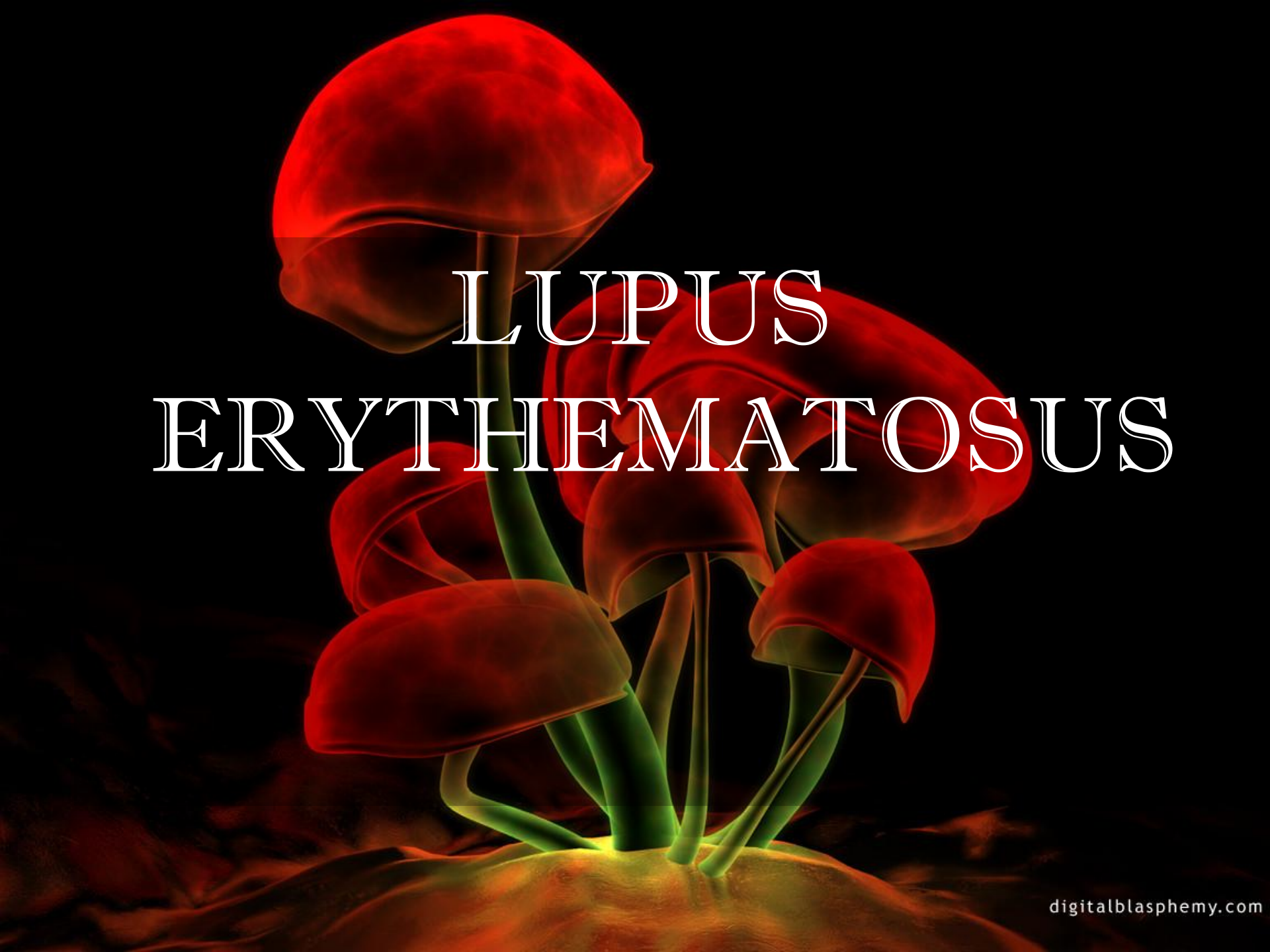
SKIN MANIFESTATIONS OF RHEUMATOLOGICAL DISEASES


LUPUS
ERYTHEMATOSUS
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LUPUS ERYTHEMATOSUS

Is the designation of a spectrum of diseases that are linked by distinct clinical findings and distinct patterns of polycolonal B cell immunity .It ranges from life threatening manifestations of SLE to the limited and exclusive skin involvement in CCLE. More than 85% of patients with LE have skin lesions, which can be classified into LE-specific & non-specific.

ABBREVIATED GILLIAM CLASSIFICATION OF SKIN LESIONS ASSOCIATED WITH LE

1- LE specific skin disease(CLE)

A.Acute cutaneous LE

1- Localized ACLE(malar rash,butterfly rash)

2- generalized ACLE (maculopapular rash,malar rash, photosensitive lupus dermatitis, bullous LE)

B- Subacute cutaneous LE (SCLE)

1- annular SCLE

2- Papulosquamous SCLE

3- syndromes commonly exhibiting similar morphology

a. neonatal LE

b. complement deficiency syndromes

c. drug induced

ABBREVIATED GILLIAM CLASSIFICATION OF SKIN LESIONS ASSOCIATED WITH LE

C. Chronic cutaneous LE (CCLE)

1. Classic discoid LE(DLE)
   a. localized DLE
   b. generalized DLE
2. Hypertrophic /verrucous DLE
3. Lupus profundus
4. Mucosal DLE
5- Lupus tumidus (urticarial plaque of LE)
6. Chilblains LE
7. Lichenoid DLE (LE/Lichen planus overlap)

2. LE non-specific skin disease.

These ranges from necrotizing and urticarial vasculitis to livedo reticularis ,raynaud's phenomenon ,dermal mucinosis like lesions in LE.

Systemis Lupus erythematosus

- It is a genetically determined multi-system auto-immune disease characterized by diverse clinical features of unknown etiology.
- The clinical manifestations include fever (90%) ,skin lesions (85%),arthritis, CNS,renal, cardiac, and pulmonary diseases.

Etiology of SLE

Host factor :

1- sex : female : male → 10:1 (90%)

* 80% in childbearing years.

2- race : SLE is more common in blacks (1:250) than in whites (1:1000). However, all ethnic groups are susceptible.

3- genetic factor:

The concordance rate in monozygotic twins is approximately 25-70%. Each patient manifests his or her disease differently.

If a mother has SLE, her daughter's risk of developing the disease is 1:40, and her son's risk is 1:250.

Etiology of SLE

4- immunological abnormalities:

- Many of the clinical manifestations of SLE are caused by the effects of circulating immune complexes on various tissues or to the direct effects of antibodies to cell surface components.
- Whether polyclonal B-cell activation or a response to specific antigens exists is unclear

Etiology of SLE

Environmental factor:

1- infections

2- Ultra-violet radiation

3- drug & chemicals

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.
- No antibodies to native DNA or hypocomplementemia are present.*
- When the drug is discontinued, the patient has resolution of clinical manifestations and reverting of abnormal laboratory values to normal.

Table 1. Drugs associated with lupus erythematosus (Source: Tierney et al)

Definite Association

Chlorpromazine	Isonizide
Hydralazine	procinamide
Methyldopa	Quinidine
Anti- TNF	Minocyclin
Penicillamin	IFN-alpha, IFN-beta

Revised ACR's Criteria for Classification of SLE

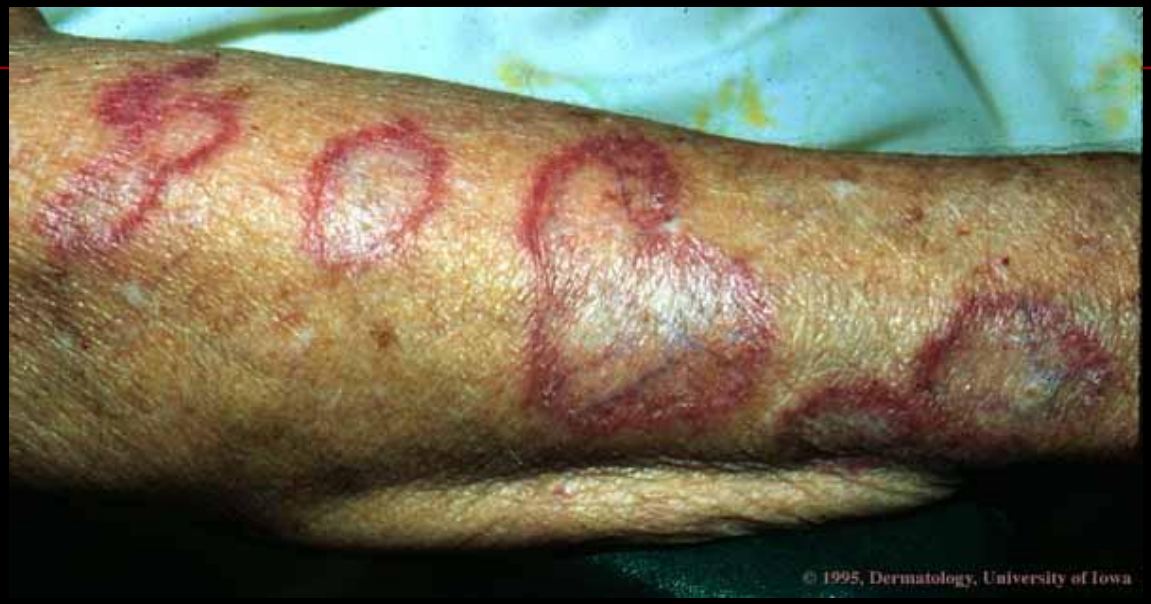
Any 4 of the following criteria are required to make the diagnosis

- Malar rash
- Discoid rash
- Photosensitivity
- Oral ulcer
- Arthritis
- Serositis
- Renal dis.
- Neurological dis.
- Hematological inv.
- Immunological dis.
- ANA

