CONNECTINE TISSUE DISEASE, VASCULITIS AND RELATED DISORDERS

CONNECTIVE TISSUE DISEASE

- Connective tissue include:

  1- extracelluler matrix

  2- support proteins (collagen , elastin)

CONNECTIVE TISSUE DISEASE

- Connective tissue disease can be difficult to define but encompasses disorders that involve the tissues connecting and surrounding organs

CONNECTIVE TISSUE DISEASE

Mechanism:

autoimmune disease

Triggering factors:

1- unkown (usually)

2-sunlight

3- infection

4- medication

5- hereditery suceptability

CONNECTIVE TISSUE DISEASE

In autoimmune disorders , immune cells may be attracted to :

1- particular target within the skin locally (pemphigus , pemphigoid).

2-acummulate at sites of connective tissues in multple organs (SLE, dermatomyositis)

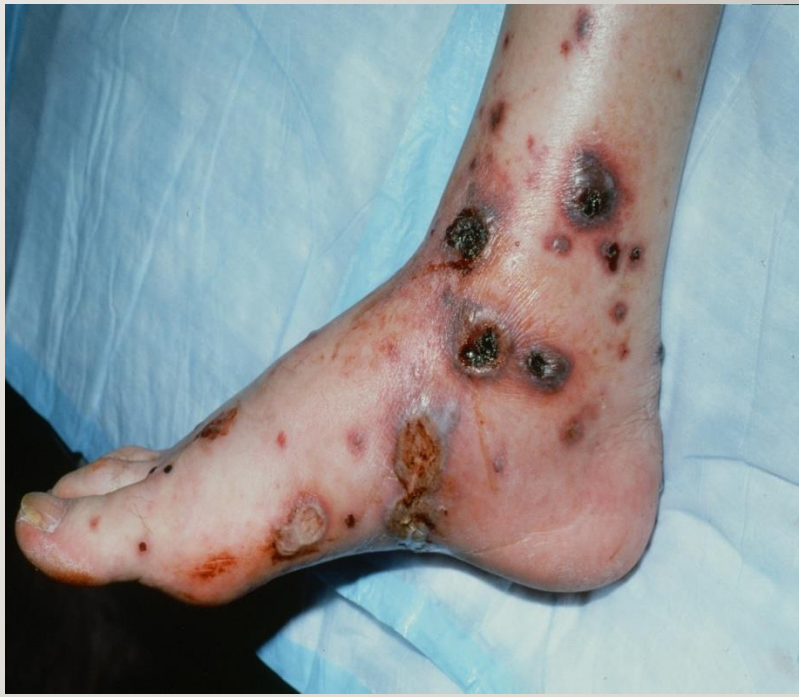
CONNECTIVE TISSUE DISEASE

Dignosis

cinically	investigations
Any symptoms combinatin of : Cutaneous lesions, joint pains ,muscle aches , malaise,weakness, photosensitivity , Raynaud's phenomenon , alopecia .	Box 9.1 **Investigations might include the following** • Full blood count (FBC) • Antinuclear antibodies (ANAs) • Extractable nuclear antibodies (ENA), (Ro, La) • Erythrocyte sedimentation rate (ESR) • Renal and liver function • ANCA (antineutrophil cytoplasmic antibodies) • Hepatitis serology • Streptococcal serology (ASOT) • Rheumatoid factor • Angiotensin-converting enzyme (ACE) • Antiphospholipid antibodies • Coagulation screen, lupus anticoagulant • Anticardiolipin antibodies • Factor V Leiden, antithrombin III, proteins S and C • Urine dipstick and microscopy • Blood pressure • Chest X ray

VASCULITIS

Complex reactions occurring specifically in the capillaries and arterioles of the skin may lead to cutaneous erythema .



VASCULITIS

Pathophysiology :

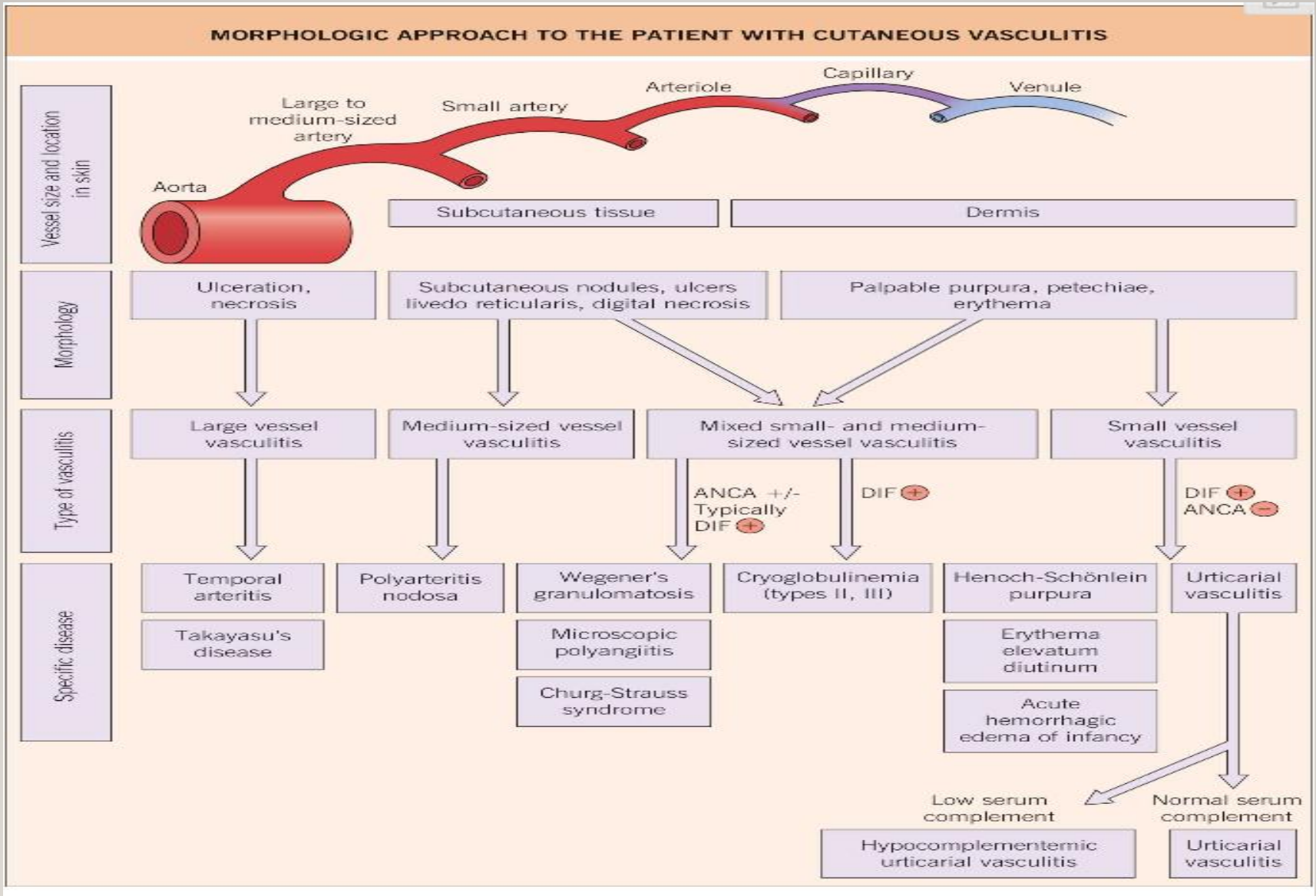
-complex and poorly characteresied.

- Antibodies or immune mediated.
- Immune complex deposition, complement activation ,inflammatory mediators release , vasodilatation , polymorph accumulation , leakage and occlusion of blood vessels , ischemia .

VASCULITIS

Skin lesions :

- Red macules, palpable purpura , blistering , ulcerated and necrotic.
- Transient or last for weeks.
- Painful and unplessant .


MORPHOLOGIC APPROACH TO THE PATIENT WITH CUTANEOUS VASCULITIS
Vessel size and location in skin
Morphology
Type of vasculitis
Specific disease
Aorta
Large to medium-sized artery
Small artery
Arteriole
Capillary
Venule
Subcutaneous tissue
Dermis
Ulceration, necrosis
Subcutaneous nodules, ulcers livedo reticularis, digital necrosis
Palpable purpura, petechiae, erythema
Large vessel vasculitis
Medium-sized vessel vasculitis
Mixed small- and medium-sized vessel vasculitis
Small vessel vasculitis
ANCA +/- Typically DIF +
DIF +
DIF +
ANCA -
Temporal arteritis
Takayasu's disease
Polyarteritis nodosa
Wegener's granulomatosis
Microscopic polyangiitis
Churg-Strauss syndrome
Cryoglobulinemia (types II, III)
Henoch-Schönlein purpura
Erythema elevatum diutinum
Acute hemorrhagic edema of infancy
Urticarial vasculitis
Low serum complement
Normal serum complement
Hypocomplementemic urticarial vasculitis
Urticarial vasculitis

VASCULITIS

- Causes:

1- infection

2- medication

3- connective tissue disorder

4-underlying malignancy

5- vascular/ coagulopathy disorder

6- IBD

7-sarcoidosis

Box 9.2 Possible causes of cutaneous vasculitis

- Drug hypersensitivity
- Hepatitis
- Endocarditis
- Inflammatory bowel disease
- Connective tissue disease
- Coagulopathies
- Behçet's syndrome
- Kawasaki disease
- Sarcoidosis

VASCULITIS

- Diagnosis:

  - skin biopsy for histology and immunofluorescence (helpful but usually not diagnostic .

