MEDICINE 1
MINI-OSCE COLLECTED SLIDES – PART 1
JU 2021

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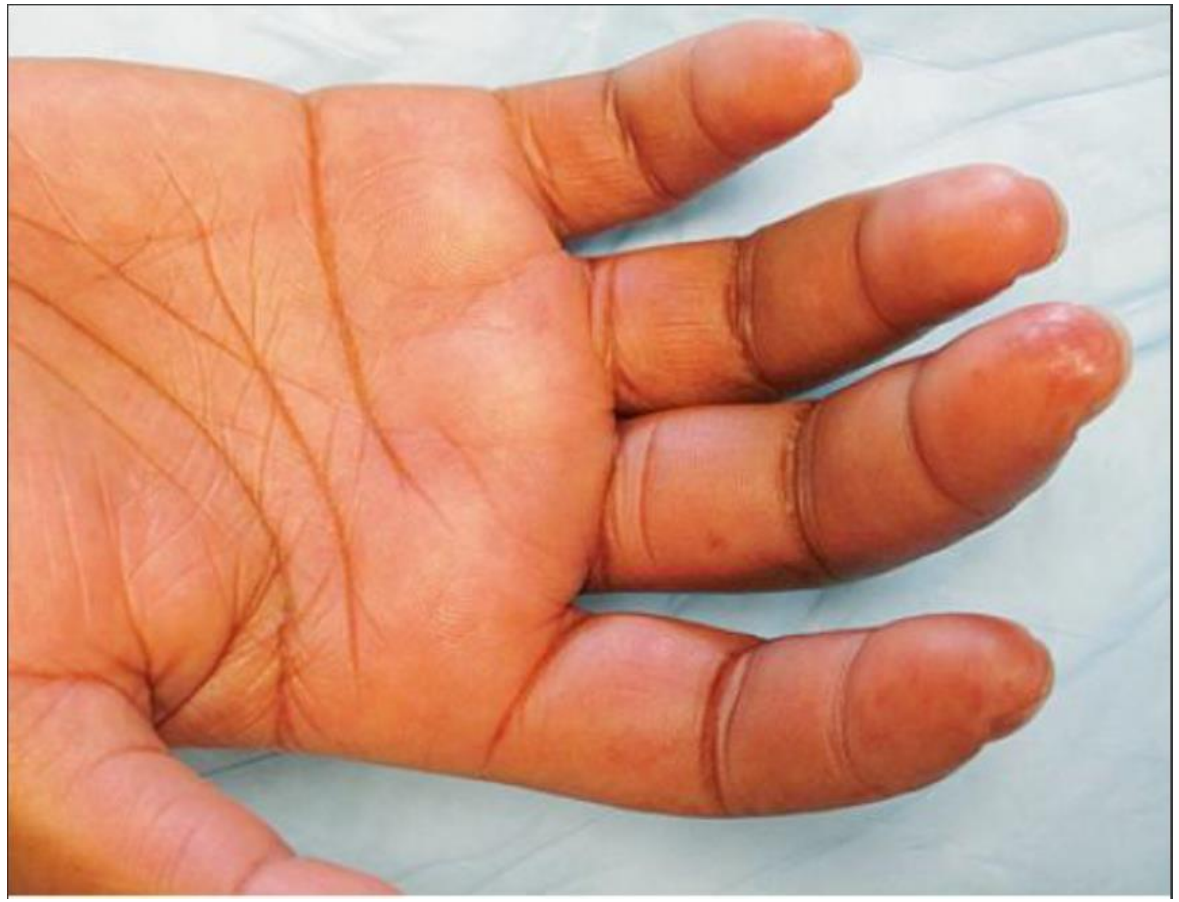
Contents

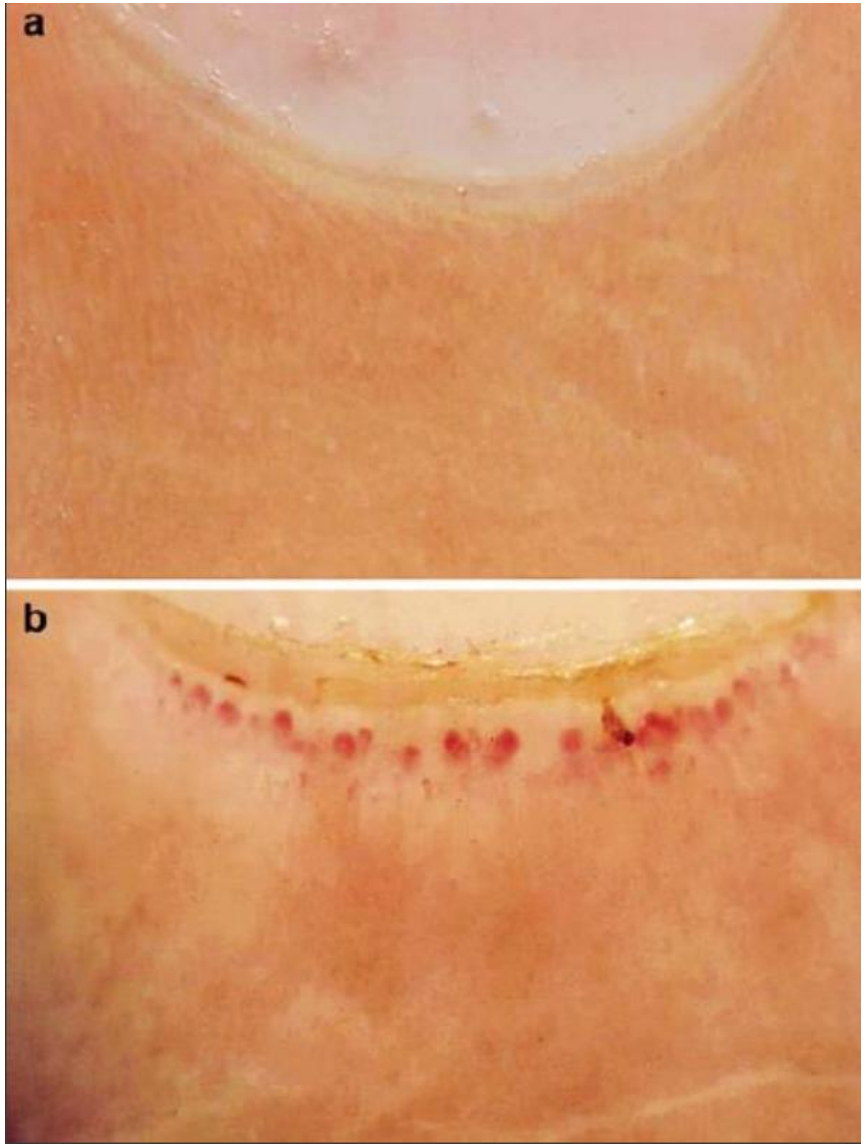
RHEUMATOLOGY

SCLERODERMA (SYSTEMIC SCLEROSIS)



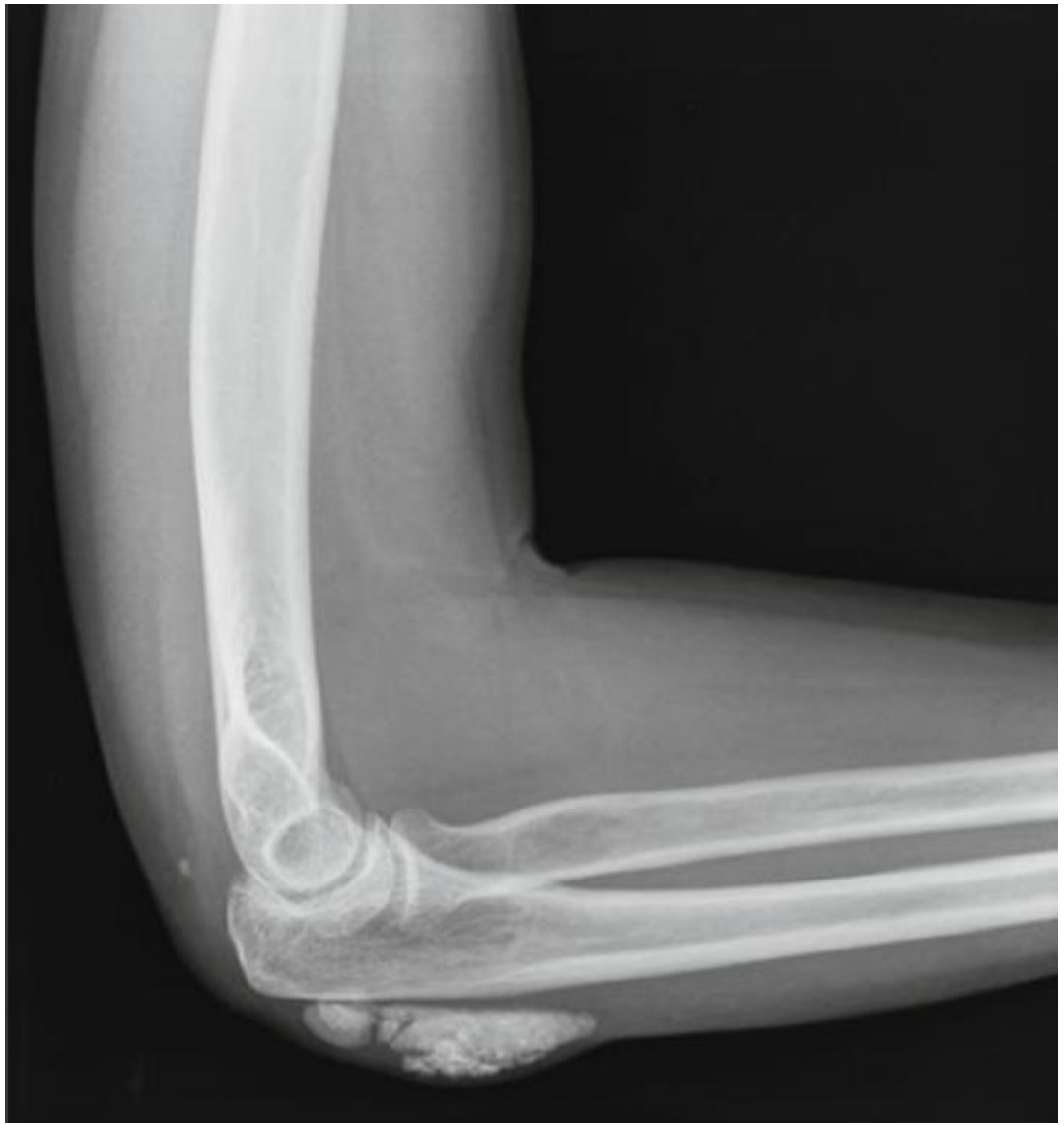
SKIN THICKENING ON THE TIPS OF THE FINGERS