Malar rash / butterfly rash

- ✓ Fixed erythema ,flat or raised ,over the malar eminences, tending to spare the nasolabial folds
- ✓ Bright red ,sharply defined erythema with slight edema & minimal scaling in a butterfly patteren

Discoid rash

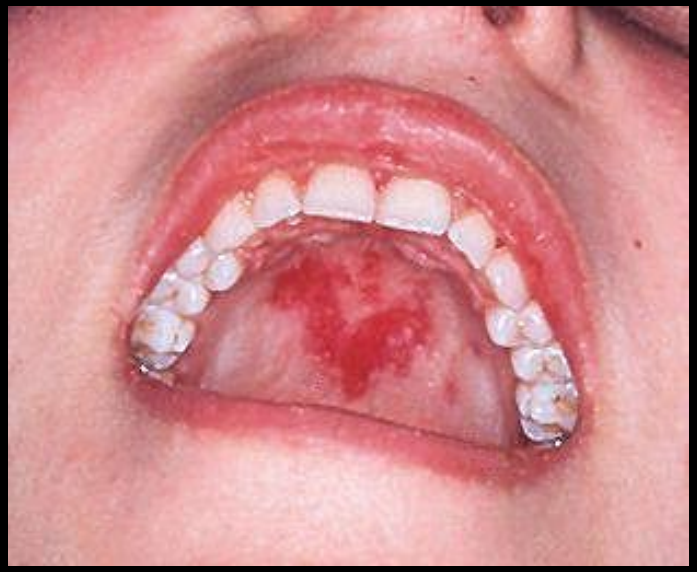


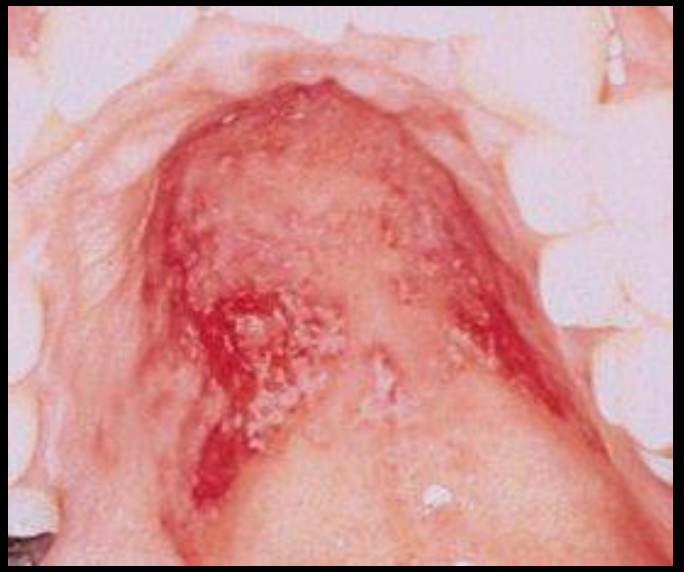
- Erythrematous patches or plaques with an adherent keratotic scale and follicular plugging ,atrophic scarring hairless patches may occur in older lesions.

photosensitivity

- Skin rash as a result of of unusual reaction to sunlight by patient history or physician observations.

Oral ulcers





- Oral or nasopharyngeal ulceration ,usually painless

CUTANEOUS LUPUS ERYTHEMATOSUS

SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS (SCLE)

- ✓ is a nonscarring non–atrophy-producing photosensitive dermatosis.
- ✓ SCLE may occur in patients with systemic lupus erythematosus (SLE), Sjögren syndrome, and deficiency of the second component of complement (C2d), or it may be drug induced.

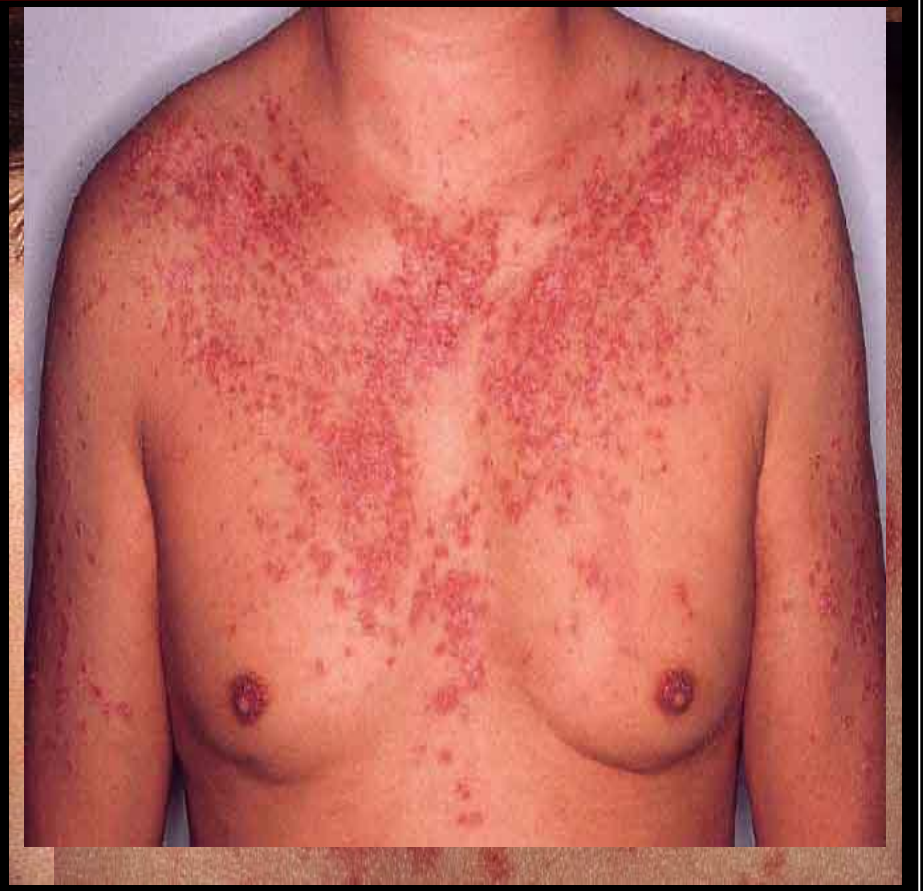
- SCLE occurs in genetically predisposed individuals, most often in patients with (HLA-B8), (HLA-DR3), (HLA-DRw52), (HLA-DQ1).
- A strong association exists with anti-Ro(SS-A) autoantibodies. The reaction is believed to be related to ultraviolet (UV) light modulation of autoantigens, epidermal cytokines, and adhesion molecules, with resultant keratinocyte apoptosis.

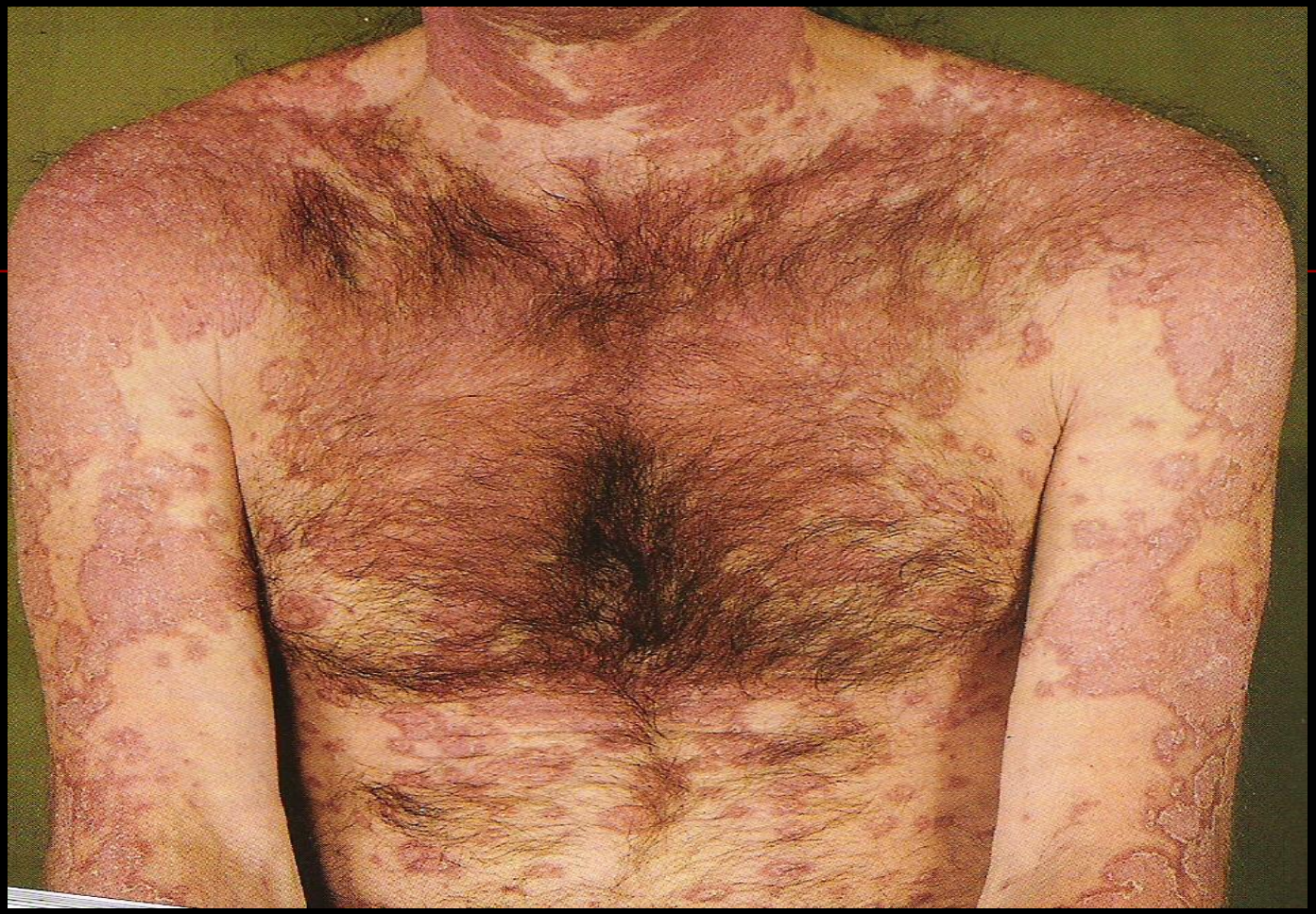
Epidemiology

- **Race:** SCLE is more common in whites (85%).
- **Sex:** Male-to-female ratio of SCLE is 1:4.
- **Age:** SCLE typically occurs in patients aged 15-70 years. The mean age is approximately 43 years.