POLYARTERITIS NODOA(PAN)

PAN is a systemic vasculitis of small to medium sized arterioles that most commonly affects the skin and joints .

POLYARTERITIS NODOA(PAN)

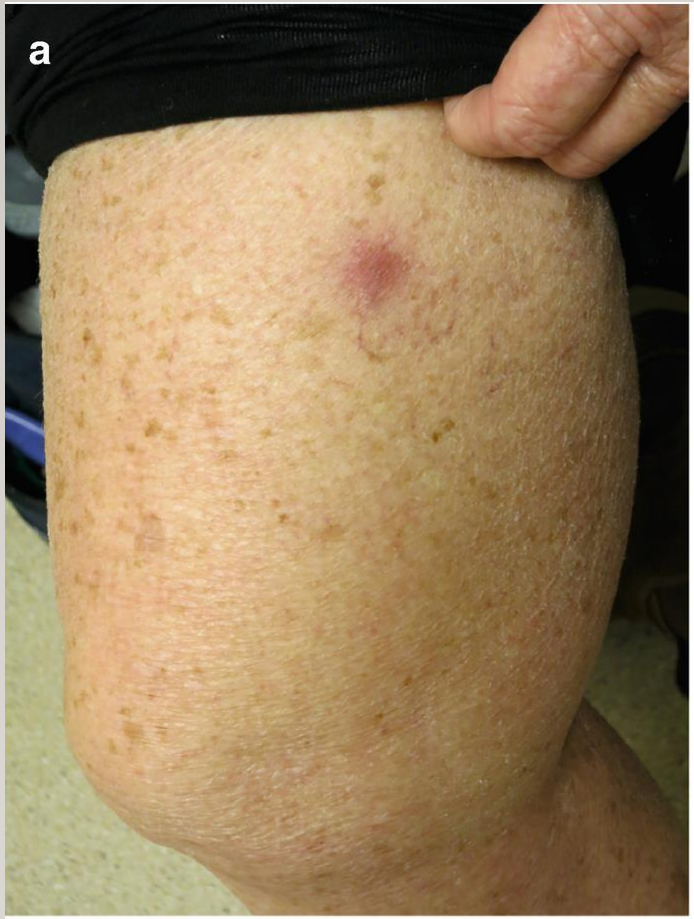
- Symptomes:

General symptoms	Cutaneous symptomes
1-general malaise 2- fever 3- weight loss 4- weakness 5- arthralgia 6- neuropathies	1-livedo reticularis 2- purpura 3- tender 4- ulceration subcutaneous nodule 5- necrosis * Particularly in the lower limb .

POLYARTERITIS NODOA(PAN)

- Pathophysiology:

- Immune complex mediated disease.
- Activating the complement cascade, inflammatory damage to the vessels, micro aneurysm , occlusion, haemorrhage .
- May be +ve ANCA.
- The most common affected site is blood vessel bifurcation.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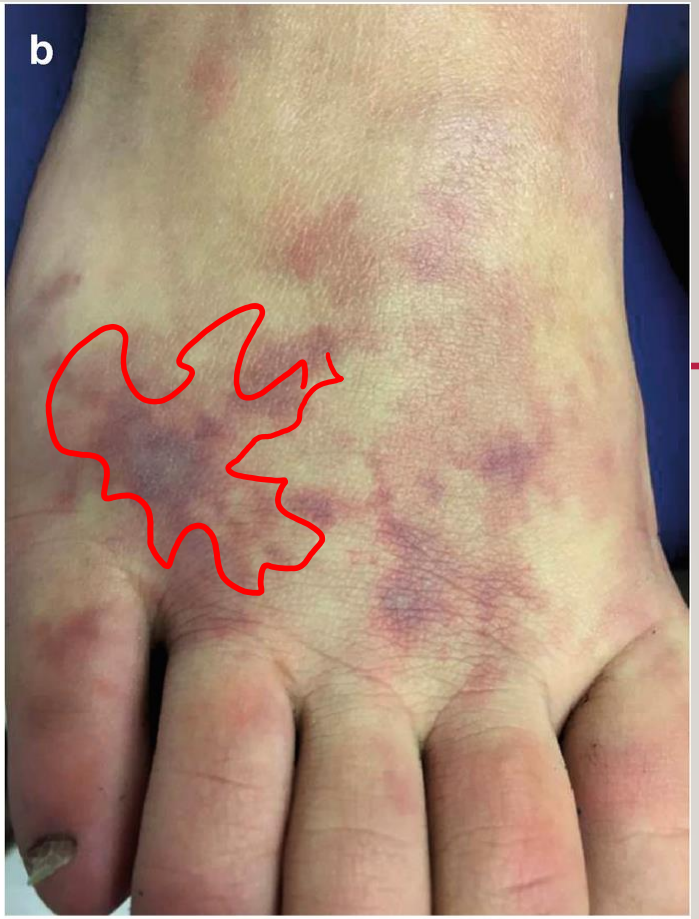
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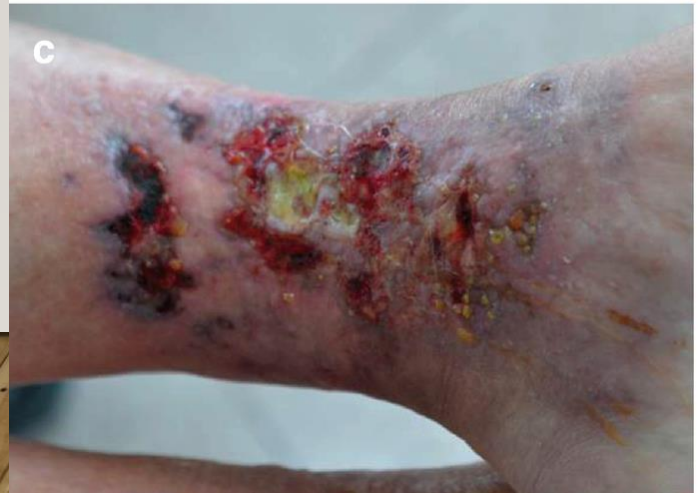
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POLYARTERITIS NODOA(PAN)

Investigations:

1- angiography

2- tissue biopsy (skin , sural nerve , muscle)

Management :

oral steroid in addition to cyclophosphamide in severe cases

.

HENOCH – SCHÖNLEIN PURPURA

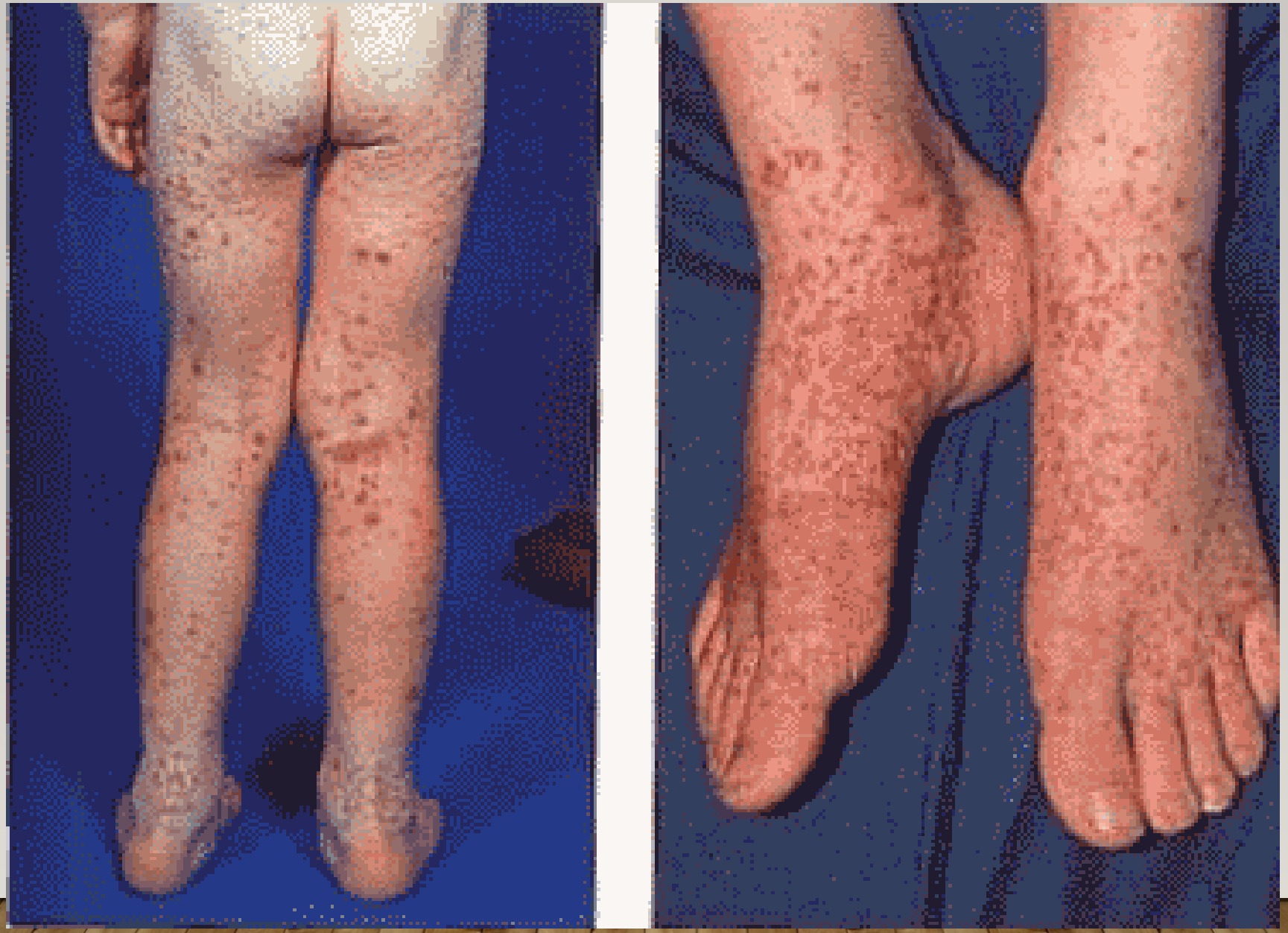
- Occurs in children (75%) or young adults .
- M>F
- Unknown aetiology but have preceding URT symptoms and +ve antistreptolysin O titer (ASOT)

