Cutaneous Manifestations Of Connective Tissue Diseases

Objectives :

- Differentiate between the various types of Lupus (clinical presentation, investigations and management)
- Learn about Dermatomyositis (clinical presentation, investigations and management)
- Learn about the clinical presentations of morphea, systemic sclerosis and their management.
- 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.

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***Sources**: FITZPATRICK color atlas + 433 male + 434 + doctors slides and notes*

[Color index : Important | Notes | Extra]

(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

We'll only mention the first 4. This is just to show you connective tissue diseases in dermatology.

1) Lupus Erythematosus (LE):

- A multisystem disorder that predominantly affects the skin. If we have a patient with a non specific skin lesions we have to put lupus in the DDx.
- Its course and organs involvement are unpredictable (**Great mimicker)**.
- 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). The three major specific types are not mutually exclusive. In a given patient, more than one type may occur.
  - **Non-specific:** Raynaud's, Livedo Reticularis, Palmar Erythema, Periungual Telangiectasias.

Risk for systemic disease:

- Acute cutaneous LE (ACLE) 100%
- Subacute cutaneous LE (SCLE) 50%
- Chronic cutaneous LE (CCLE) (**DLE**) 10%

- **Epidemiology: (females more affected)**
- Incidence of CLE in Sweden and USA is 4/100,000.
- The female to male ratio is about 6:1 for ACLE and about 3:1 for both DLE and SCLE
- Almost 80% of systemic LE patients have skin involvement.
- DLE (CCLE) is common among **African Americans** and SCLE is common in Caucasians.
- DLE is the most common subset (80%).

- **SLE patients in Saudi Arabia**
- A study including 624 showed that 566 were females and 58 males with a mean age of 34.3 (range 8-71) years and mean age at disease onset of 25.3 years (range 0.08-67).

- **Discoid lupus erythematosus in a Saudi population**
- (THIS STUDY HAS BEEN DONE BY OUR KKUH DERMATOLOGY DEPARTMENT)
- Of the 56 DLE patients, females outnumbered males by 1.5:1. Mean age of onset was 36.5 ± 13.7 years and mean duration of the disease was 18.5 ± 24.6 **months**. Majority of patients (91.1%) had atrophic type. The **scalp** and **face** were the commonest sites of involvement.

◆ Pathogenesis Of CLE:

- Remains unclear
- CLE is multifactorial and polygenic.
- Complex interactions between **genetics**, **environment**, and cells.
- Ultraviolet radiation Play a role **(sun exposure)**

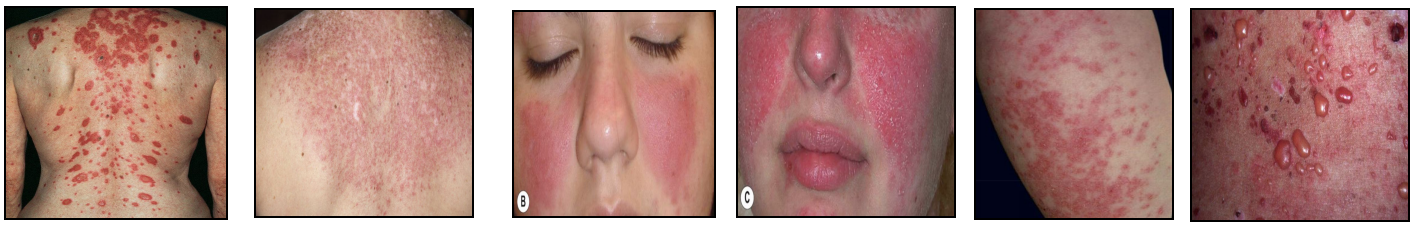
◆ Classification:

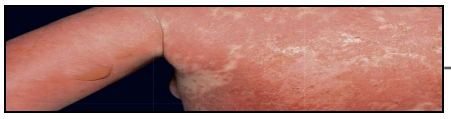
1. **Systemic form (SLE) (almost always associated with skin manifestations)**
2. **Cutaneous form (CLE)**. further divided base on histopathological findings
    a. **Histopathologically <u>specific</u> CLE:** will be talked about in detail
        i. Acute cutaneous LE (ACLE)
        ii. Subacute cutaneous LE (SCLE)
        iii. Chronic cutaneous LE (CCLE) or (**DLE,** Tumid lupus, lupus panniculitis) (most common)
    b. **Histopathologically <u>non-specific</u> LE-skin manifestations**
        i. which are not exclusive to LE disease
        ii. Raynaud's, livedo reticularis, palmar erythema, periungual telangiectasia

Note: **SLE and CLE can occur simultaneously or separately**

Acute cutaneous lupus erythematosus (ACLE):

- **These patients must be evaluated carefully for evidence of internal disease**. ACLE usually indicate systemic disease. **Always** check for systemic involvement.
- The lesions tend to be **<u>transient</u>**, follow **<u>sun exposure</u>**, and resolve **<u>without scarring.</u>**
- Bilateral Malar erythema (Butterfly rash). **Sparing of the nasolabial folds** helps differentiate lupus from rosacea.
- The morphology ranges from mild erythema (hard to be noticed by the physician) to intense edema.
- **Telangiectasias, erosions, dyspigmentation and epidermal atrophy** help distinguish the malar erythema from other facial rashes. Could be scaly like picture c.
- The duration may range from a few hours to several weeks.
- Sometimes may be more widespread in distribution. Rarely involves areas other than the face.
- What I want you to know about ACLE is malar rash and it usually indicates systemic involvement.