Skin manifestations

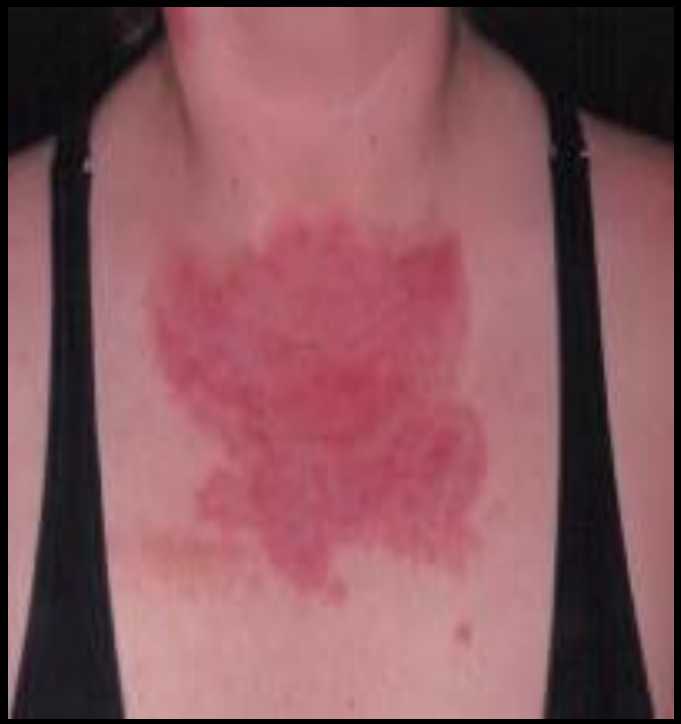
- The primary lesion of SCLE is an erythematous papule or a small plaque with a slight scaling.
- Primary lesions expand and may merge and eventually form either plaques with scaling in the papulosquamous variant or annular and/or polycyclic lesions in the annular variant
- Photosensitivity is prominent in about half of patients.



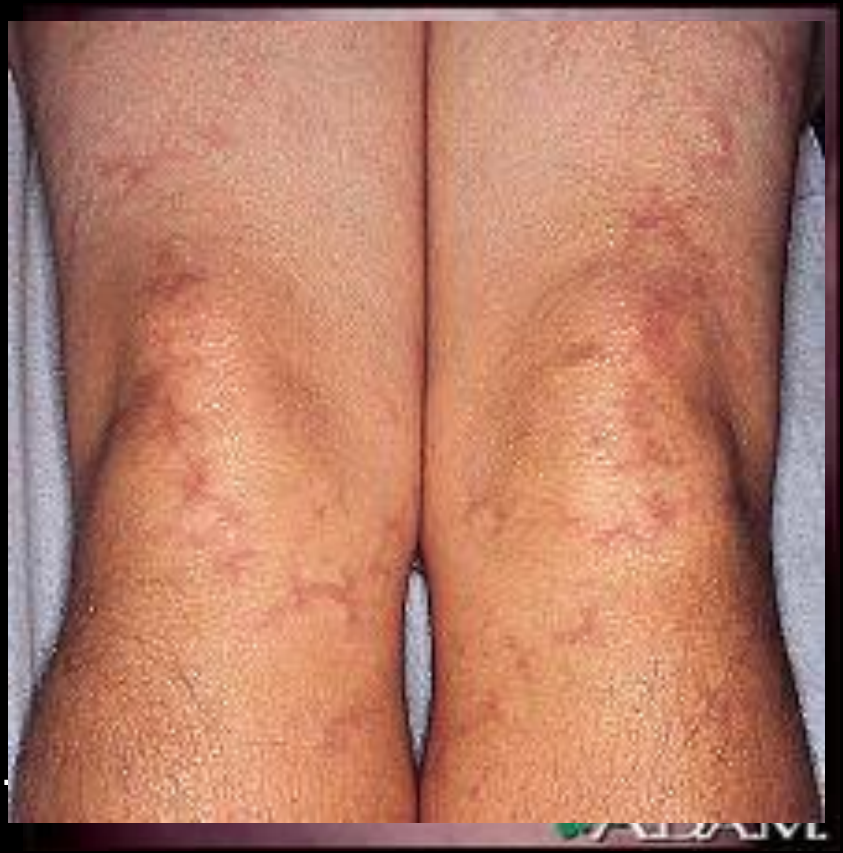


- ✓ SCLE: widely scattered ,erythematous to violaceous scaly,well demarcated plaques on the trunk, neck and arms

- Papulosquamous lesions may mimic psoriasis or lichen planus
- while annular lesions may mimic erythema annulare centrifugum. Most patients exhibit one predominant type of lesion, and some also manifest isolated lesions of DLE (20 % of patients).
- SCLE lesions primarily are photodistributed. When they occur on the lower extremities, they often are purpuric.



- Patients with SCLE may have systemic manifestations.
  - arthritis/ arthralgia (20%)
  - Leukopenia
  - Positive ANA (80%)
- Patients also may have nonspecific cutaneous manifestations of lupus erythematosus (LE), such as livedo reticularis, palpable purpura, urticaria, ischemic changes of the distal fingertips (resulting from Raynaud phenomenon), or mucosal leukoplakic or ulcerative lesions.

