Lecture (5)
Cutaneous Manifestations Of Connective Tissue Disease (Lupus, Dermatomyositis and Scleroderma)

Objectives:

1. Differentiate between the various types of CLE.
2. How to diagnose and investigate CLE.
3. Identify all of the current treatment options available for CLE.
4. To learn how to diagnose and investigate dermatomyositis.
5. How to manage dermatomyositis.
6. To learn the presentation of morphea and systemic sclerosis and ways to manage them.

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Color index: slides, doctor notes, extra explanation.

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Lupus Erythematosus (LE)

➔ Is a chronic, autoimmune disease that includes a broad spectrum of clinical manifestations.Its course and organs involvement are unpredictable.

➔ **LE is divided into:** (can occur both together or separately)
- ◆ Systemic lupus erythematosus (SLE).
- ◆ Cutaneous lupus erythematosus (CLE).

➔ Cutaneous form (CLE) can be divided based on histopathological findings into:
- ◆ **Histopathologically specific CLE:**
  - Acute cutaneous LE (ACLE).
  - Subacute cutaneous LE (SCLE).
  - Chronic cutaneous LE (DLE) Also Known as Discoid lupus.

- ◆ **Histopathologically non-specific LE:**
  - skin manifestations which are not exclusive to LE disease.

➔ **Risk of systemic disease:**
- ◆ Acute cutaneous LE → 100% .
- ◆ Subacute cutaneous LE → 50% .
- ◆ Chronic cutaneous LE → 10% .
  - Localized (Head and neck only) → Risk 5%.
  - Generalized → Risk 20% .

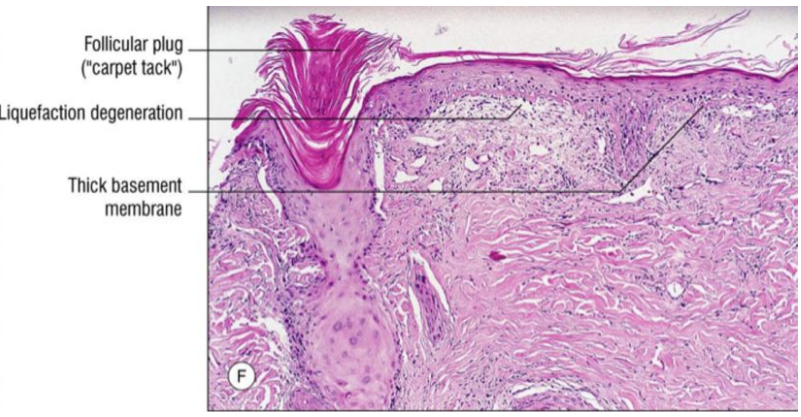
➔ **Epidemiology:**
- ◆ The female to male ratio is about 6:1 for ACLE and about 3:1 for both DLE and SCLE.
- ◆ DLE is common among African Americans and SCLE is common in Caucasians.
- ◆ Skin involvement is seen in about 70 to 80% of LE patients.
- ◆ DLE is the most common subset (80%).

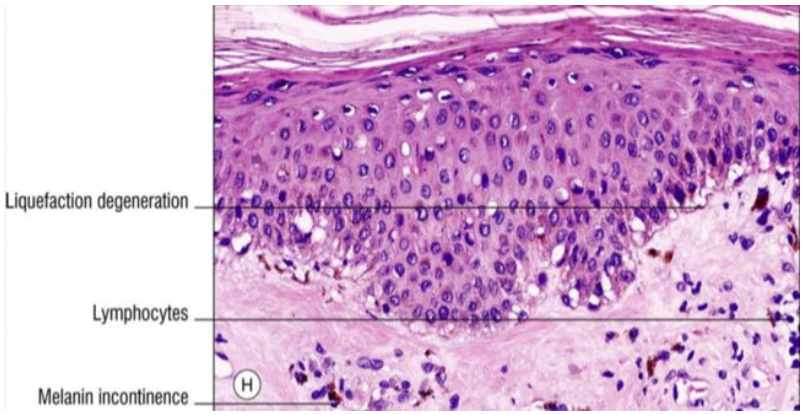
➔ **Pathogenesis:**

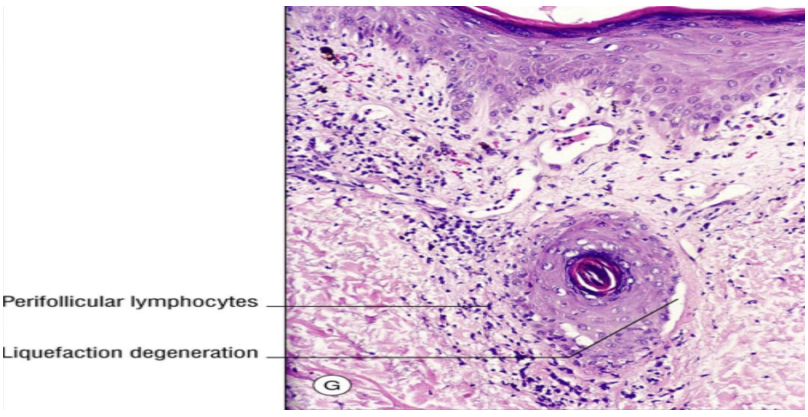
- ◆ Pathogenesis of CLE remains unclear
- ◆ CLE is multifactorial and polygenic.
- ◆ Complex interactions between genetics, environment (Ultraviolet light), and cells.
- ◆ Drug-induced subacute CLE and DLE: hydrochlorothiazide (Thiazide), terbinafine (antifungal medication), TNF-α inhibitors, antiepileptic, minocycline (tetracycline antibiotic) and proton-pump inhibitors.