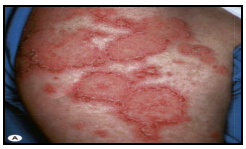




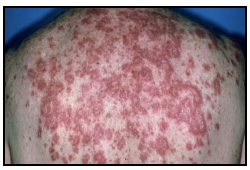
Toxic epidermal necrolysis-like eruption of acute lupus erythematosus.This presentation has also been referred to as a form of acute syndrome of apoptotic pan-epidermolysis (ASAP)

-If other parts of the body are involved (other than the face, e.g. back) it means that the disease is very aggressive
-Erythema multiforme-like skin lesions > Rowell's syndrome. Rowell syndrome is a rare disease consisting of erythema multiforme-like lesions associated with lupus erythematosus. The syndrome occurs mostly in middle-aged women.

Subacute cutaneous lupus erythematosus (SCLE):



Lesions are most commonly seen on the sun-exposed aspects of the upper extremities. The margins of the annular lesions may have scale-crust



Numerous erythematous annular plaques on the back, some of which have associated white scale. Note the photodistribution.

- Typically **Photosensitive**, lesions confined to sun-exposed skin.
- The **midfacial skin is usually spared** (difference between SCLE and ACLE), 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 **1) annular configuration** (first picture, Raised red borders and central clearing) or a **2) papulosquamous/ Psoriasiform type (more likely to progress to systemic)** (second picture,Eczematous or psoriasiformappearance) presentation.
- Lesions often result in dyspigmentation (mainly hypopigmentation) but **do not scar.**
- 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 (SSA) autoantibody** and anti-la. (Approximately 70%)

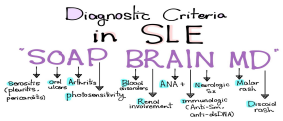
Drug induced SCLE:

- SCLE lesions can appear after receiving certain medications including:
  - **Hydrochlorothiazide and terbinafine** antifungal (most common)
  - Calcium channel blockers
  - NSAIDs (naproxen)
  - Griseofulvin antifungal
  - Antihistamines
  - TNF-α inhibitors, antiepileptic, minocycline and proton-pump inhibitors.
- The lesions may or may not clear once the medication is discontinued

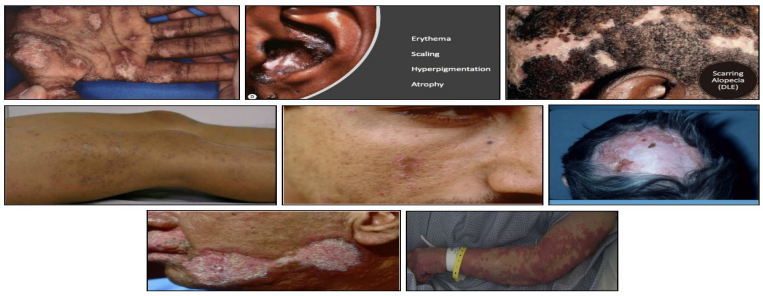
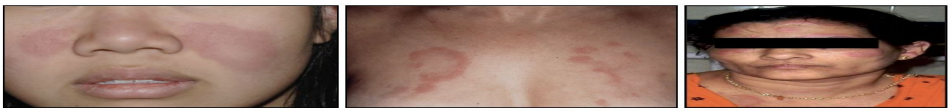
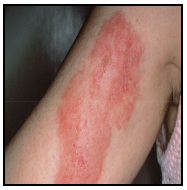
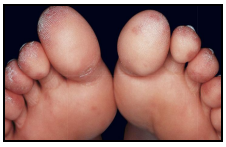
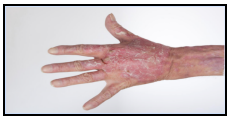
Chronic CLE:

1- Discoid lupus erythematosus (DLE):

One of the **most common** skin manifestations of Lupus.

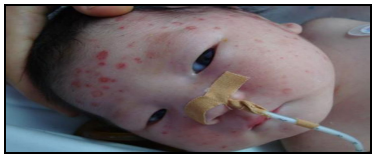
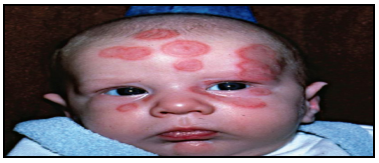
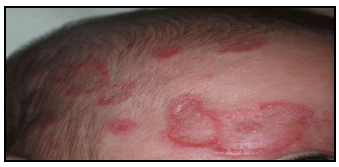


- Most often involves the **face,scalp and ears.**
- 60-80% is **localized** form above the neck and 20-40% is **generalized** form.
- Unusual to present below the neck without lesions present above the neck.
- Have a chronic course, less chance of remission. More difficult to control
- No clear association between sun exposure and developing DLE lesions.
- DLE lesions have the **potential for scarring**. If left untreated.
- Active lesions tend to feel indurated on palpation.
- **Follicular plugging** and **scarring alopecia** Irreversible hair loss.
- **Dyspigmentation** (Hypo in the central area and hyper at the periphery).
- Only 5-15% of DLE patients eventually develop clear-cut SLE.
- The risk is higher in patients with widespread discoid lesions. The more widespread lesions the higher is the chance of developing SLE.
- Remember: Discoid lesions represent 1 of the 11 ARA criteria for SLE. (mentioned in page 11)
- Hypertrophic DLE is an unusual variant (Thick, scaly) mostly on the arms
- Scarring vs non scarring alopecia: look with a magnifying glass, if hair follicles are seen hair might grow back (non scarring)