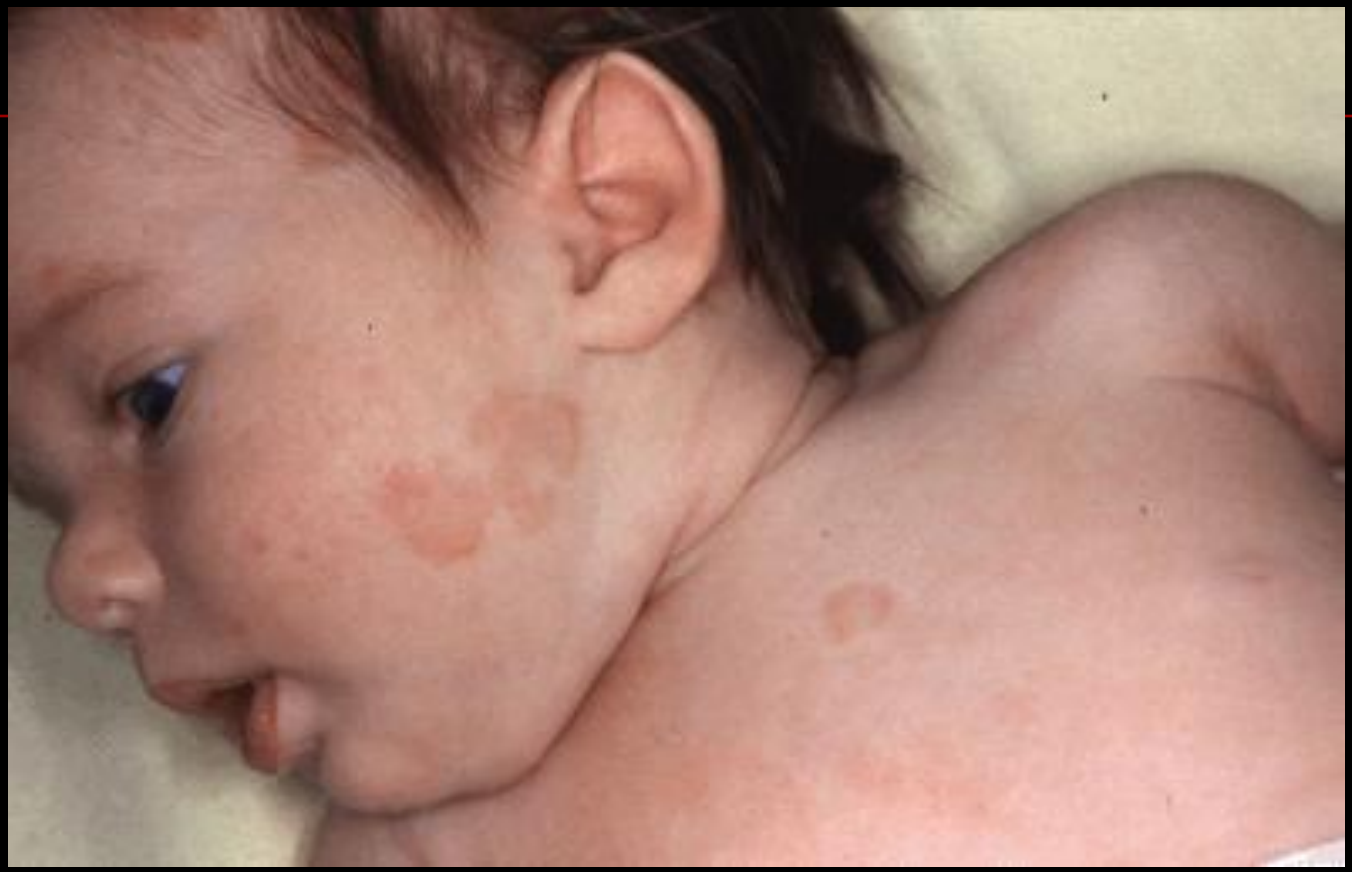


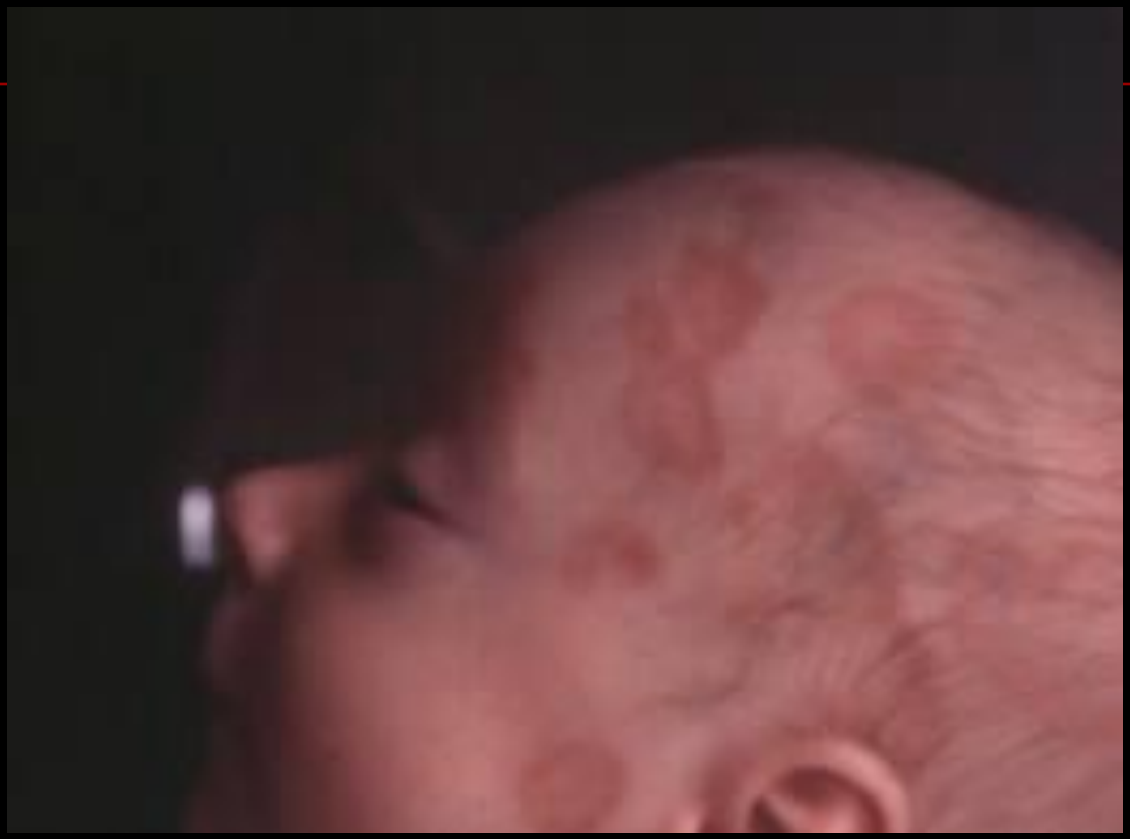
Neonatal lupus erythematosus:

- Most infants are girls born to mothers who carry the Ro/SSA antibody.
- They don’t have skin lesions at birth, they develop them during the 1st few weeks of life.
- Annular erythematous macules and plaques may appear on the head and extremities.
- Lesions usually heal spontaneosly by 6 months of age and usually heal without significant scarring.

Neonatal lupus erythematosus:

- Half of the patients have an associated isolated congenital heart block, usually 3rd degree which is permanent.
- In patients with cutanoeus disease, thrombocytopenia and hepatic disease may occur as frequently as cardiac disease.
- There is a strong association with Ro/SSA antibodies.
- In women with anti-Ro antibodies only 1-2 % will have an infant with neonatal LE.
- The risk of a second child developing neonatal LE is 25%.





Chronic cutaneous lupus erythematosus

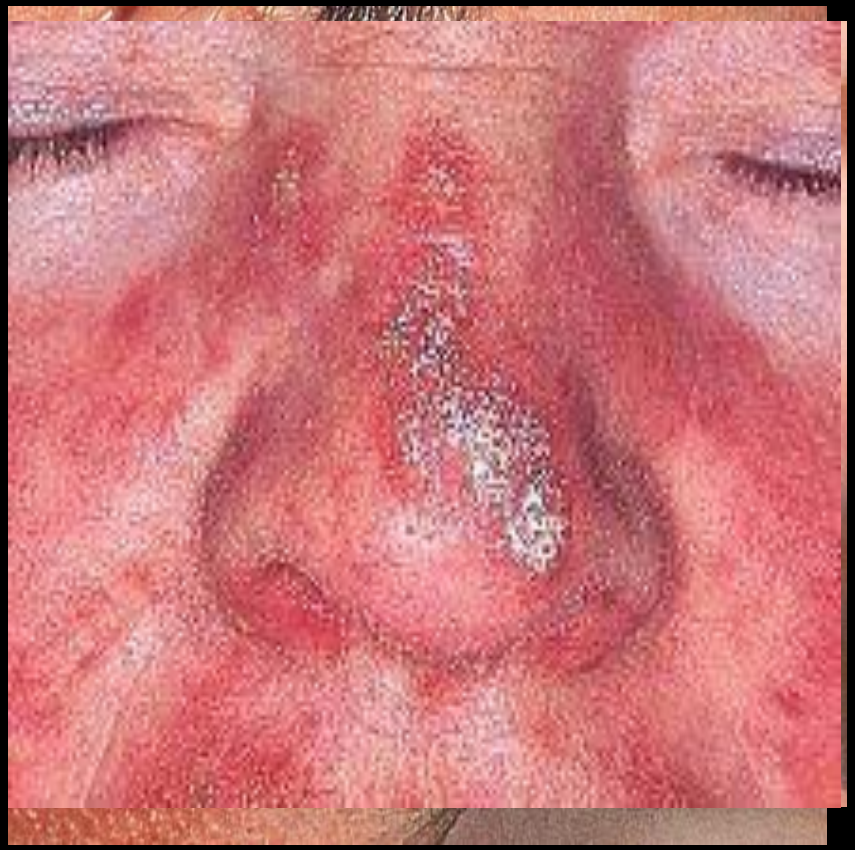
- (DLE) is a chronic, scarring, atrophy producing, photosensitive dermatosis. DLE may occur in patients with systemic lupus erythematosus (SLE), and some patients (<5%) with DLE progress to SLE. Some patients also have the lesions of subacute cutaneous lupus erythematosus (SCLE), and some may have a malar rash.

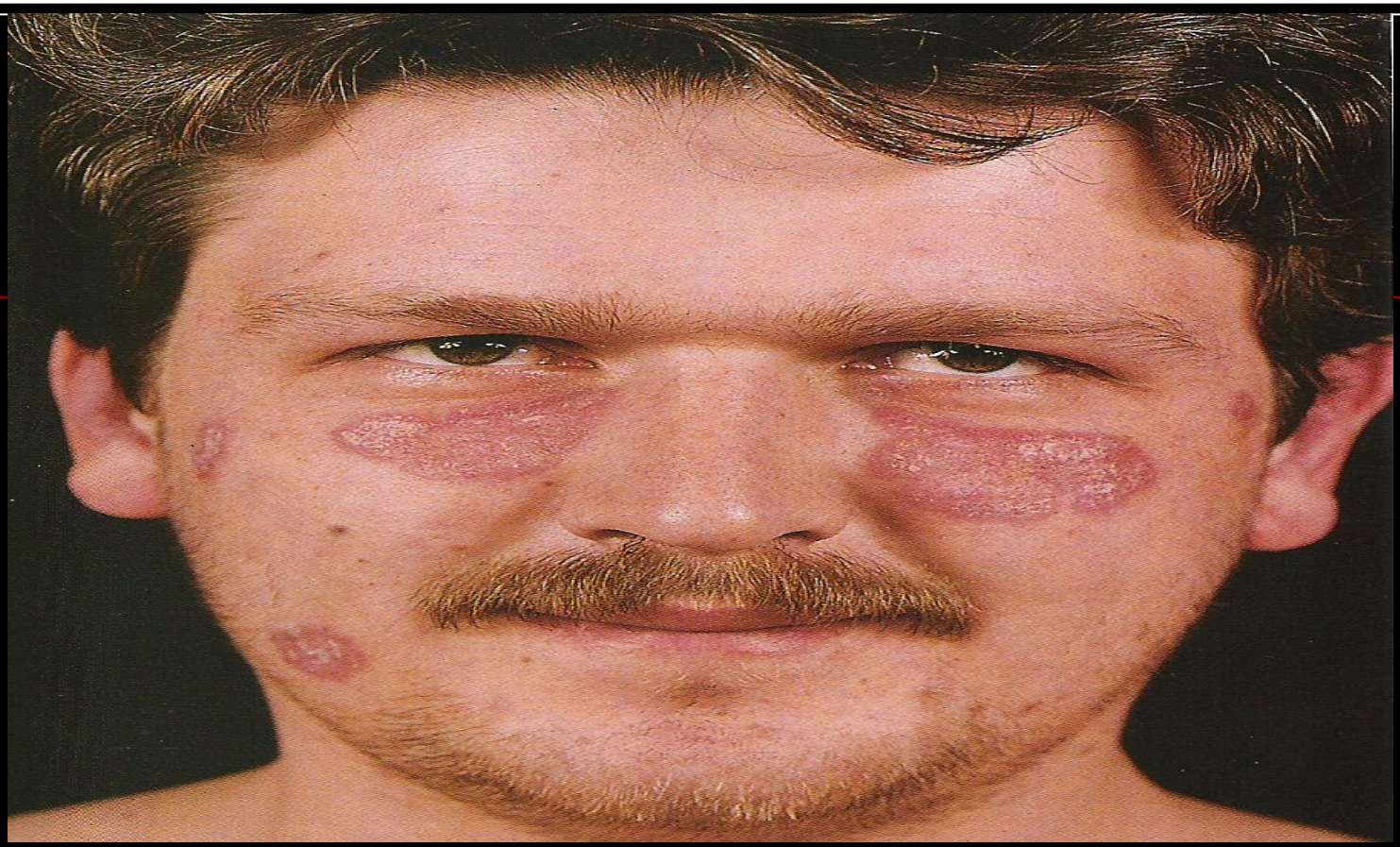
- Serologic abnormalities are uncommon.
- **Race:** DLE is slightly more common in African Americans than in whites or Asians.
- **Sex:** Male-to-female ratio of DLE is 1:2.
- **Age:** DLE may occur at any age but most often occurs in persons aged 20-40 years. The mean age is approximately 38 years.