➔ **Histopathology: (Features seen in histopathological specific CLE)**

a) Focal or continuous epidermal atrophy.
b) Follicular keratin plugs.
c) Vacuolar degeneration along the dermoepidermal junction zone.
d) Individual necrotic keratinocytes.
e) Pigment incontinence (melanin incontinence).
f) Thickening of basement membrane.
g) Moderate to dense superficial and deep lymphocytic infiltrate (Perivascular).
h) Abundant interstitial mucin deposits in the reticular dermis.







Histopathological LE-specific skin manifestations

(Pictures are in the end of the this section)

1. Acute CLE:
   Almost always associated with systemic disease.
   - Localized (Head and neck)
     - Malar rash (erythema that spares the nasolabial folds)
   - Generalized (more aggressive & uncommon)
     - Generalized maculo-papular exanthema or Photosensitive lupus dermatitis.
     - sun-exposed areas also associated with a previous sun exposure.
     - Sometimes it forms bullae.

2. Subacute CLE:
   - well-defined cutaneous and serological features.
   - Photosensitivity is a triggering factor.
   - it heals withOUT scarring
   - Two Forms:
     - Psoriasiform type (More likely to progress to Systemic lupus)
     - Annular, polycyclic type (more benign)
   - Subacute CLE is strongly associated with the anti- Ro/SSA and anti-la.
   - Subtype of SCLE:
     - Neonatal lupus:
       - Transient (6 months) condition caused by the transmission of the antibodies (Anti-Ro and Anti-LA) to the baby by the placenta.
       - More likely to exhibit the annular form of SCLE and also associated with complete heart block (90%) requiring a pacemaker.

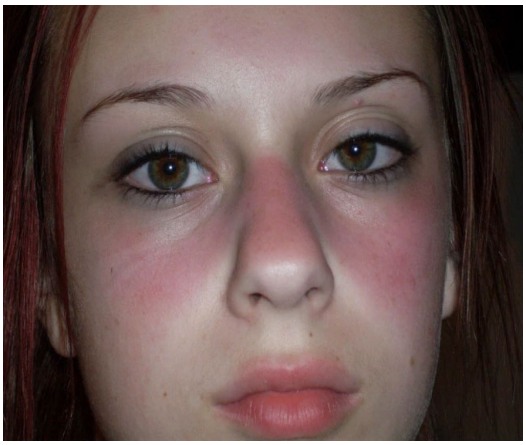
3. Chronic CLE: include the following subtypes:
    - **Discoid lupus erythematosus (DLE)**
        - **4 Clinical features:** Element of scars, Hypopigmentation hyperpigmentation (usually in the periphery) and telangiectasia.
        - Two types:
            - Localised (Head and neck)
            - Generalized.
        - If it involves the scalp it affects the hair follicles and may lead to alopecia.
        - Scalp, ears and cheeks are the most commonly involved areas.
        - Starts as subtle erythematous with scales and ends with a scar.

    - **Verrucous or hypertrophic LE**
        - Wart-like lesions most often on the arms and/or hands
        - Increased incidence of squamous cell carcinoma
        - Hyperkeratosis, thick layer of epidermis.

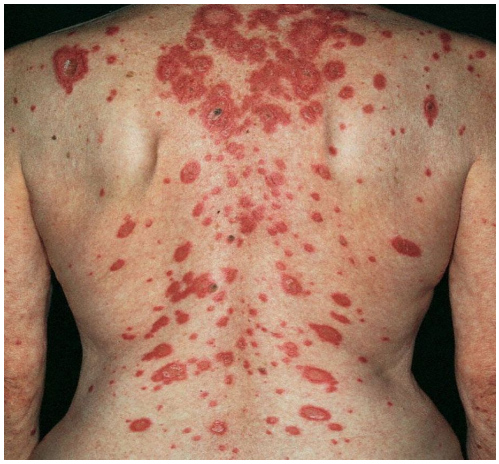
    - **Lupus profundus (panniculitis)**
        - Rare type of lupus that starts in the subcutaneous tissue rather than the usual site. (which is the the epidermis).
        - Destruction of the subcutaneous fat → atrophy of the skin.
        - Multiple painful, firm, subcutaneous nodules or plaques

    - **Chilblain lupus**
        - Predominantly in women.
        - Symmetrically erythematous to violaceous painful plaques over dorsal and lateral aspects of hands and feet, appearing during cold.
        - Microvascular injury secondary to exposure to cold and possibly hyperviscosity from immunological abnormalities.

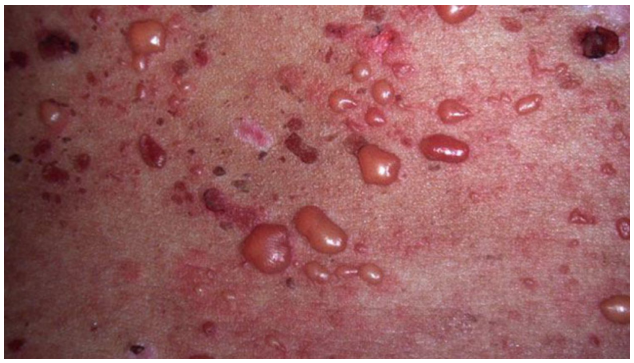
    - **Lupus Erythematosus Tumidus**
        - Erythematous, edematous, urticarial-like plaques usually over face.
        - Respond very well to treatment and doesn't leave scar.



