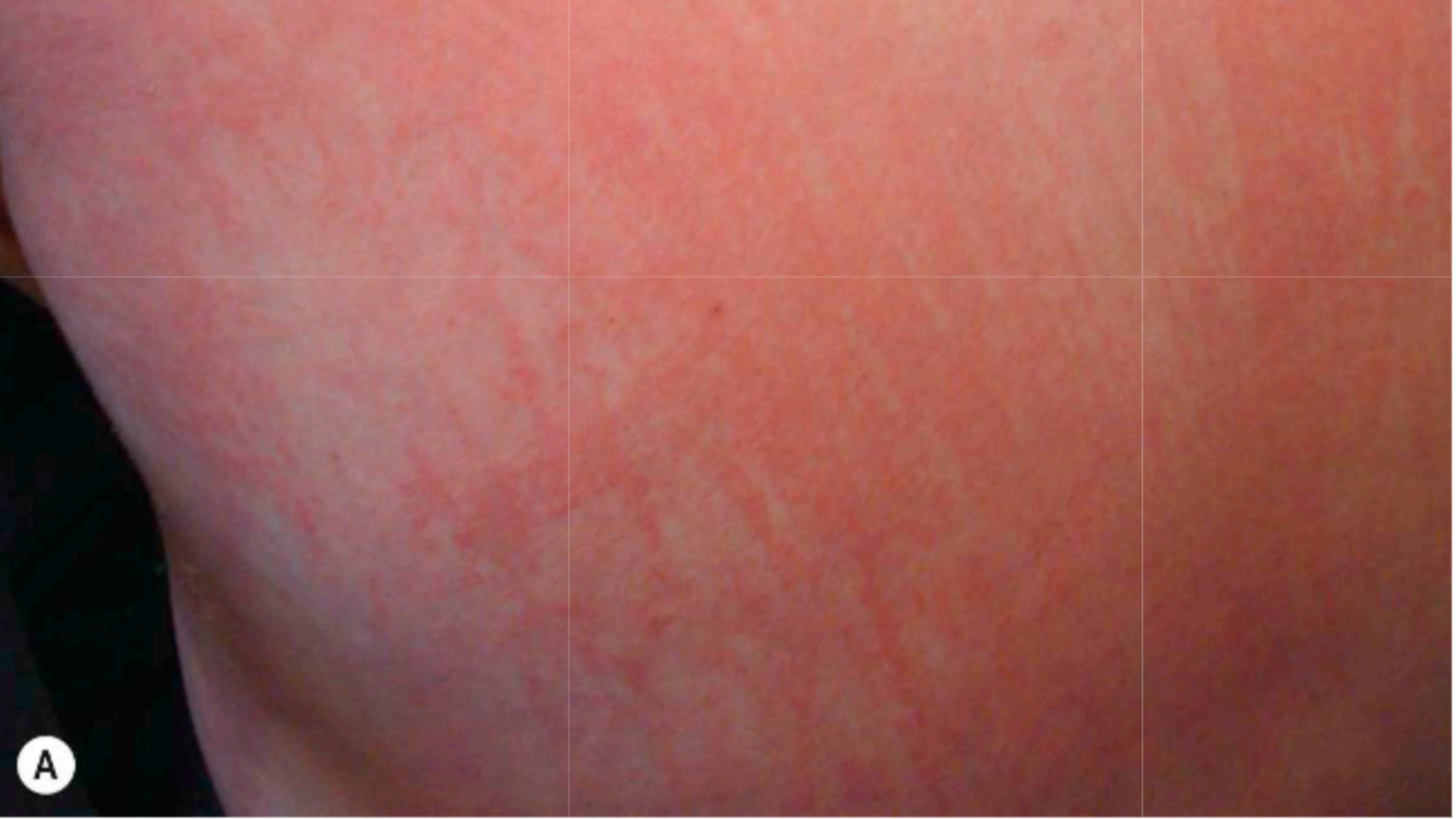




Shawl sign



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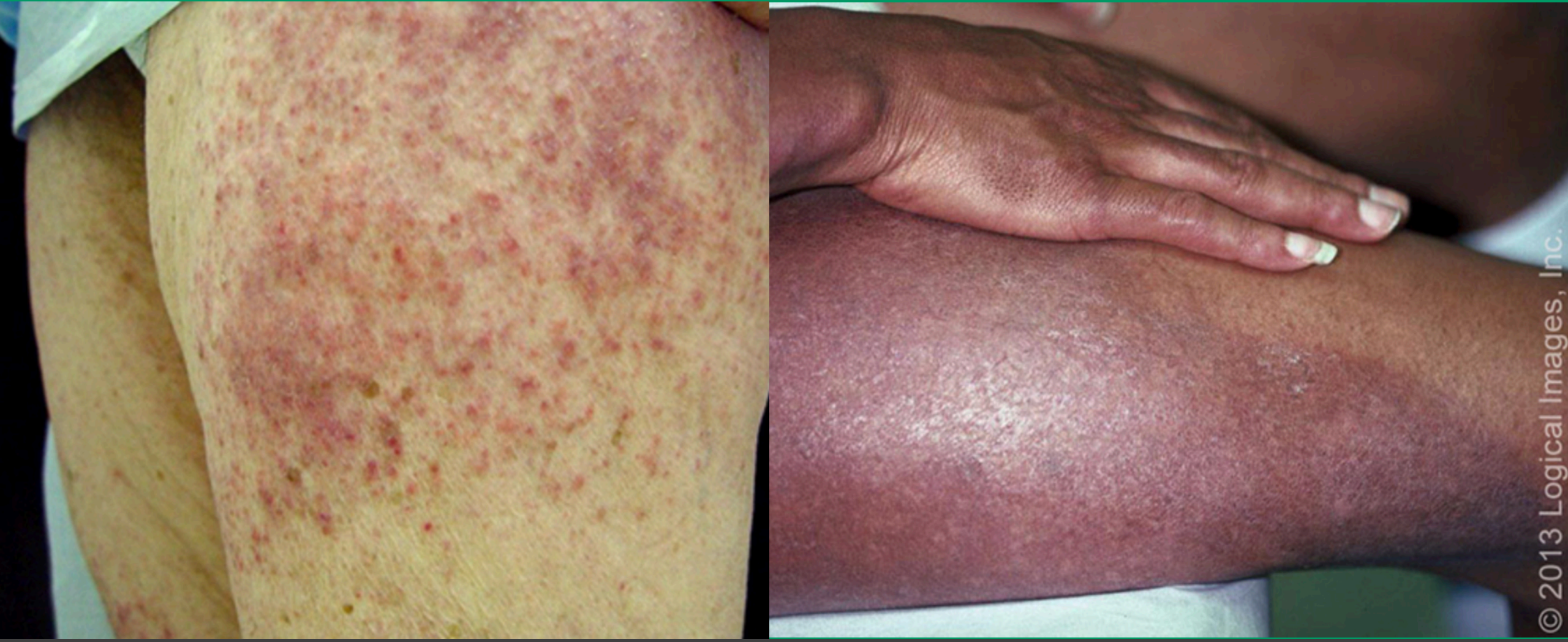

Holster sign

Systemic manifestations of Dermatomyosisits

- Myopathy: affects **proximal** muscle groups, mainly the extensor groups (Triceps and quadriceps) in a symmetric fashion.
- Calcinosis: **More common in Juvenile DM**, favors sites of trauma and can be painful.
- Pulmonary disease: 15-30%, generally presents as diffuse interstitial fibrosis. Patients may also develop ARDS.
- Cardiac disease: Usually asymptomatic (Arrhythmias, conduction defects)
- Gastrointestinal: Symptoms such as dysphagia should prompt investigation for overlap with scleroderma.

Malignancy

- 10% to over 50% in adults.
- Amyopathic DM also appears to be at increased risk of malignancy.
- Most common are: **Ovarian**, and **colon** cancer but can include: breast, lung, gastric, pancreatic, lymphomas.
- The risk of malignancy may return to normal after 2-5 years.
- Screening:
  - Urinalysis, occult blood stool testing.
  - Serum PSA (men), Serum CA125 (women)
  - Mammogram & Transvaginal U/S (women)
  - CT of chest, abdomen and pelvis.
  - Colonoscopy if age appropriate or iron deficiency anemia or symptoms.
  - Upper endoscopy if colonoscopy negative in the setting of iron def. anemia or symptoms.

Evaluation

- History, physical exam.
- Skin: Biopsy (suggestive but not diagnostic)
- Serology: Autoantibodies.
- Muscle: Serum CK, Aldolase, EMG, muscle biopsy)
- Pulmonary: PFT, chest X-ray and/or high resolution chest CT.
- Cardiac: ECG, if symptomatic → Echo.
- Esophageal: If symptomatic → Barium swallow.
- Malignancy screening.

Autoantibodies

- High specifity for DM/PM:
- P155 → increased risk of malignancy.
- Mi-2 → good prognosis.
- Jo-1 (20%) → Antisynthetase syndrome.
- SRP → Fulminant DM, cardiac involvement.

- Low Specifity for DM/PM:
- ANA (40%)

Treatment

- Systemic therapy:
- Oral prednisone, slow taper (50% by 6 months, zero by 2-3 yrs)
- Methotrexate
- Others: IVIG, Azathioprine, cyclosporine..

- Cutaneous DM or amyopathic DM:
- Topical steroids, topical calcineurin inhibitors.
- Antimalarials.
- Methotrexate.
- Surgical excision or diltiazem can be used to treat calcinosis cutis.

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  - Lupus Erythematosus Tumidus
  - Lupus Panniculitis
  - Neonatal Lupus Erythematosus
- **Dermatomyositis**
- **Scleroderma (systemic sclerosis)**
- **Morphea & Lichen Sclerosus**
- **Other Rheumatologic Disease**
  - Still's disease
  - Relapsing Polychondritis
  - Sjogren's syndrome
  - Mixed connective tissue disease

Systemic Sclerosis

Systemic Sclerosis

- An autoimmune connective tissue disease of unknown etiology that affects the skin, blood vessels and internal organs.
- Two major clinical subtypes: **Limited** and **diffuse**.
- Women are affected 3-4 times as often as men.
- Onset typically between 30-50 years old.
- Significant mortality rate, overall 10 yr survival of less than 70%.

Diagnostic criteria of systemic sclerosis

- Either one **Major** criterion

- Symmetric cutaneous sclerosis proximal to the MCP or MTP joints.

- Or Two or more **Minor** criterion:

- Sclerodactyly.
- Digital pitted scars.
- Loss of substance from finger pads.