- Childhood DLE:
  - Lack of female predominance.
  - Low frequency of photosensitivity
  - Higher progression of SLE.

Skin manifestations

- DLE lesions frequently are characteristic. The primary lesion is an erythematous papule or plaque with slight-to-moderate scaling.
- As the lesion progresses, the scale may thicken and become adherent, and pigmentary changes may develop, with hypopigmentation in the central or inactive area and hyperpigmentation at the active border.

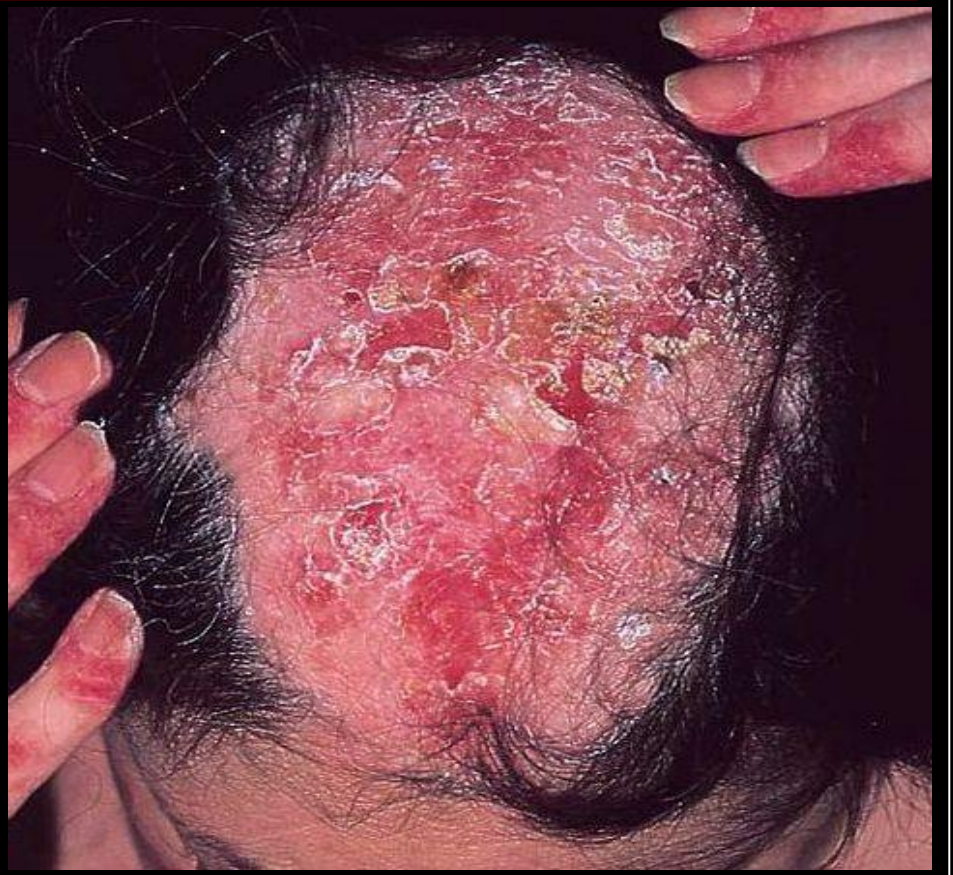




- CCLE : well demarcated ,erythematous ,hyperkeratotic plaques with atrophy, follicular plugging , and adherent scale on both cheeks
- (classic presentation of CDLE)
- Perifollicular erythema and the presence of easily extractable anagen hairs are signs of active disease.

Skin manifestations

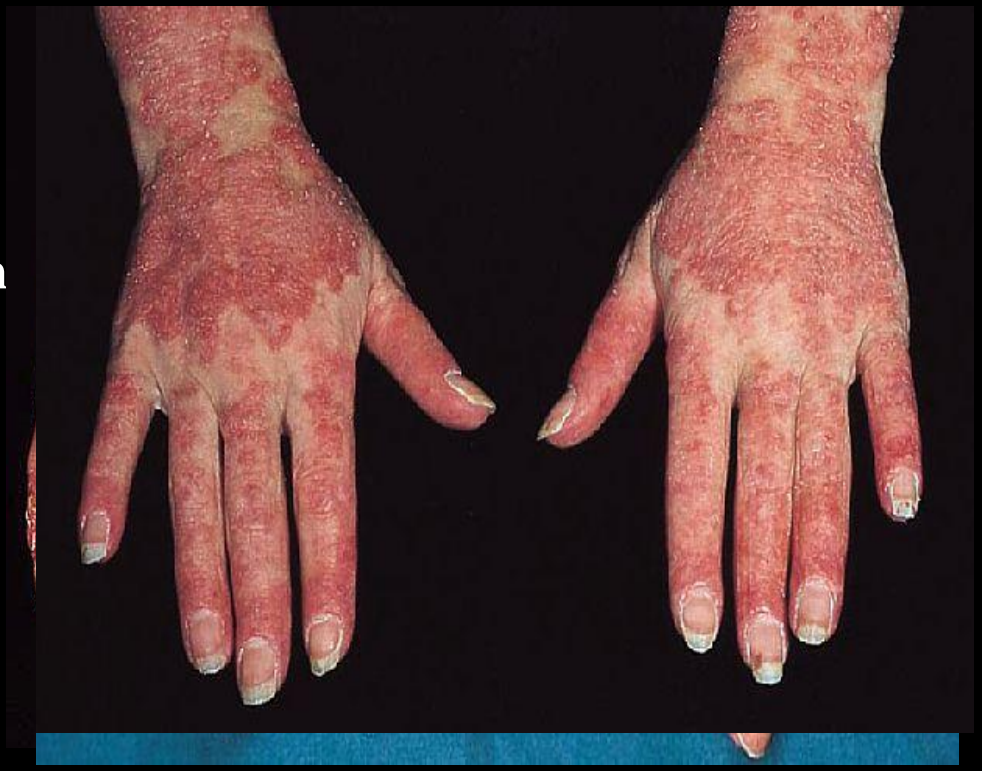
- The scalp is a common area of involvement, and permanent alopecia may result
- Well defined erythermatous plaque with area of follicular plugging & scarring alopecia



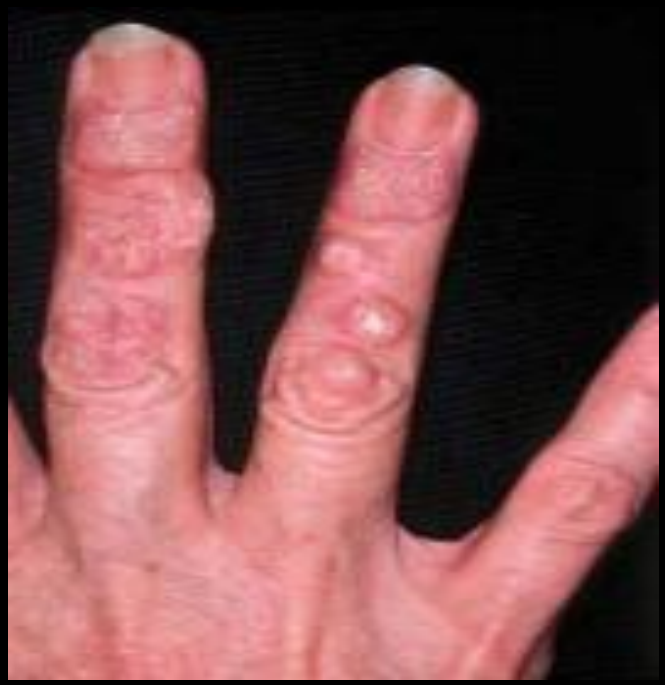
Skin manifestations

- Palms and soles may be affected, but this occurs in fewer than 2% of patients
- Periungual involvement with CCLE lesions
- Severe hand involvement:

  several depressed scars surrounded by an active erythematous border (CCLE).