RAYNAUD PHENOMENON

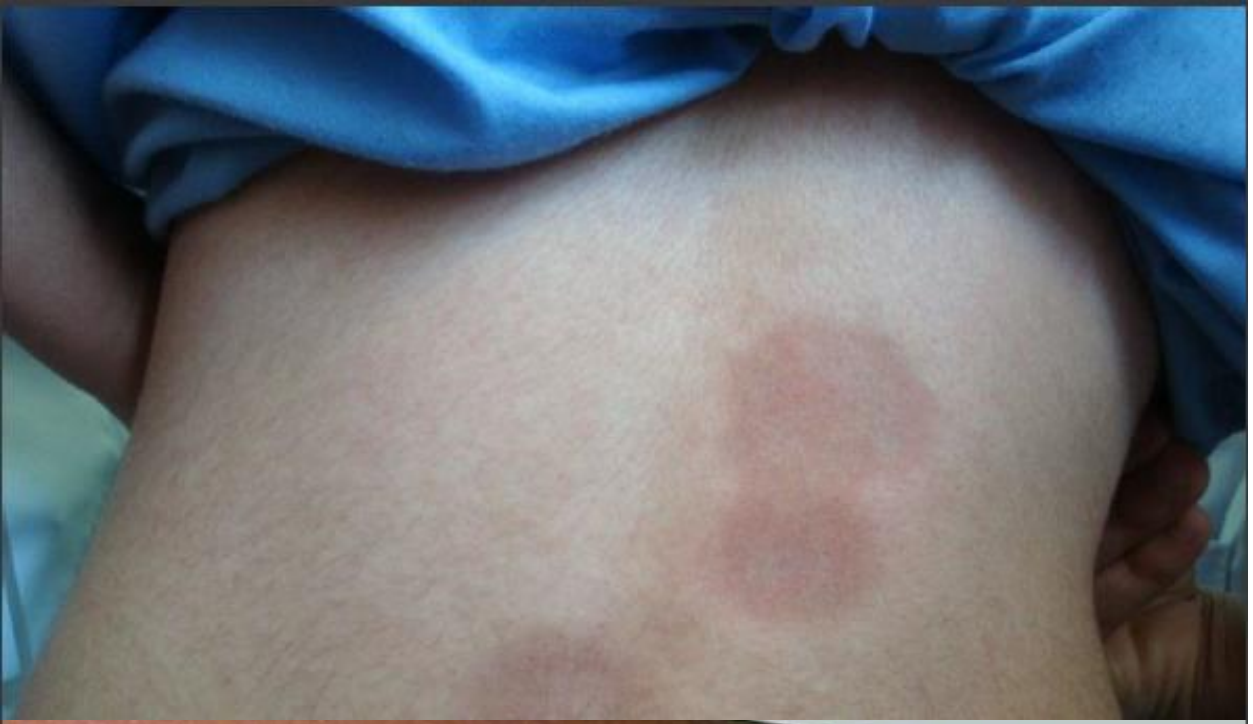


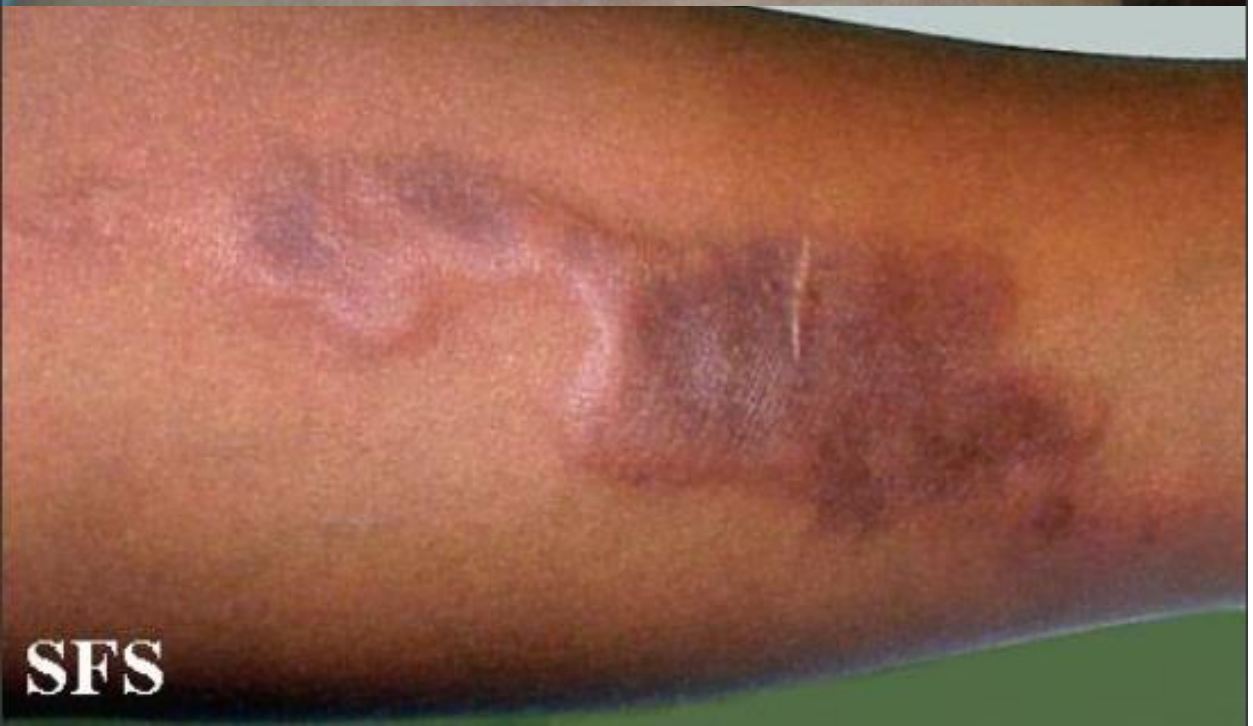
CAPILLARIES DILATION AND HEMORRHAGE

When seen along with Raynaud's phenomenon it indicates connective tissue disease.



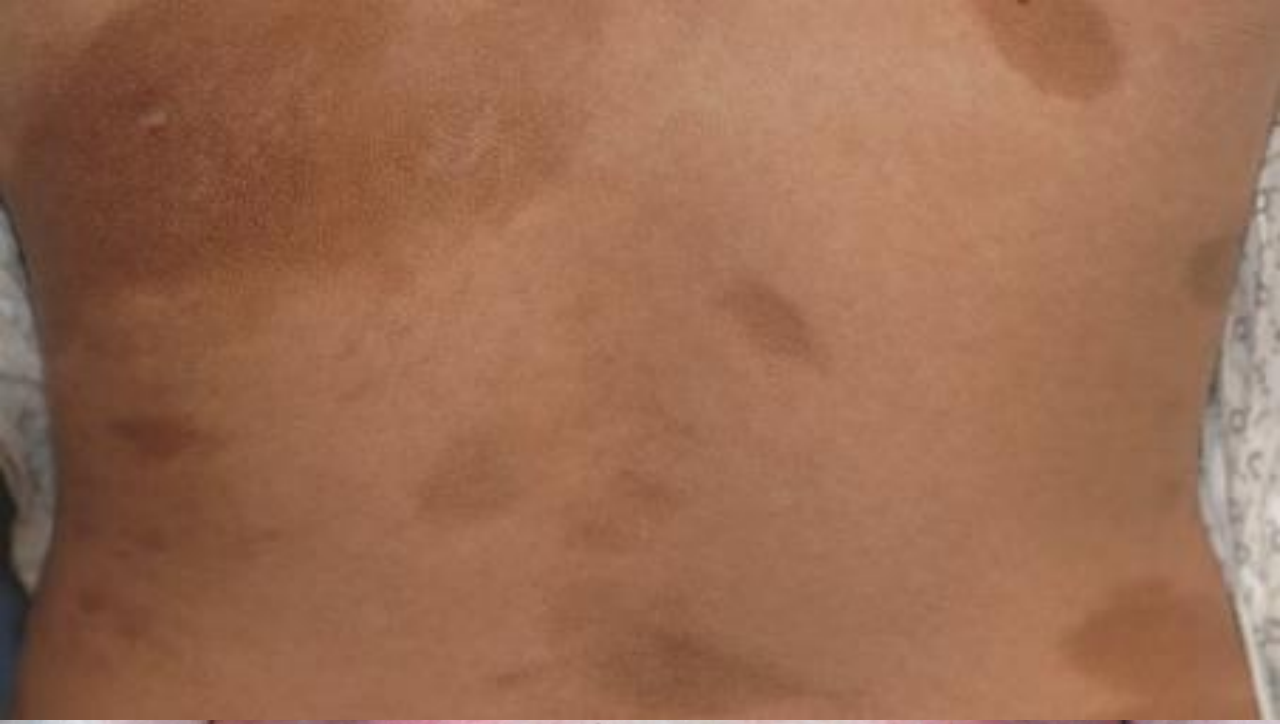
CALCIFICATIONS IN SCLERODERMA

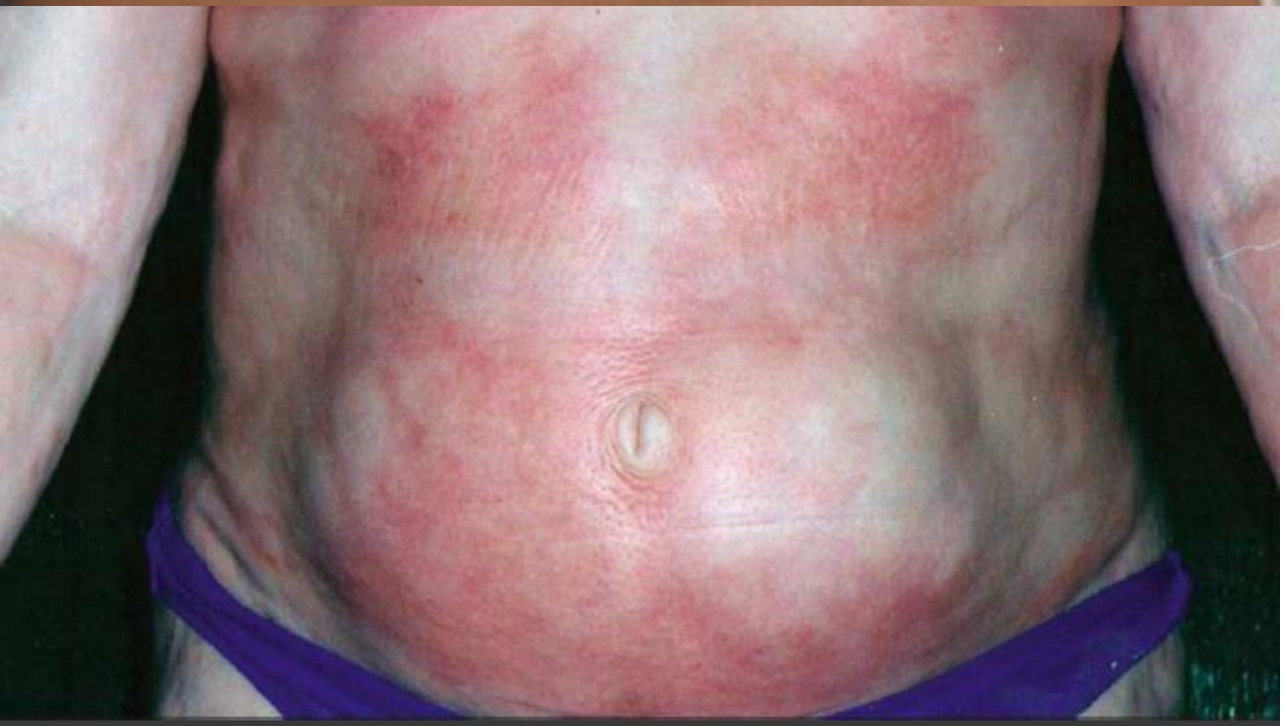




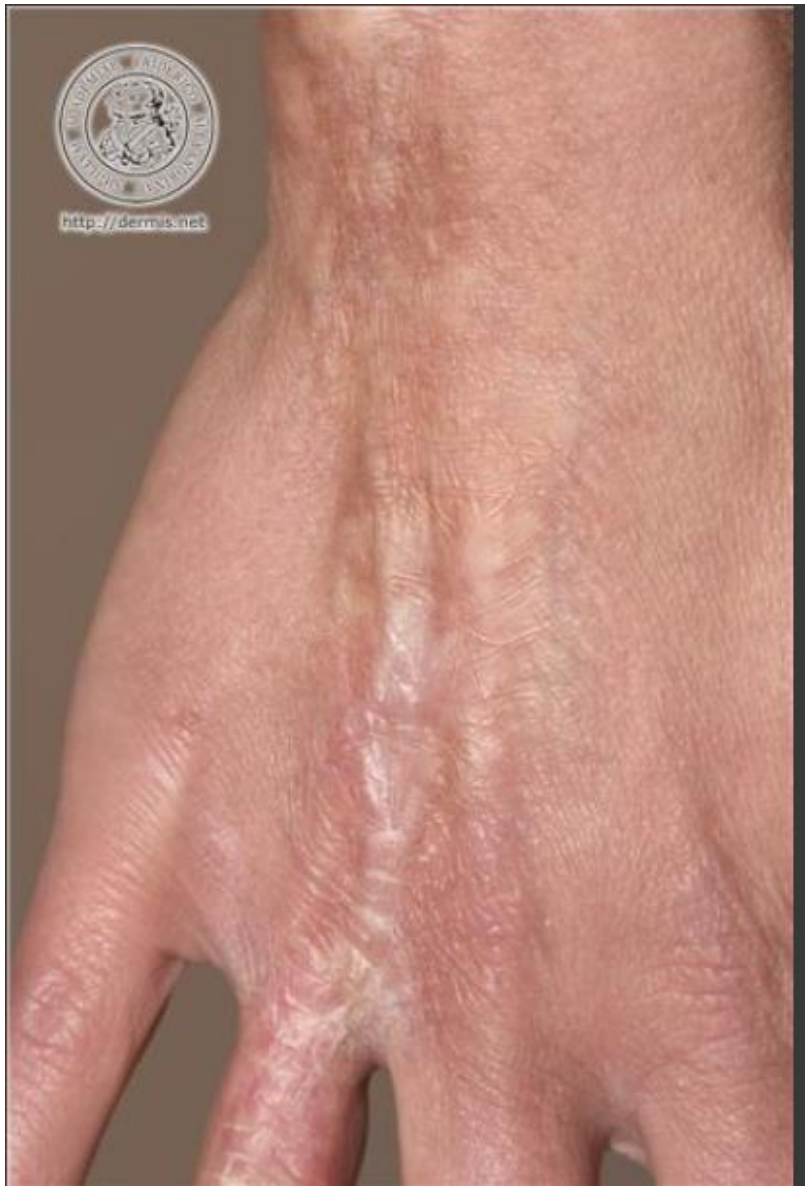
MORPHEA

- A solitary or multiple circular patches of thickened skin and less commonly widespread induration (Generalized Morphea).
- It is the main issue seen in **LOCALIZED SCLERODERMA**
- Localized Scleroderma: A group of localized fibrosing skin disorders that primarily affect children.