HENOCH – SCHÖNLEIN PURPURA

- Pathophysiology:

- Deposition of IgA, complement and immune complexes in small vessels (arterioles, capillaries , venules) leading to systemic vasculitis.

- Skin , kidney ,GI tract and joints are mainly affected .



HENOCH – SCHÖNLEIN PURPURA

Investigations:

Skin biopsy may demonstrate deposition of IgA on immunofluorescence , which can support the diagnosis.

HENOCH – SCHÖNLEIN PURPURA

- Management:

in persistent conditions , systemic corticosteroids have been used to treat skin , GI and arthritis symptoms not been shown to prevent or treat renal disease .

MANAGEMENT OF CUTANEOUS VASCULITIS

a- treat any underlying causes .

b- for mild to moderate cutaneous involvment potent topical steroid can be applied to the affected skin .

c- support hosiery should be used and the leg elevated on sitting .

d- in severe cases systemic corticosteroid , anticoagulation with warfarin or heparin .

e- in persistent cases , alternative immunosuppressant (Methotrexate or Azthioprine) may needed .

RAYNAUD'S PHENOMENON

Recurrent reversible vasospasm of peripheral arterioles secondary to cold exposure leads to transient ischemia of the digits associated with an underlying autoimmune disease , most commonly associated with sclerosis , mixed connective tissue disease , SLE and cryoglobulinemia .

primary vs secondary

Primary symmetric, before 30 years old, no skin manefestations

Secondary asymmetric, ANA, digital ulcerations

RAYNAUD'S PHENOMENON

Symptoms:

1- change in colour (white – blue – red).

2- pain

3- numbness

*the condition most frequently affects the finger in symmetrical pattern but may also affects toes, nose and ears.

Normal Circulation

Constriction of a small blood vessel

Raynaud's Phenomenon

White due to lack of blood flow

Blue due to lack of oxygen

Red when blood flow returns

RAYNAUD'S PHENOMENON

- Investigations:

1- full blood count

2-LFT and KFT

3- coagulation profile

4- thyroid function

5- serum glucose

6- creatin kinase

7- hepatitis serology

8-antinuclear antibodies

RAYNAUD'S PHENOMENON

- Management :

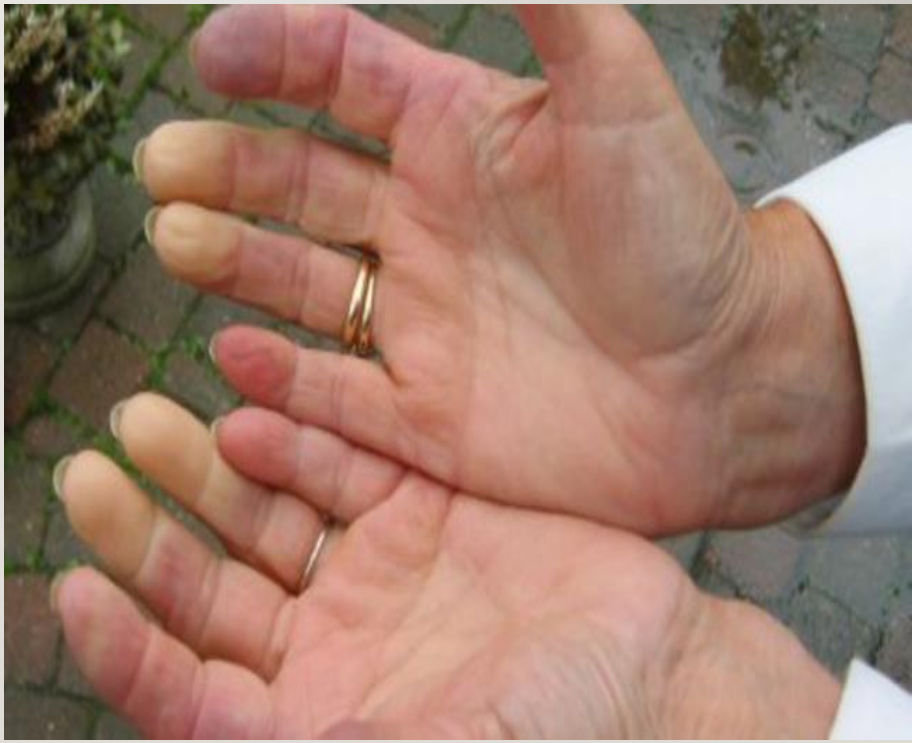
  1- keeping peripheries warm

  2- nifedipine

  3- iloprost (prostacycline analogue)

SYSTEMIC SCLEROSIS (SSC)

Excessive collagen deposition and fibrosis of the subcutaneous tissues in the fingers and toes as well as around the mouth (scleroderma), with similar changes affecting the internal organs particularly the lung and kidneys.



SYSTEMIC SCLEROSIS (SSC)

Types:

Main:

1- limited systemic sclerosis(lSSc)

2- disseminated systemic sclerosis (dSSc)

other

1- undifferentiated connective tissue disease

2- CREAST syndrome.

- Limited systemic sclerosis: Raynaud starts many years before, Anticentromereantibody, skin scleorosis distally does not cross the elbows and knees, slowly progressing , CREST is an example
- Diffuse systemic sclerosis: Raynaud starts 1-2 years before, Antobodies ANA, Scl-70, sclerosis crosses elbows and knees, fast progress with internal orgns involvement (heart , kidneys, lungs)

SYSTEMIC SCLEROSIS (SSC)

Sign and symptoms :

1- Raynaud's phenomenon

2- telengectasia (mouth and finger)

3-tethring of skin on the fingers/toes which become very tight with waxy appearance and considerable limitation of movement .