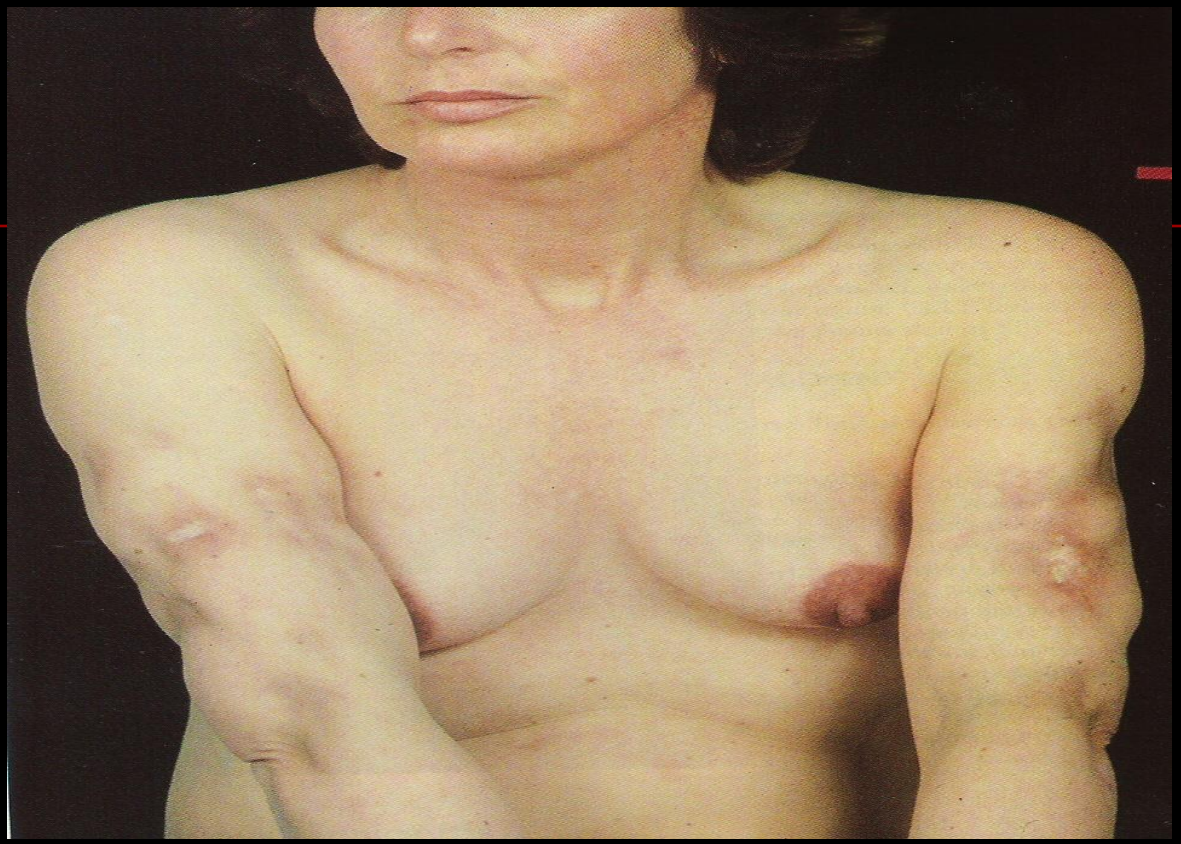


- CCLE lesions may become hypertrophic or verrucous ,This subset is manifested by wartlike lesions, most often on the extensor arms. Hypertrophic lesions of LE must be differentiated from warts, keratoacanthomas, or squamous cell carcinoma..



Chronic lupus panniculitis

- It is a form of CCLE in which there is firm ,circumscribed subcutaneous nodules on the face, scalp, breast, upper arms, thighs and buttocks. Most but not all patients also have typical lesions of DLE. Usually a form of cutaneous lupus , but may occur in SLE.



- Chronic panniculitis with atrophy of the subcutaneous tissues ,resulting in large sunken areas of overlying skin ,representing resolving lesions. Where erythema is still visible , palpation reveals firm subcutaneous nodules and plaques . Also some lesions reveal scarring in the center.

Diagnosis

- Diagnosis made on the basis of clinical findings,histopathology,lupus band test and serology within the frame work of the revised ARA criteria for SLE
- CBC: anemia, leukopenia,thrombocytopenia.
- ESR
- urine analysis

Diagnosis

- Serology testing:

1- rheumatoid factor : +ve in 30%

2- ANA :+ve in 95% ,VERY SENSITIVE BUT NOT SPECIFIC

3- Anti-dsDNA (anti- native DNA):

Specific but not very sensitive, indicates high risk for renal disease.

4- Anti-Ro (SS-A) :+ve in 90% of SCLE

Anti- La (SS-B) often present in lesser percentage

Diagnosis

5- Anti-smith : most specific +ve in 30%

6- anti-histone AB*

7- C3,C4: : low levels indicate active disease, often with renal involvement.

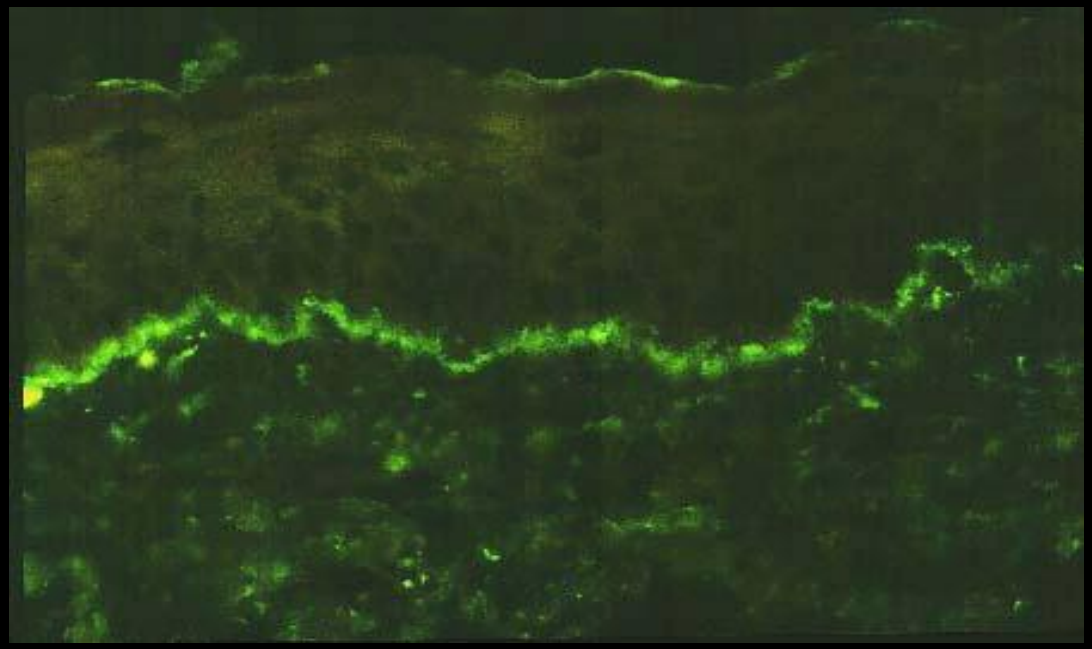
Diagnosis

- LUPUS BAND TEST:

  Testing of nonlesional nonexposed skin is termed the lupus band test (LBT).

  Deposition of immunoglobulin and/or complement at the dermal-epidermal junction is a characteristic feature of LE.

Lupus Band Test



Direct immunofluorescence microscopic examination after staining with fluorescein-coniugated antihuman antiserum shows a continuous homogeneous band of immunoreactant at the dermo-epidermal junction.

Diagnosis

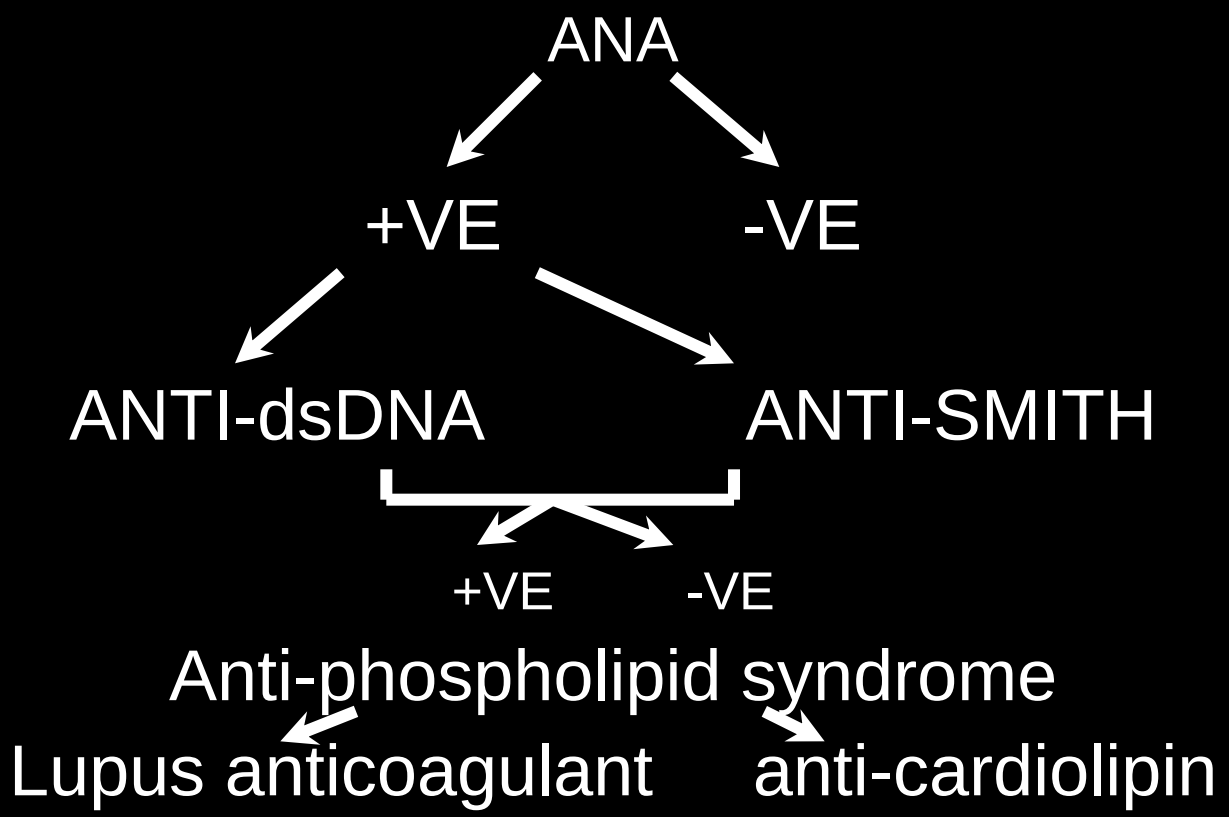
- **Histologic Findings:**

Characteristic histopathologic alterations observed in LE include:

(1) vacuolar alteration of the basal cell layer

(2) inflammatory cell infiltrate (usually lymphocytic) around vessels (perivascular), around appendiceal structures (periappendiceal), and in a subepidermal location. Epidermal changes, such as atrophy, are common, but follicular plugging is less frequent than in patients with DLE. An abundance of mucin often is seen within the dermis.