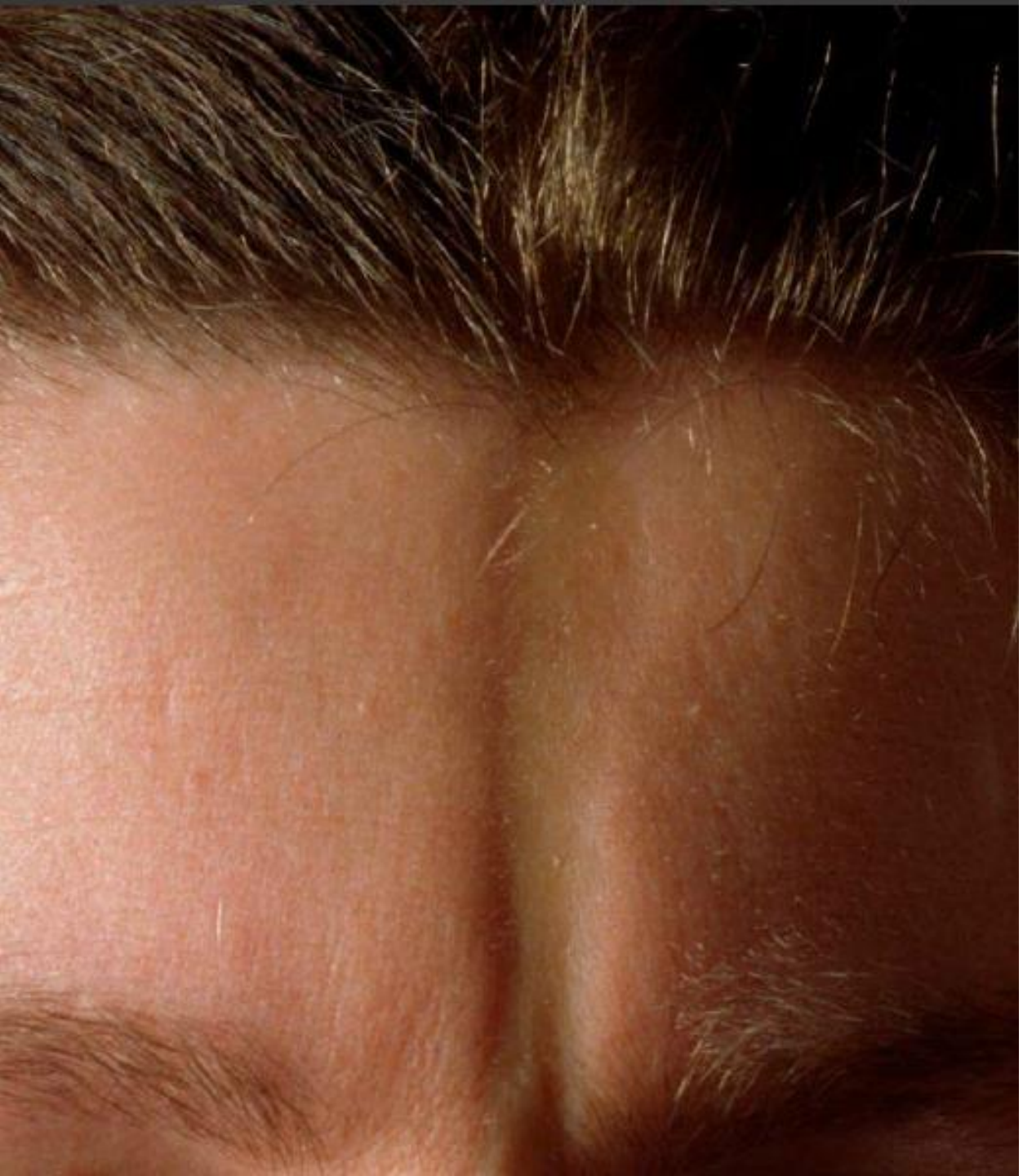


GENERALIZED MORPHEA



LINEAR SCLERODERMA

- Also Seen in **LOCALIZED SCLERODERMA**
- Streaks of thickened skin typically in on or both lower extermities.
- In children, it can affect the growth of long bones.
- When they cross joints, they may lead to the development of Contractures.



EN COUPE DE SABRE

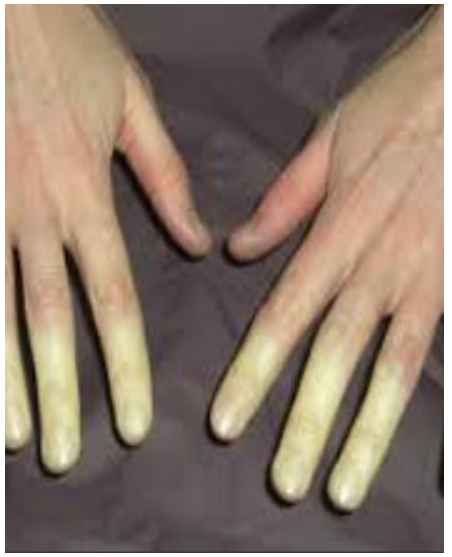
- Seen in **Localized Scleroderma**

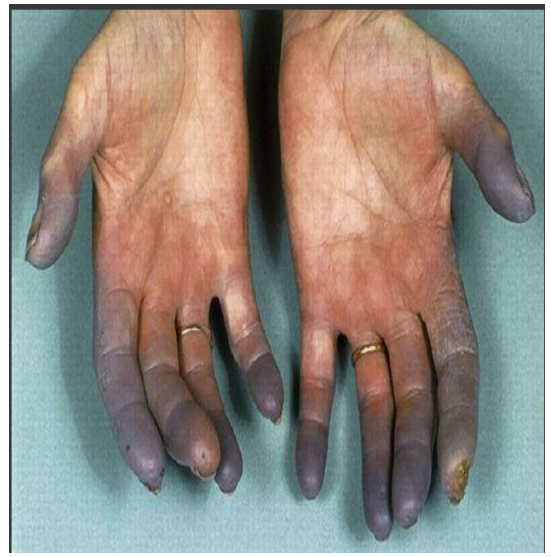
Raynaud phenomenon

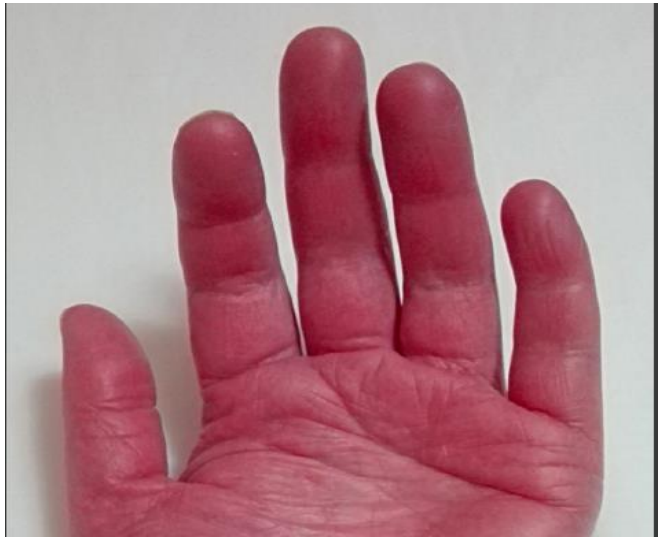
- Color changes in Raynaud phenomenon occurs in 3 stages:

1- Blanching (Pallor) 2- Cyanosis 3- Redness (Reactive Hyperemia).

- Seen in Systemic Sclerosis.
- Can be either Primary (not associated with autoimmune or CT diseases) or Secondary (associated with Scleroderma, SLE, Sjogren, Cryoglobulinaemia, Vibrating tools use, Beta Blockers, Bleomycin and Cisplatin



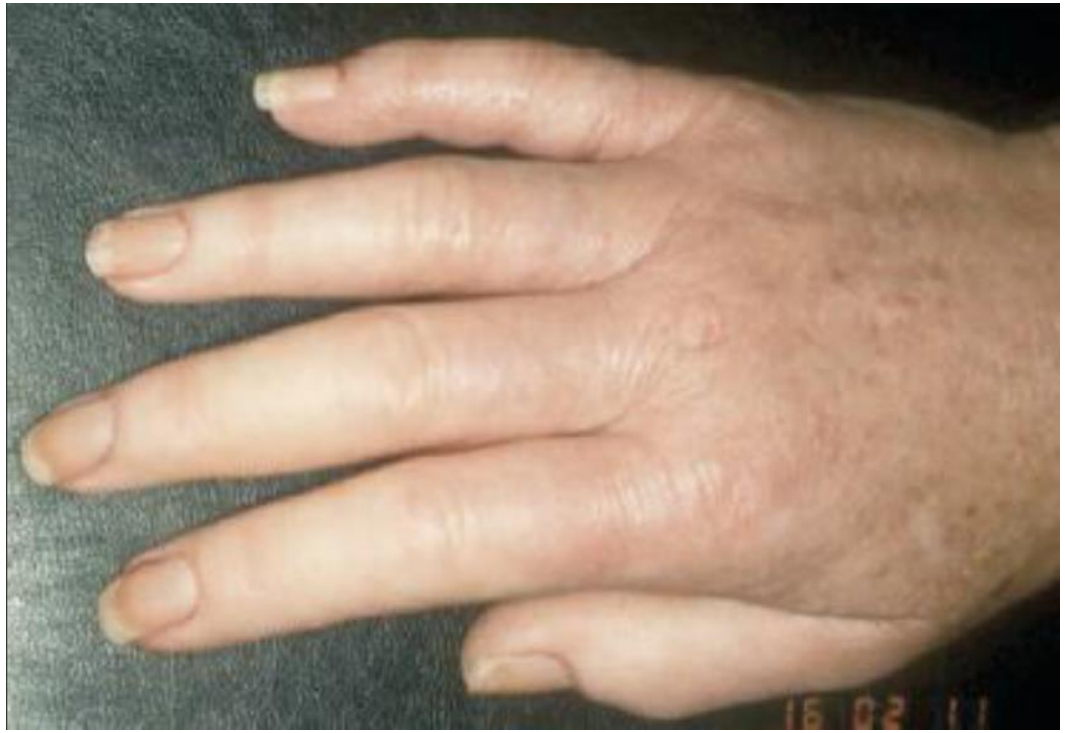




COMPARISON BETWEEN PRIMARY AND SECONDARY RAYNAUD'S

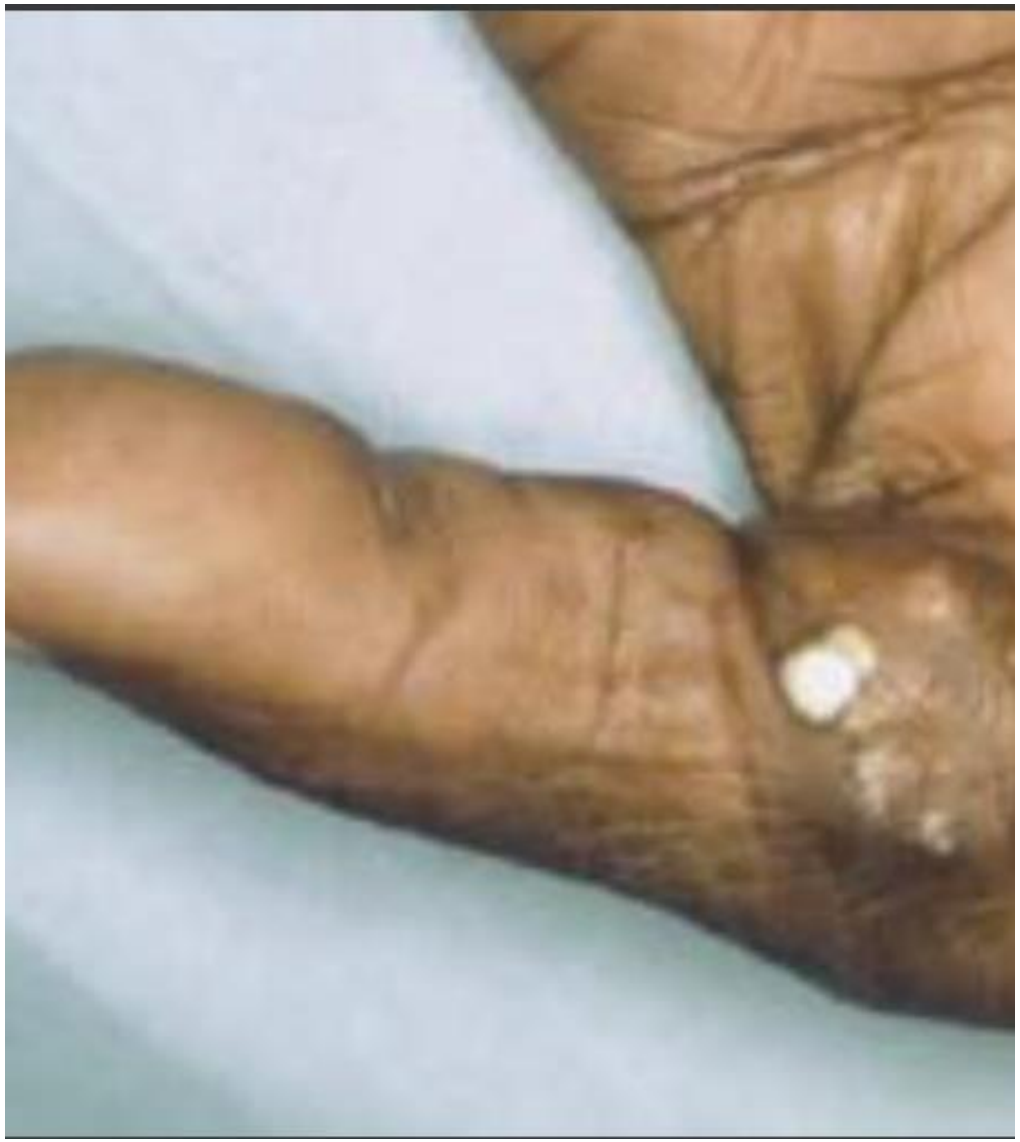
Raynaud's Phenomenon

	Primary	**Secondary**
Sex	Female	Male and Female
Age of Onset	Menarche	Mid 20's or later
Finger Edema	No	Frequent
Periungual erythema	Rare	Frequent
Arthritis	No	Frequent
Nail fold capillaroscopy	Normal	Dilated tortuous capillaries
Autoantibodies	Absent	Present