Clinical types of Systemic Sclerosis

- Two major clinical subtypes:

1) Limited:

- Induration is limited to the distal extremities and face.
- Tend to develop internal involvement late in the course of disease (decades)

2) Diffuse:

- Distal and proximal of the extremities plus the trunk and face
- Typically associated with early internal organ involvement (within 5 yrs of onset) and a worse prognosis.

CREST syndrome

- Describes the clinical features in a subset of patients with limited SSc.

Calcinosis

Raynaud's phenomenon

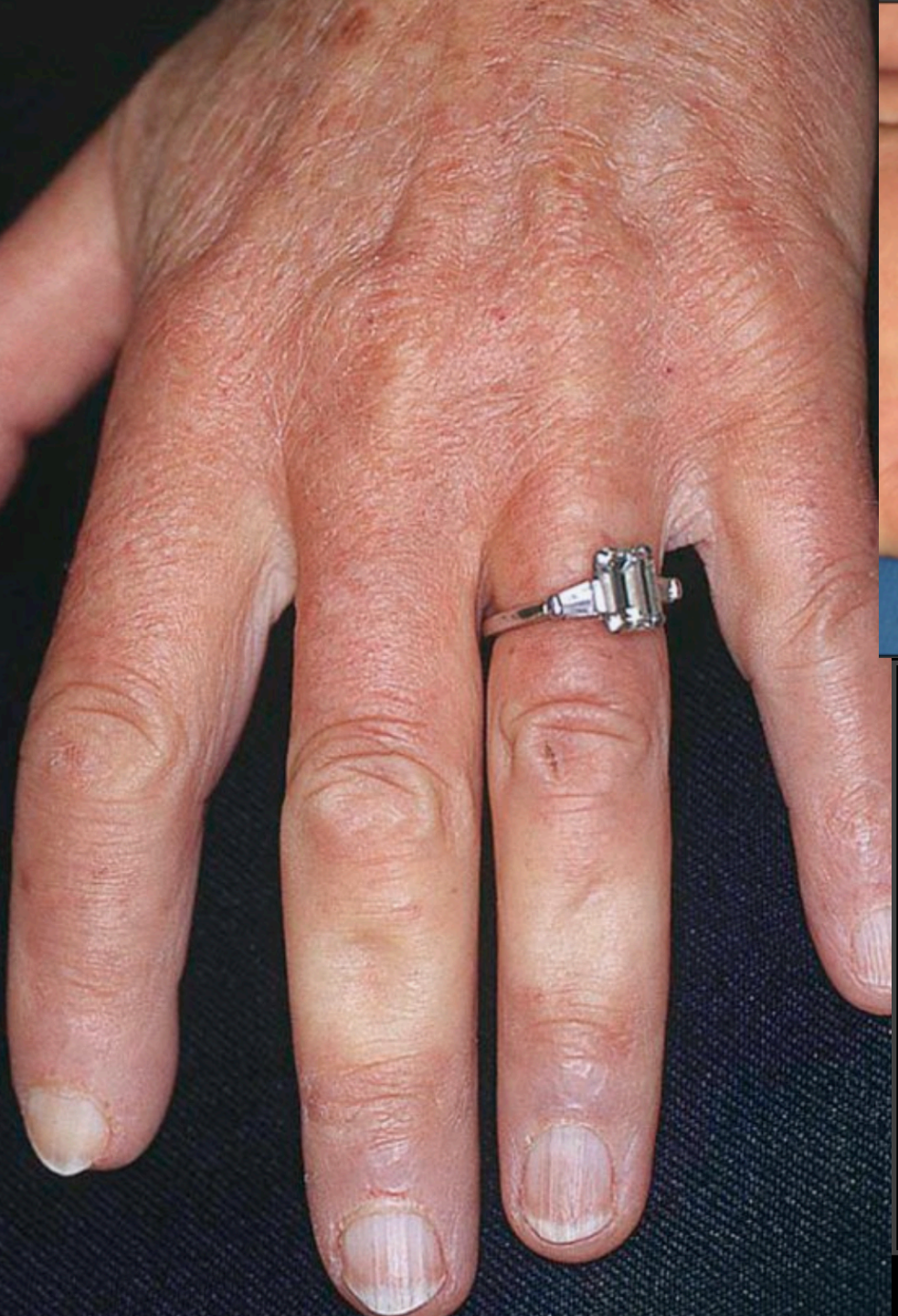
Esophageal involvement

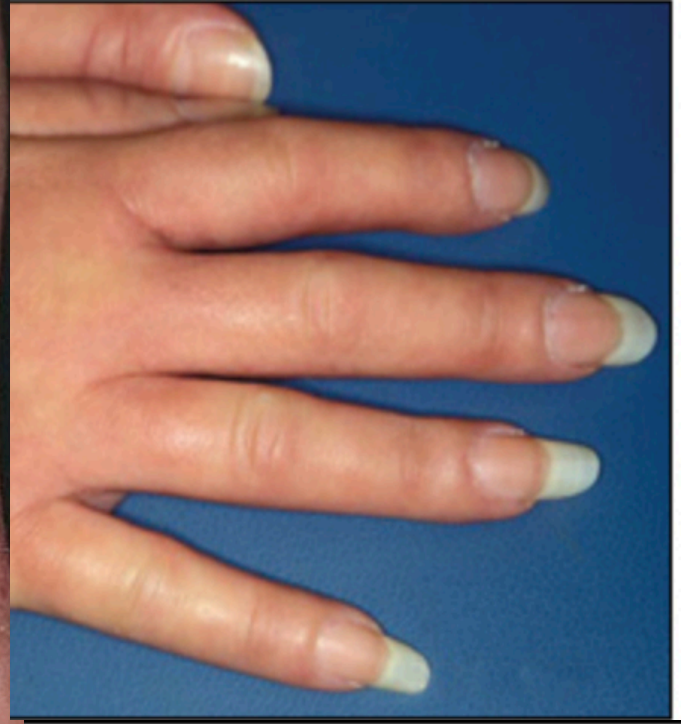
Sclerodactyly

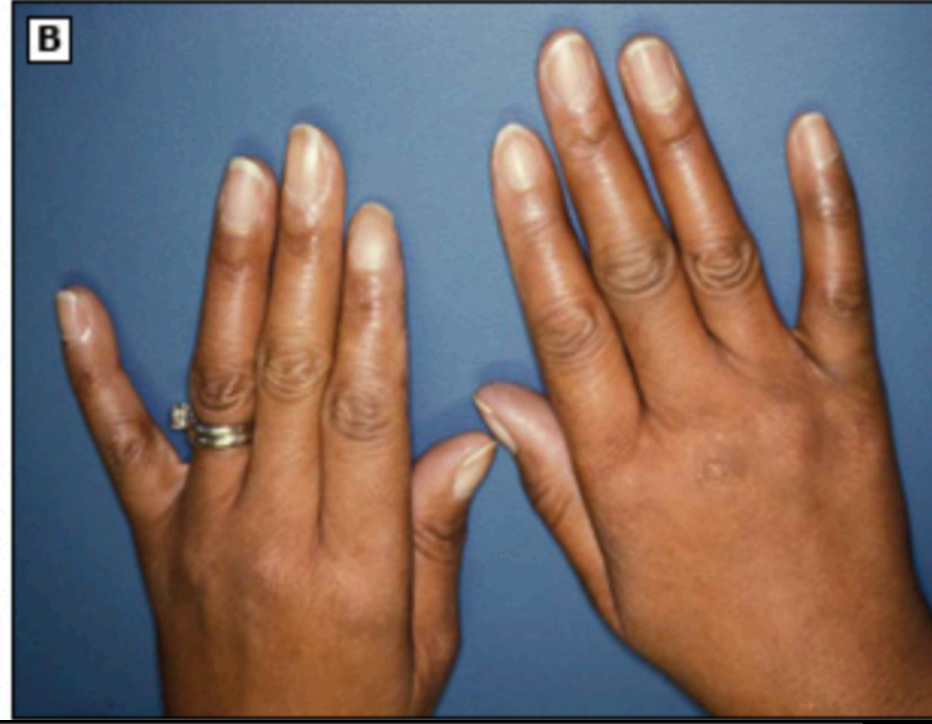
Telangiectasia

Cutaneous features of systemic sclerosis

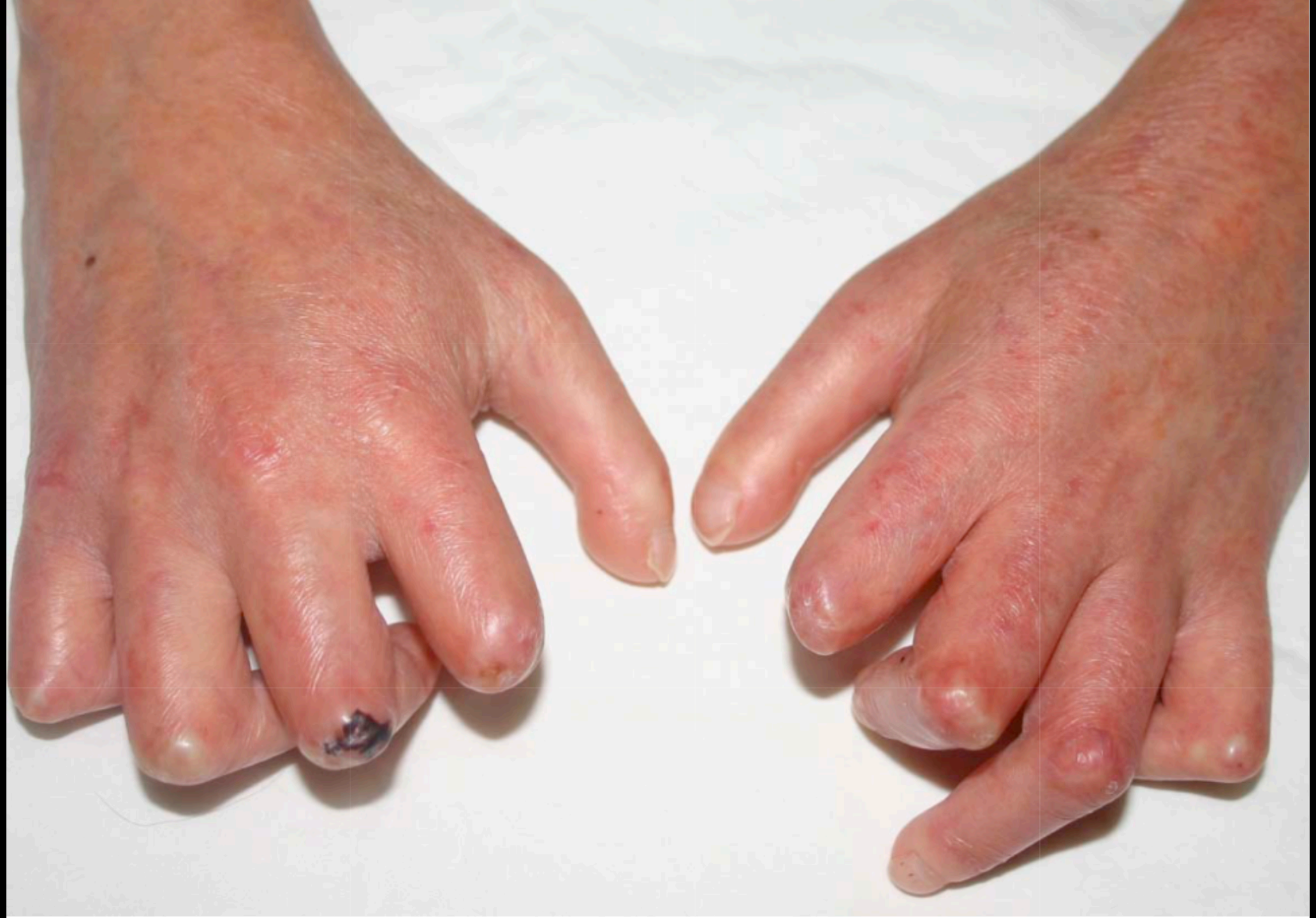
- **Digits:** Early pitting edema, hardening, taut and shiny appearance.
- **Face:** Beaked nose, microstomia and a youthful appearance.
- **Dyspigmentation:** Salt & pepper.
- **Telangiectasias:** Matted (Squared off) on the Face, lips and palms.
- **Nailfold capillary abnormalities:** in 90% (Capillary drop out alternating with dilated loops).
- Dystrophic Calcinosis Cutis.
- Raynaud's phenomenon.
- Cutaneous ulcers