	 DLE:Lesions, which favor the head and neck region, may show erythema, scaling, atrophy and dyspigmentation in addition to scarring (and alopecia). Less common sites include the palms. 1st pic on the right: Discoid lupus lesions with dyspigmentation and scarring alopecia.Hypopigmentation often develops centrally with hyperpigmentation at the periphery.
2- Lupus erythematosus tumidus (LET):	• Induration and erythema **without scaling and follicular plugging.** • Photosensitivity > 70% (severe type). • **Erythematous, edematous,** urticarial-like plaques usually over face • The **epidermis is uninvolved** but has intense dermal inflammatory infiltrate. • Appears on the face and trunk. • **Negative serology**, does not lead to systemic disease.  Annular pink plaques on the chest and pink–violet plaques on the face.None of the lesions have epidermal change.
3- Lupus panniculitis (LEP):	• Rare presentation of CCLE • Involvement of deeper areas of the skin all the way down to the **fat**. • 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) • Very firm and indurated. Can have secondary changes. • Multiple painful, firm, subcutaneous nodules or plaques.  Pic : Erythematous plaque on the upper arm. The lesions may resolve with lipoatrophy
4- Chilblain lupus:	• **Chilblains** are small, itchy swellings on the skin that occur as a reaction to cold temperatures. 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**. Appears after exposure to cold weather. • The lesions may represent the concurrence of ordinary chilblains with LE,although, with time, the lesions may develop a discoid lesion.  pic : Violaceous plaques, some with scale, on toes. If there is a family history of this disorder, the possibility of mutations in TREX1, which encodes a DNA exonuclease, can be considered.
5- Verrucous hypertrophic LE	• **Wart-like** lesions most often on the arms and/or hands • Typical DLE lesions elsewhere • Differential diagnosis – warts, KeratoAcanthoma, **SCC** 

Neonatal lupus: (NLE)

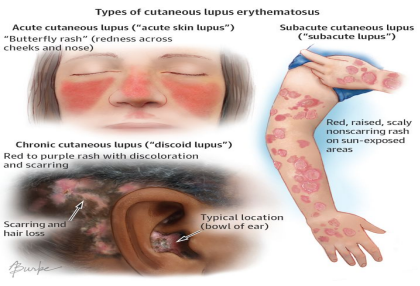
- May occur in infants whose mothers have **anti-Ro autoantibodies** anti-La/SSB antibodies and more rarely Ribonucleoprotein(RNP) antibodies.
- In babies who have NLE, the SCLE-like lesions are histologically identical to those of SCLE in adults.
- Transmission of antibodies over the placenta which can **cause congenital heart block** and cutaneous manifestations
- Resolve spontaneously as the titers of maternal antibodies degrade within the first 6 months
- **Almost 100% of babies with NLE have anti-Ro (SSA) 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.
- 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 (cardiac changes), CBC (thrombocytopenia) and LFT (liver involvement).
- Lesions look similar to SCLE (annular). > annular erythematous plaques
- Cutaneous signs include a SCLE-like rash, erythematous, non-scarring annular plaques most typical occurrence in the face and especially periorbital (“raccoon or owl eye”)

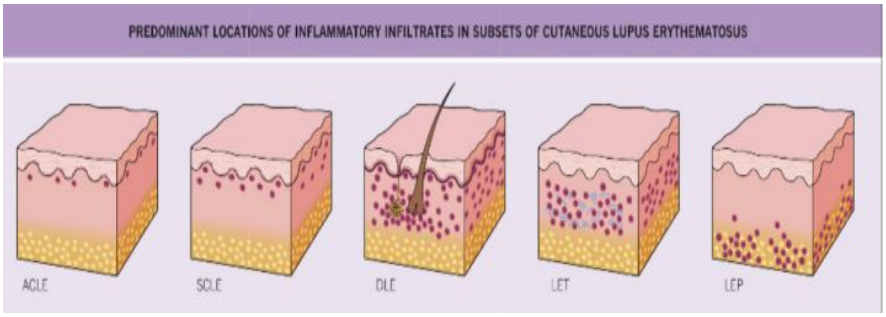




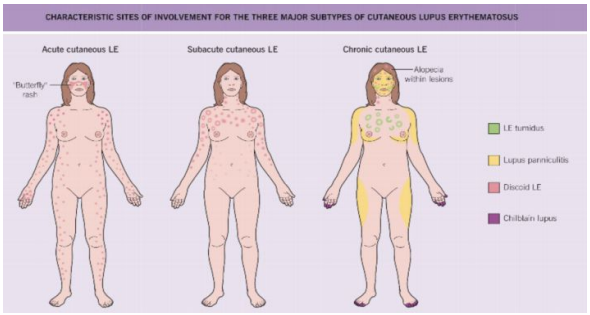
Drug induced lupus:

- 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…

- Quick summary: ACLE → butterfly rash SCLE → red raised scaly non scarring rash in sun exposed areas DLE → involves face, scalp, and ears
  - ACLE and SCLE: epidermal and upper dermal
  - DLE: superficial and deep dermis and around hair follicles
  - Lupus tumidus: superficial and deep dermis
  - Lupus panniculitis: subcutaneous fat



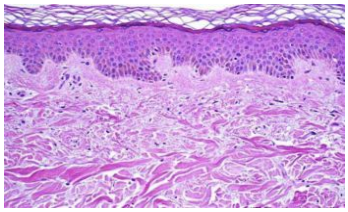
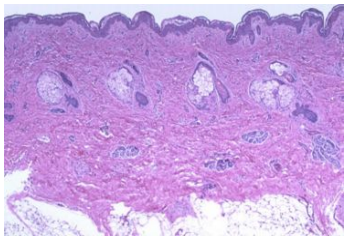
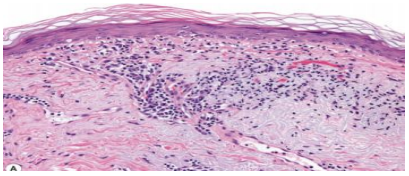
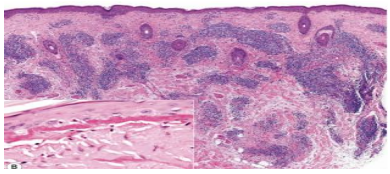