SYSTEMIC SCLEROSIS (SSC)

Diagnosis:

1- ANA (90% of patients with SSc will have at least one +ve ANA)

2-CRP / ESR (raised)

3- high resolution CT scan of the lung (thickening of the alveolar walls)

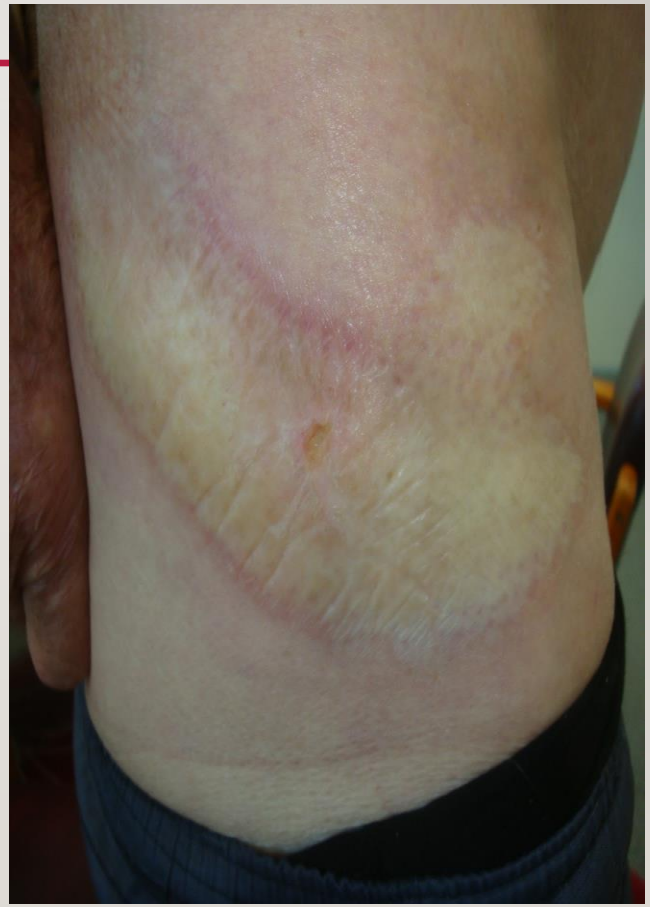
4- PFT (impaired ventilation – perfusion)

5- skin biopsy (fibrotic changes seen in histology)

SYSTEMIC SCLEROSIS (SSC)

Morphaea :

- benign form of localised systemic sclerosis in which there is localised sclerosis with very slight inflammation .
- early stages : dusky appearance of skin.
- late stages : discolored skin and feels very firm .
- Localised morphoea in the frontoparietal area is associated with alopecia and sunken groove of firm sclerotic skin .



CREST SYNDROME (CALCINOSIS,RAYNAUD, OESOPHGEAL DYSMOTILITY, SCLERODACTYLYL, TELANGECTASIA)

Symptoms:

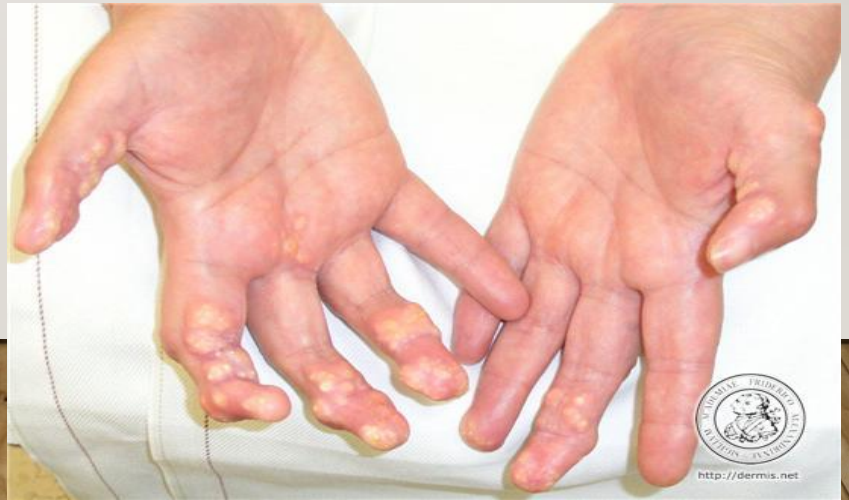
1-Raynaud's phenomenon (first complain)

2-thickining of the skin of the digit (sclerodactyly)

3- calcium deposits in the skin are seen as chalky white material which can be painful

4- multiple telengectasia (first seen in the face)

5- dysmotality of the oesophagus (late)



CREAST SYNDROME

Investigations:

FBC , ANA , anticentromere antibody and anti Scl-70

Management:

1-psychological support

2-patients should keep themselves warm

3-calcium- channel blockers

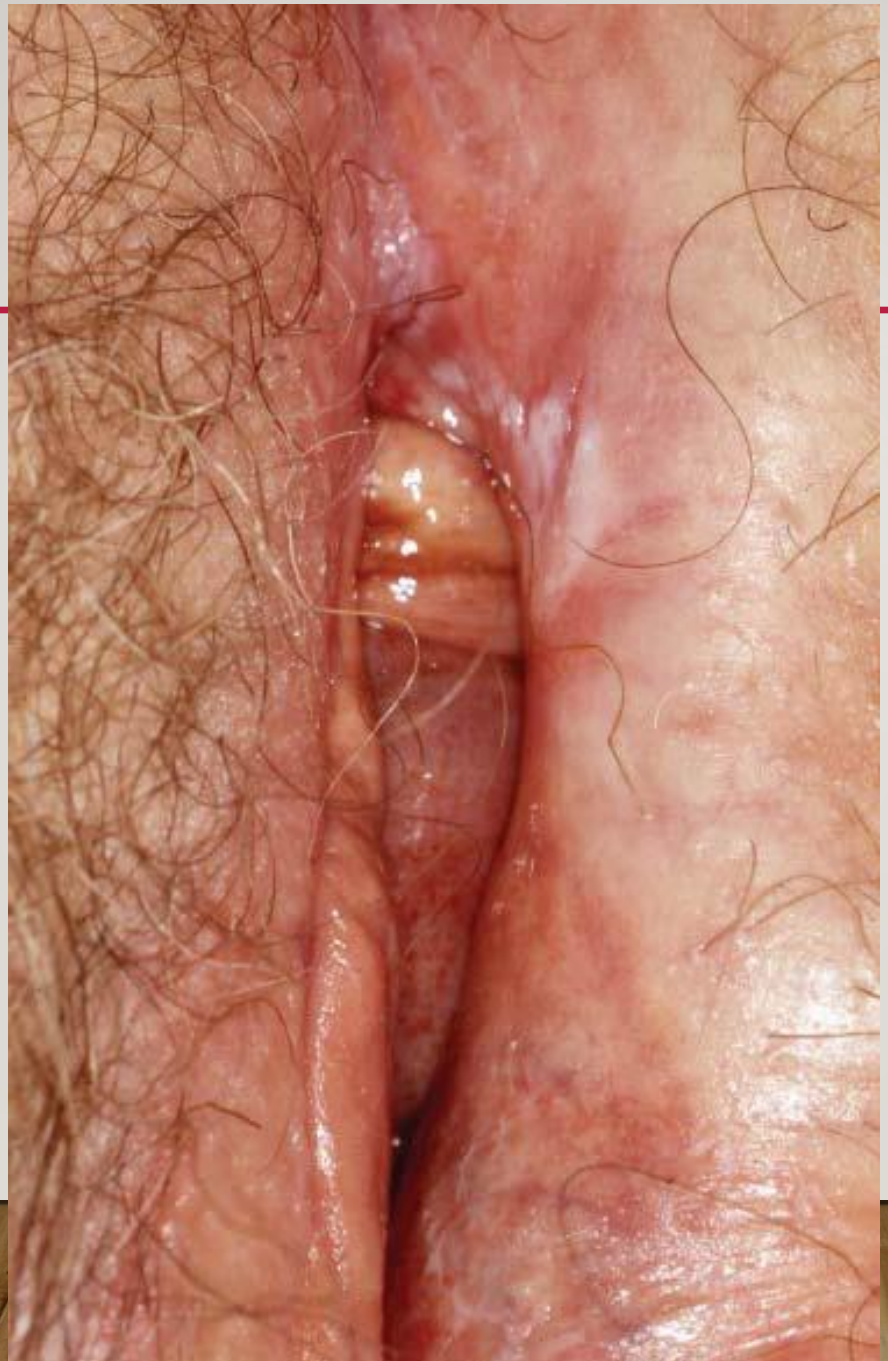
4- prostaglandins

5-calcitriol

6- pulsed dye laser

LICHEN SCLEROSUS

- itchy eruption which mainly affects the genital and perineal regions in women.
- well-demarcated atrophic patches and plaques with a distinctive ivory white colour.
- fibrosis of the underlying tissues with associated loss of normal genital architecture
- frequently affects the vulva and perineum, but may also affect the penis and extragenital skin



- Children : acute, resolves
- Adults ; chronic , rarely be associated with the development of squamous cell carcinoma (SCC).
- Pathophysiology : unknown, but in early lesions there is an

infiltrate of lymphocytes with CD3, CD4, CD8 and CD68 markers.