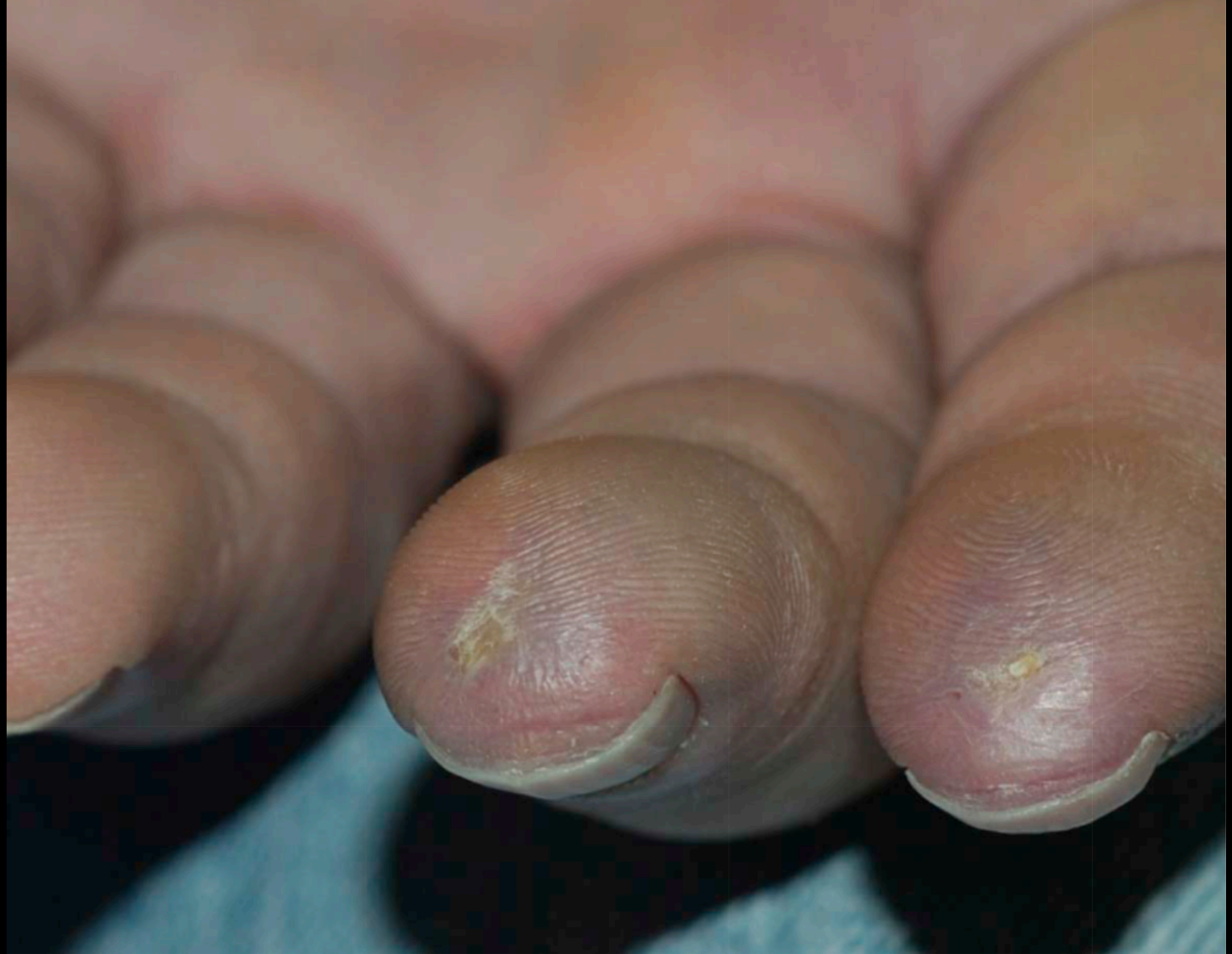


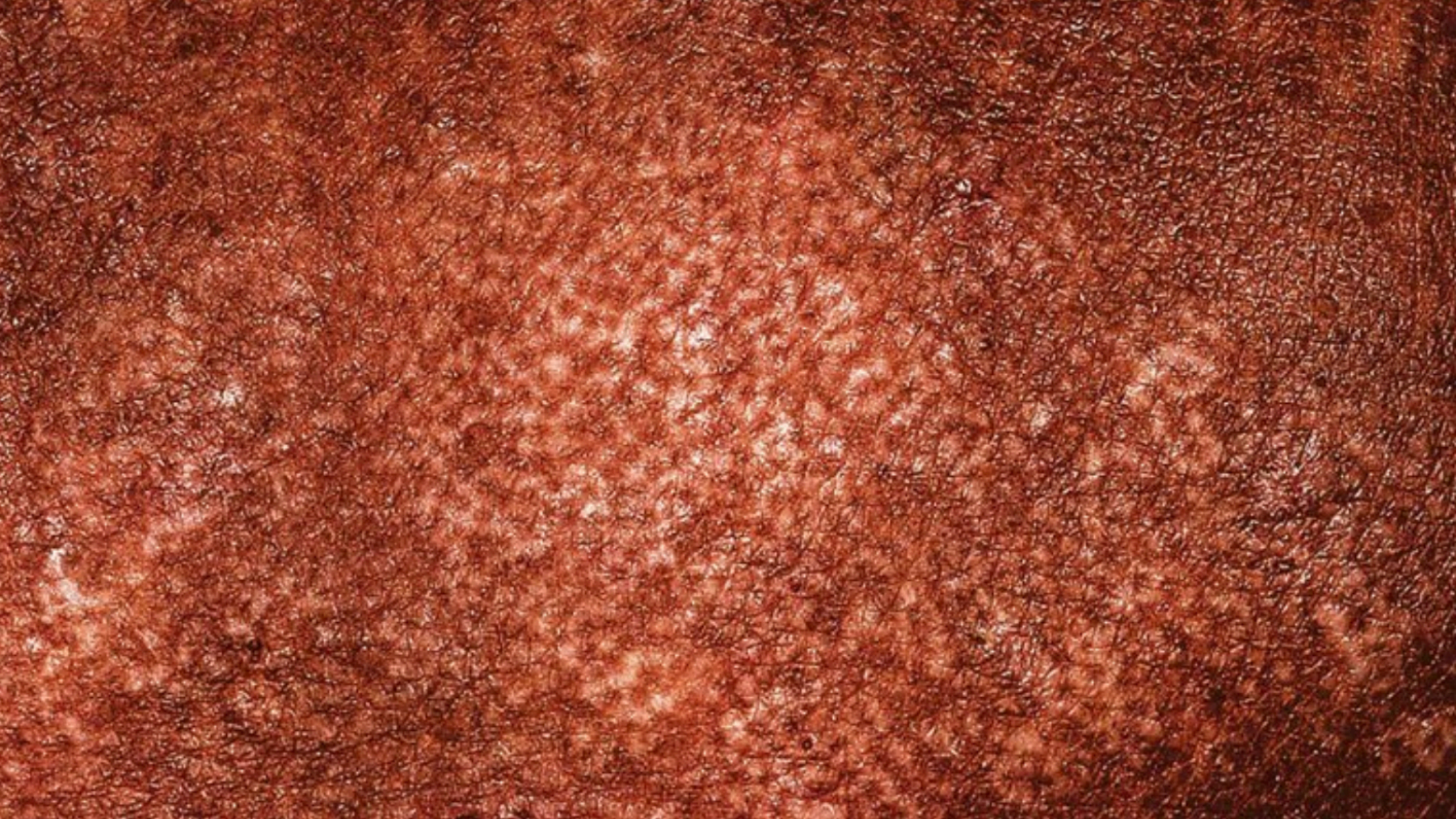


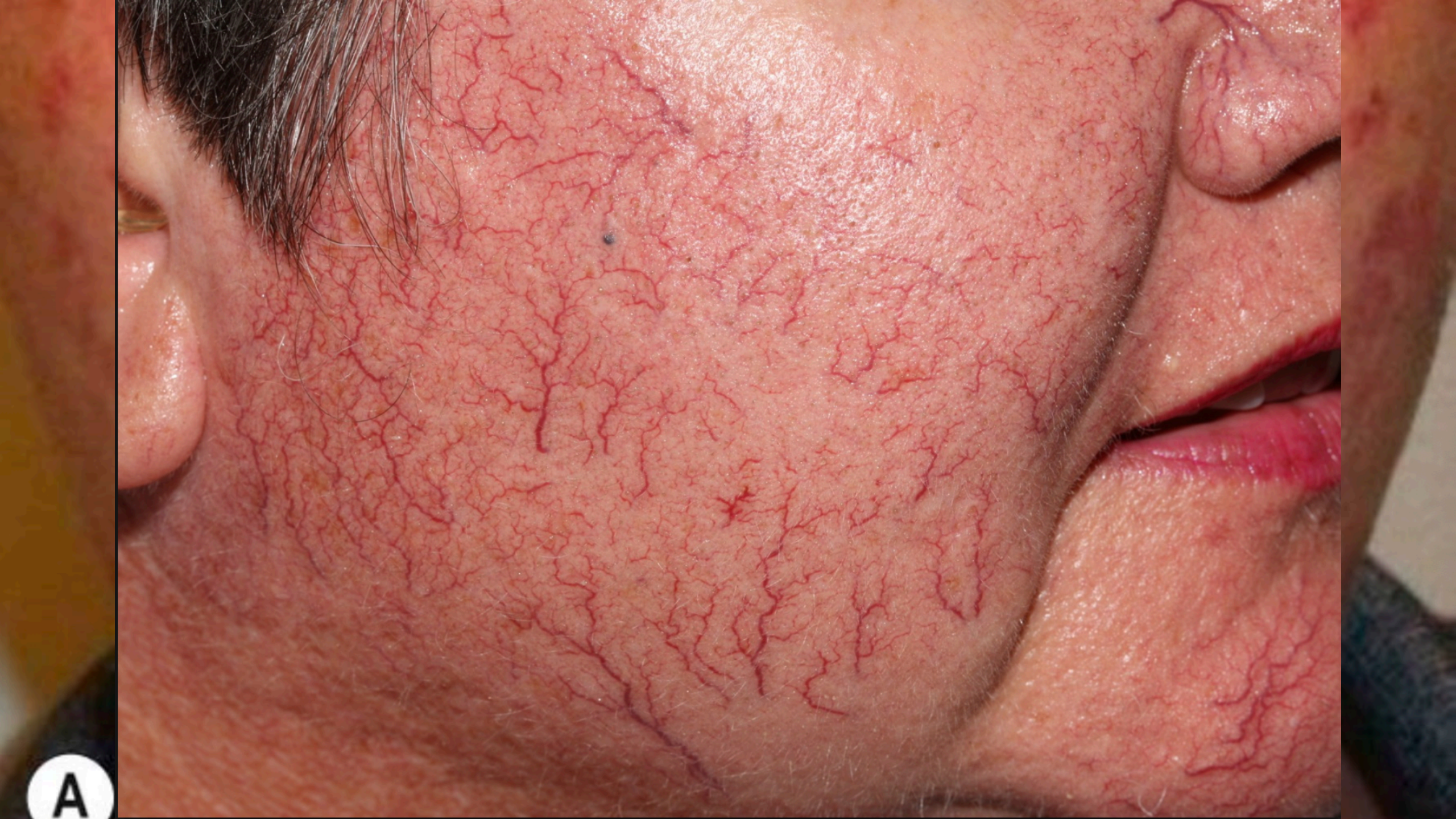


Early phase of SSc





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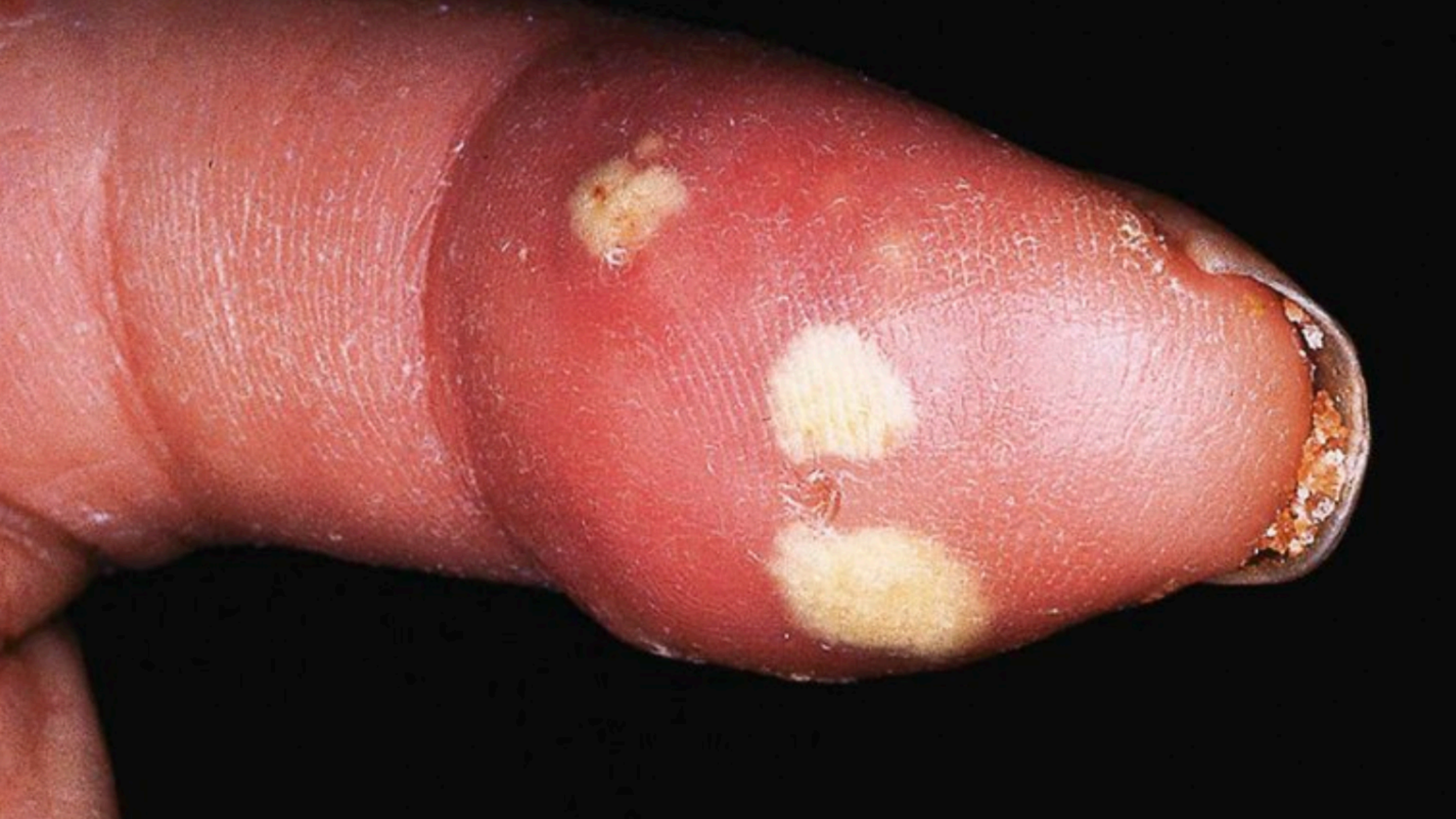
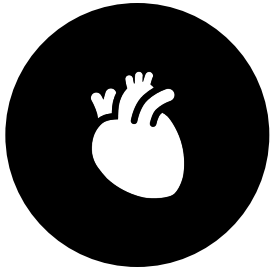
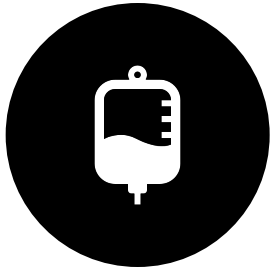