Predominant locations of inflammatory infiltrates in subsets of cutaneous lupus erythematosus. The types of cutaneous lupus erythematosus are: (ACLE),(SCLE), (DLE),(LET) and (LEP); the latter three are forms of chronic cutaneous lupus erythematosus. The primary locations of the infiltrates are as follows: superficial dermis, ACLE and SCLE; superficial plus deep dermis and periadnexal, DLE; superficial and deep dermis, LET; and subcutaneous fat, LEP. The final diagnosis requires clinicopathologic correlation

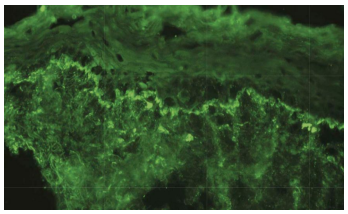
◆ Diagnosis:

- History and physical examination.
- Skin biopsy (+/- DIF). Almost all cases will need skin biopsy.
- Autoantibodies (ANA, Anti-DsDNA, Anti-Sm)
- CBC with differential.
- Urinalysis, BUN, Creatinine.
- ESR, CRP.
- Complement levels (C3, C4). The lower the complement level the higher the chance of having nephritis.

Skin biopsy (lesional): The most valuable diagnostic test		
Normal	**ACLE**	**DLE**
 	 • Inflammatory cells near the epidermal-dermal junction • Basal layer vacuolization (white halo) • Acute cutaneous LE showing interface dermatitis with vacuolization of basal keratinocytes and sparse superficial lymphoid infiltrates	 • Inflammation around hair follicles and adnexal structures (dark areas) • Thickening of basement membrane • Chronic discoid LE showing focal interface dermatitis and dense perivascular and periadnexal lymphoid infiltrates throughout the entire dermis. A thickened basement membrane is a characteristic finding and can be highlighted by PAS staining.
Direct Immunofluorescence (DIF)		
• Done to support the diagnosis, negative results does not exclude dx. • Lesional DIF: Granular deposition of IgG/IgM in the DEJ(Dermoepidermal junction) and around hair follicles. • Non-lesional DIF (Normal skin) is referred to as ''**Lupus band**'' test. Positive reaction usually indicates systemic SLE.		

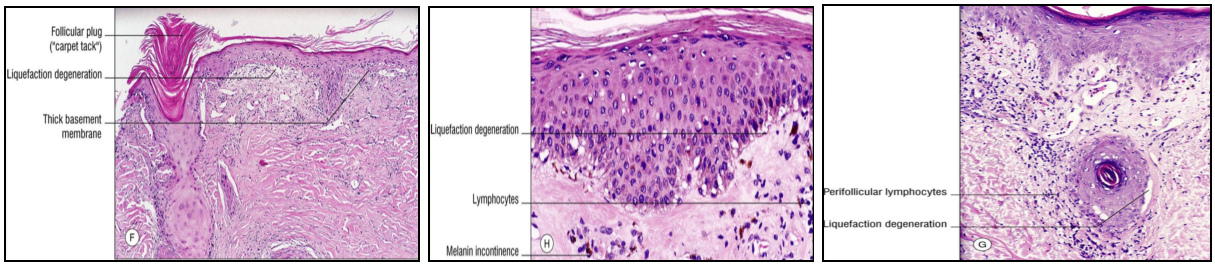
Direct immunofluorescence of cutaneous lupus.

Granular deposits of IgM are present at the dermal–epidermal junction within lesional skin. Antibody deposits at the dermal–epidermal junction are the most characteristic immunohistologic finding in lesions of cutaneous lupus and normal skin of patients with systemic lupus erythematosus.



◆ CLE Histopathology IMP (DR. SAID IN THE EXAM) (Not mentioned by F2 doctor)

- Focal or continuous epidermal atrophy (epidermal thinning)
- Follicular keratin plugs (around hair follicles)
- Vacuolar degeneration along the dermo-epidermal junction zone (we will see a gap)
- Individual necrotic keratinocytes
- Thickening of basement membrane (one of the major criteria)
- Abundant interstitial mucin deposits in the reticular dermis
- Moderate to dense superficial and deep perivascular and periadnexal lymphocytic infiltrate (inflammatory cells)
- Note (melanocyte produce melanin which goes to keratinocytes the question is what will happen if the keratinocytes are destroyed where will the melanin go? It will go to the demis Its called melanin incontinence the dermis will be pigmented



◆ Histopathologically non-specific LE-skin manifestations (not mentioned by F2 doctor)

- Photosensitivity
- Vasculitis: Palpable and nonpalpable purpura Urticarial-like vasculitis (Hypocomplementemic urticarial vasculitis)
- Vasculopathy: Raynaud's phenomenon, Livedo reticularis, Erythromelalgia
- Urticaria
- Non-scarring alopecia: telogen effluvium, Alopecia Areata, lupus hair imp
- Scarring alopecia (discoid lupus) imp
- Oral lesions aphthous ulcers
- Bullous lesions (non-specific)
- Acanthosis nigricans
- Mucinous infiltration
- Porphyria cutanea tarda.
- Acanthosis nigricans.
- Calcinosis Cutis

◆ 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

◆ Diagnostic criteria of SLE:

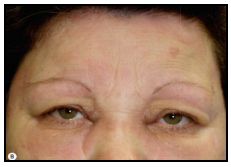
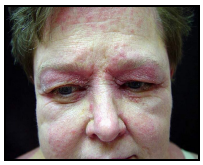
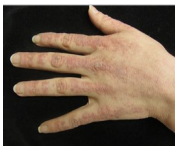
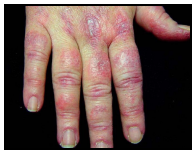
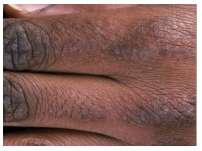
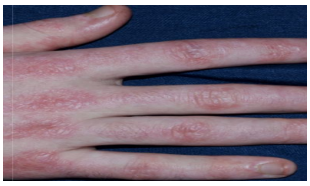
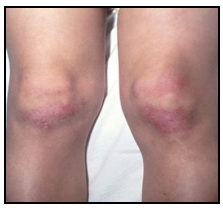
- **<u>ACR criteria for diagnosis of SLE (4 out of 11):</u>**
  - **Malar Rash**
  - **Discoid Rash**
  - Photosensitivity
  - Oral ulcers
  - Arthritis
  - Serositis (Pleuritis OR Pericarditis)
  - Renal disorder (Proteinuria OR Cellular casts)
  - Neurologic disorder (Seizures OR Psychosis)
  - Hematologic disorder (Anemia OR leukopenia OR lymphopenia OR thrombocytopenia)
  - **Immunologic disorder (Anti-DNA OR Anti-Sm OR antiphospholipid AB's)**
  - **Antinuclear antibody (ANA)**

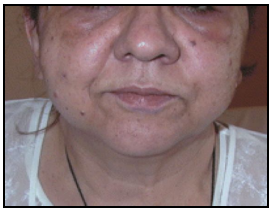
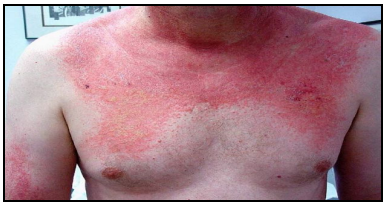
◆ CLE Management:

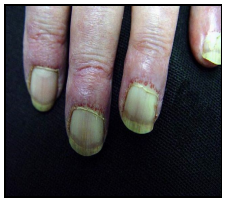
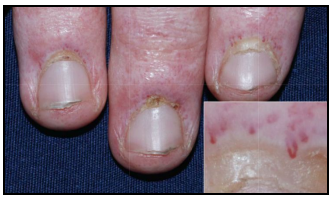
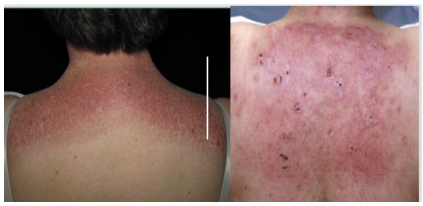
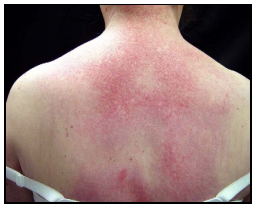
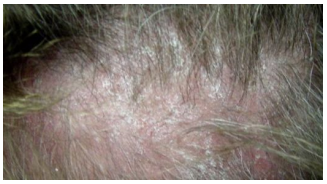
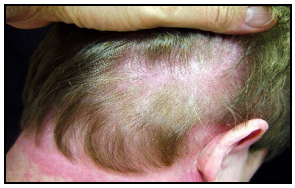
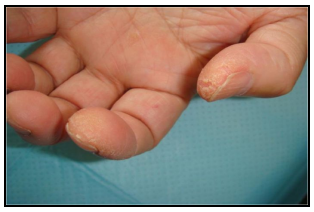
- **Sun protection** very important!
- Topical therapy
  - Topical steroids
  - Topical Calcineurin inhibitors e.g. Tacrolimus
  - ILK injections (intralesional kenalog ''steroid'' injection)
- Systemic Therapy
  - 1st line: Antimalarials (Hydroxychloroquine, Chloroquine, Quinacrine), Systemic steroids
    - Antimalarials side effect: xerosis, exanthematous or lichenoid drug eruptions, urticaria, blue-gray skin hyperpigmentation, **ocular toxicity, gastrointestinal upset**, myopathy, cardiomyopathy, and rare central nervous system side effects (dizziness, headache, insomnia, psychosis).
  - Others (Retinoids, Thalidomide, Mycophenolate, azathioprine, systemic steroids….)

2) Dermatomyositis:

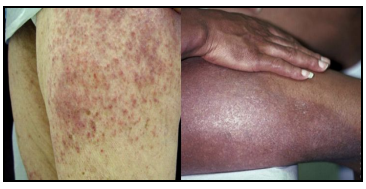
- A subtype of idiopathic inflammatory myopathies (IIMs)
- Characterized by **skin rash, proximal** muscle weakness, and inflammatory infiltrates in the muscle tissue.
- A relatively rare disease of presumed autoimmune pathogenesis that mainly affects the skin and muscles.
- Bimodal age distribution.
- 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)
- Some pts don't have muscle symptoms but if you test them there's inflammation (Hypomyopathic dermatomyositis)

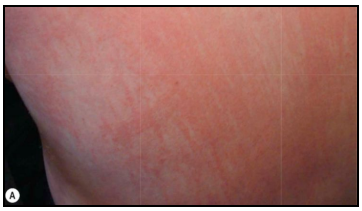
Clinical presentation	
Pathognomonic Cutaneous manifestations: Only one is enough for diagnosis	
1. **Heliotrope rash** : violaceous to dusky erythematous rash with or without edema in a symmetrical distribution involving upper palpebra skin.	 
2. **Gottron's papules:** slightly elevated, violaceous papules and plaques over extensor surface of finger joints Gottron's papules are erythematous to violaceous papules that occur symmetrically over the extensor (dorsal) aspects of the metacarpophalangeal (MCP) and interphalangeal (IP) joints	  
3. **Gottron's sign:** symmetric, non-scaling, violaceous to erythematous macules or patches, often atrophic, in the same distribution as Gottron's papules. Some people define them as gottron's papules but patches not bumps and some define them as gottron's papules in areas other than the hand.	 