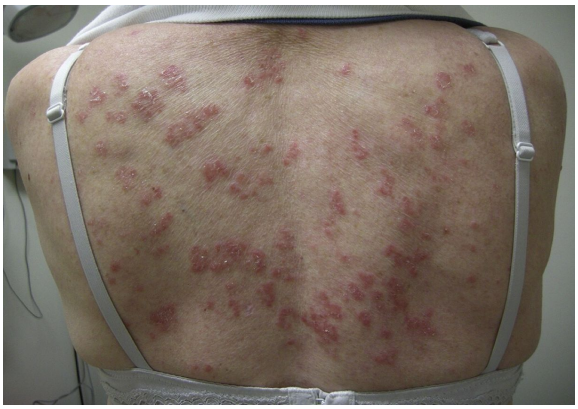
Localized acute CLE (malar rash)



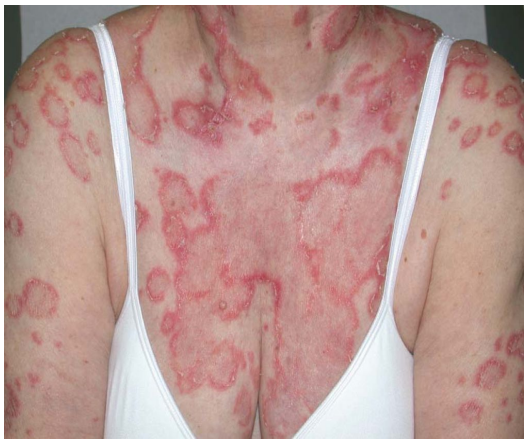
Generlized acute CLE



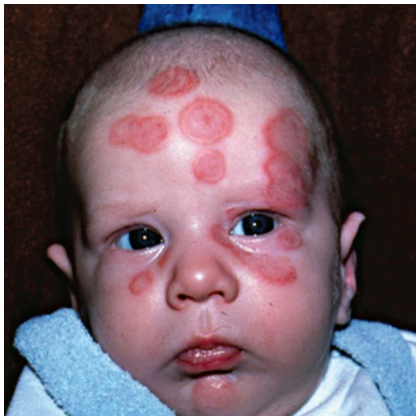
Generlized Acute CLE with bullae



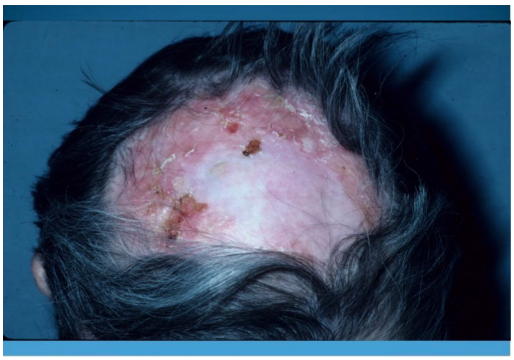
Psoriasiform type of subacute CLE



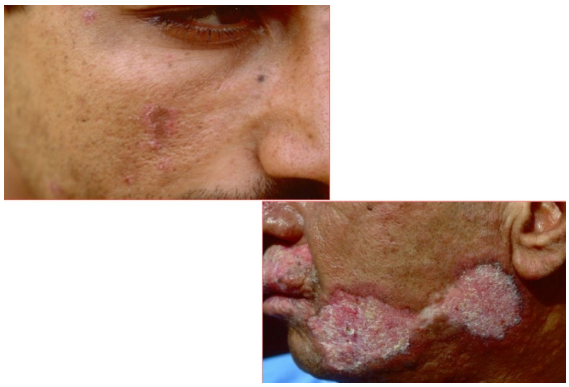
Annular form of SCLE



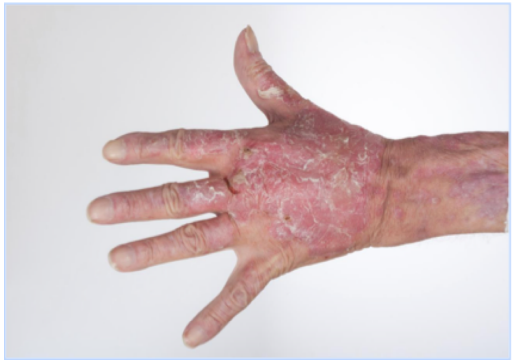
Neonatal lupus

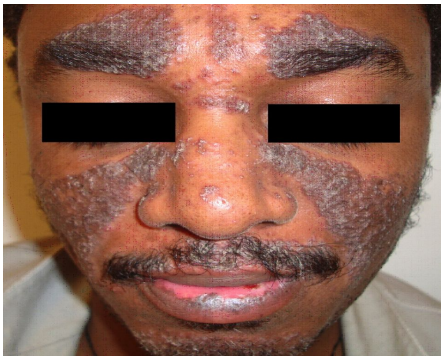


Discoid Chronic CLE with scarring alopecia

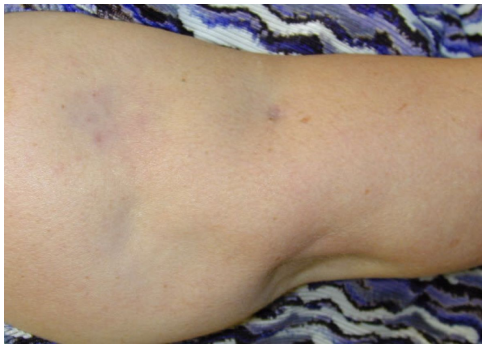


Discoid chronic CLE

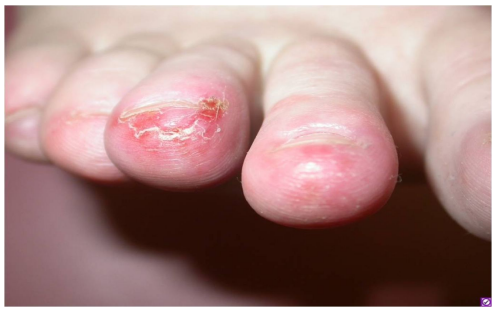




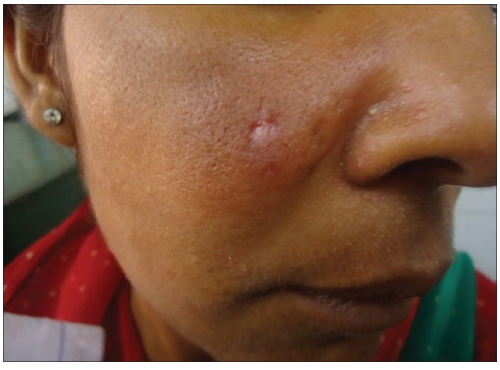
Verrucous or hypertrophic LE



Profundus chronic CLE (notice the atrophy)