- Histologically, there are some similarities between LS

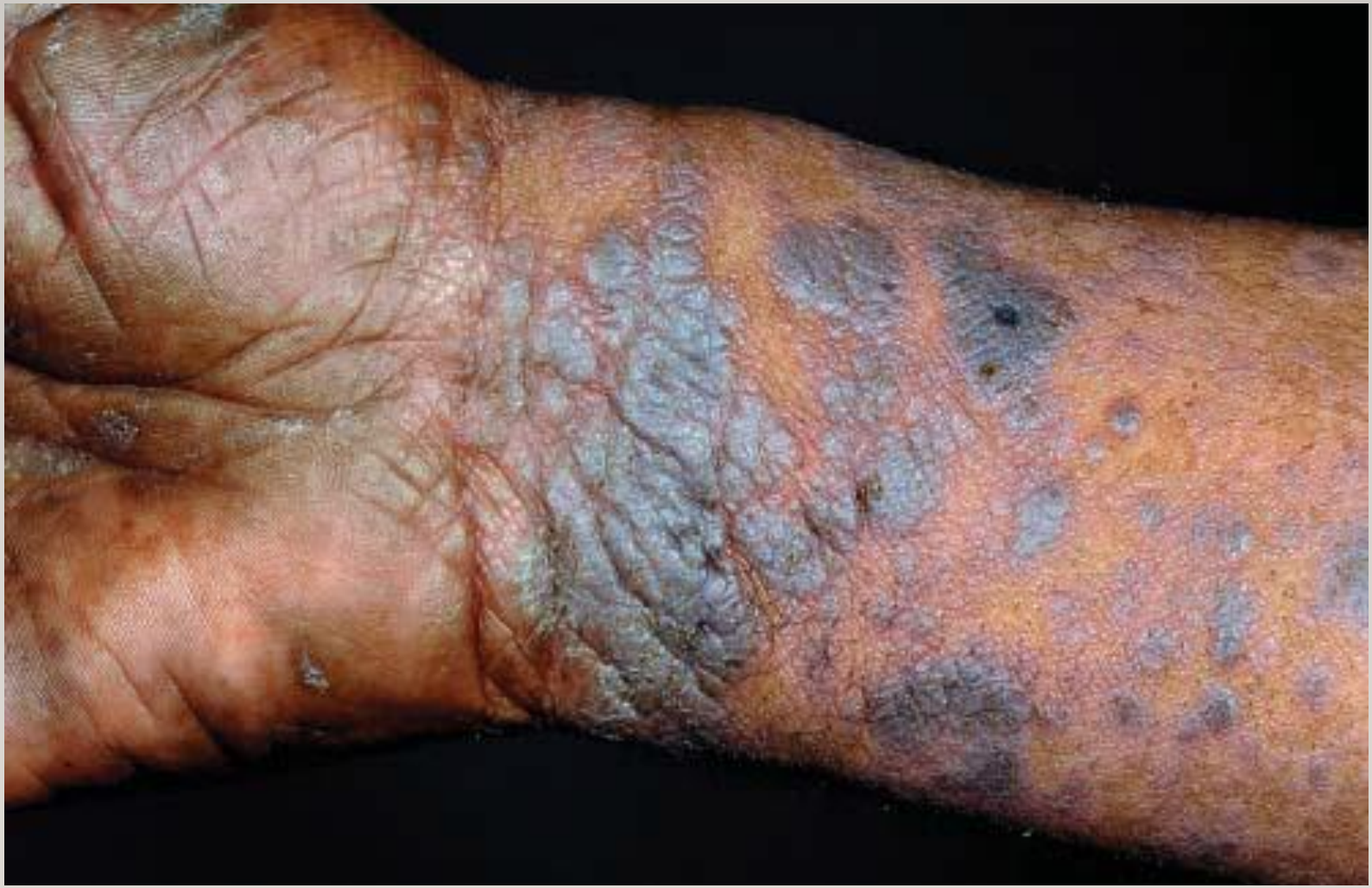
and lichen planus, but different clinical picture.

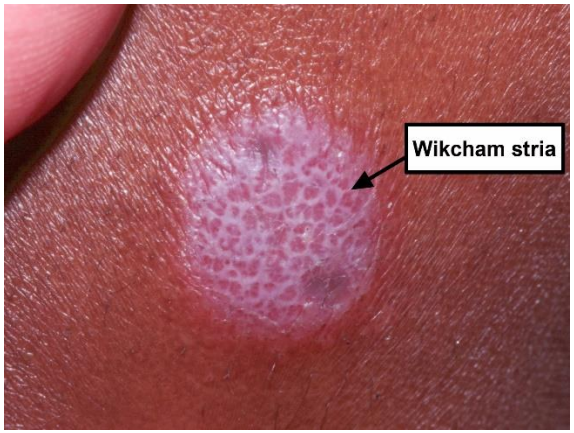
- Treatment is with intermittent potent topical steroids, which usually controls the itching.
- If pruritus is not controlled by potent topical steroids or soreness develops, then review by an experienced dermatologist is indicated to rule out the development of SCC.

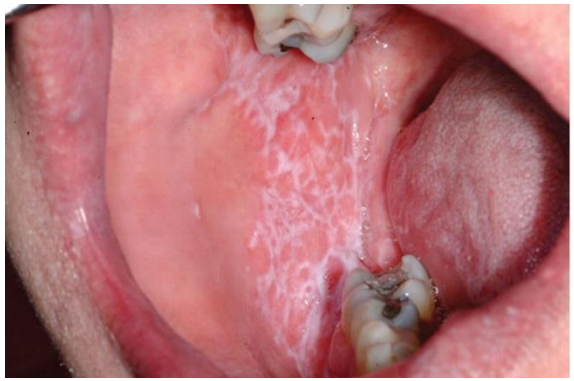
LICHEN PLANUS

- itchy eruption consisting of shiny purple-coloured flat-topped papules
- Appear on the wrists and ankles.
- White lines called Wickham's striae may appear on the surface of the lesions at any site
- Lesions may appear in clusters or in linear scratches/surgical scars(Koebner phenomenon)
- Aetiology unkown , immune mediated
- histological features are characterised by a band of lymphocytes attacking the basal keratinocytes which results in oedema, subepidermal clefts and death of some keratinocytes

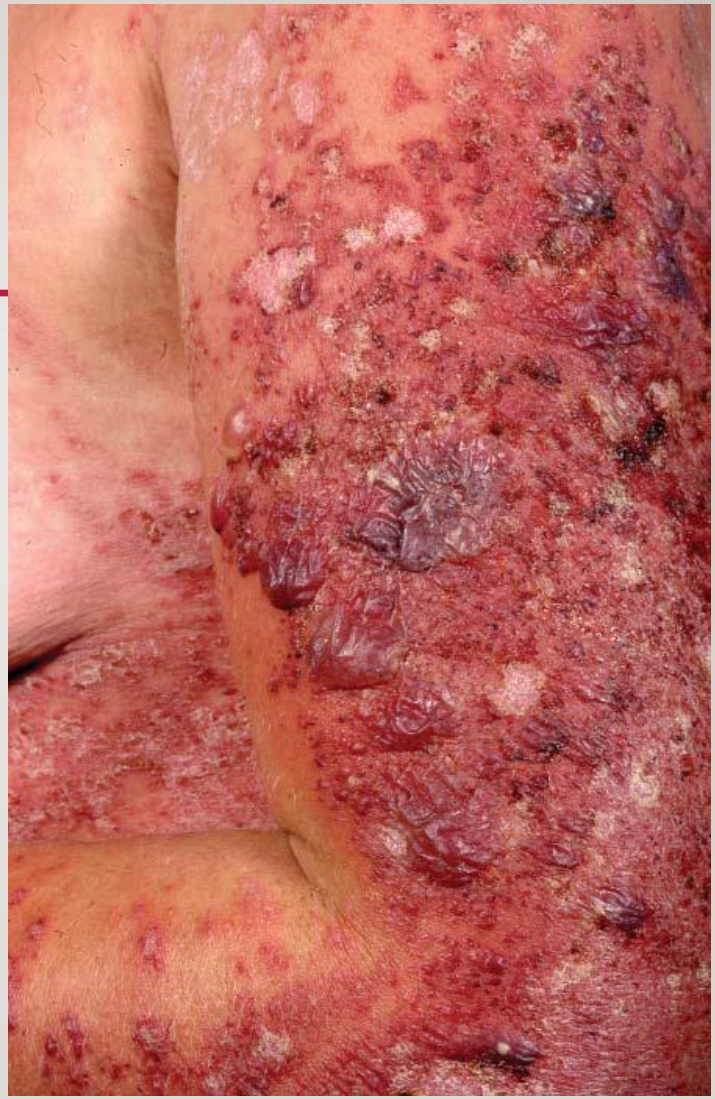
- In patients withblack skin, LP may be very hypertrophic and heal with marked post-inflammatory hyperpigmentation.
- Mouth (buccal mucosa), genitals (erosions on labia minora) may also be involved
- distinctive linear ridges may affect the nails.
- Scalp lesions are often scaly with marked follicular plugging that may result in scarring alopecia.
- Most cases resolve over 1–2 years. Hypertrophic LP may, however, persist for decades.




Wikcham stria



- Severe acute lichen planus can manifest as bullous lesions
- Severe lichen planus can be treated with systemic corticosteroids,mycophenolatemofetil, methotrexate or azathioprine.



- Treatment :
- Potent topical steroid applied to the itchy active lesions
- Occlusion of the steroid for treatment of hypertrophic

lesions is usually more effective than steroid alone

LICHENOID DRUG ERUPTIONS

- clinically similar to LP
- lesions are usually more extensive and oral involvement is rare .
- Lesions only resolve very slowly after the drug is
- stopped, generally taking 1–4 months to settle and usually leaving hyperpigmentation on the skin.
- Examples :
- **Antihypertensives – ACE inhibitors, beta-blockers, nifedipine, methyldopa**

LUPUS ERYTHEMATOSUS (LE)

Clinical variants of lupus erythematosus

- Systemic
- Subacute cutaneous
- Discoid
- Neonatal

- Diagnostic criteria for SLE include four of the following at any given time:

- • malar rash
- • serositis
- • discoid plaques
- • neurological disorders
- • photosensitivity
- • haematological changes
- • arthritis
- • immunological changes
- • mouth ulcers
- • antinuclear antibodies
- • renal changes.