Characteristic Cutaneous features but not Pathognomonic	
	
A- Facial erythema and edema	**B-Poikiloderma** a photosensitive distribution: **V-sign** Poikiloderma a rash that has: hyperpigmentation, hypopigmentation, atrophy, and telangiectasia

 	 
C-Periungual and cuticular changes Dilation of capillary loops at the proximal nailfold Ragged and thickened cuticles, cuticular overgrowth, and periungual erythema.	**D-Poikiloderma** over the upper back **(shawl sign)** Poikiloderma refers to skin that demonstrates both hyperpigmentation and hypopigmentation, as well as telangiectasias and epidermal atrophy. In DM, patients may demonstrate poikiloderma in any photo-exposed site; however, classic areas of involvement are the upper back (shawl sign)
 	
E- Scalp: Erythematous to violaceous, **psoriasiform** dermatitis	**F. Mechanic's hand** :Cracking and fissuring of the skin of the fingerpads

- **Common:**
  - Heliotrope sign
  - Eyelid edema
  - Gottron's papules
  - Gottron's sign
  - Photodistributed Poikiloderma (V-sign, Shawl sign, Facial erythema)
  - Psoriasiform scalp rash
  - Nailfold changes (Ragged cuticles nail fold telangiectasia)
  - Calcinosis Cutis (Juvenile DM)
  - Pruritus.
- **Uncommon:**
  - Cutaneous erosions or ulcerations
  - **Holster sign** (first picture) poikiloderma of the lateral thigh
  - **Flagellate Erythema** (picture A) seen in the back
  - Vesiculobullous lesions
  - Exfoliative erythroderma
  - Panniculitis
  - Gingival Telangiectasia
  - Pustular eruption of the elbows and knees
  - Lipoatrophy
  - Small vessel vasculitis





◆ Systemic DM manifestations:

- 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.
  - Ask questions like: are you able to comb your hair? Are you able to sire to your feet from a sitting position? Also cover a full systematic review to check for systemic involvement of DM and/or overlap with over CTDs.

◆ 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.

Juvenile (childhood) DM

Major differences of from adult dm include:

- **More Calcinosis imp**
- **More Vascular inflammation imp**
- Lipodystrophy accompanied by insulin resistance

Drug-induced DM

- Quinidine
- **NSAID**
- **D-penicillamine**
- isoniazid and
- TNF antagonist

◆ Investigations:

- History, physical exam
- Skin: Biopsy (suggestive but not diagnostic)
- Serology: Autoantibodies.
- Muscle: Serum CK, Aldolase, EMG, muscle biopsy) **(serum enzymes are important for diagnosis and even for management) low results mean that treatment is effective**
- 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 specificity for DM/PM:
  - P155 → increased risk of malignancy
  - Mi-2 → good prognosis
  - Jo-1 (20%) → Antisynthetase syndrome
  - SRP → Fulminant DM, cardiac involvement.
- Low Specificity 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.

3) Systemic Sclerosis:

- An autoimmune connective tissue disease of unknown etiology that affects the skin, blood vessels and internal organs.
- The hallmark of the disease is thickening and tightness of the skin.
- characterized by fibrosis of the skin as well as internal organs, e.g. lung, heart, gastrointestinal tract, and kidneys.
- 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%. This is why It's very important to diagnose and treat early.

◆ Epidemiology:

- Rare disease
- Incidence: 50 cases per million in USA.
- Peak occurrence in the 30-40 years age group
- F: M 4:1
- Very rare in childhood

◆ Diagnostic criteria:

- **Either one Major criterion**
  - Symmetric cutaneous sclerosis proximal to the MCP or MTP joints.
- **Or Two or more Minor criterion:**
  - Sclerodactyly (localized thickening and tightness of the skin of the fingers or toes).
  - Digital pitted scars.
  - Loss of substance from finger pads.

◆ Pathogenesis:

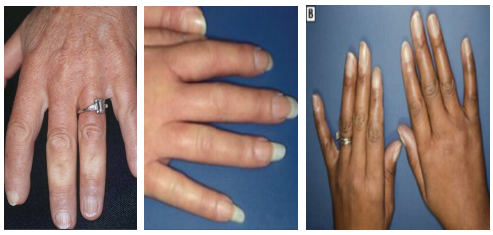
- Individual genetic background
- Exposure to environmental triggers(virus, drugs, vinyl chloride, silica and nanoparticles from traffic-derived pollution).
- Inducing vascular damage and fibroblast
- Activate cells that have ability to give origin to endothelial cells, or collagen producing cells
- 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 SScare activated and produced anti-topoisomerase I and anti-centromere antibodies

◆ Classification:

Limited	Diffuse
○ Induration is limited to the distal extremities and face. ○ Tend to develop internal involvement late in the course of disease (decades) ○ **CREST Syndrome:** describes the clinical features in a subset of patients with limited SSc. ■ **C**alcinosis ■ **R**aynaud's phenomenon ■ **E**sophageal involvement ■ **S**clerodactyly ■ **T**elangiectasia ○ Pulmonary hypertension ○ Positive anticentromere antibodies	○ Distal and proximal of the extremities plus the trunk and face ○ Typically associated with early internal organ involvement (within 5yrs of onset) and a worse prognosis. ○ Pulmonary fibrosis and Renal Crisis are more common. ○ Positive antitopoisomerase antibodies (anti scl-70)

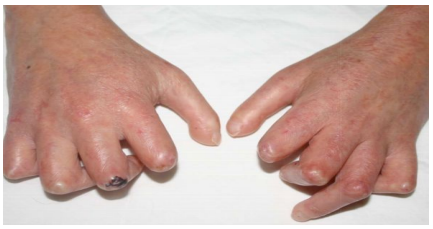
◆ Cutaneous features of systemic disease:

- **Digits**: Early pitting edema (early on), hardening, taut and shiny appearance (later on).
- **Face**: Beaked nose, microstomia (small mouth) 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 ulcer



Early phase of SSc

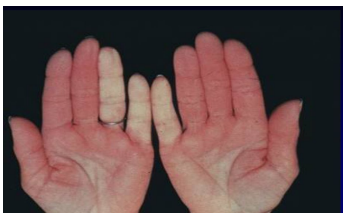
- Early, edematous phase of systemic sclerosis.
- Note the demonstration of pitting edema on two of the digits.
- Edematous and shiny fingers
- Swelling and sclerosis reduce hand movements, so patients may be unable to make a fist, or to place the palmar surfaces together - the 'prayer sign'.
- Fingertips may have pitting, ulcers or loss of bulk from finger pads



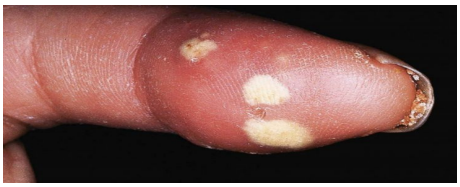
Late phase

Contractures, thick skin, ulceration and scars

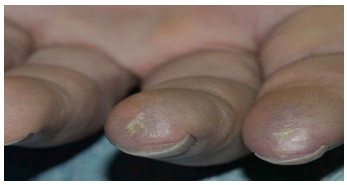
Late stage of systemic sclerosis with diffuse cutaneous scleroderma. Note the fixed flexion contractures, sclerodactyly, and the digital ulceration overlying the third proximal interphalangeal joint



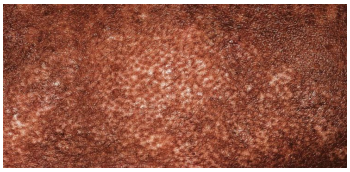
Raynaud's phenomenon:
Vasospasm of the digital microvasculature resulting in:
- digital ischemia (pallor)
- digital hypoxia (cyanosis)
- digital reactive hypermedia (erythema)



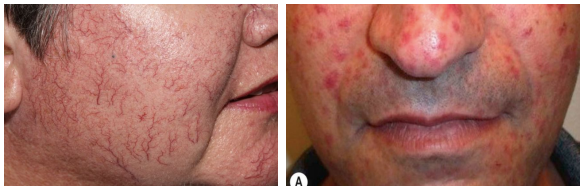
Calcinosis cutis
white spots or ulcerations and may be quite painful.



Pitted scars scars of the digital pulp
that form in distal areas



Salt and pepper pigmentation
Areas of hyper and hypopigmentation
The "salt and pepper" sign. Leukoderma with retention of perifollicular pigmentation in a patient with systemic sclerosis.



1st picture: regular telangiectasia (long and tortuous) seen in rosacea and other skin conditions.
2nd picture: matted telangiectasia seen in scleroderma (flat and rounded)

◆ Extracutaneous features of systemic disease:

- Pulmonary
- Cardiac
- Renal
- Gastrointestinal

◆ Autoantibodies:

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

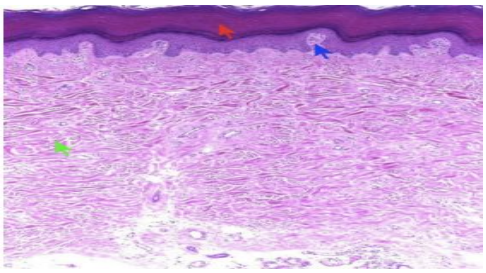
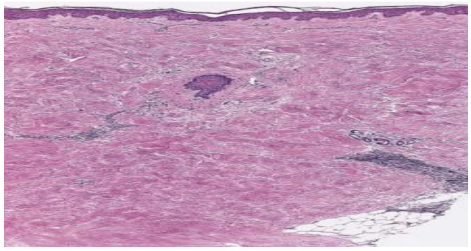
Specific Antibodies

Autoantibody	Subtype (% subtype with antibody)	Clinical Characteristics
Antinuclear antibody	Limited cutaneous & diffuse cutaneous (95% nucleolar pattern is most specific)	Pulmonary arterial hypertension; Interstitial lung disease
Anticentromere antibody	Limited cutaneous (60 – 80%)	Pulmonary arterial hypertension
	Diffuse cutaneous (2 - 5%)	Digital ulcerations or digital loss
Antitopoisomerase-1 antibody (anti-Scl-70)	Diffuse cutaneous (20 - 40%)	Rapidly progressive skin thickening; Scleroderma renal crisis; Pulmonary fibrosis

- Extra picture from boys' slides

◆ Pathology:

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

	
Normal skin	Systemic sclerosis Not a lot of epidermal changes Thick areas (collagen) in the dermis and trapping of adnexal structures and loss of fat

◆ Treatment:

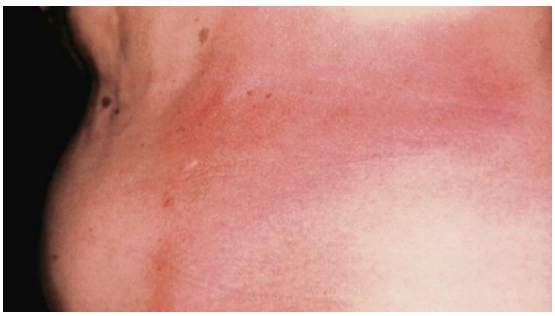
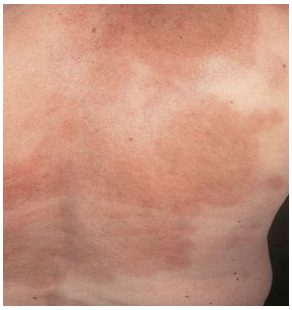
- Most interventions focus on internal organs and unfortunately, have no significant impact on cutaneous manifestations.
- Raynaud's → Keep warm, CCB (Nifedipine), Angiotensin II receptor blockers (Losartan), Phosphodiesterase type inhibitors (Sildenafil).
- ACE inhibitors is used to treat scleroderma renal crisis.
- Cyclophosphamide → ILD. interstitial lung disease
- Oral immunosuppressants.
- Matted Telangiectasias → Pulse dye laser.
- Cutaneous ulcers → Bosentan(approved in Europe but not US)

4) 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.
- Some people consider morphea as a subtype of scleroderma (localized scleroderma) and some people consider it as a different entity. The doctor likes to consider it as a different disease.
- **Clinicaltypes:**
  - plaque type (56%).
  - Linear (20%).
  - Generalized (13%).
  - Deep morphea (11%).