Chilblain lupus



Lupus erythematosus tumidus

Histopathological LE- nonspecific skin manifestations

- Lupus is one of the great imitator (تتخفى في اي شئ).
- It may present as:
  - Vascular manifestation (Vasculitis) → purpura.
  - Vasculopathy → Raynaud's phenomenon, livedo reticularis, erythromelalgia (response to heat, opposite to raynaud's)
  - Photosensitivity
  - Three hair manifestation seen in Lupus:
    - Scarring alopecia
    - telogen effluvlum
    - Lupus hair (ماكلته العث يصير مهتري ومتقطع)
  - Oral lesions (recurrent ulcers)
  - Acanthosis nigricans
  - Bullous lesions(non-specific)
  - Porphyria cutanea tarda.
  - Calcinosis Cutis[1]

Differential diagnosis

- Acute CLE → Rosacea, drug-induced photosensitivity,Dermatomyositis , atopic dermatitis, seborrheic dermatitis.
- SCLE → Erythema annulare centrifugum, Psoriasis.
- Chronic → Psoriasis, sarcoidosis, Lichen planus.

[1] **Calcinosis cutis** (or cutaneous calcification) is a type of **calcinosis** wherein calcium deposits form in the skin.

Workup

1. Detailed history.
2. Detailed examination
3. Skin biopsy
4. Basic investigation : CBC, LFT's (liver function test), ESR[2], urinalysis.
5. Serology: ANA, dsDNA, complement (C3, C4, total), anti-phospholipid Abs, Anti-Ro and Anti-La.
6. Planning to start treatment you should do:
    a. Send the patient to ophthalmologist → if you are using hydroxychloroquine .
    b. Do the workup for the immunosuppressive if you're planning to use them.

Management

1. Prevention
    a. **Educate the patient and reassurance**
    b. **Heat, sun and drug avoidance**.
    c. Strict sunscreen adherence
    d. Strict sunscreen adherence is a critical component of therapy.
2. Acute → systemic therapy.
3. Subacute depends if it is associated with systemic manifestation or not.
4. Chronic depends if it is localized or generalized
    a. Localized → topical therapy
    b. Generalized → hydroxychloroquine (Systemic therapy)

5. Topical therapy:
    a. steroids
    b. calcineurin inhibitors.
6. Systemic therapy:
    a. First LINE → Hydroxychloroquine sulfate (Antimalarial Drug)
        i. Side effects: urticaria, blue-gray skin hyperpigmentation, ocular toxicity, gastrointestinal upset, myopathy, cardiomyopathy. (Not mentioned by the doctor)
    b. Second LINE → Systemic steroids: prednisone.
    c. Third LINE → Immunosuppressive therapy (Azathioprine,methotrexate)
    d. Best to treat lupus is thalidomide but because of the side effects it is not used (teratogenicity, irreversible peripheral neuropathy)

[2] Erythrocyte sedimentation rate

Dermatomyositis (DM)

1. A subtype of idiopathic inflammatory myopathies (IIMs).
2. Characterized by skin rash, proximal muscle weakness, and inflammatory infiltrates in the muscle tissue.
3. Rare disease.
4. 10 /1,000,000 in adults.
5. Adult F:M is 2:1
6. Two peaks of onset: ages 10-15, 45-55

➔ **Pathognomonic Cutaneous manifestations:**

- Heliotrope rash: violaceous to dusky erythematous rash with or without edema in a symmetrical distribution involving upper palpebra skin.
- Gottron's papules : slightly elevated, violaceous papules and plaques over extensor surface of finger joints.
- Gottron's sign: symmetric, non-scaling, violaceous to erythematous macules or patches, often atrophic, in the same distribution as Gottron's papules.

➔ **Cutaneous features are characteristic of the disease but not pathognomonic:**

- Facial erythema and edema.
- Poikiloderma in a photosensitive distribution: V-sign in upper chest.
- Poikiloderma over the upper back (shawl sign).
- Periungual erythema and cuticular changes.
- Scalp: Erythematous to violaceous, psoriasiform dermatitis.
- Mechanic's hand: Cracking and fissuring of the skin of the finger pads.

➔ **Other skin manifestations:** Non specific

- Photosensitivity.
- Vasculitis.
- Nonscarring alopecia.
- Calcinosis cutis.
- Vesiculobullous eruption.

➔ **Non-cutaneous DM manifestations:**

- Fever.
- elevated serum C-reactive protein level and ESR.

- Muscle pain on grasping or spontaneous pain.
- Proximal muscle weakness (upper or lower extremity and trunk).
- Nondestructive arthritis or arthralgias.
- Elevated serum creatine kinase or aldolase level.
- Myogenic changes on electromyography.
- Positive anti-Jo-1 antibody test (histidyl-tRNA synthetase).
- Pathologic findings compatible with inflammatory myositis.

Juvenile (childhood) DM

➔ Major differences of juvenile DM from adult DM include:

- Calcinosis.
- Vasculitis.
- Lipodystrophy accompanied by insulin resistance.

Drug-induced DM

Quinidine, NSIND, d-penicillamine, isoniazid and TNF antagonists.

Dermatomyositis and malignancy

- Older patients.
- Ovarian carcinoma, lungs, pancreas, breasts and gastrointestinal tract.