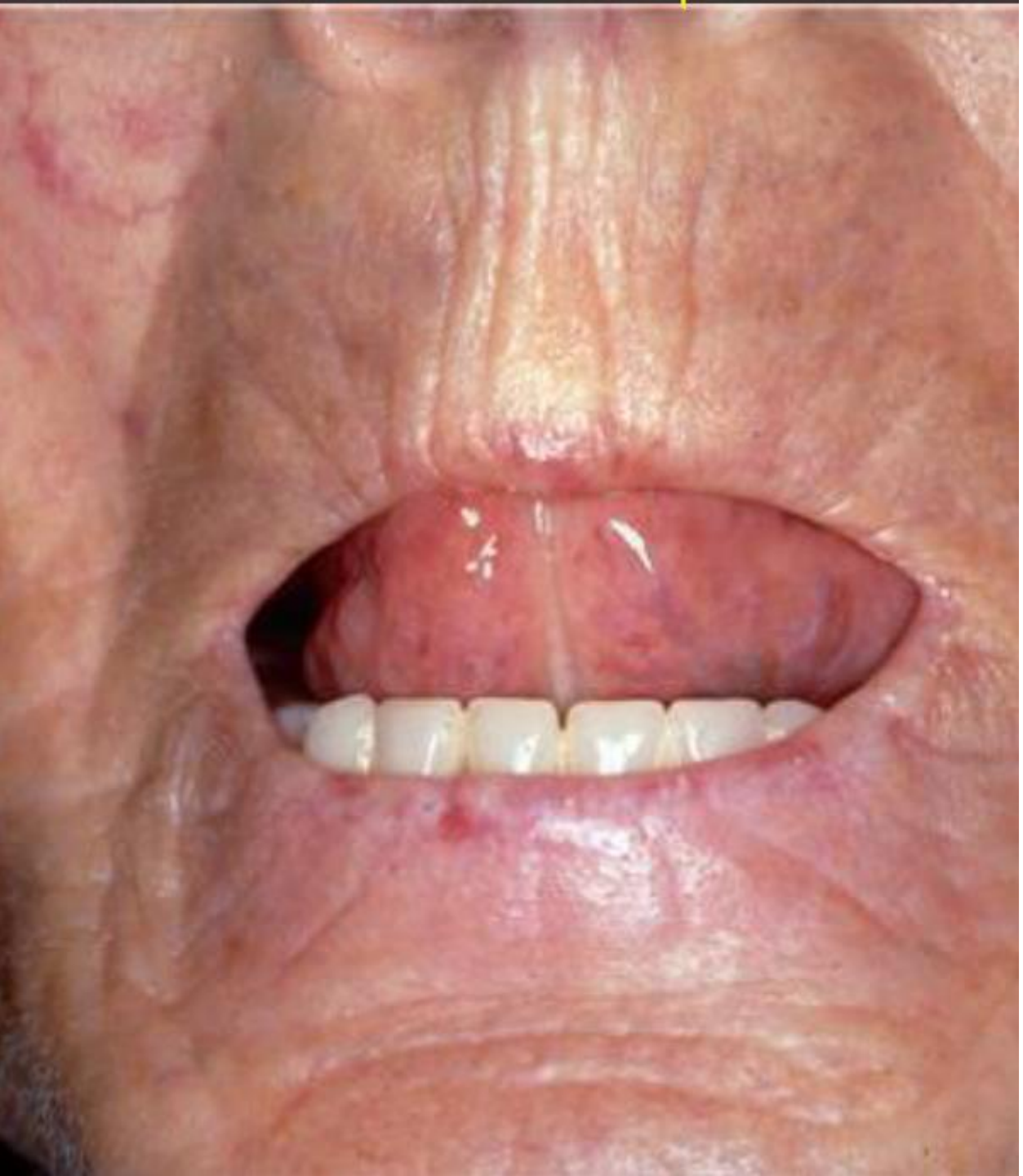
TIGHT CREASES OVER PIP (BUFFY FINGERS)

- One of the Skin Changes seen in Systemic Sclerosis.
- Always Symmetrical and Bilateral



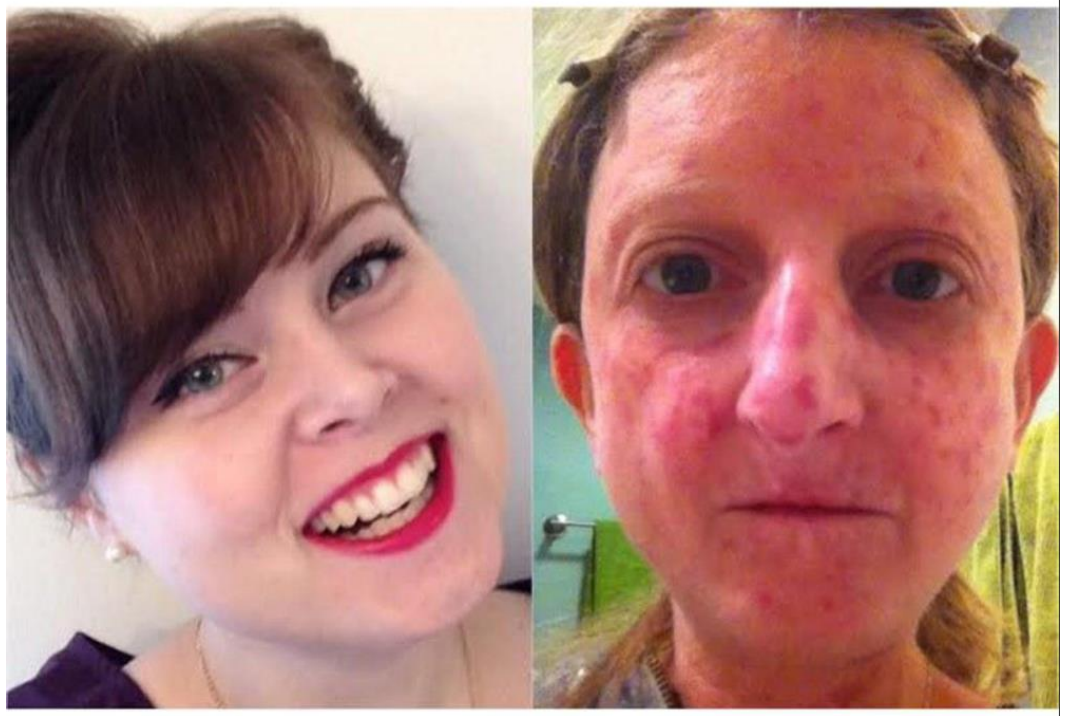
CALCINOSIS

One of the Skin changes seen in scleroderma



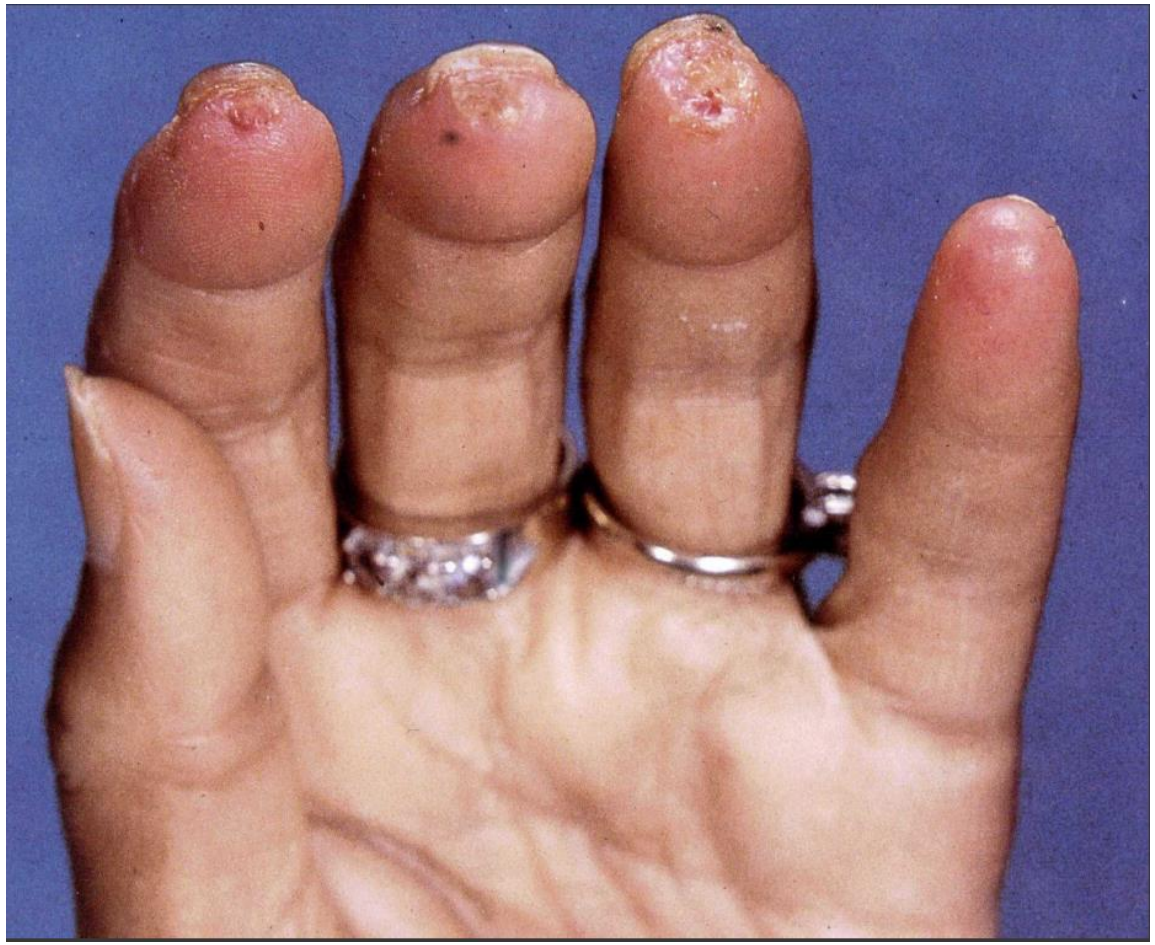
MICROSTOMIA (SMALL MOUTH / FISH MOUTH APPEARANCE)

- One of the skin changes seen in Scleroderma.
- Note that the skin of the face looks taut and shiny.



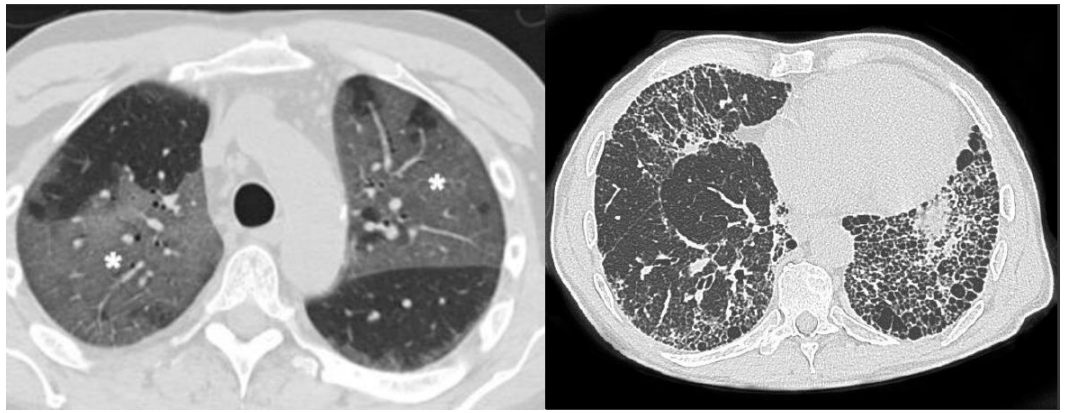
BEAKED NOSE + TELANGIECTASIA + MICROSTOMIA

- Skin Changes Seen in Scleroderma.
- Note that the skin of the face looks taut and shiny
- Telangiectasias are usually seen on face, hands, lips and oral cavity.