Summary


ANA
+VE
-VE
ANTI-dsDNA
ANTI-SMITH
+VE
-VE
Anti-phospholipid syndrome
Lupus anticoagulant
anti-cardiolipin

Management of SLE:

- Advice patient to avoid sun exposure and modify cardiovasular risk factors

NSAIDS	Arthalgia, arthritis, fever, sinusitis
Antimalarial	Mild skin disease, fatigue , arthalgia
Steroid & immunosuppr-essants	-More severe disease (GN- vasculitis- cerbral dis- blood dyscrasias) -Symptoms poorly controlled

Management of-Cutaneous Lupus Erythematosus

Treatment agent	Comment
Sun block	Blocks both UVA and UVB radiation
Antimalarials	Use of combination antimalarial therapy (hydroxychloroquine [Plaquenil] and quinacrine) or chloroquine (Aralen), which has more risk of retinopathy, is sometimes necessary
Dapsone	G6PD status should be checked
Retinoids	Avoid using in pregnant women
Corticosteroids	Use of corticosteroids may be necessary as part of initial therapy for severe discoid lupus or for lupus vasculitis; intradermal corticosteroids are helpful for individual discoid lesions, especially in the scalp
Immunosuppressive drugs	Methotrexate (Rheumatrex) or azathioprine (Imuran) is used as steroid-sparing drug
Thalidomide (Synovir)	One of the most effective drugs for treatment of discoid lupus, but teratogenicity and neuropathy will limit its acceptance and use

Future therapy

- **CTLA-4- Ig and anti-CD154 monoclonal antibodies –immunotherapy with anti-CD20 antibody ??**

  Agents which interfer with T-cell –B-cell collaboration are theoretically attractive but randomized trials are absent or disappointing .recently immunotherapy with rituximab has shown promise.


DERMATOMYOSITIS
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Dermatomyositis

- (DM) is an idiopathic inflammatory myopathy (IIM) with characteristic cutaneous findings. DM is a systemic disorder that frequently affects the joints, the esophagus, the lungs, and, less commonly, the heart.

Dermatomyositis

- In 1975, Bohan and Peter first suggested a set of criteria to aid in diagnosing and classifying DM and polymyositis (PM). Of the 5 criteria, 4 relate to the muscle disease; these include:

- Progressive proximal symmetrical weakness
- Elevated muscle enzyme levels
- Abnormal findings on electromyograms
- Abnormal findings from muscle biopsy.
- Compatible cutaneous disease.

Diagnosis :

Proximal muscle weakness with two of the three laboratory criteria

Epidemiology

- Race: **black patients** are 4 times more frequently affected than white patients
- Sex: Females are affected twice as often as males.
- Age: **has a bimodal peak .**

Causes

The cause of DM is unknown.

Factors that have been implicated :

- ✓ A genetic predisposition
- ✓ Immunologic abnormalities are common
- ✓ Infectious agents, including viruses (particularly coxsackievirus, echovirus, human T-lymphotropic virus 1 [HTLV-1], and human immunodeficiency virus [HIV]), *Toxoplasma* species, and *Borrelia* species, have been suggested as possible triggers of the disease.

- Several cases of drug-induced disease have been reported.
- DM-like skin changes have been reported with hydroxyurea in patients with chronic myelogenous leukemia or essential thrombocytosis.
- Other agents that may trigger the disease include penicillamine, statin drugs, quinidine, and phenylbutazone
  - DM may be initiated or exacerbated by silicon breast implants or collagen injections. However, this evidence is anecdotal and has not been verified in case-control studies.

Clinical manifestations:

- ✓ Ranges from DM with only cutaneous inflammation (amyopathic DM) to polymyositis with only muscle inflammation.
- ✓ Cutaneous involvement occurs in 30 to 40% of adults,

  95% of children
- ✓ Patients often present with skin disease as one of the initial manifestations. In as many as 40% of patients, the skin disease may be the sole manifestation at the onset. Muscle disease may occur concurrently, it may precede the skin disease, or it may follow the skin disease by weeks to years.
- ✓ Patients often notice an eruption on exposed surfaces. The disease is often pruritic, and, sometimes, intense pruritus may disturb sleep patterns. Patients may also complain of a scaly scalp or diffuse hair loss

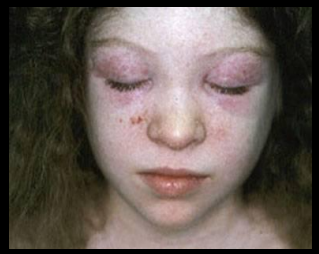
Clinical manifestations

- Muscle involvement manifests as proximal muscle weakness*
- Systemic manifestations may occur; therefore, a review of systems should assess for the presence of arthralgias, arthritis, dyspnea, dysphagia, arrhythmias, and dysphonia
- Malignancy is possible in any patient with DM, but it is much more common in adults older than 60 years*.

Skin manifestations

The characteristic and possibly pathognomonic cutaneous features of DM :

- ✓ The heliotrope rash
- ✓ Gottron papules



What is Heliotrope rash?

- The heliotrope rash consists of a violaceous to dusky erythematous rash with or without edema in a symmetrical distribution involving the periorbital skin.

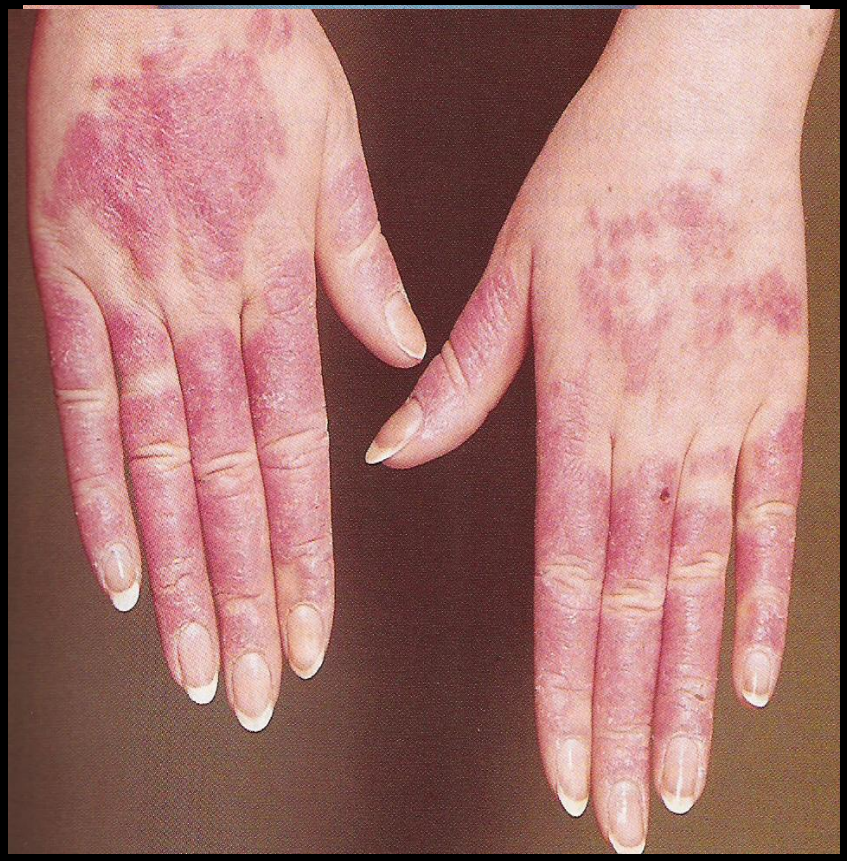
What is the difference between Gottron papules and Gottron sign?

- Gottron's sign: a pink to reddish purple atrophic or scaling eruption often over the knuckles, knees and elbows.
- Gottron's papules: are flat topped, polygonal violecous papules over the knuckles (less common but highly chracteristic)

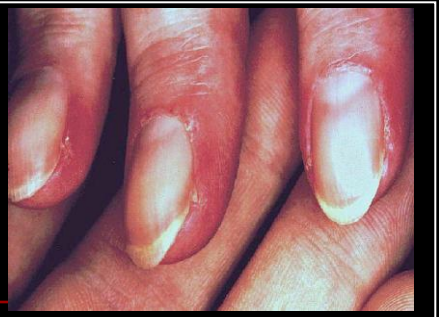
Skin manifestations

- Violaceous erythema and gottron's papules on the dorsum of the hands and fingers,especially over MCPJ & IPJ .periungual erythema and telengectasis

- Red to violaceous ,well demarcated papules and plaques on the dorsum of the fingers and hands ,characteristically sparing the skin overlying the joints.*



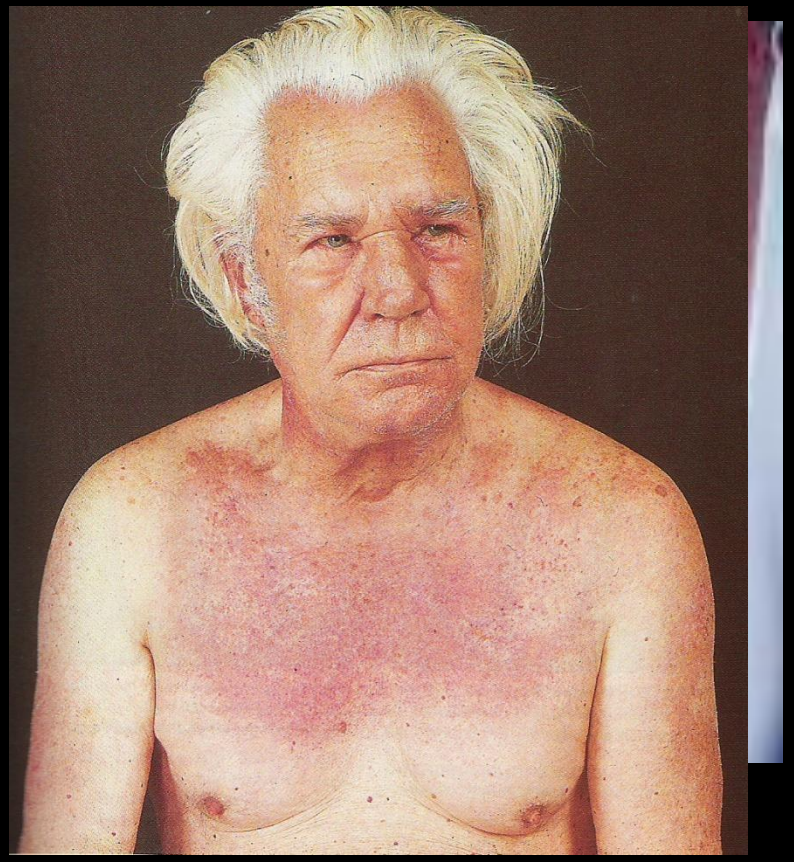
Skin manifestations



- ✓ Other cutaneous features are characteristic of the disease despite not being pathognomonic.
- ✓ Nail fold changes consist of periungual telangiectases and/or a characteristic cuticular change with hypertrophy of the cuticle and small, hemorrhagic infarcts in this hypertrophic area .
- ✓ Periungual telangiectases may be clinically apparent, or they may be appreciated only by capillary microscopy.