Systemic complications/associations:

- Cardiomyopathy and Cardiac conduction defects.
- Aspiration pneumonia secondary to respiratory muscle weakness.
- Diffuse interstitial pneumonitis/fibrosis.
- Muscle calcification.
- Ocular complications including iritis, nystagmus, cotton-wool spots, optic atrophy, conjunctival edema and pseudopolyposis.
- Internal malignancy.

DM Investigations:

- Muscle enzyme elevation: Serum CK, aldolase, ALT, LDH.
- CK is useful to monitor the treatment of DM.
- Autoantibodies: ANA levels, anti Jo-1: most common antisynthetase.
- Magnetic resonance imaging (MRI).
- Electromyography.
- Muscle biopsy.
- Skin biopsy.

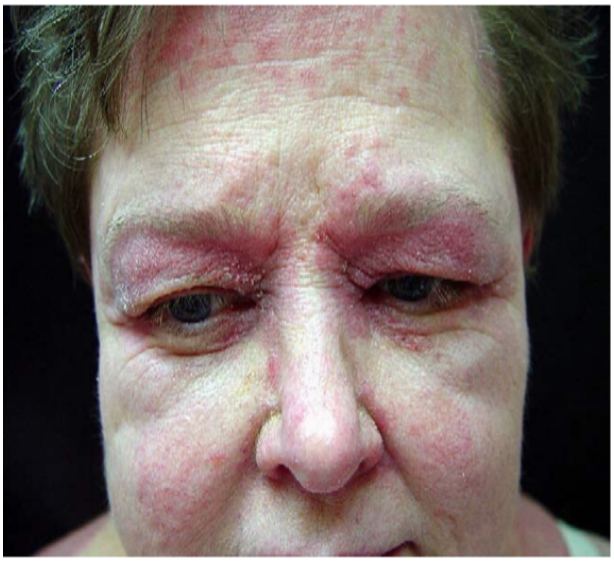
DM diagnostic Criteria:

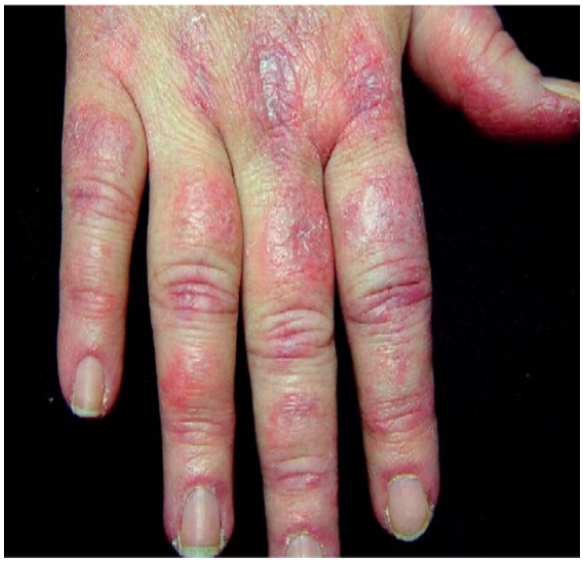
1. Symmetric proximal muscle weakness.
2. Biopsy evidence of myositis (MRI can subst).
3. Increased serum skeletal muscle enzymes.
4. Characteristic EMG pattern.
5. Typical DM skin lesions.

   DM possible (5 + any two of 1-4), probable (5 + any 3), definite (all 1-5)

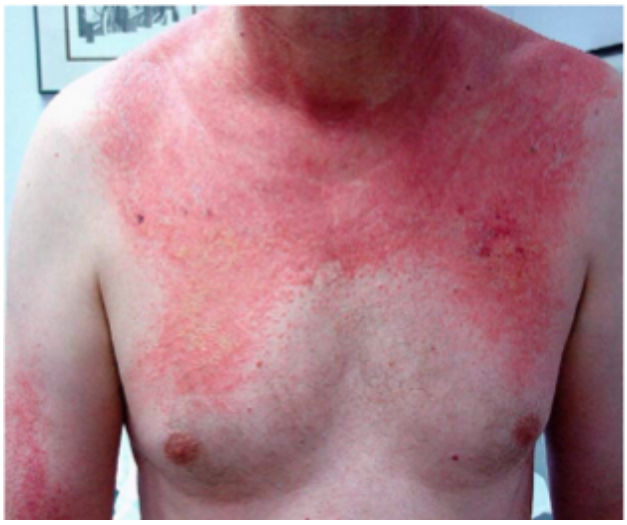
DM treatment:

- Oral prednisone (to prevent more muscle destruction): 0.5 to 1.5 mg/kg/day until serum creatine kinase normalizes, then slowly taper over 12 months.
- Methotrexate oral: 7.5 to 10 mg per week, increased by 2.5 mg per week to total of 25 mg per week.
- Azathioprine: 2 to 3 mg per kg per day tapered to 1 mg per kg per day once steroid is tapered to 15 mg per day. Reduce dosage monthly by 25-mg intervals. Maintenance dosage is 50 mg per day.
- Cyclosporine.
- Hydroxychloroquine.
- Topical steroids.