New ACR and EULAR criteria for classification of SLE

All patients classified as having systemic lupus erythematosus must have a serum titer of antinuclear antibody of at least 1:80 on human epithelial-2–positive cells or an equivalent positive test. In addition, a patient must tally at least 10 points from these criteria. A criterion is not counted if it has a more likely explanation than SLE. Occurrence of the criterion only once is sufficient to tally the relevant points, and the time when a patient is positive for one criterion need not overlap with the time when the patient is positive for other criteria. SLE classification requires points from at least one clinical domain, and if a patient is positive for more than one criterion in a domain only the criterion with the highest point value counts:

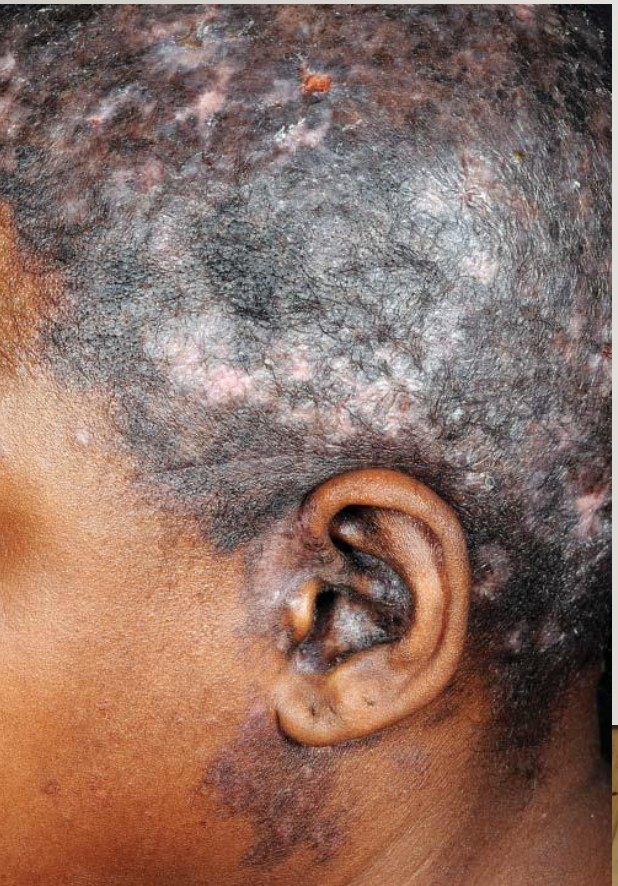
Clinical domains	Points
Constitutional domain	
Fever	2
Cutaneous domain	
Nonscarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus	4
Acute cutaneous lupus	6
Arthritis domain	
Synovitis in at least two joints or tenderness in at least two joints, and at least 30 min of morning stiffness	6
Neurologic domain	
Delirium	2
Psychosis	3
Seizure	5
Serositis domain	
Pleural or pericardial effusion	5
Acute pericarditis	6
Hematologic domain	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Renal domain	
Proteinuria >0.5g/24 hr	4
Class II or V lupus nephritis	8
Class III or IV lupus nephritis	10

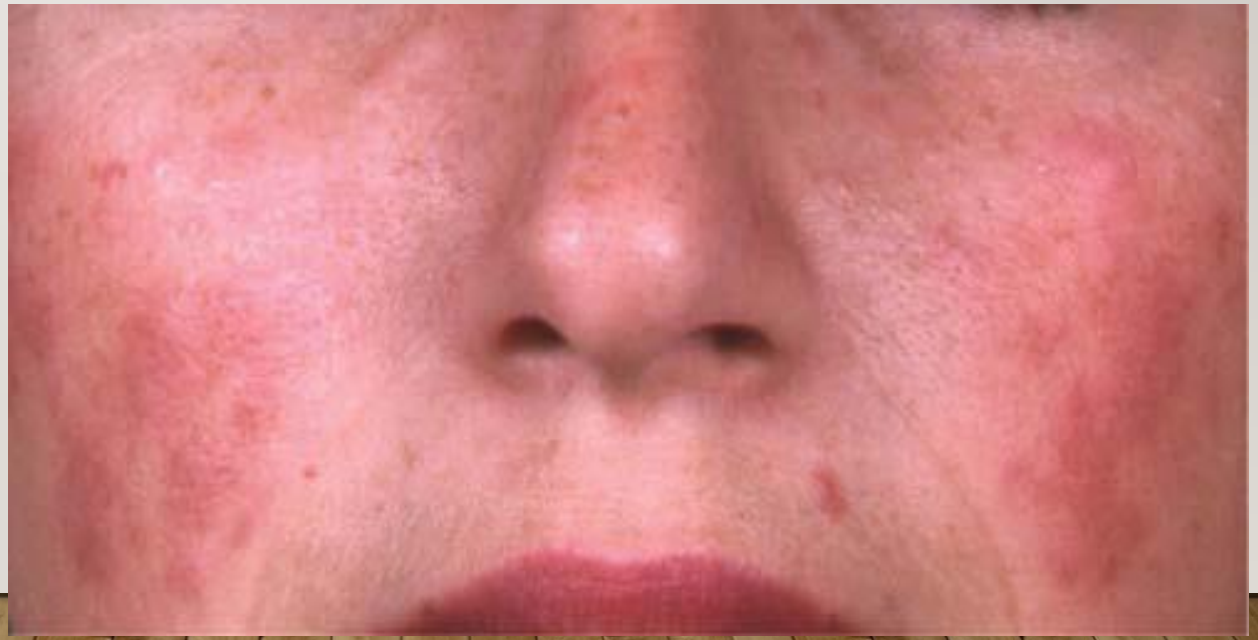
Immunologic domains	Points
Antiphospholipid antibody domain	
Anticardiolipin IgG >40 GPL or anti-β2GP1 IgG >40 units or lupus anticoagulant	2
Complement proteins domain	
Low C3 or low C4	3
Low C3 and low C4	4
Highly specific antibodies domain	
Anti-dsDNA antibody	6
Anti-Smith antibody	6

MDedge News

Source: Dr. Johnson

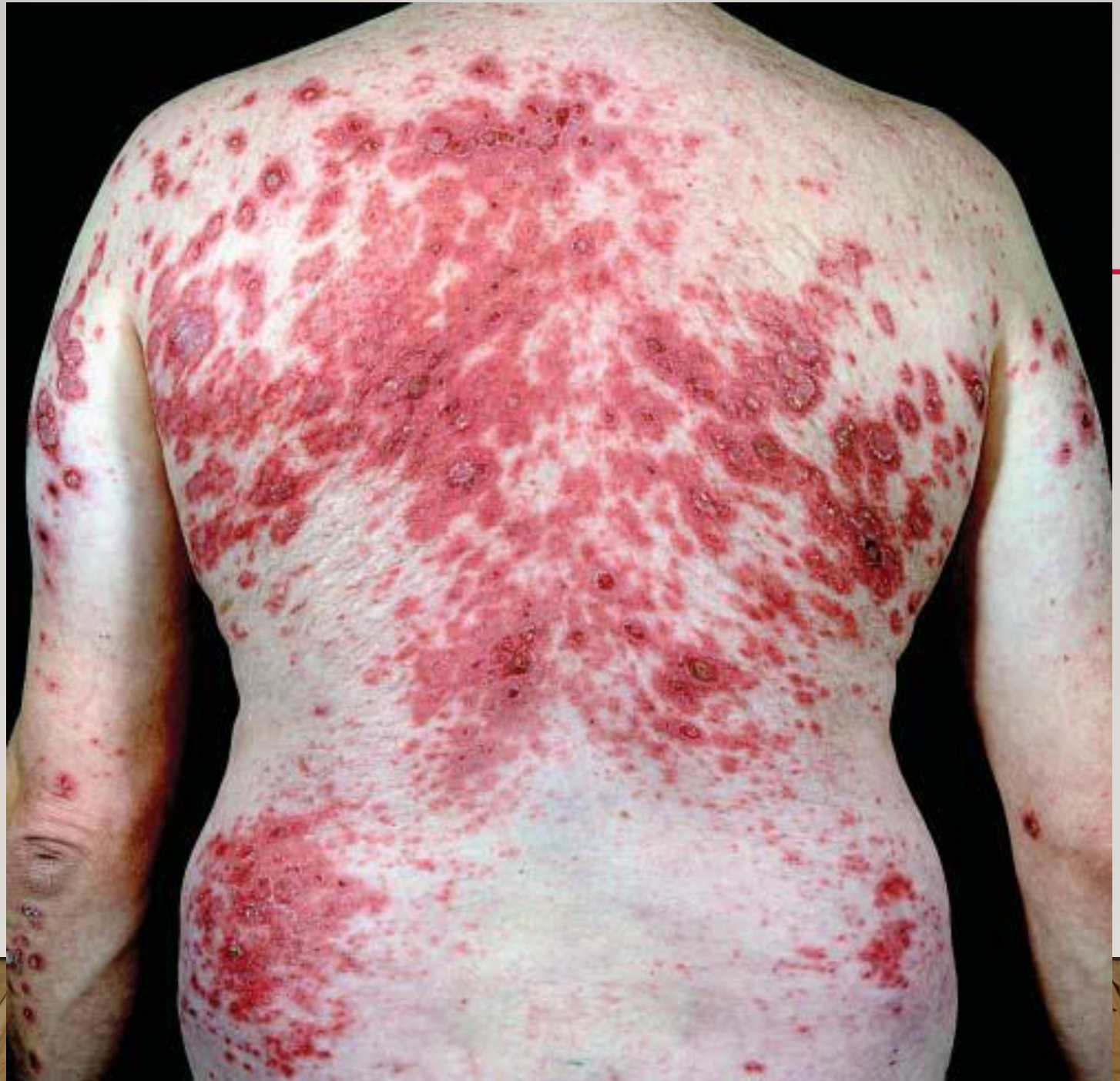
- 75% of patients have skin involvement, most commonly an erythematous 'butterfly' distribution rash on the face , Photosensitivity, hair loss and areas of cutaneous vasculitis.
- As the disease progresses the cutaneous manifestations can become extensive Systemic changes include fever, arthritis and renal involvement, but
- there may be involvement of a wide range of organs