DIGITAL ULCERATIONS ON THE TIPS OF THE FINGERS

- One of the skin changes seen in scleroderma.
- They’re related to Raynaud phenomenon and Ischemia.
- They’re slowly healing and may become infected

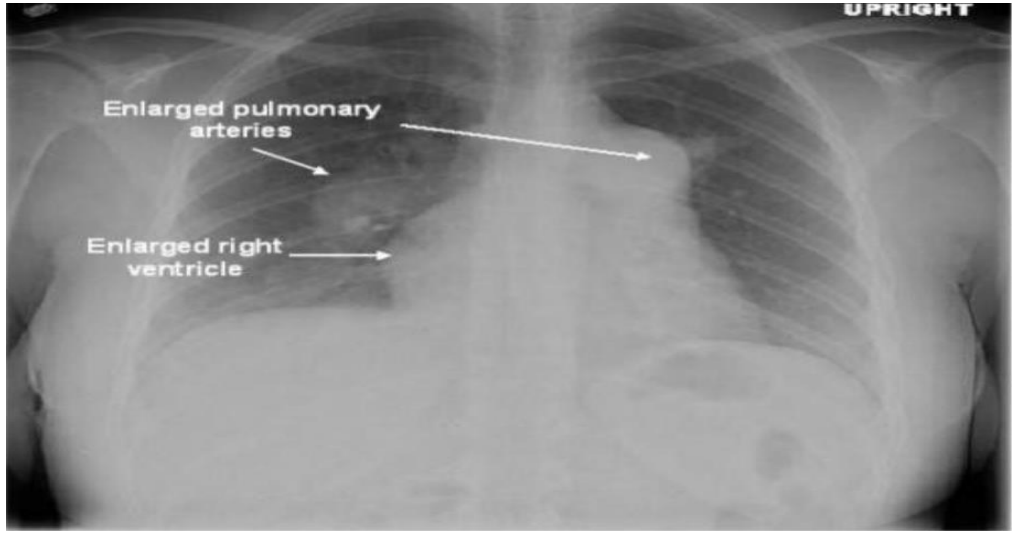


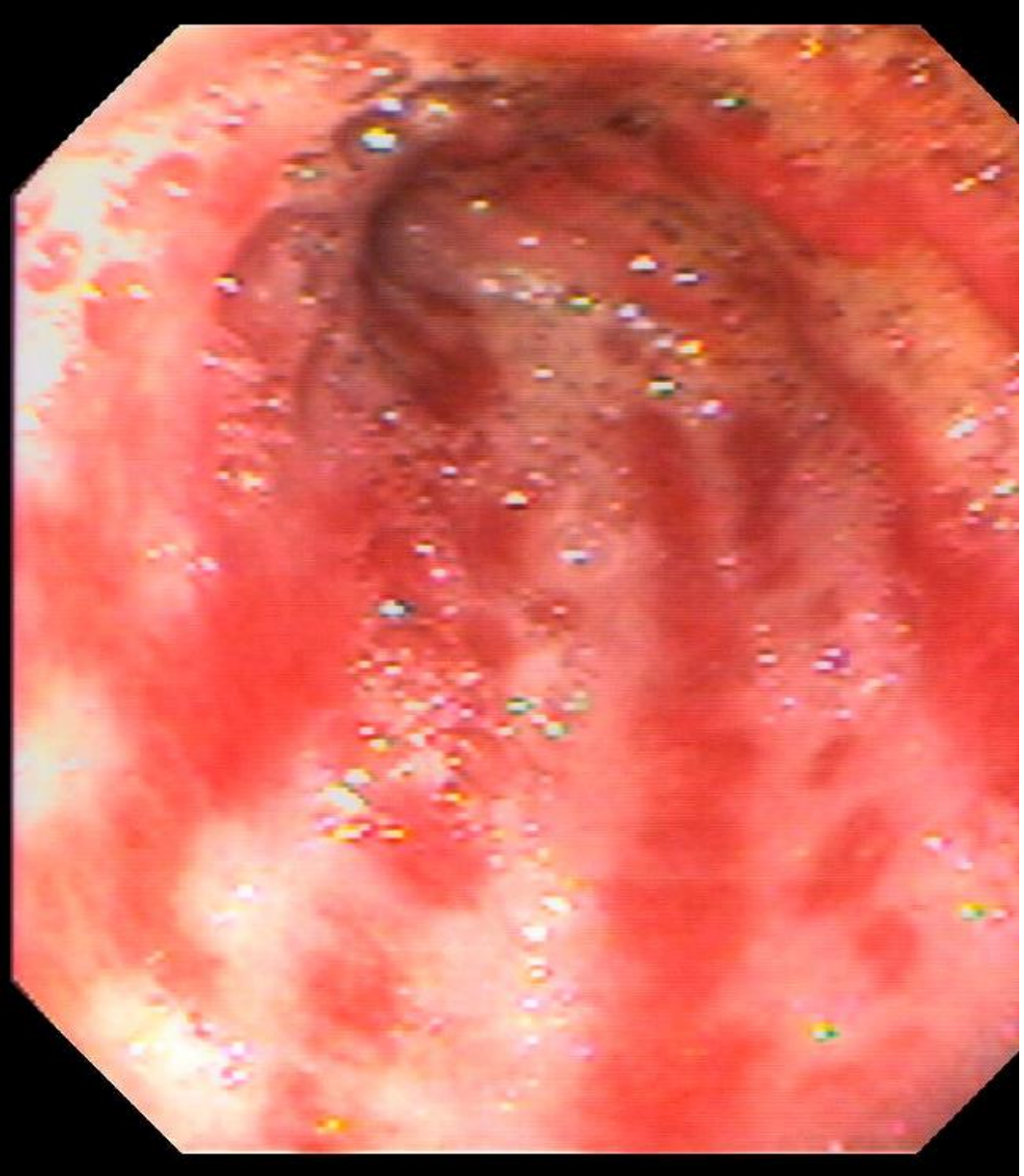
INTERSTITIAL LUNG DISEASE

- The most common cause of death from Scleroderma along with Pulmonary HTN.
- More common in Diffuse Scleroderma.
- Associated with SCL-70 positivity.
- Diagnosed by PFTs (decreased FVC and DLCO, but unaffected flow rates) and CT scans.
- Notice the Ground Glass appearance on the CT scan.

Enlarged Pulmonary Artery on CXR

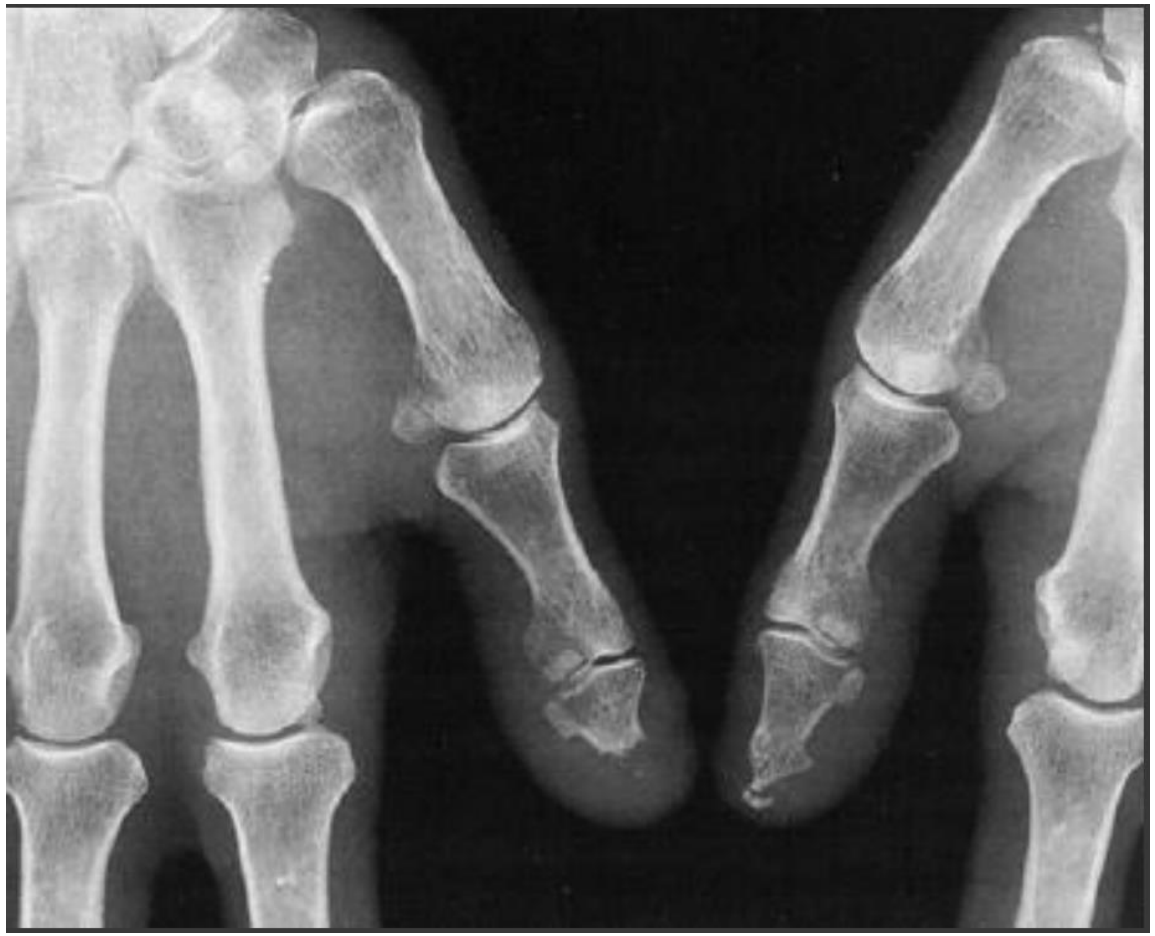
- Suggestive of Pulmonary Arterial Hypertension, seen in Scleroderma and is the most common cause of death along with ILD.
- More common in Limited Scleroderma.
- Associated with Anticentromere and RNP positivity.
- Late age of onset.
- Severe Raynaud phenomenon (both share the same pathophysiology).
- Diagnosed by PFTs (Isolated reduction in DLCO) and CXR (Enlarged Pulmonary Artery).





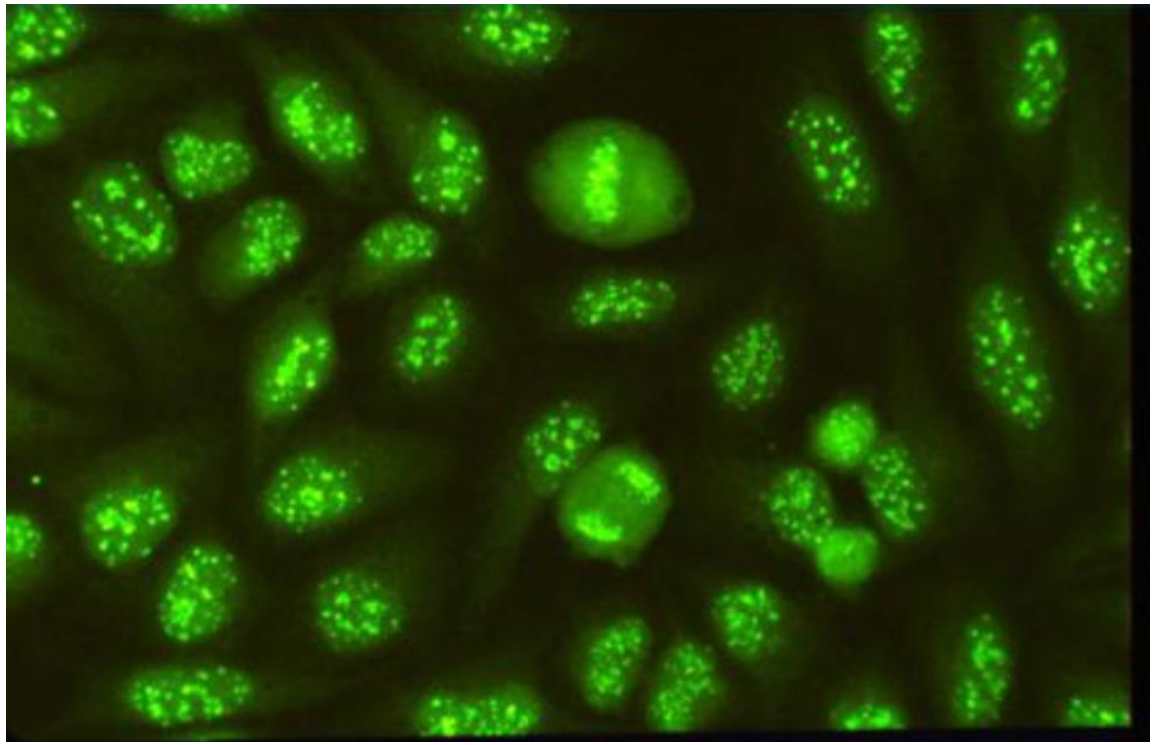
WATERMELON APPEARANCE OF THE STOMACH

- Caused by Telangiectasias.
- Can cause Bleeding and eventually leads to anemia.
- Associated with Bloating, Distension, GERD, Hematemesis, Chronic Diarrhea and dysphagia.



ACRO-OSTEOLYSIS

- One of the musculoskeletal changes seen in Scleroderma.
- It is a bone resorption in the terminal phalanges caused by Ischemia.