Extracutaneous features of Systemic Sclerosis

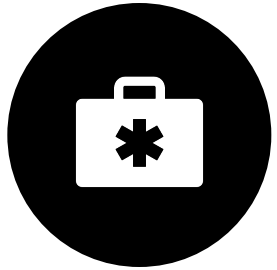
PULMONARY



CARDIAC



RENAL



GASTROINTESTINAL

Autoantibodies

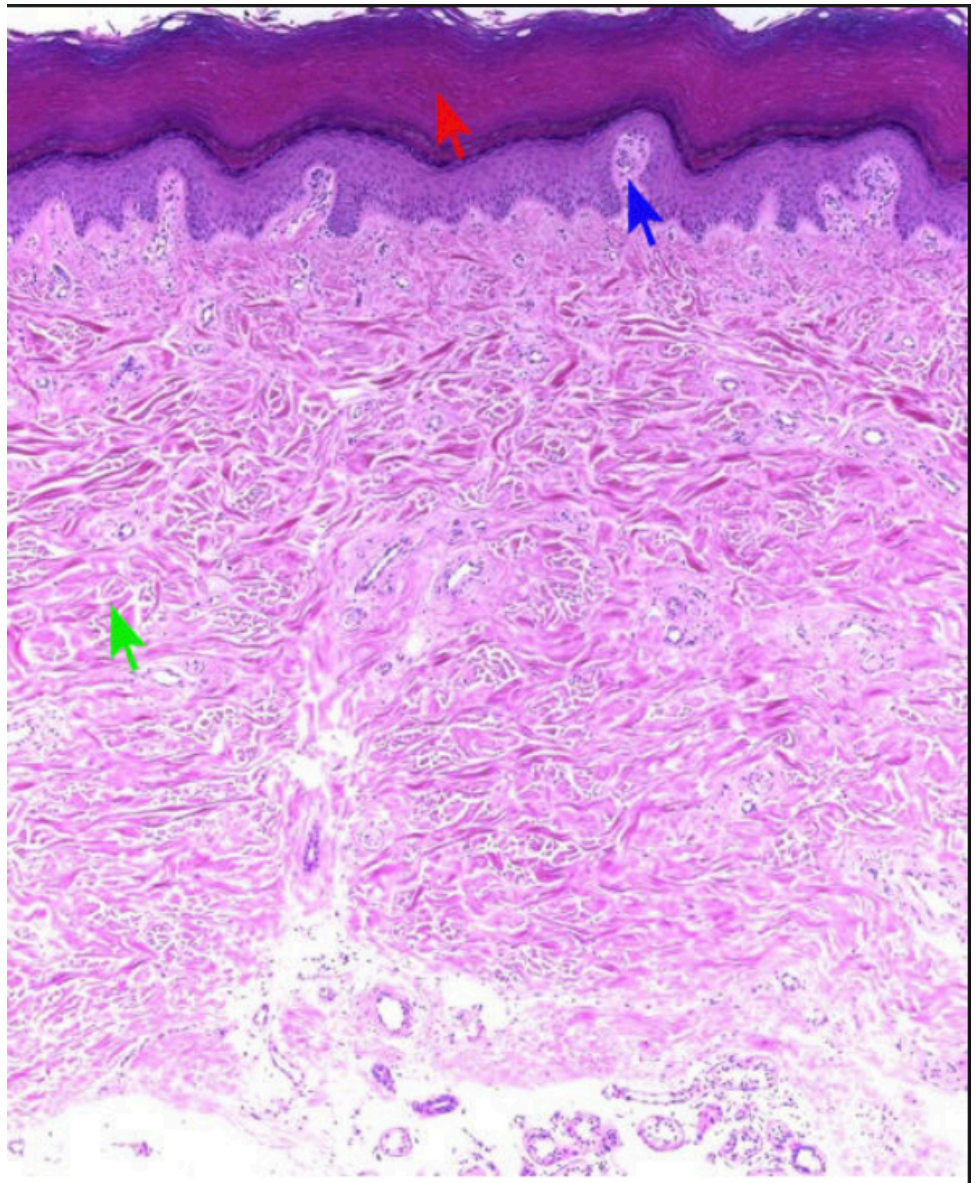
- ANA (Nucleolar and speckled patterns).
- Topoisomerase (Scl-70) --> diffuse disease, ILD.
- Anticentromere → Limited disease (CREST syndrome)
- RNA polymerase → Diffuse disease.