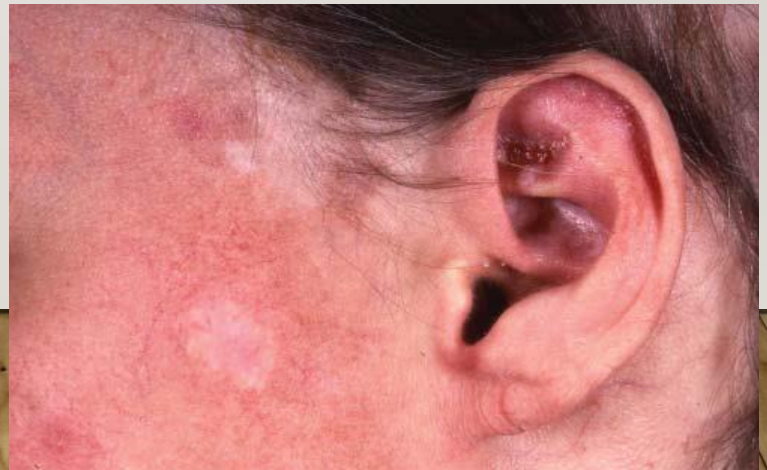
SUBACUTE LUPUS ERYTHEMATOSUS (SLE)

- erythematous annular and serpiginous eruption on the skin
- Systemic involvement is less common/severe than in SLE.
- high incidence of neonatal lupus erythematosus in children born to mothers with the condition
- ENA(extractable nuclear antigen) test is positive in 60% and anticytoplasmic antibodies are present in 80% of patients



DISCOID LUPUS ERYTHEMATOSUS (DLE)

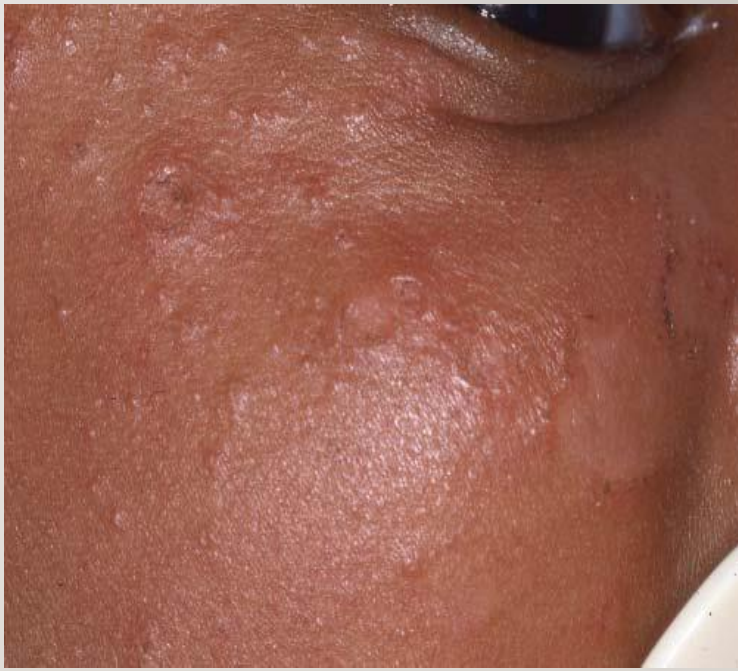
- photosensitive disorder
- well-defined erythematous lesions with atrophy, scaling and scarring occur on the face, scalp (alopecia, follicular plugging) and occasionally arms
- circulating antinuclear antibodies are very rare and only 5% of patients go on to develop SLE
- should be treated with potent and super-potent topical steroids to limit scarring



NEONATAL LUPUS ERYTHEMATOSUS

- caused by transplacental passage of maternal lupus antibodies (particularly Ro/La) to the neonate
- skin lesions characterised by annular scaly and inflammatory lesions on the face/scalp
- congenital heart block (whichmay require pacing).
- Skin lesions may require topical steroid but usually resolve spontaneously as the level

of autoantibody depletes



- Treatment of SLE with threatened or actual involvement of organs is important.

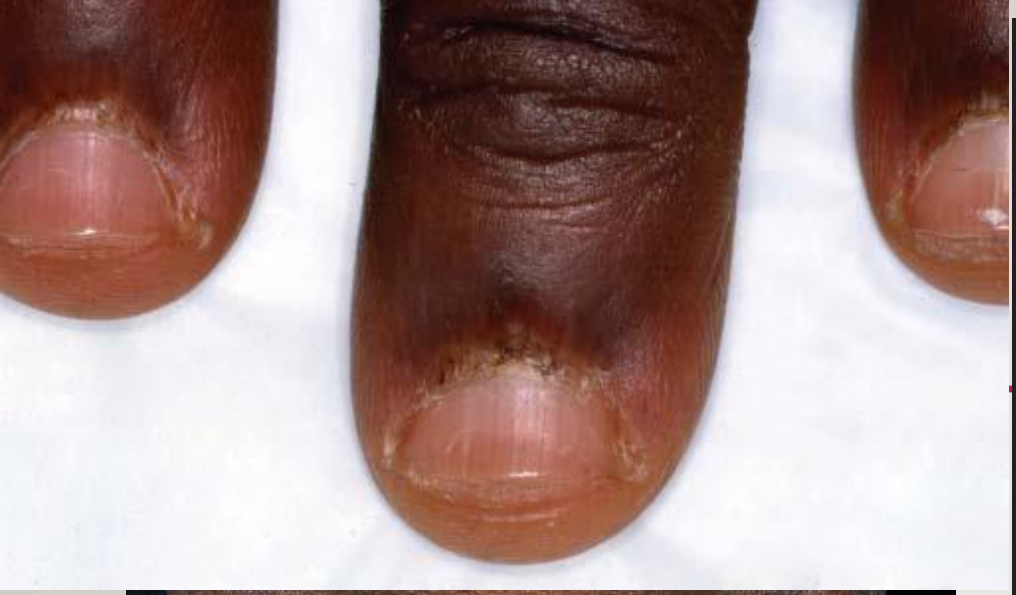
Prednisolone is usually required and sometimes immunosuppressant drugs such as azathioprine as well.