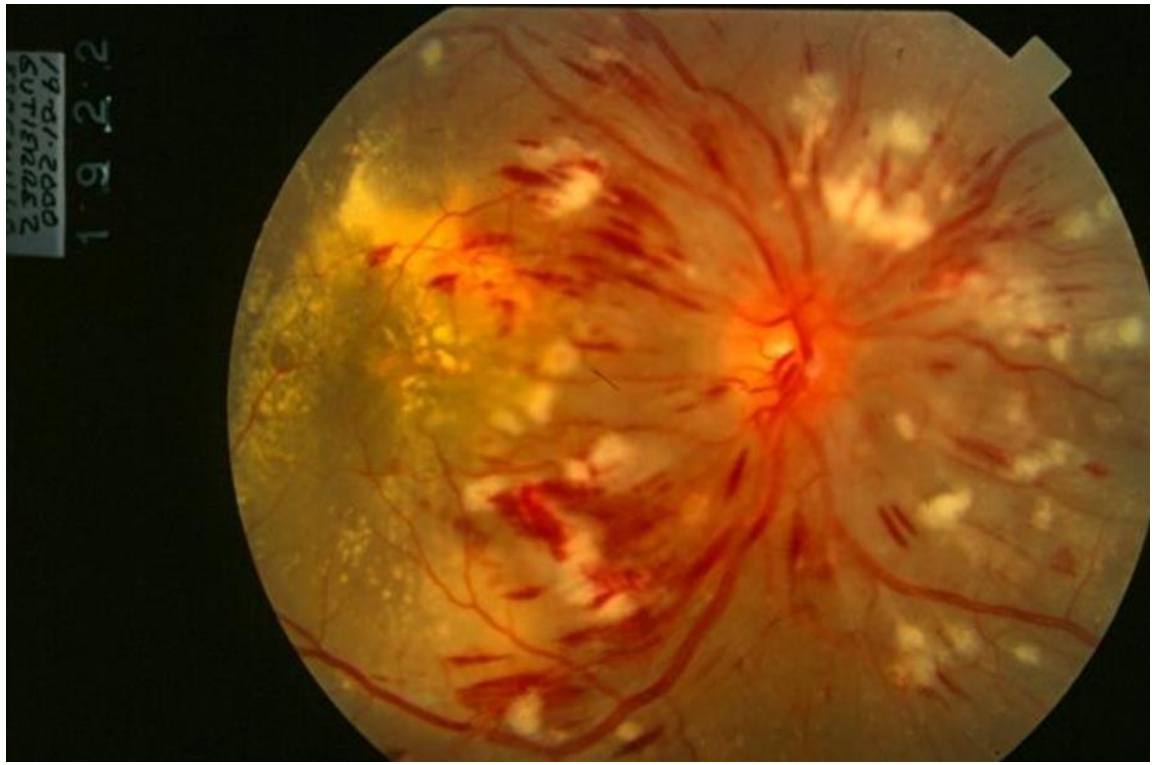
CENTROMERE PATTERN ANA

- Suggestive of Limited Scleroderma.
- Other lab findings:

1- normocytic anemia 2- normal ESR

3- Positive ANA

- Anti SCL-70 (anti topoisomerase 1) is only positive in diffuse Scleroderma



HARD EXUDATES, COTTON WOOL SPOTS AND FLAME SHAPED HEMORRHAGE ON THE FUNDUS

- Suggestive of renal crisis and Hypertension in diffuse scleroderma.

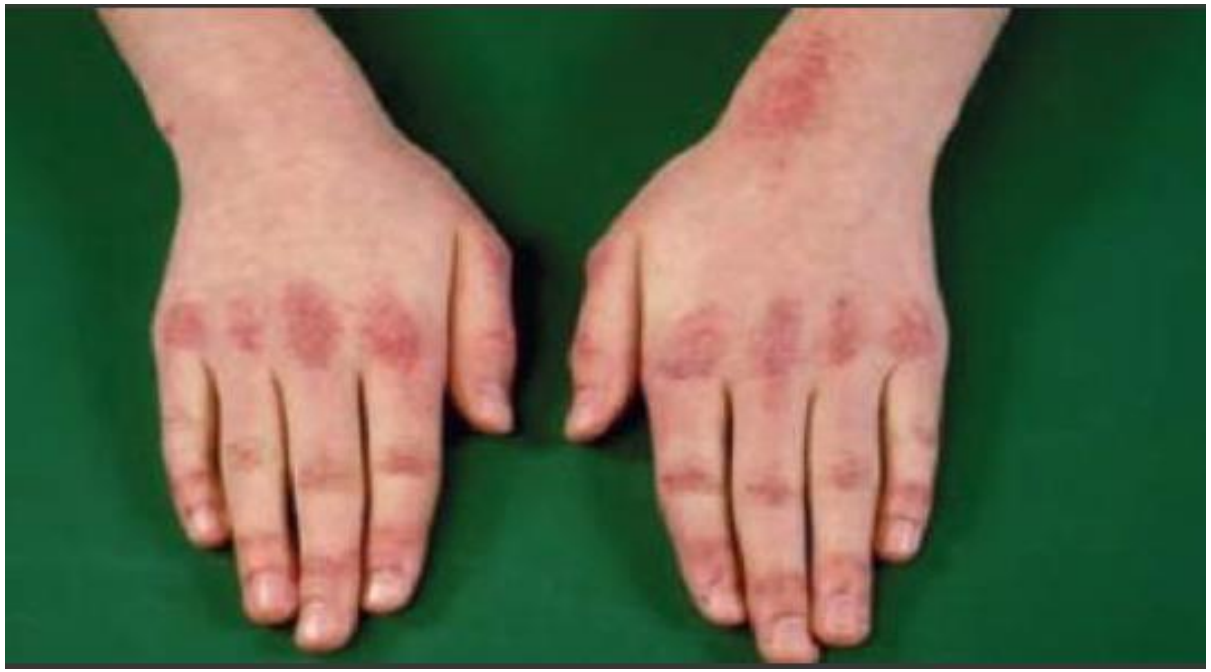
COMPARISON BETWEEN DIFFUSE AND LIMITED SCLERODERMA

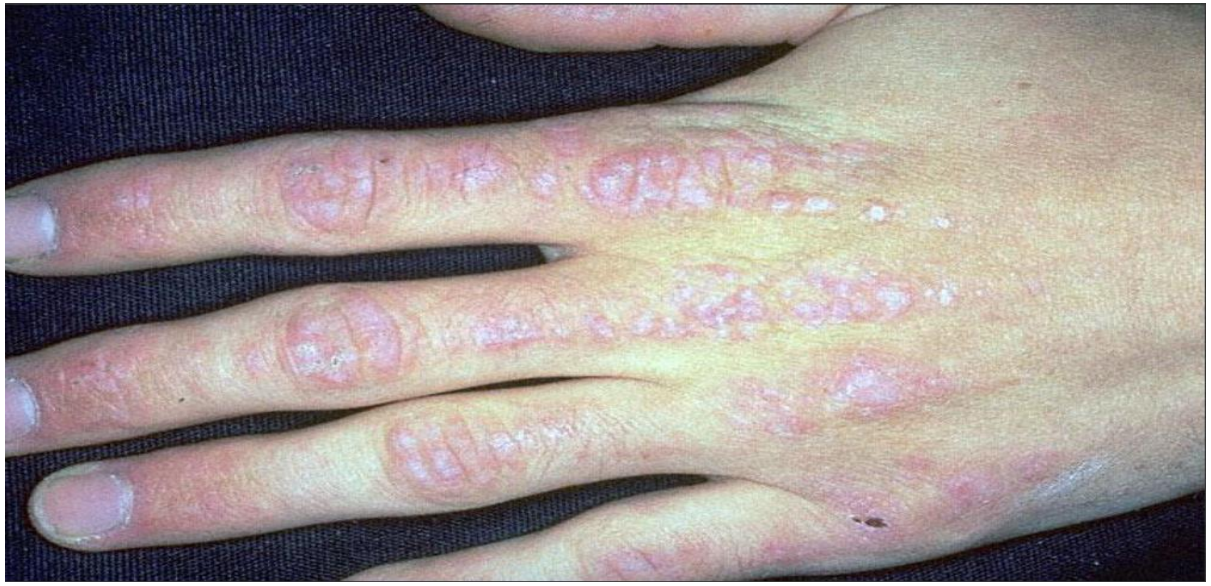
SUBSETS OF SYSTEMIC SCLEROSIS (SSc): LIMITED CUTANEOUS SSc VERSUS DIFFUSE CUTANEOUS SSc		
FEATURES	**LIMITED CUTANEOUS SSc**	**DIFFUSE CUTANEOUS SSc**
Skin involvement	Limited to fingers, distal to elbows, face; slow progression	Diffuse: fingers, extremities, face, trunk; rapid progression
Raynaud's phenomenon	Precedes skin involvement; associated with critical ischemia	Onset contemporaneous with skin involvement
Pulmonary fibrosis	May occur, moderate	Frequent, early and severe
Pulmonary arterial hypertension	Frequent, late, may be isolated	May occur, associated with pulmonary fibrosis
Scleroderma renal crisis	Very rare	Occurs in 15%; early
Calcinosis cutis	Frequent, prominent	May occur, mild
Characteristic autoantibodies	Anticentromere	Antitopoisomerase I (Scl-70)

INFLAMMATORY MYOPATHIES

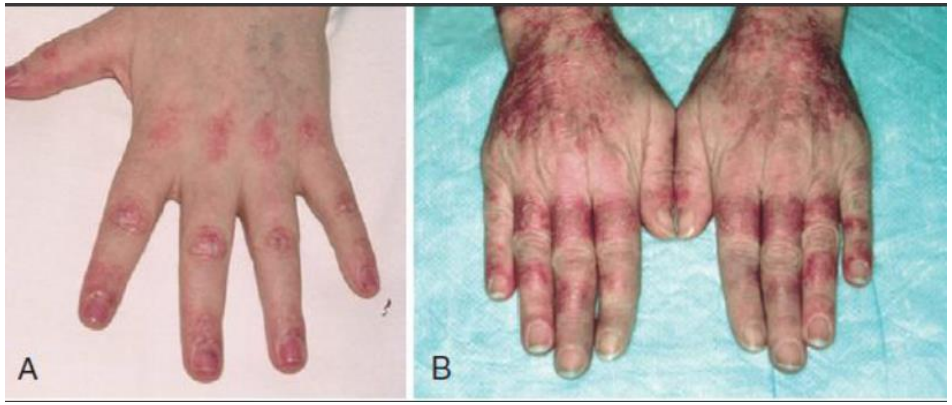
Gottron's papules

- Skin rash on the dorsal aspect of the knuckles (MCP, PIP, DIP), they're shiny, erythematous and Pinkish-Purplish in color.
- One of the skin changes seen in Idiopathic inflammatory myopathies specifically **DERMATOMYOSITIS**





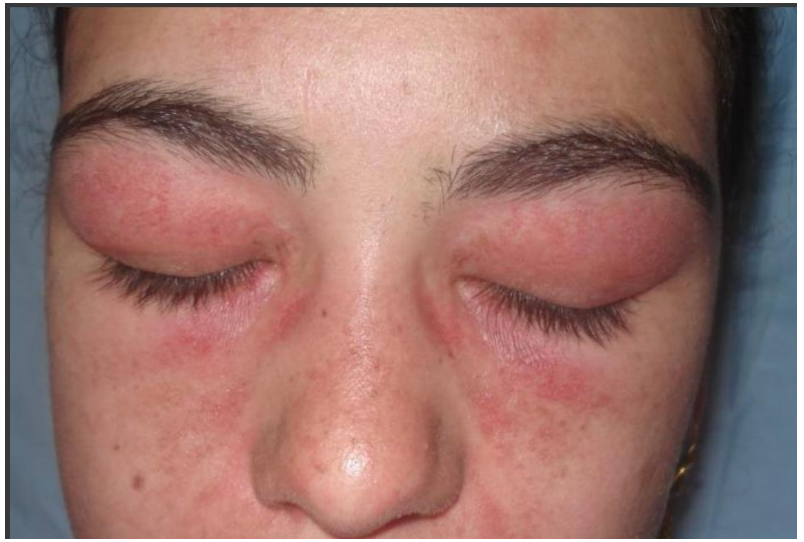
The difference between Skin rash in dermatomyositis and Lupus