Skin manifestations

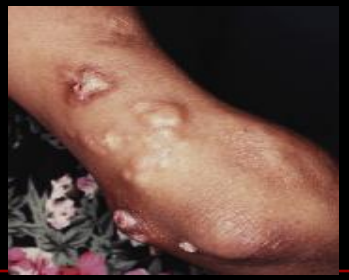
- Poikiloderma may occur on exposed skin, such as the extensor surfaces of the arm, the V of the neck (or the upper part of the back (Shawl sign).
- Shawl sign: highly associated with interstitial lung disease



Skin manifestations

- Facial erythema may also occur in DM. This change must be differentiated from lupus erythematosus, rosacea, seborrheic dermatitis, or atopic dermatitis.
- Scalp involvement in DM is relatively common and manifests as an erythematous to violaceous, psoriasiform dermatitis.

Skin manifestations



- Calcinosis of the skin or the muscle is unusual in adults, but it may occur in as many as 40% of children or adolescents with DM.
- Calcinosis cutis manifests as firm, yellow or flesh-colored nodules, often over bony prominences.
- Occasionally, these nodules can extrude through the surface of the skin, in which case, secondary infection may occur.

Differential Diagnosis:

- Lupus erythematosus
- Mixed connective tissue disease
- Steroid myopathy
- Toxoplasmosis

Laboratory studies:

Chemistry:

During acute active phase :

- ✓ elevations of creatine phosphokinase 65%
  Most specific for muscle disease
- ✓ Aldolase 40%
- ✓ Glutamic oxaloacetic transaminase
- ✓ Lactate dehydrogenase

Serology :

- ⇨ Myositis-specific antibodies (MSAs).
- ✓ ANA in < 60%..
- ✓ Anti-Jo-1 (anti-histidyl-t-RNA synthase) in 30%..
- ✓ Anti-Mi-2 is highly specific for DM, but it lacks sensitivity because its present only 25% of patients with DM, indicates good prognosis.

Other Invx:

- ✓ Urine :

  Elevated 24hr creatine excretion >200mg/24hr)
- ✓ EMG
- ✓ Muscle biopsy :
- ⇨ Inflammatory cell infiltrations & necrosis of muscle cells.
- ✓ MRI
- ✓ Barium study

Management:

- Prednisone 0.5 to 1 mg/kg /day

Increasing to 1.5mg/kg if lower dose ineffective taper when muscle enzyme approach normal

Best If combined with azthioprine 2 to 3 mg/kg/day

Alternatives:

- Methotrexate
- Cyclophosphamide
- High dose IV IG bolus therapy at monthly intervals


Scleroderma
(systemic sclerosis)
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Scleroderma(systemic sclerosis)

- Chronic multi-system disease which predominantly affects the skin & usually accompanied by Raynaud's phenomenon
- It is 3 to 5 times more common in women than men & present before the age of 50 years.

Etiology

- Unknown , although many abnormalities in both cellular & humoral immunity have been documented.
- There is an increase in dermal collagen & decrease in the elastic tissues which leads to typical thickening & immobility

Classifications

- ⇨ Limited cutaneous scleroderma (lSSc) 60% of cases
- This start initially with Raynaud's phenomenon ,often prior to the development of cutaneous manifestations
- The skin changes that dominate this disease are usually limited to hand , face & feet (acrosclerosis)
- High incidence of anticentromeric antibodies.
- ISSc include CREST syndrome (calcinosis, raynaud's phenomenon, esophageal involvement ,sclerodactyly, telangiectasia)
- Systemic involvement may not appear for years.

⇨ Diffuse cutaneous scleroderma (40% of cases) dSSc

- The skin changes develop more rapidly after the development of raynaud's phenomenon and are more wide spread.
- There is early involvement of other organs.
- Anti-centromere antibodies are uncommon but Scl-70 (antitopoisomerase 1) antibodies are present.

Skin manifestations in Scleroderma

Hands/Feet

- Early : Raynaud's phenomenon with triphasic color changes ,i.e.pallor ,cynosis, rubor , precedes sclerosis by months and years.

What is Raynaud's Phenomenon ?

It is digital ischemia that occurs on exposure to cold and/ or as a result of emotional stress.

causes:

1- Rheumatic disorders(SS 85%,SLE 35%, DM 30%, RA, PAN)

2- Diseases with abnormal blood proteins (cryoprotein, macroglobulins)

3- Drugs (b-adrenergic blockers, nicotine,cyclosporine)

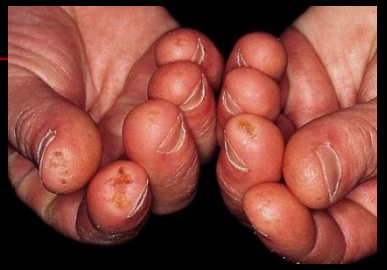
4- Arterial disease (atheriosclerosis obliterans)

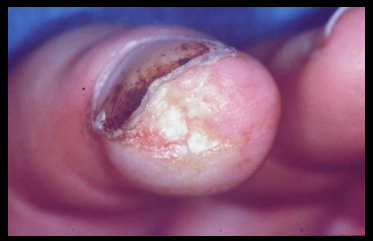
5- Carpel tunnel syndrome.

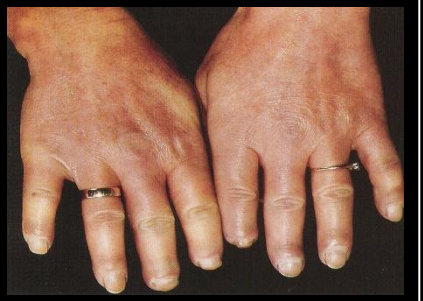
Skin manifestations in Scleroderma

2- Nonpitting edema of the hands & feet.

3- Painful ulceration at fingertips (rat bite necrosis),knuckles heal with pitted scars.





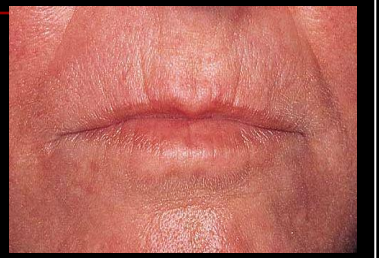


Skin manifestations in Scleroderma

Late :

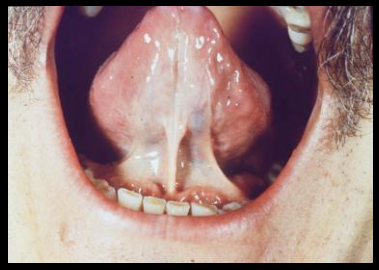
- ✓ Sclerodactyly with tapering of fingers (madonna fingers),with waxy ,shiny hardened skin,which is tightly bound down & doesn't permit folding or wrinkling
- ✓ Leathery crepitation over joints ,flexion contracture,periungual telangectasia
- ✓ Nails grow claw like over shortened distal phalanges.
- ✓ Bony resorption and ulceration results in loss of distal phalanges
- ✓ A sclerosis proceeds proximally , there is loss of sweat glands with anhidrosis and thinning and complete loss of hair on distal extremities.

Skin manifestations in Scleroderma



Face

- ✓ Early: periorbital edema
- ✓ Late : edema & fibrosis result in loss of normal facial lines (mask like) patient looks younger than they are.
- ✓ Thinning of lips, microstomia, radial perioral furrowing , small sharp nose, telangectasia and diffuse hyperpigmentation.



Trunk

- In dSSc the chest & proximal upper and lower extremities are involved early. Tense ,stiff & waxy appearing skin, that can't be folded
- Other changes: cutaneous calcification occurs on finger tips or over bony prominences or any sclerodermatous site , may ulcerate & extrude white paste.

Color changes

- Hyperpigmentation that may be generalized`and on extremities may be accompanied by perifollicular hypopigmentation.

Mucus membranes

- Sclerosis of sublingual ligament ,uncommonly ,painful induration of gums ,tongue.

Investigations

The diagnosis of scleroderma is primarily based upon the presence of characteristic skin changes.

- CBC
- ESR
- Autoantibodies
- ANA are often positive
- Anticentromeric AB occur in 21% ofdSSc
  71% of lSSc
- Scl-7 occur in 33% of dSSc
  18% of CREST
- Dermatopathology

Management

- ✓ Is symptomatic . There is no specific treatment.
- ✓ Systemic glucocorticoids may be of benefit for limited periods early in the disease.
- ✓ All other systemic ttt (EDTA, aminocaproic acid , D-penicillamine, para-aminobenzoate,colchicine ,immunosuppressive drugs),Have not been shown to be of lasting benefit.
- ✓ Presently interferon gamma is being tested clinically as photopheresis.

Thank YoU !!