Pathology

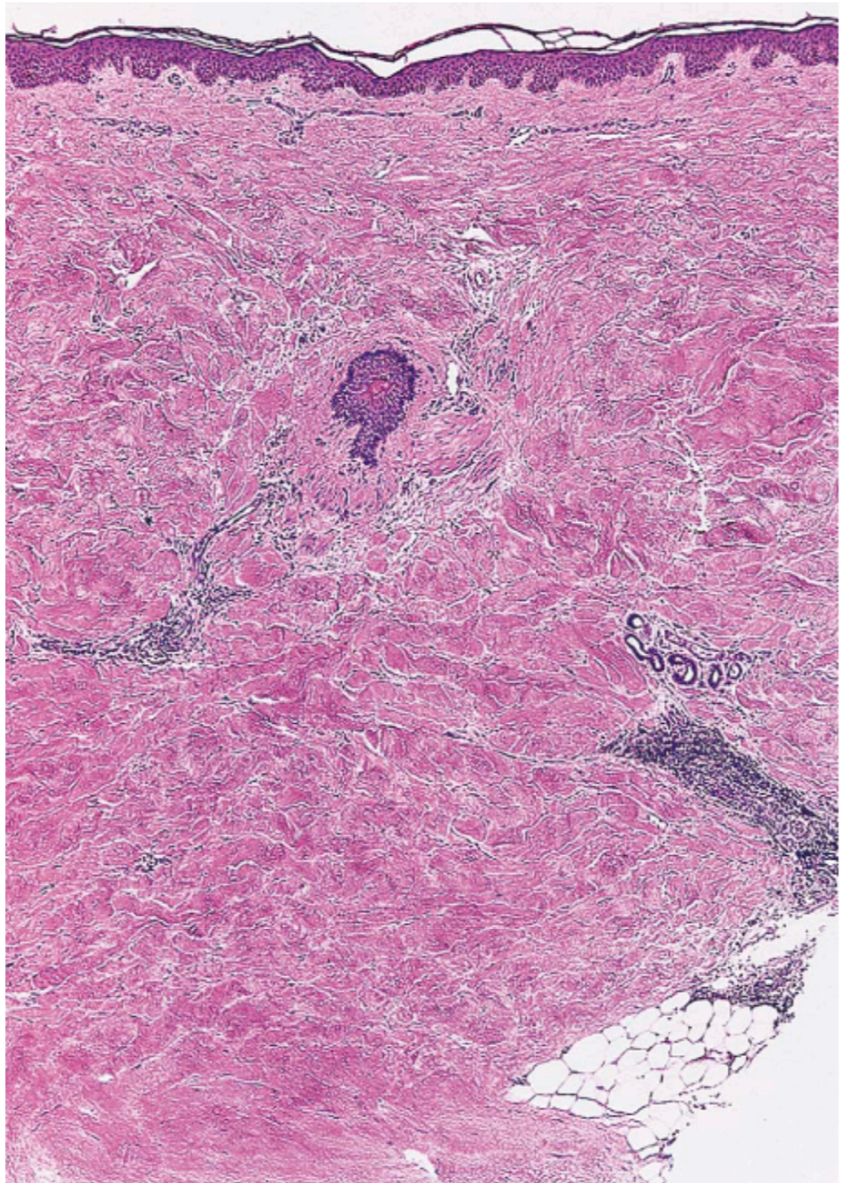
- Skin biopsy: compact collagen, loss of subQ fat, deep lymphocytic infiltrate and trapped adnexal structures.
- DIF → usually negative.

Skin Biopsy

Normal Skin



Systemic Sclerosis



Treatment

- Most interventions focus on internal organs and unfortunately, have no significant impact on cutaneous manifestations.
- Raynaud's --> Keep warm, CCB (Nifedipine), Angiotensin II receptor blockers (Losartan), Phosphodiesterase type inhibitors (Sildenafil).
- ACE inhibitors is used to treat scleroderma renal crisis.
- Cyclophosphamide --> ILD.
- Oral immunosuppressants.
- Matted Telangiectasias → Pulse dye laser.

Connective Tissue Diseases

- **Lupus Erythematosus**
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  - Mixed connective tissue disease


Morphea

Morphea

- An inflammatory skin disease that primarily affects the dermis and may extend to subcutaneous structures and lead to scar-like sclerosis.

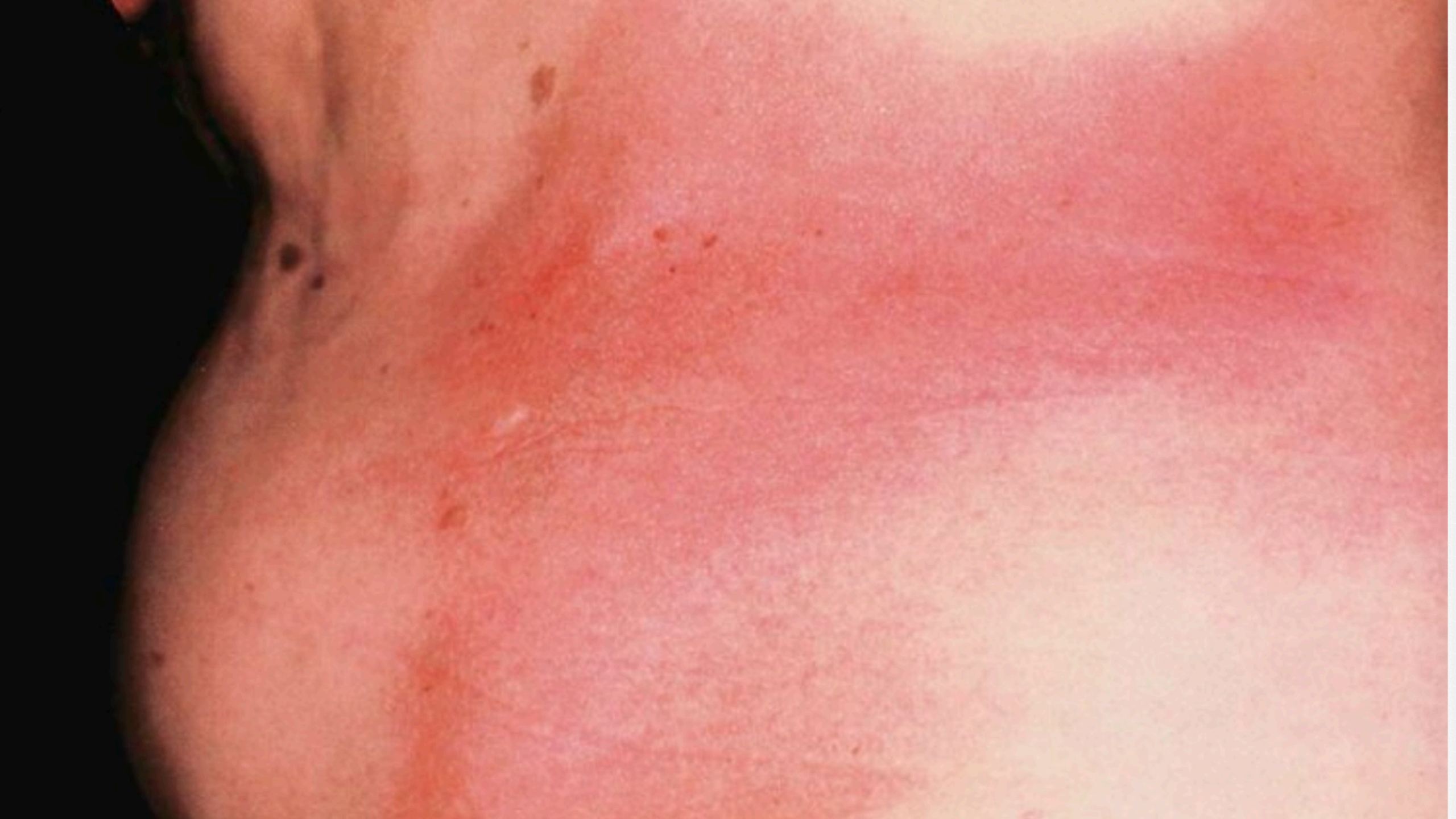
- Does not lead to involvement of internal organs.