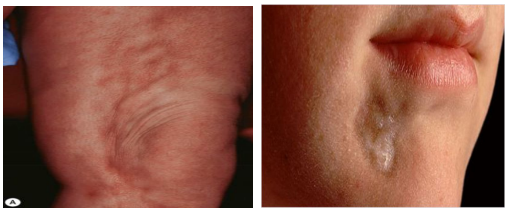
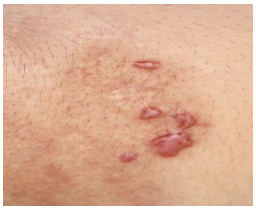
◆ Plaque Morphea:

- Most common type of morphea
- 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 arrest and eventually resolves spontaneously. (residual atrophy/pigmentation are commonly observed)

	
Early-stage lesion presenting as an erythematous edematous plaque not very specific	Plaque-type morphea of the back.Multiple, large hyperpigmented plaques, several of which have an inflammatory border. Advanced lesion Red and violaceous lesions

◆ Other variants of morphea: Not important

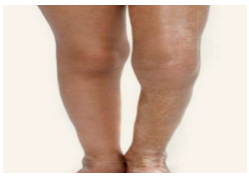
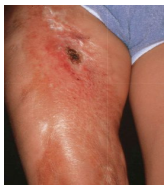
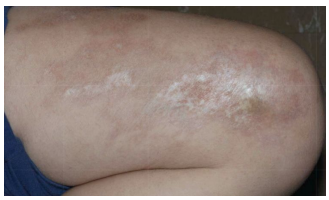
- Guttate Morphea: multiple, nummular, small plaques.
- Atrophoderma of Pasini and Pierini: hyperpigmented patches on the posterior trunk.
- Deep Morphea: Deep dermis and fat (or deeper). May impair motility of the skin and calcify (osteoma cutis).
- Nodular/Keloid Morphea: keloid-like nodules.
- Bullous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

	
Deep morphea	Keloidal morphea

severe atrophy up to the subcutaneous tissue	

◆ Linear morphea: IMP

- **<u>En coup de sabre:</u>**
  - A term used for linear morphea of the forehead and scalp. Basically, morphea of the forehead and scalp
  - Normally unilateral and extends from the forehead into the frontal scalp and leads to hair loss.
  - Paramedian location is more common than a median location.
- **<u>Hemifacial atrophy (Parry-Romberg syndrome):</u>**
  - A very severe variant of linear morphea. Some people consider it as a different entity
  - Progressive loss of subcutaneous fat, but little or no sclerosis.
  - Linear morphea tends to involve the underlying fascia, muscle and tendon

	En coup de sabre Linear depressions and sclerosis are more frequently paramedian (rather than midline) and can be wide or narrow. Note the prominent veins and loss of the medial eyebrow
	Hyperpigmentation and loss of subcutaneous fat, leading to facial asymmetry, Hemifacial atrophy Loss of fat in the checks and pigment changes
 	Linear morphea Pic on the left: Linear morphea of the leg in two adolescents. A Extensive induration of the left leg with hypoplasia and an obvious flexion contracture of the knee; there is also involvement of the right foot. B Linear distribution of coalescing sclerotic plaques on the thigh; note the lilac-colored border.
	Linear distribution of coalescing sclerotic plaques on the thigh; note the lilac-colored border.

◆ 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.

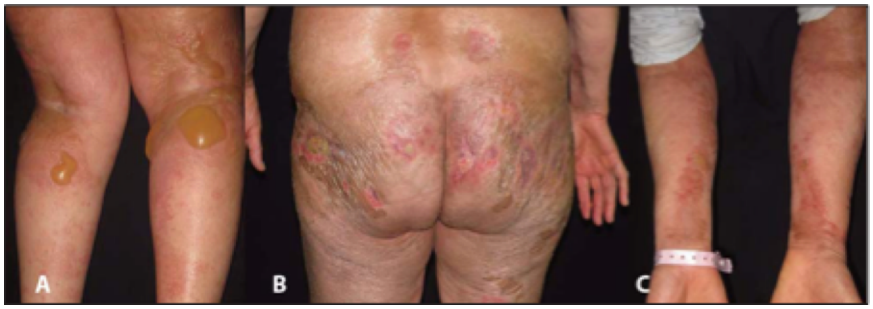
- More severe (4 or more), characterized by extension of skin damage and its association with muscle damage.

◆ Childhood morphea:

- 20% of Morphea patients are children and teenagers.
- 2:1 female to male ratio, mean age of disease onset is 7 years.
- **⅔ 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.

◆ Bullous morphea:

- is characterized by tense sub-epidermal bullae in the presence of typical morphea or deep morphea. sometimes comes with severe inflammation causing bullae.



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 sample.

Treatment:

- **Phototherapy**
- **Topical therapy:**
  - Calcineurin inhibitors
  - Corticosteroids (Class I)
  - ILK injections
- **Systemic therapy:**
  - Systemic steroids
  - Methotrexate