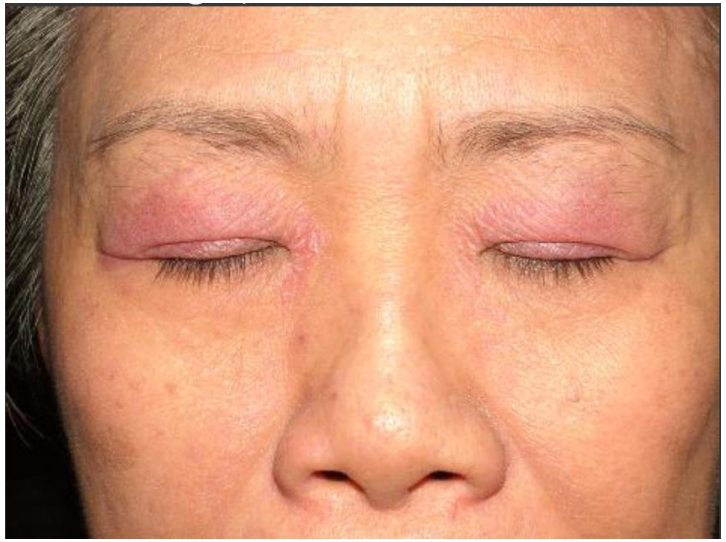


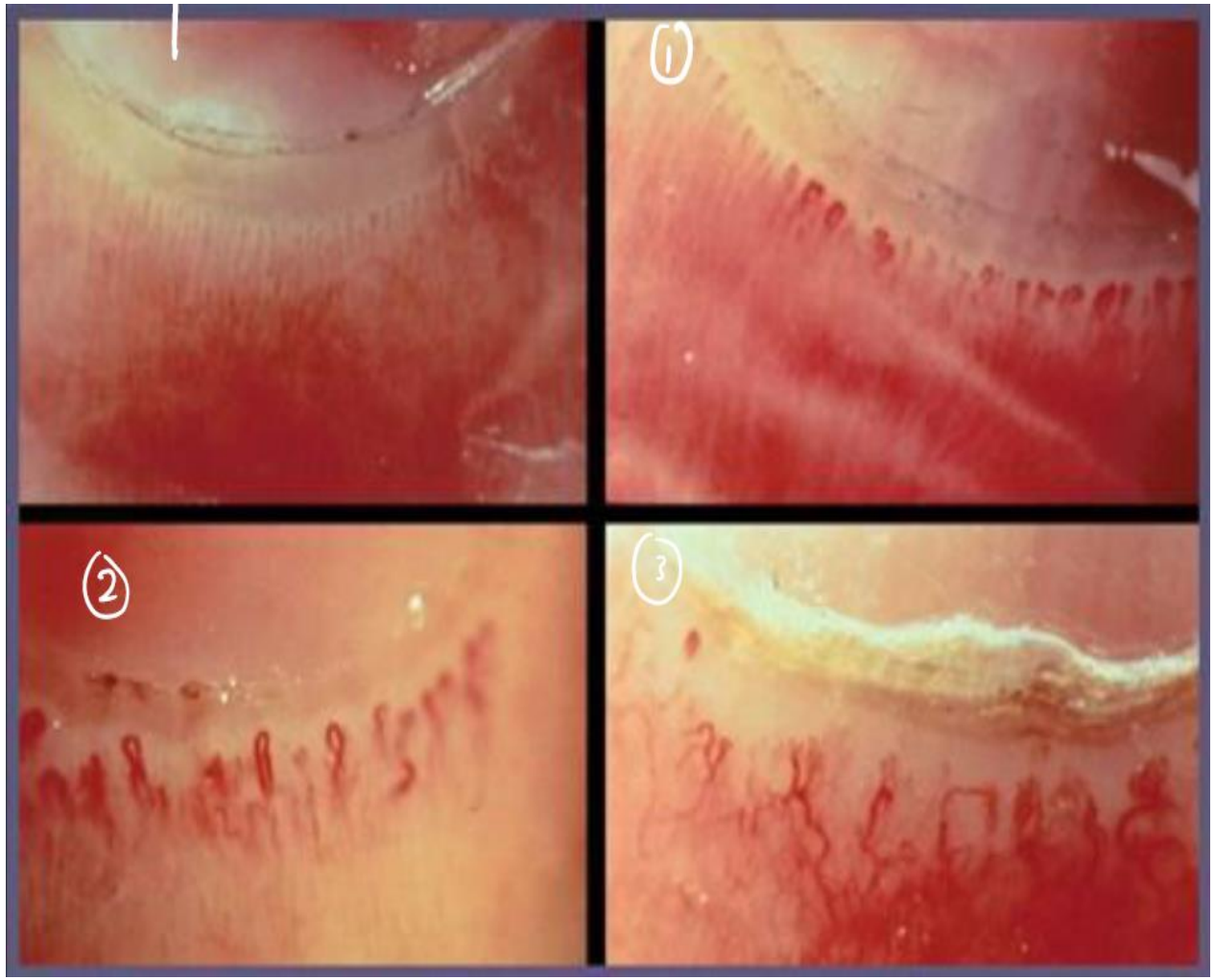
- Notice that in Dermatomyositis (the picture on the left) the rash is on the dorsal aspect of all MCPs, PIPs, and DIPs.
- While in Lupus (the picture on the right) we have intra-articular dermatitis with the rash found between MCPs and PIPs.

HELIOTROPE RASH (BUTTERFLY RASH)

- A skin change seen specifically in Dermatomyositis.
- Found around the eyelids, bridge of nose and cheeks.
- Associated with swelling of the eyelid and fine telangectasia.

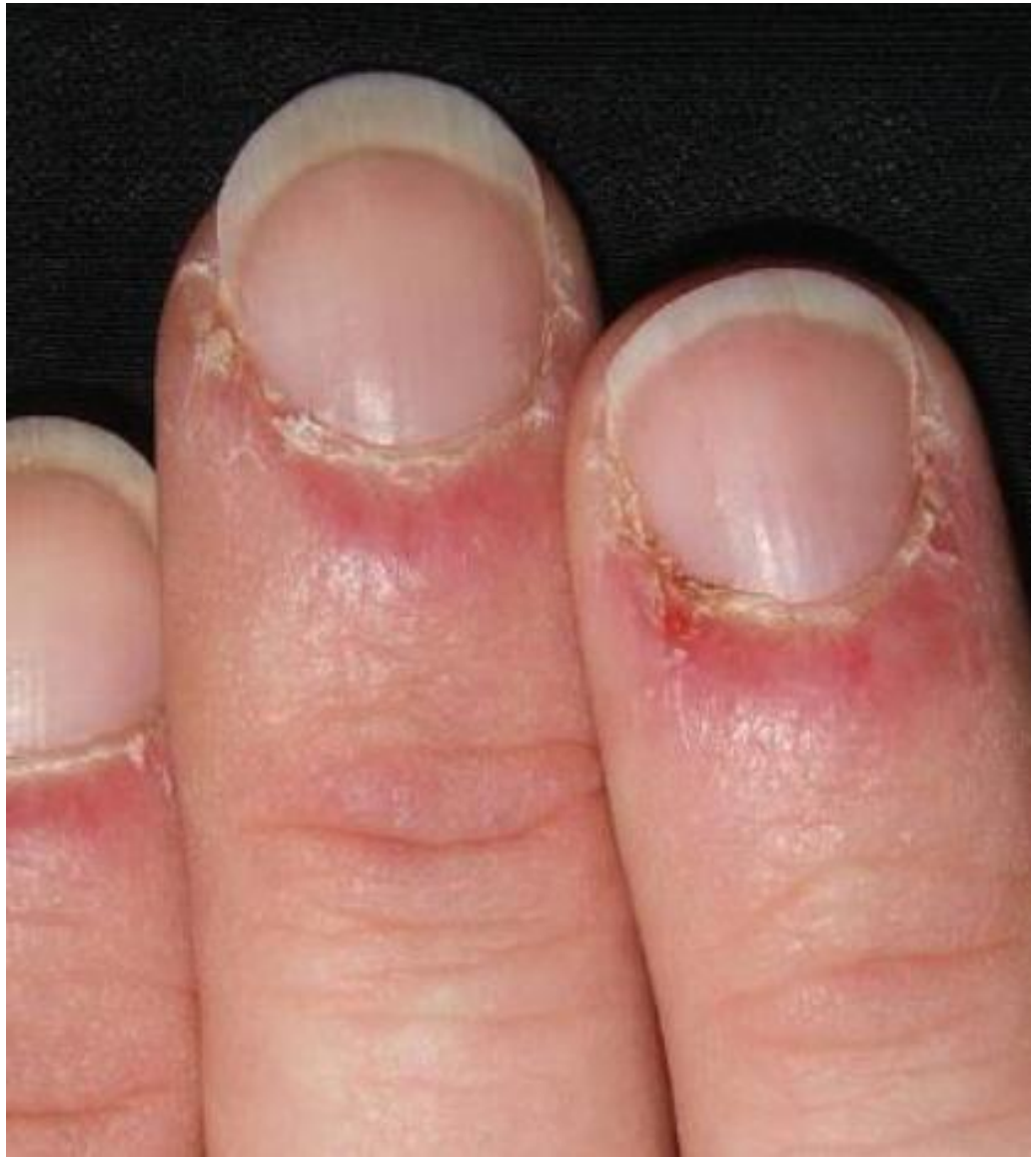






Nail fold capillary changes

- Also seen specifically with Dermatomyositis.
- Consequent dilation and drop out of the nail fold capillaries, seen with the naked eyes in pictures 1-3

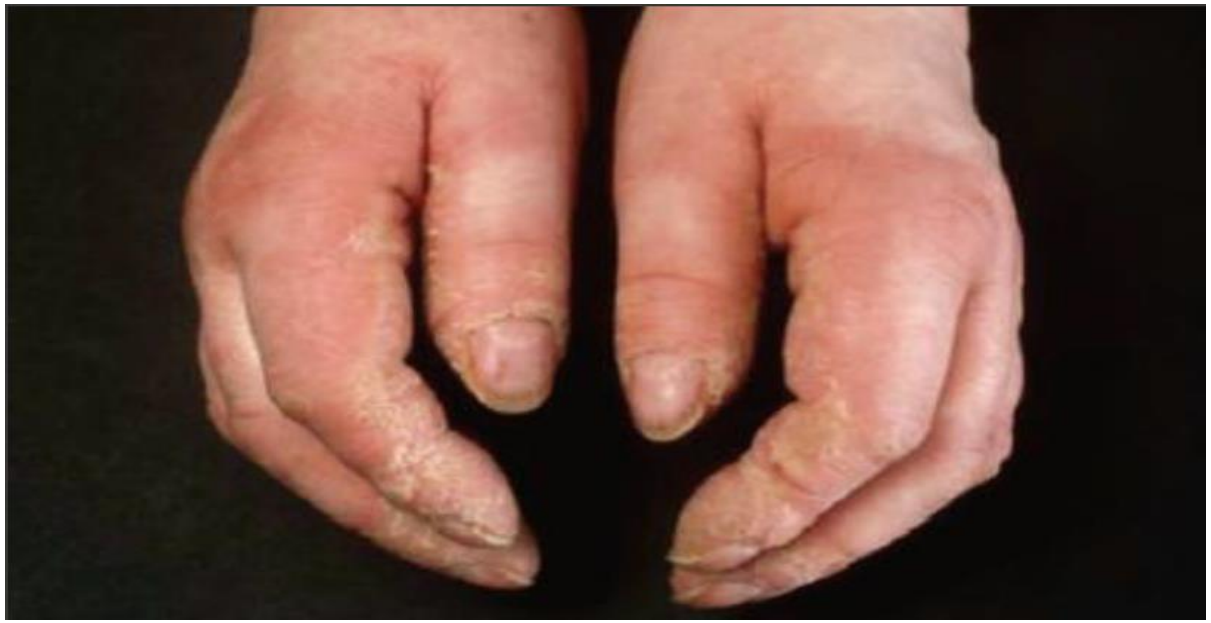


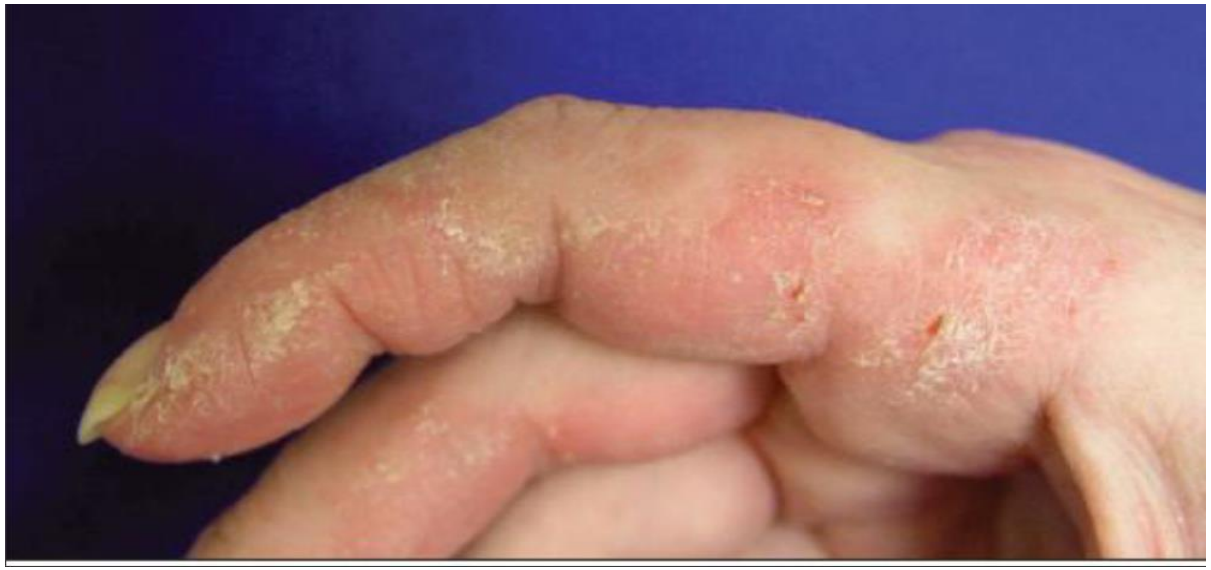
Cuticular overgrowth with periungual erythema and capillary dilation

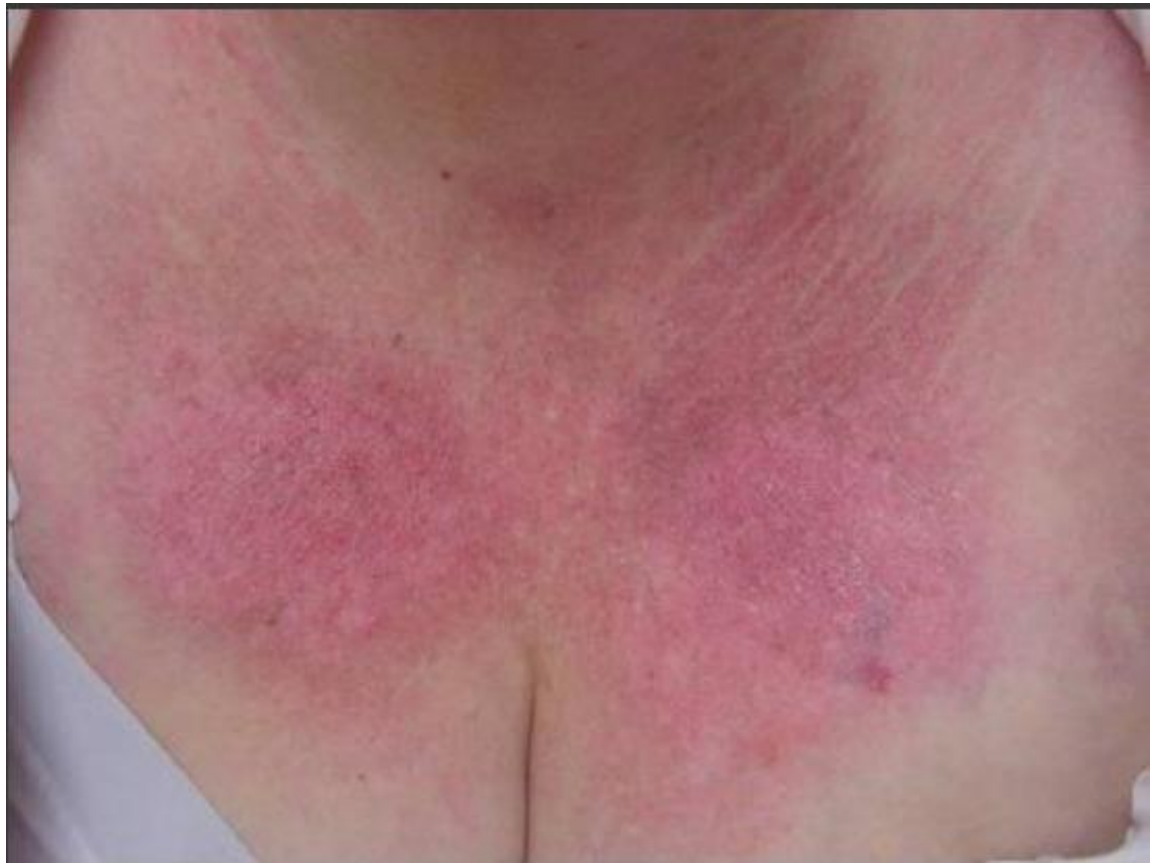
- Seen, Specifically in Dermatomyositis.
- Redness around nail-fold and ragging of the cuticle and skin is very dry + small infarctions may occur.