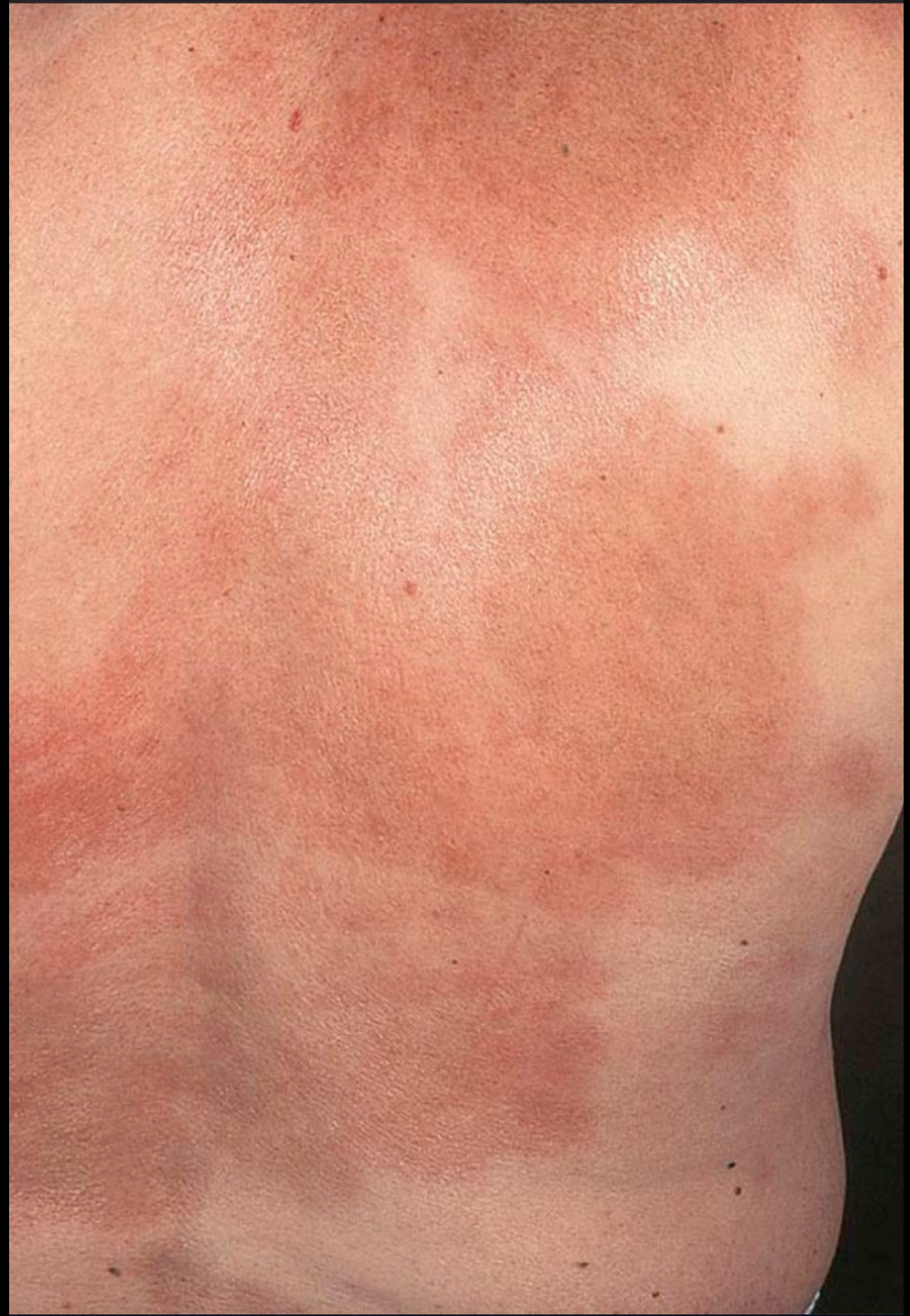
- Clinical types:

- plaque type (56%).
- Linear (20%).
- Generalized (13%).
- Deep morphea (11%).

Clinical features of Morphea "Plaque-Type"

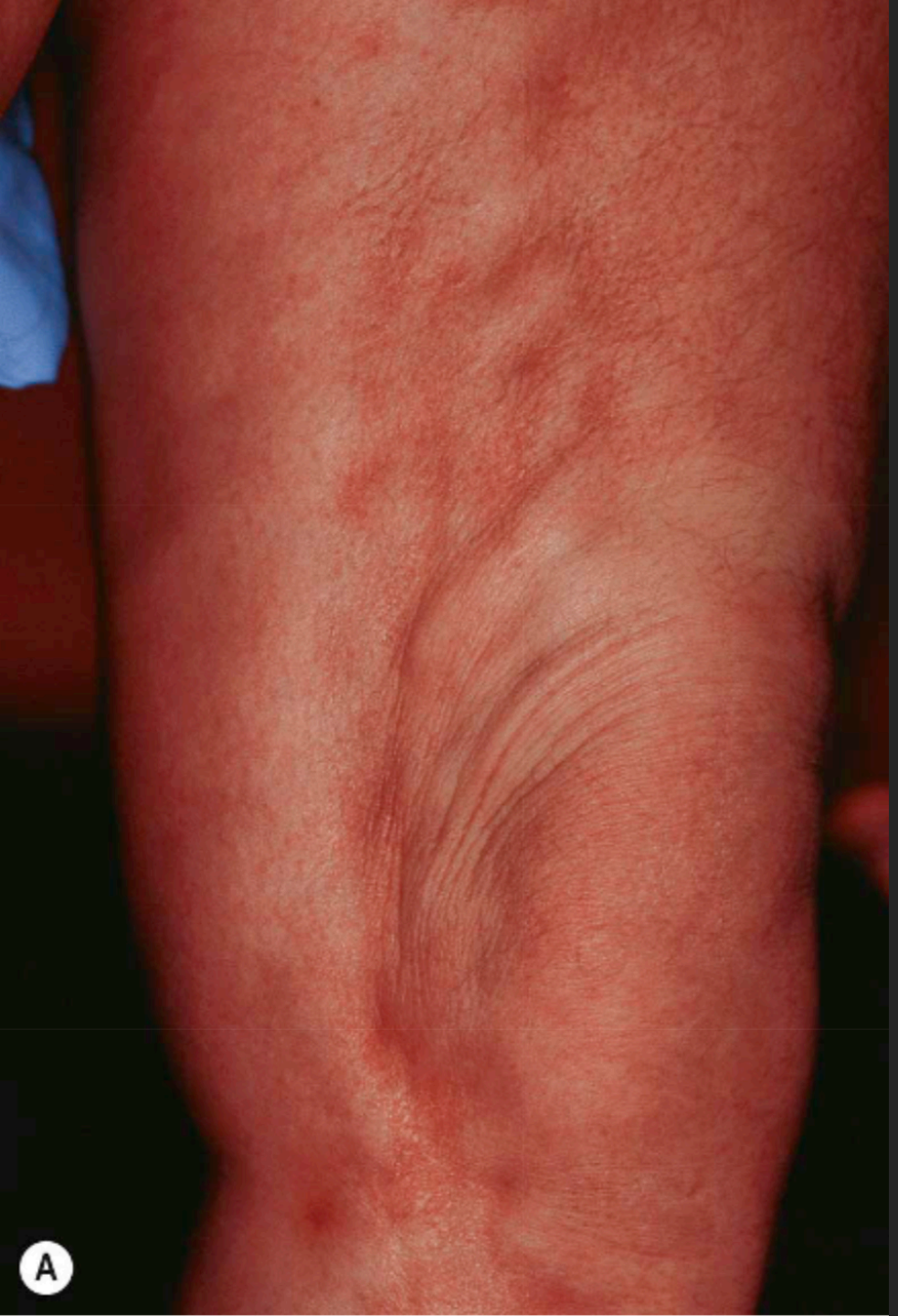
- Insidious onset of a slightly elevated, erythematous or violaceous, somewhat edematous plaque that undergoes centrifugal expansion.
- Asymptomatic, can go unnoticed by the patient.
- The central part of the progressing lesion starts to transform into sclerotic, scar-like tissue and the skin becomes more indurated.
- Centrally, it can acquire a shiny white color, and peripherally, a violaceous or "Lilac" Ring.
- As the lesion matures, post-inflammatory hyperpigmentation dominates the center over the white sclerosis.
- Most commonly affects the trunk, usually multiple and asymmetric.
- In most patients, morphea progresses over 3-5 years, then arrests and eventually resolves spontaneously. (residual atrophy/pigmentation are commonly observed)



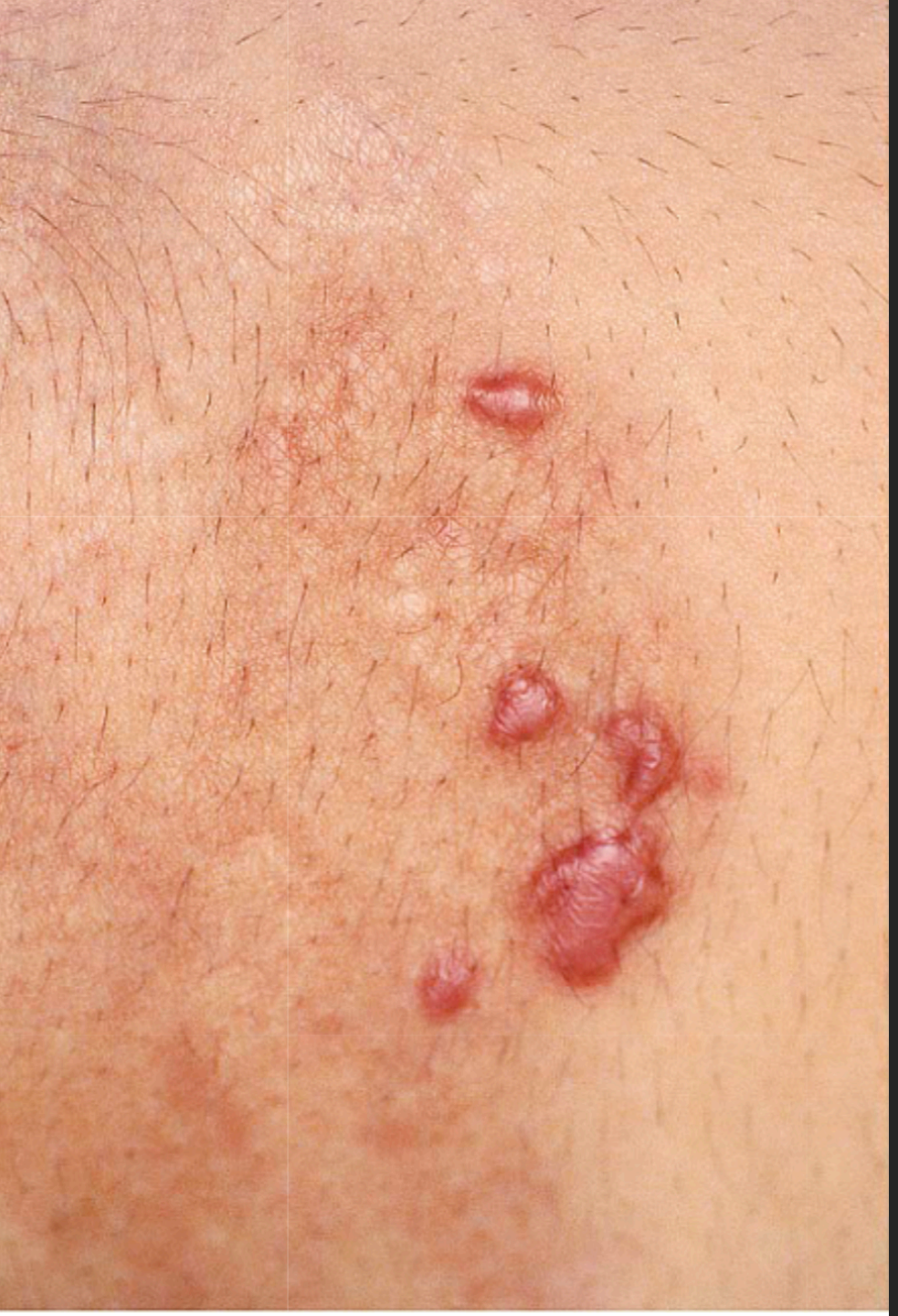


Variants of Morphea

- Guttate Morphea: multiple, nummular, small plaques.
- Atrophoderma of Pasini and Pierini: hyperpigmented patches on the posterior trunk.
- Deep Morphea: Deep dermis and fat (or deeper). May impair motility of the skin and calcify (osteoma cutis).
- Nodular/Keloid Morphea: keloid-like nodules.
- Bullous Morphea: Very rare.