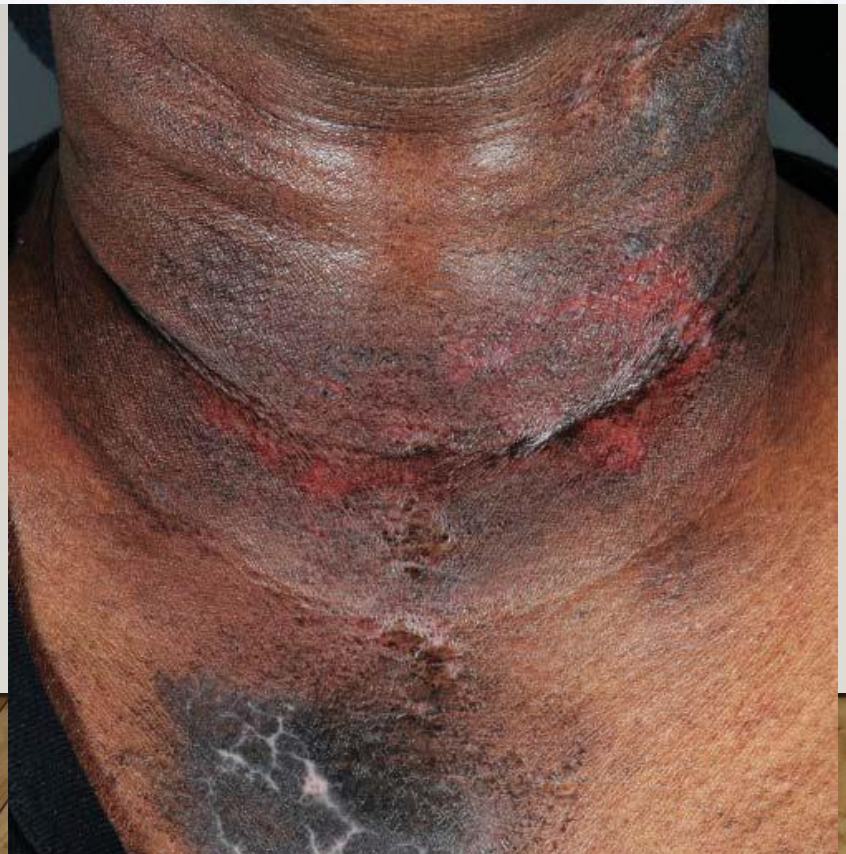
- Treatment of DLE is generally with topical steroids and sunscreen.
- Hydroxychloroquine 200mg twice daily can be effective.
- hydroxychloroquine can cause ocular toxicity; however, patients should be asked to report any visual disturbance

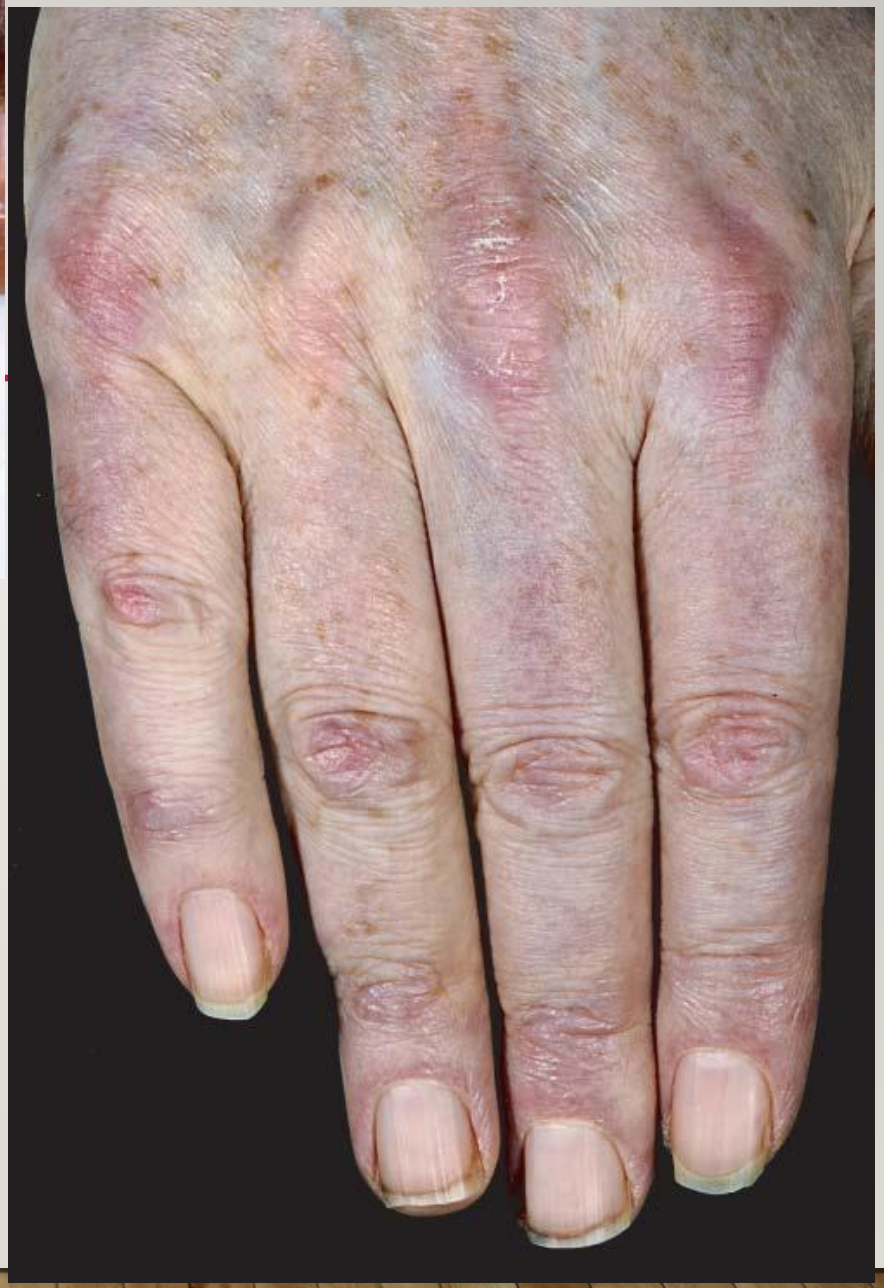
DERMATOMYOSITIS

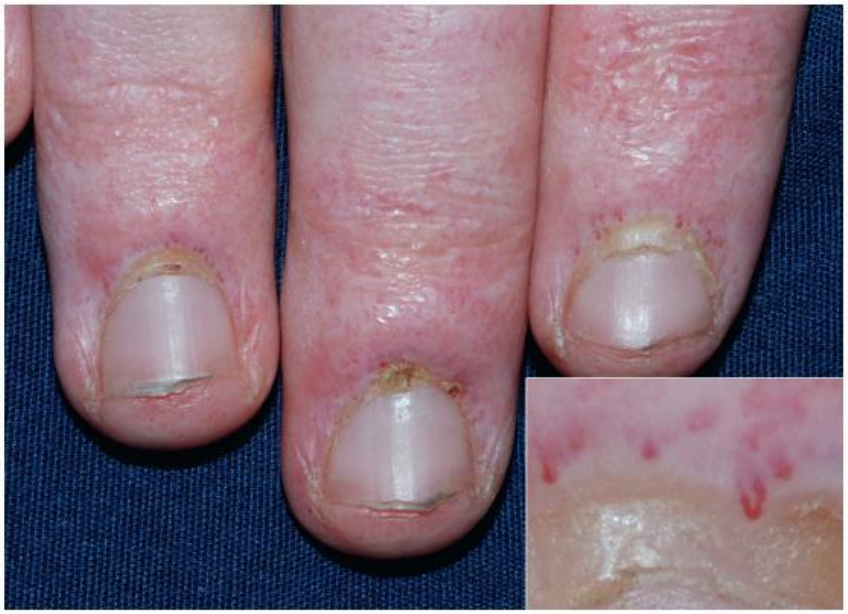
- rare disorder that affects the skin, muscle and blood vessels.
- in adults may precede the diagnosis of an underlying tumour(most commonly breast, lung, ovary or gastrointestinal tract)
- Clinically, there is a rash in a mainly photosensitive distribution
- characterised by a purple hue (heliotrope) on the upper eyelids, cheeks and forehead. The anterior 'V' and posterior aspect (shawl sign) of the neck ,The dorsal surface of the fingers may be affected by the erythematous eruption and purplish (Gottron's) papules may predominate over the dorsal finger joints .
- Ragged cuticles and dilated nail-fold capillaries may also be seen .There is a variable

association with muscle discomfort and weakness, which is mainly in the proximal limbs but bulbar and respiratory muscles maybe affected.









Courtesy, Julie V Schaffer, MD.

- investigations include creatine phosphokinase (CK), ESR,anti-Jo-1 antibody,and skin and muscle biopsy. Electromyography and MRI can help demonstrate myositis

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- Treatment with high dose systemic corticosteroids (60–100mg
- daily) or pulsed methyl prednisolone (1 g daily for 3 days) helps achieve rapid control of symptoms.
- Pulsed cyclophosphamide, azathioprine, methotrexate and mycophenolate mofetil

. Treatment of any underlying malignancy will usually lead to resolution of these skin signs.

MIXED CONNECTIVE TISSUE DISEASE (MCTD)

- overlapping features of systemic lupus, scleroderma and myositis with characteristic autoantibodies
- they usually have Raynaud's phenomenon, sclerodactyly/swollen hands, arthritis/ arthralgia, Sjogren syndrome, myositis, malaise, oesophageal dysmotility, trigeminal neuralgia and pulmonary hypertension
- positive antibodies to U1-ribonucleoprotein (RNP) and small nuclear ribonucleoprotein (snRNP)
- NSAIDs are used to reduce pain and inflammation and the newer cyclooxygenase 2 (COX-2) inhibitor celecoxib is increasingly used to help reduced arthritis and myositis.
- Hydroxychloroquine can also be used and for more refractory disease low dose oral corticosteroids and methotrexate