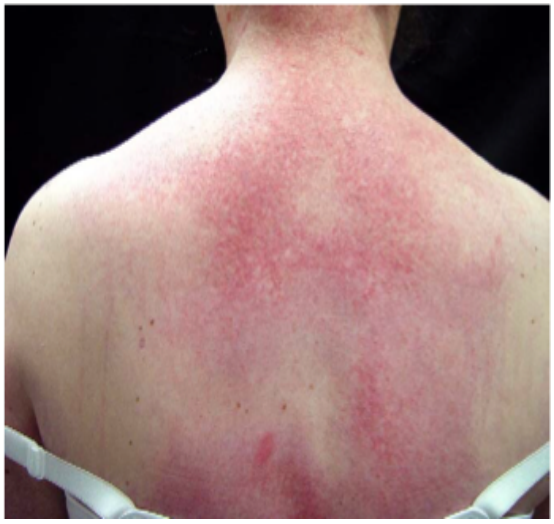




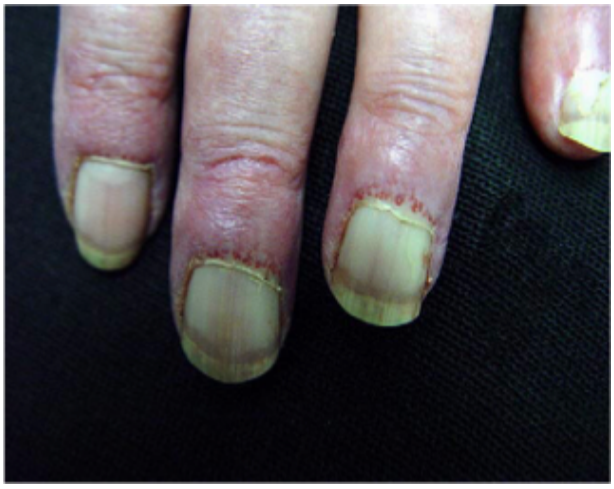
Heliotrope rash



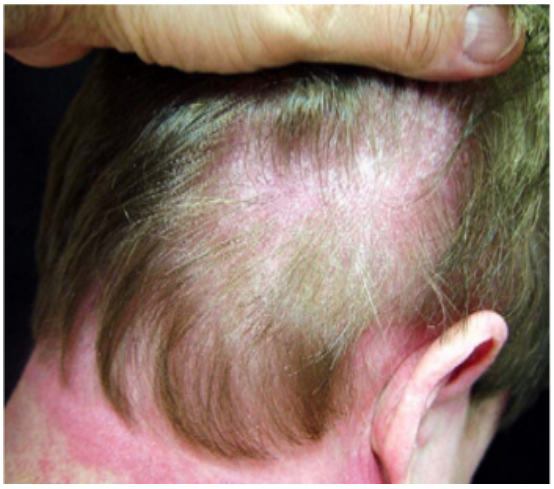
V-sign



Shawl sign



Periungual & Cuticular changes



Scalp

Scleroderma

- Chronic multisystem autoimmune disease.
- The hallmark of the disease is thickening and tightness of the skin. (Increased collagen+ inflammation- in place of skin appendages).
- Characterized by fibrosis of the skin as well as internal organs, e.g., lung, heart, gastrointestinal tract, and kidneys.
- Rare disease.
- Incidence: 50 cases per million in USA.
- Peak occurrence in the 30-40 years age group.
- F: M 4:1

1-Systemic scleroderma:

➔ Characterized by tissue fibrosis and immune abnormalities.

➔ Three cardinal pathogenetic features:

- ◆ microvascular involvement (vasodilation).
- ◆ activation of the immune system.
- ◆ increase of extracellular matrix deposition in the skin and internal organs

-Pathogenesis:

➔ Individual genetic background.

➔ Exposure to environmental triggers.

➔ Inducing vascular damage and fibroblast.

➔ Activate cells that have ability to give origin to endothelial cells, or collagen producing cells.

➔ These cells will migrate into injured tissues to differentiate into both endothelial cells and fibroblasts, to cause defective vasculogenesis or fibrosis or both, and to have immunomodulatory effects.

➔ The B cells in SSc are activated and produced anti-topoisomerase I and anti-centromere antibodies.

-Histopathology:

➔ Normal epidermis.

➔ Increased number of blood vessels.

➔ Huge amount of collagen.

➔ Absence of skin appendages.

-Serology:

- ➔ Antinuclear antibody--- positive for both (Limited & diffuse)
- ➔ Anticentromere antibody--- positive for Limited Cutaneous.
- ➔ Antitopoisomerase-1 antibody (anti-Scl-70)--- positive for Diffuse.

A-Limited Scleroderma:

- 45.5%
- Raynaud's phenomenon for years.
- Sclerosis limited to the extremities and face.
- Can involve perioral skin thickening (pursing of lips).
- Less organs involvement.
- Pulmonary hypertension.
- Centromere antibodies.
- Relatively good prognosis, >70% survival at 10 years.
- CREST syndrome: Calcinosis, Raynaud's phenomenon, Esophageal, dysmotility, Sclerodactyly, Telangiectasia.

B-Diffuse Scleroderma:

- 32,7%
- Raynaud's phenomenon for a few months.
- Diffuse sclerosis.
- Tendency to rapid progression of skin change.
- Early internal manifestations.
- Pulmonary fibrosis and Renal Crisis are more common.
- Variable but overall poor prognosis, survival 40-60% at 10 years.
- Scl-70 antibodies.

C-Overlap Syndrome 10,9%
D-Undifferentiated (very early) SSc 8,8%
E-Sclerosis sine Scleroderma 1.5%

-Cutaneous manifestations:

- ➔ Raynaud's phenomenon: Triggered by cold
  - ◆ Vasospasm of the digital microvasculature resulting in:
    - digital ischemia (pallor).
    - digital hypoxia (cyanosis).
    - digital reactive hypermedia (erythema).

- Hand features:
  - Swelling (non-pitting edema) of fingers and toes - a common early sign.
  - Sclerodactyly.
  - Swelling and sclerosis reduce hand movements, so patients may be unable to make a fist, or to place the palmar surfaces together - the 'prayer sign'.
  - Fingertips may have pitting, ulcers or loss of bulk from finger pads.
- Painful ulcerations. Due to tightness not ischemia
- Calcinosis: cause white spots or ulcerations and may be quite painful.
- Facial features:
  - Spider veins (telangiectasia).
  - Tightening of facial skin.
  - Tight lips (microstomia) - can make dental hygiene difficult.
- Truncal features:
  - Salt and pepper appearance of skin, due to areas of hypopigmentation and hyperpigmentation.
  - Dry or itchy skin; reduced hair over affected skin areas.