Deep Morphea



Keloidal morphea

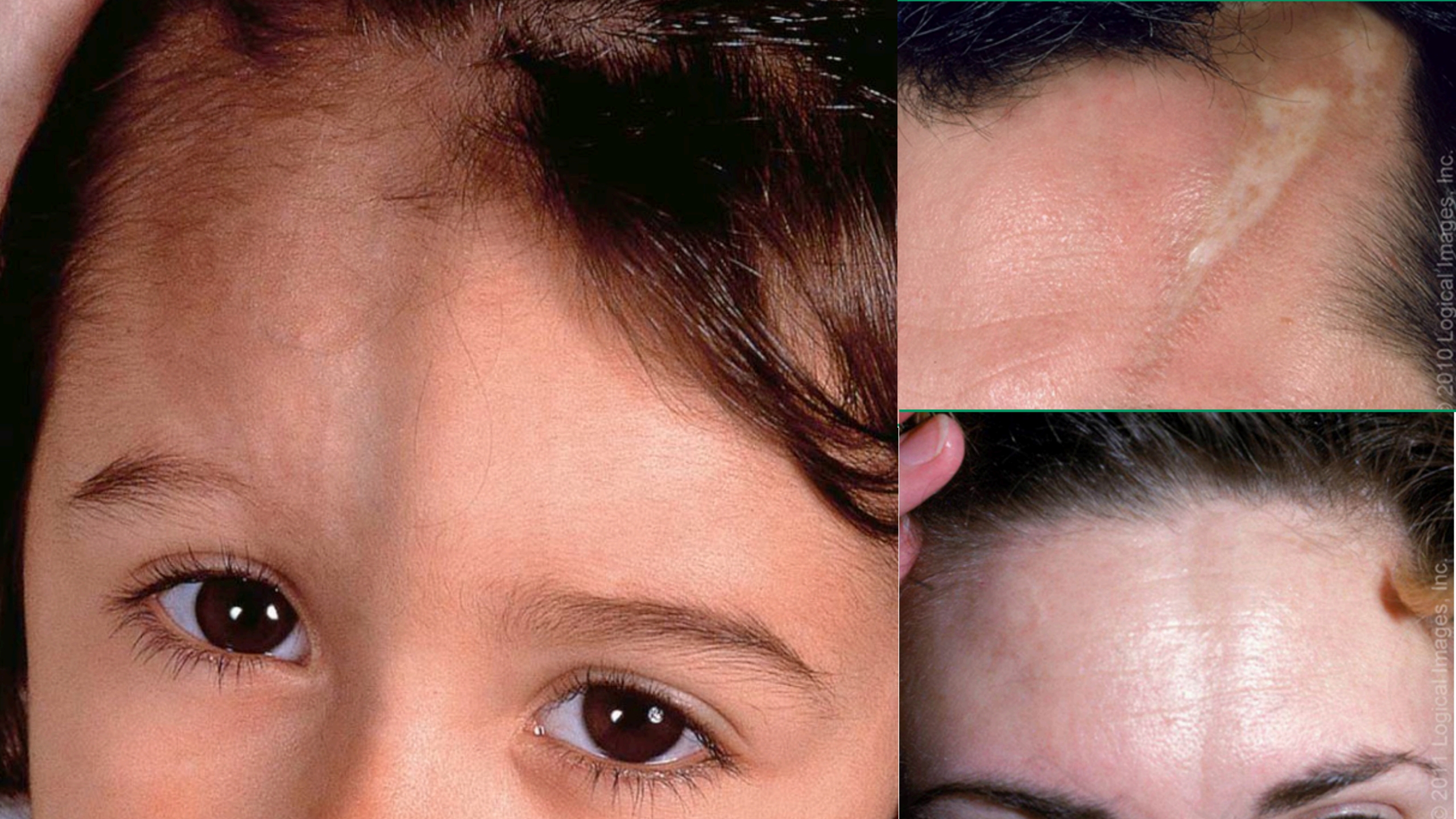
Linear Morphea

- ***<u>En coup de sabre:</u>***

- A term used for linear morphea of the forehead and scalp.
- Normally unilateral and extends from the forehead into the frontal scalp.
- Paramedian location is more common than a median location.

- **<u>Hemifacial atrophy (Parry-Romberg syndrome):</u>**

- A very severe variant of linear morphea.
- Progressive loss of subcutaneous fat, but little or no sclerosis.
- Linear morphea tends to involve the underlying fascia, muscle and tendons.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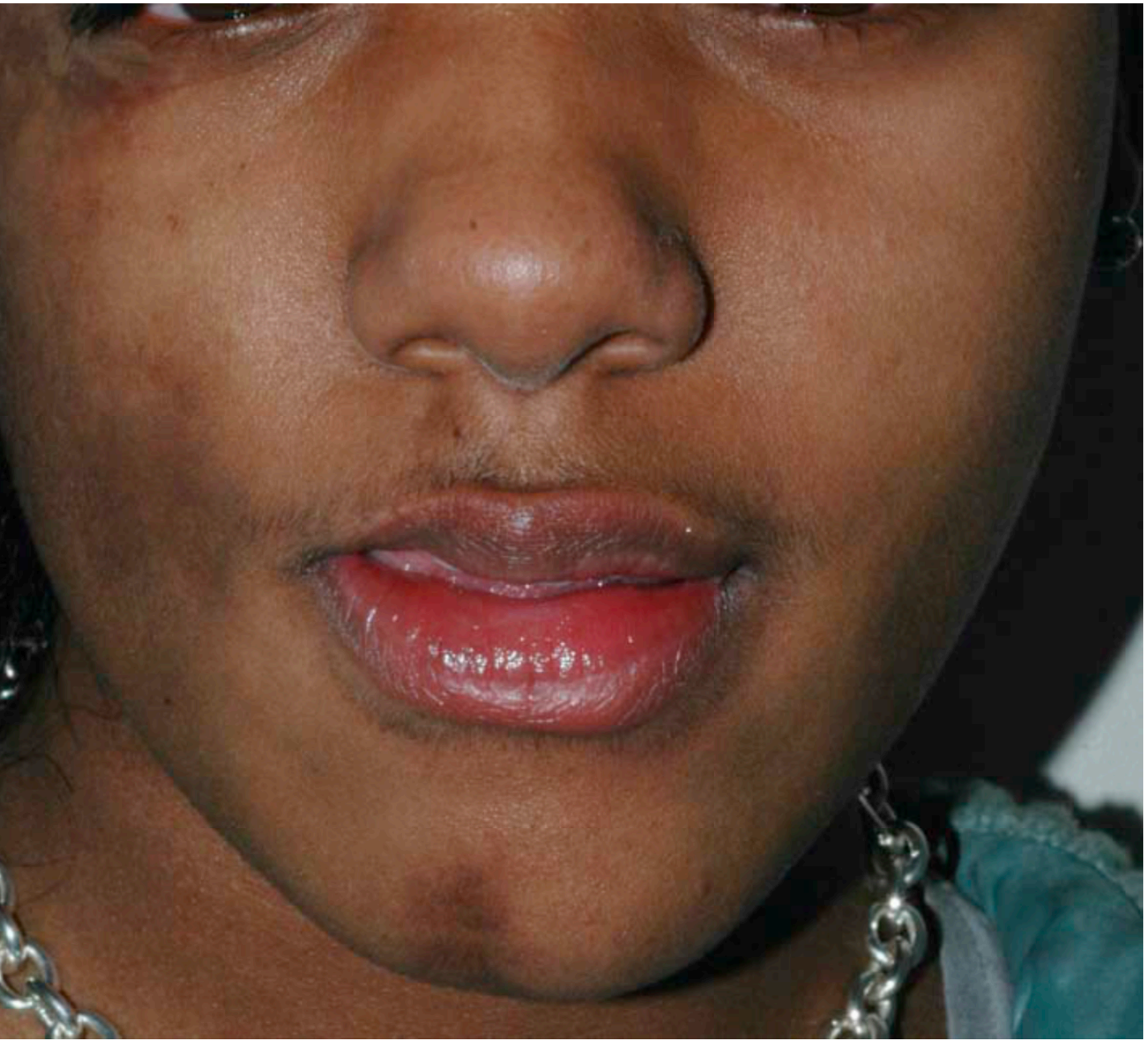
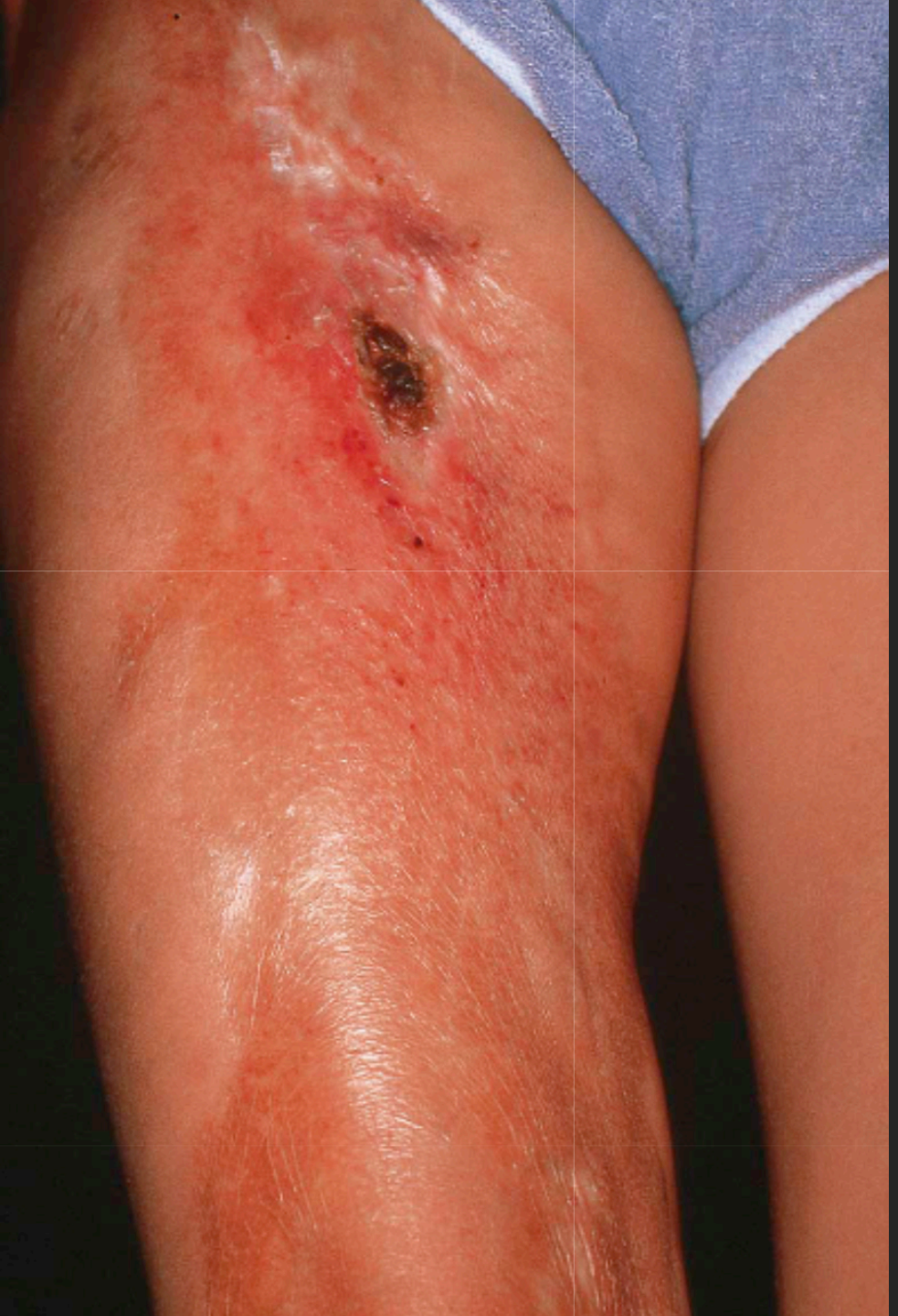