2-Localized scleroderma:

-CLASSIFICATION:

1-Plaque morphe:

- < 2.7 cases /100000
- F/M 2.4
- 40-50 years old.
- Caucasians.
- Positive personal or family history of autoimmune diseases.
- Role of trauma in the distribution of morphea lesions.
- Well-circumscribed oval-round red-brown plaques
- Trunk and limbs
- Different stages:
  - Inflammatory (Erythema)- take biopsy if + treat aggressive.
  - Typical.
  - Post-inflammatory hyperpigmentation.

2-Generalized morphea:

More severe (4 or more), characterized by extension of skin damage and its association with muscle damage.

3-Bullous morphea:

Characterized by tense subepidermal bullae in the presence of typical morphea or deep morphea.

4-Linear scleroderma (morphea):

Characterized by one or more linear streaks and induration that can involve dermis, subcutaneous tissue, muscle, and bone. It occurs on the extremities, face, or scalp of children and adolescents.

5-Deep morphea:

Subcutaneous morphea, morphea profunda, disabling pansclerotic morphea of childhood.

-INVESTIGATIONS:

- ➔ Skin biopsy
- ➔ Basic investigations:
  - ◆ ANA, RF.
  - ◆ Anti-Scl-70 (DNA topoisomerase I) antibody.
  - ◆ Anticentromere antibody.
  - ◆ Anti RNA polymerase III Ab: 10- 25% in Diffuse SSc, Renal Disease.

-Treatment of localized scleroderma

- ➔ Circumscribed:
  - ◆ Topical potent steroid
  - ◆ Tacrolimus (Calcineurin inhibitor)
- ➔ Generalized: (or early linear morphea)
  - ◆ nbUVB
  - ◆ MTX

-Diagnosis

RheumTutor.com

2013 ACR / EULAR Criteria For The Classification Of Systemic Sclerosis (Scleroderma)*

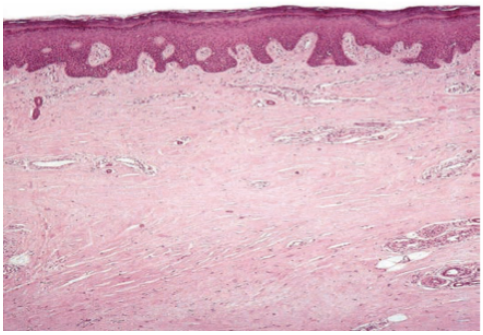
Item	Sub-items(s)	Weight/score †
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	-	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	-	3
SSc-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) *(maximum score is 3)*	Anticentromere 3 Anti–topoisomerase I Anti–RNA polymerase III	3

* The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).

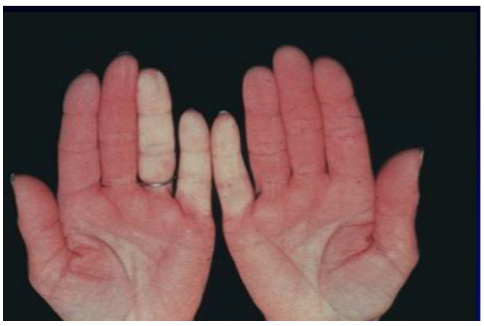
† The total score is determined by adding the maximum weight (score) in each category.
Patients with a total score of ≥ 9 are classified as having definite scleroderma.

Sensitivity 91% Specificity 92%

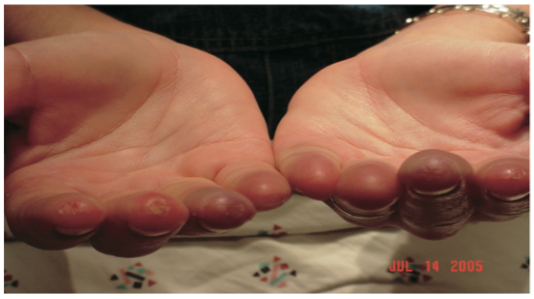
Van den Hoogen et al. 2013 Classification Criteria for Systemic Sclerosis. Arthritis and Rheumatism. Vol. 65, No. 11, November 2013, pp 2737–2747



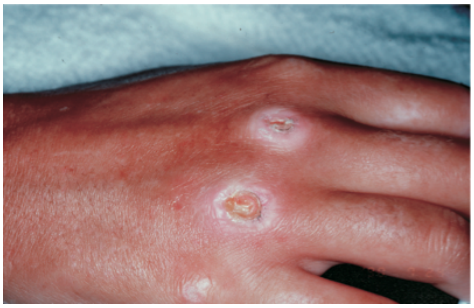
Histopathology



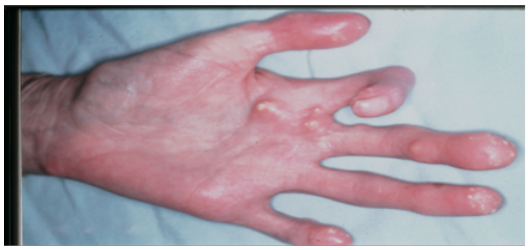
Raynaud's phenomenon



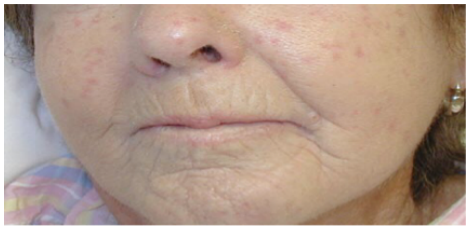
Hand features



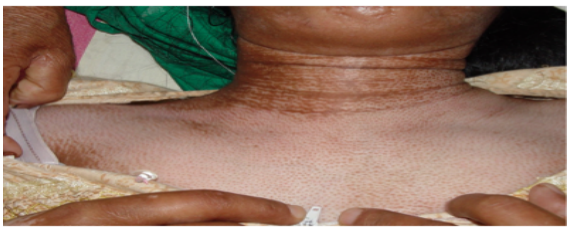
Painful ulcer

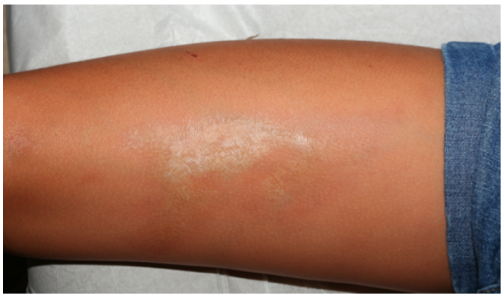


Calcinosis

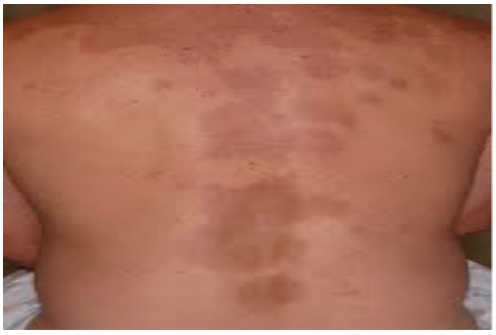


Face features

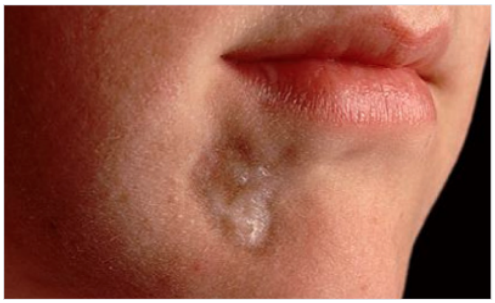




Truncal features

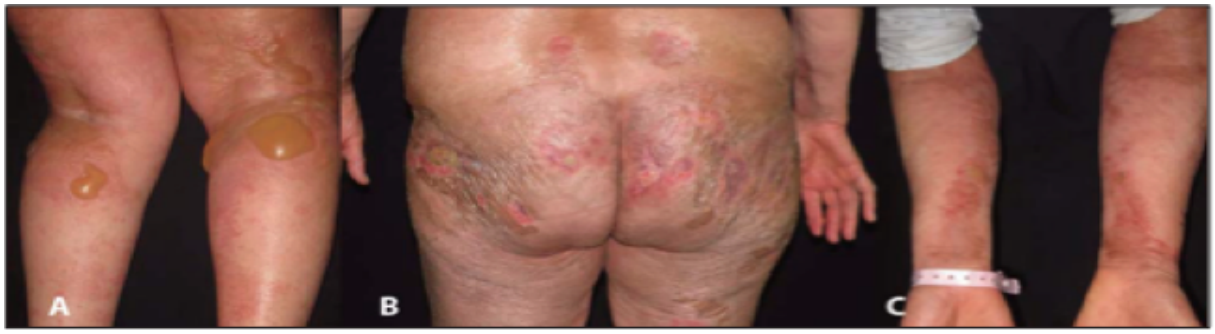


2nd stage plaque morphe

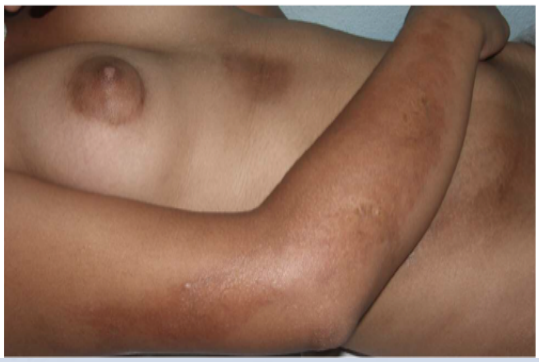


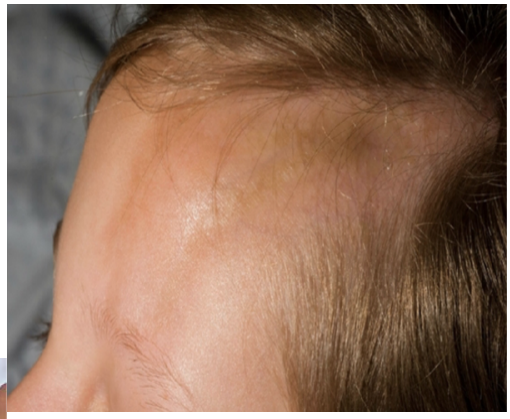
Generalized morphe

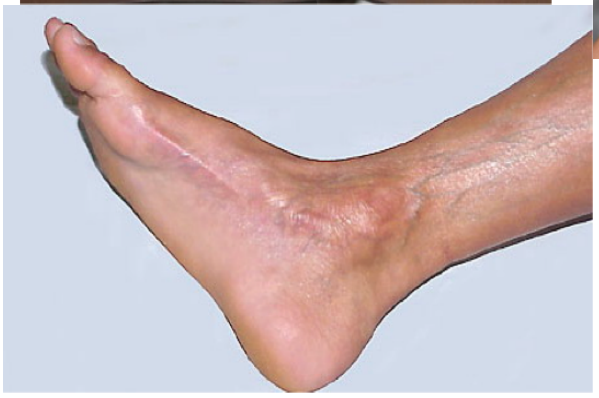
Deep morphe



Bullous morphe







Linear morphe all 3