Perry Romberg syndrome



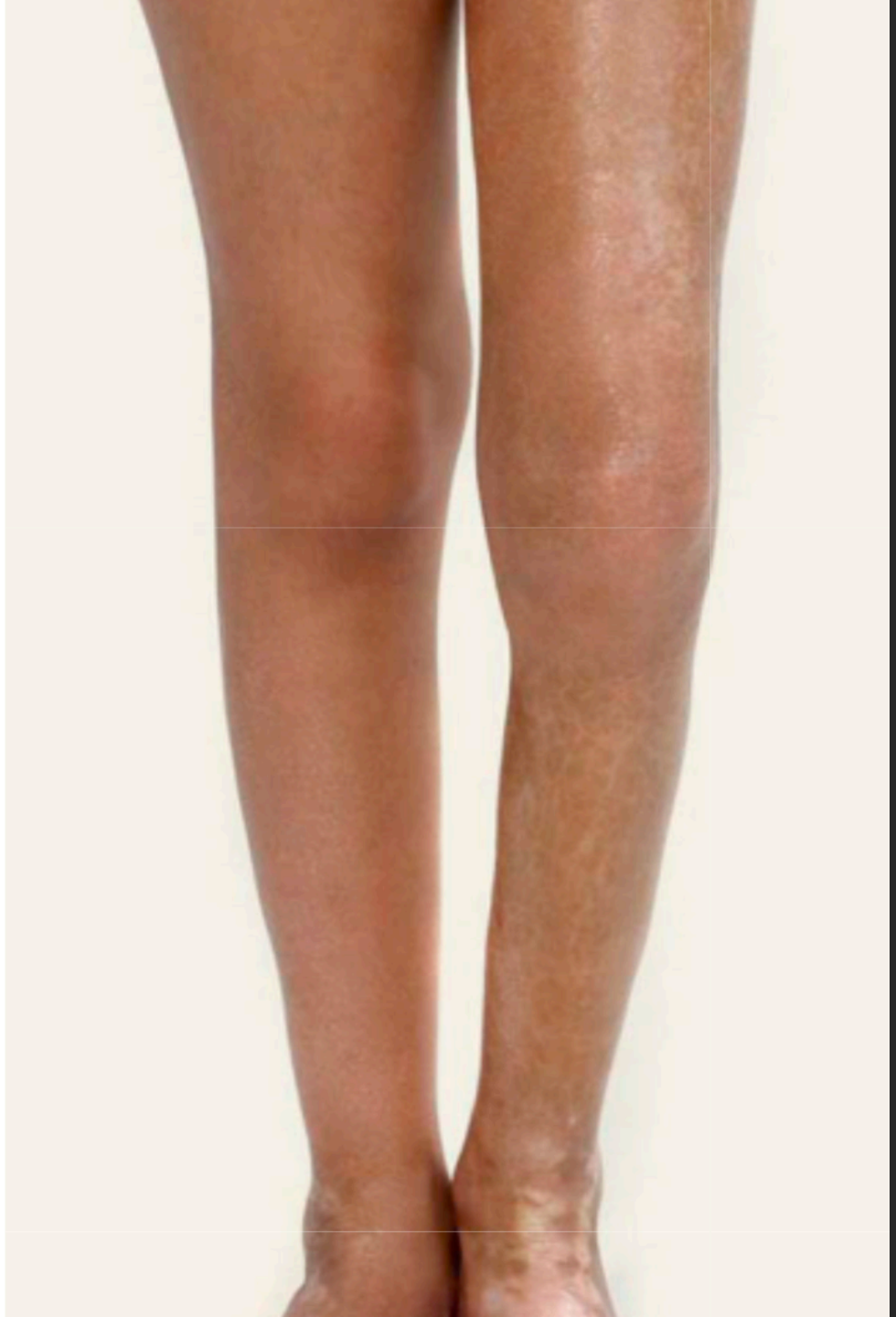
Linear Morphea

Generalized Morphea

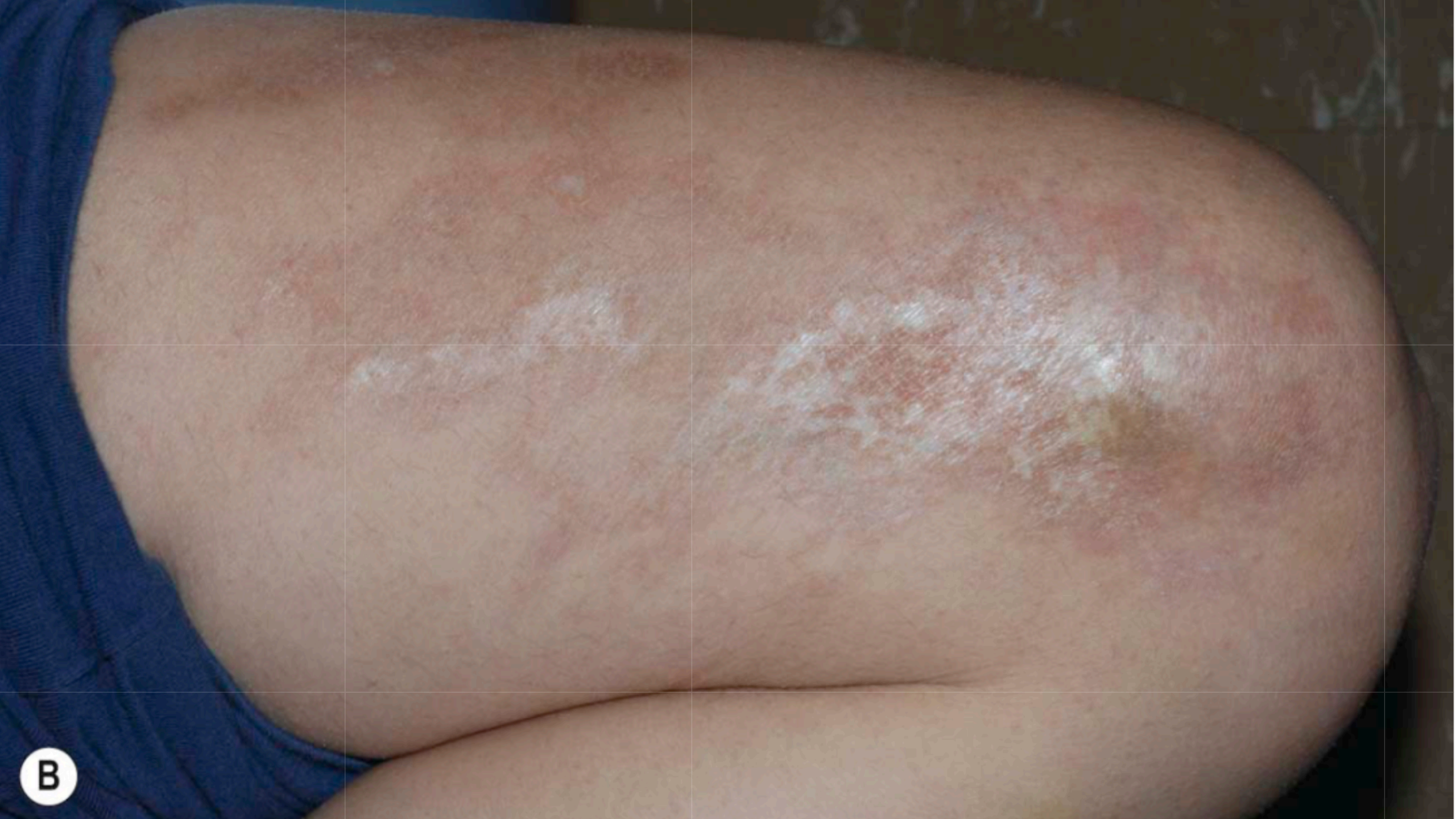
- Rare
- Starts as regular plaque morphea but does not stop expanding.
- May even cause difficulty breathing due to impaired thoracic mobility.
- The disease usually persists despite aggressive treatments.

Childhood Morphea

- 20% of Morphea patients are children and teenagers.
- 2:1 female to male ration, mean age of disease onset is 7 years.
- 2/3 of of linear morphea patients are under the age of 18.
- Linear morphea in children can affect the growth of a limb and lead to limb asymmetry as well as decrease range of motion of joints.



Linear Morphea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Investigations

- Lab-work is usually negative in Morphea except generalized & Linear Morphea (ANA +ve in 40-80%*)*
- Pathology: Helpful (similar to systemic sclerosis). Must be deep.

Treatment of Morphea

- **Phototherapy**

- **Topical therapy:**
- Corticosteroids (class I)
- ILK injections
- Calcineurin inhibitors

- **Systemic therapy:**
- Systemic steroids
- Methotrexate

I'm going to the dermatologist for a weird rash on my ankle. But I really just want to talk about wrinkles.

Amadani1@ksu.edu.sa