MECHANICS HANDS.

- Seen in Dermatomyositis.
- Patient with normal skin start to have edematous skin changes and dryness due to intense labor work.
- In this case we should suspect myositis especially with lung involvement (ANTI-SYNTHETASE / ANTI-JO1 SYNDROME)

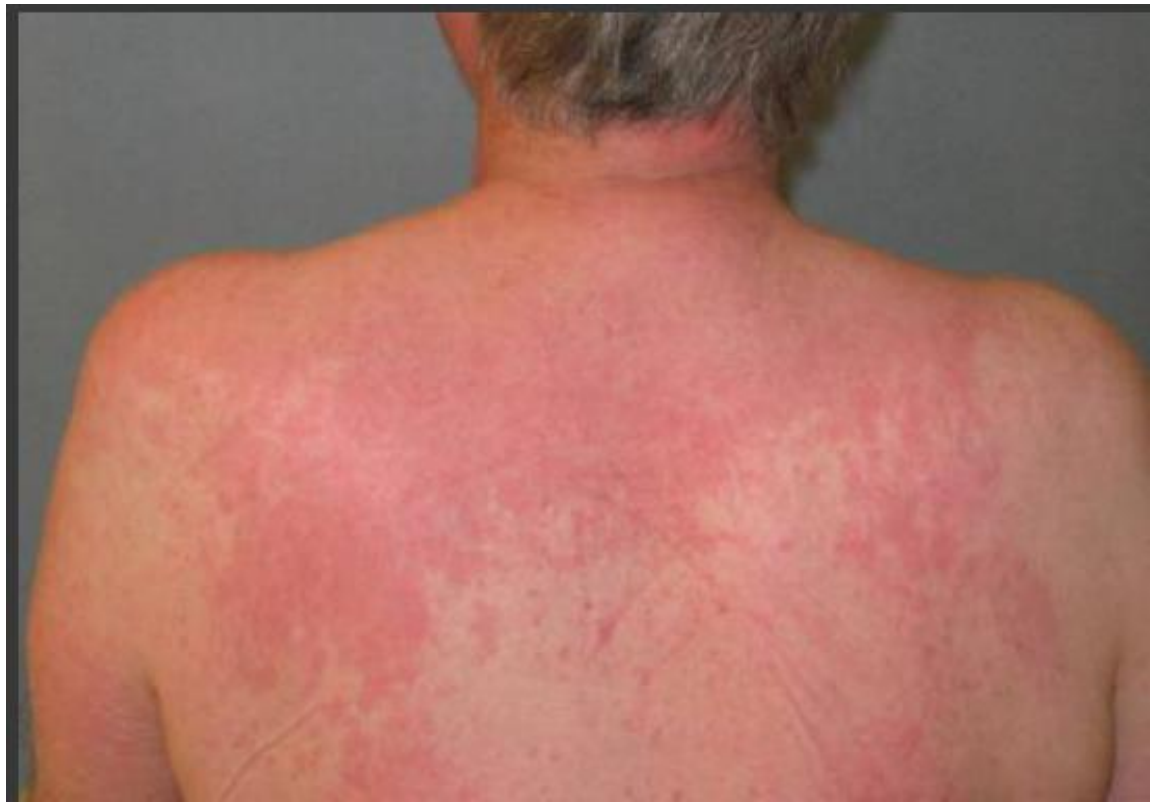






V SIGN

- Specific to Dermatomyositis.
- Photosensitive Rash on the Face, Neck, and Anterior chest.

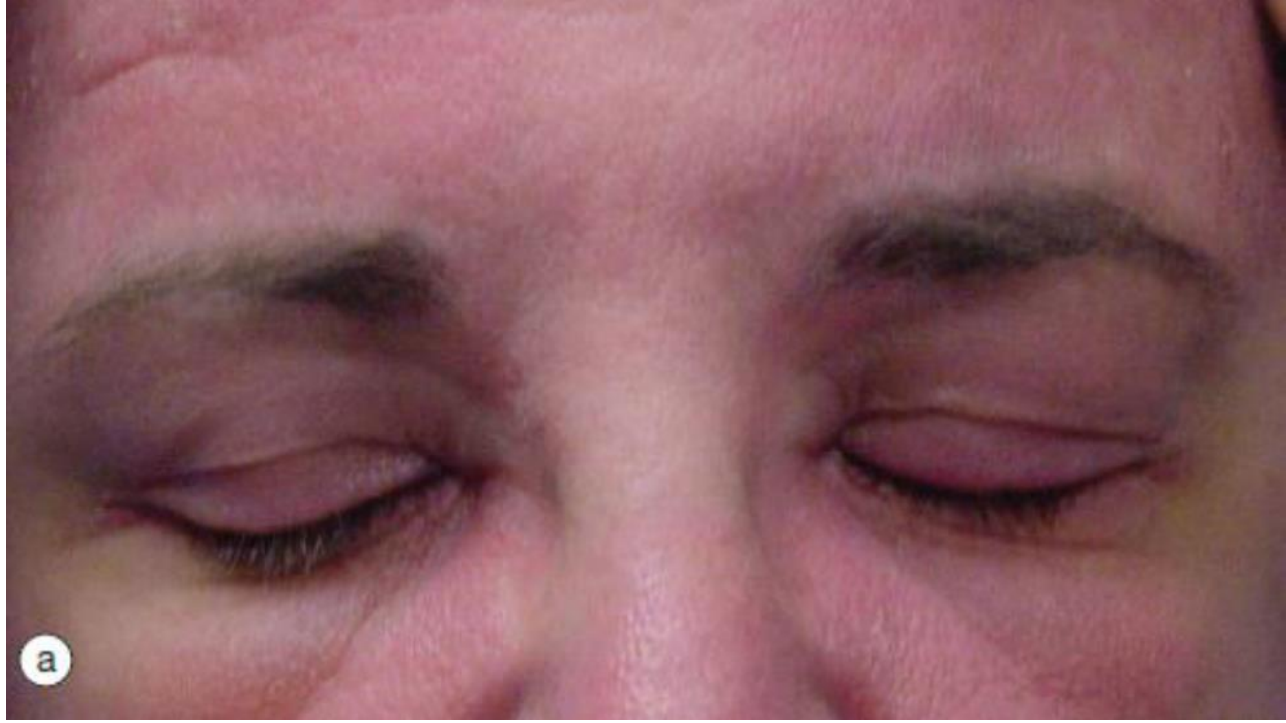


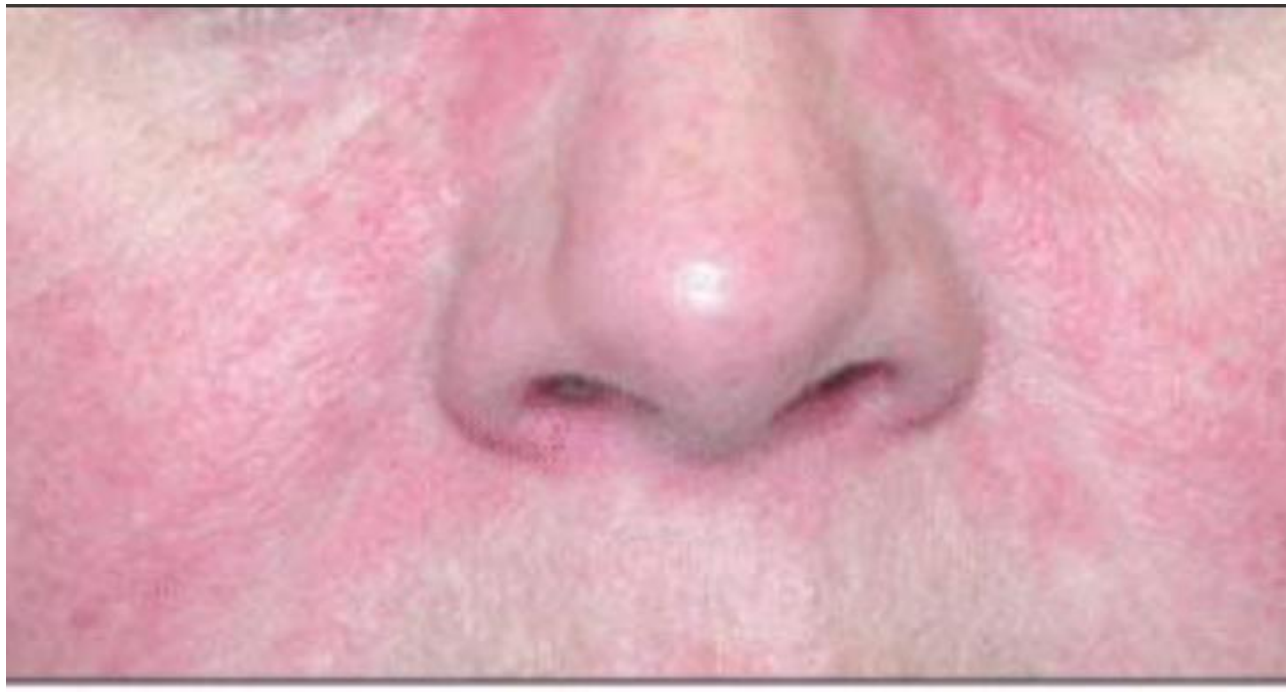
SHAWL SIGN

- Specific to Dermatomyositis.
- Rash on the Shoulders, Upper back, Elbows, and Knees.

PHOTOSENSITIVE RASH IN DERMATOMYOSITIS

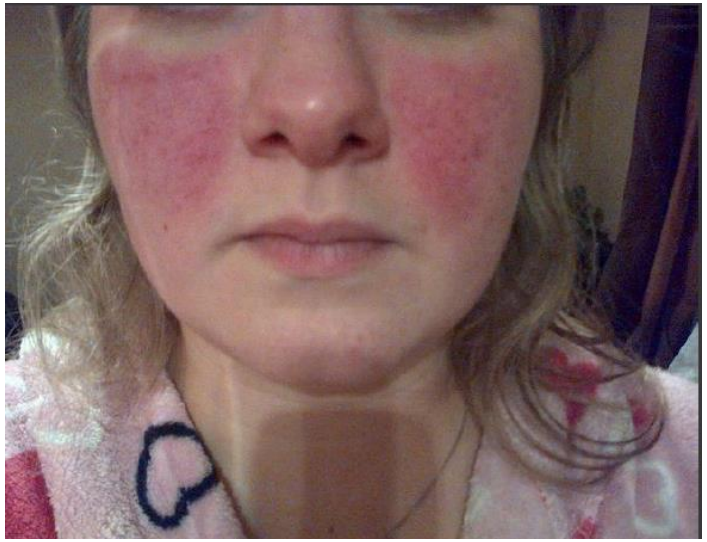
- Involvement of the Forehead and Nasolabial area distinguishes Dermatomyositis from SLE.

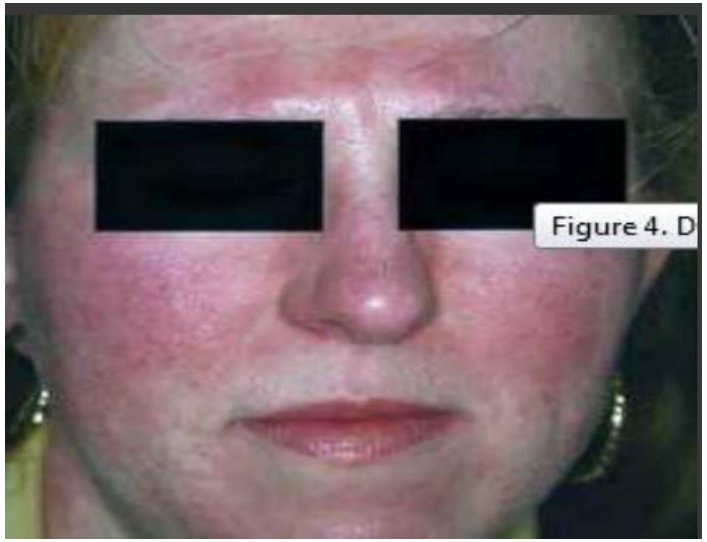


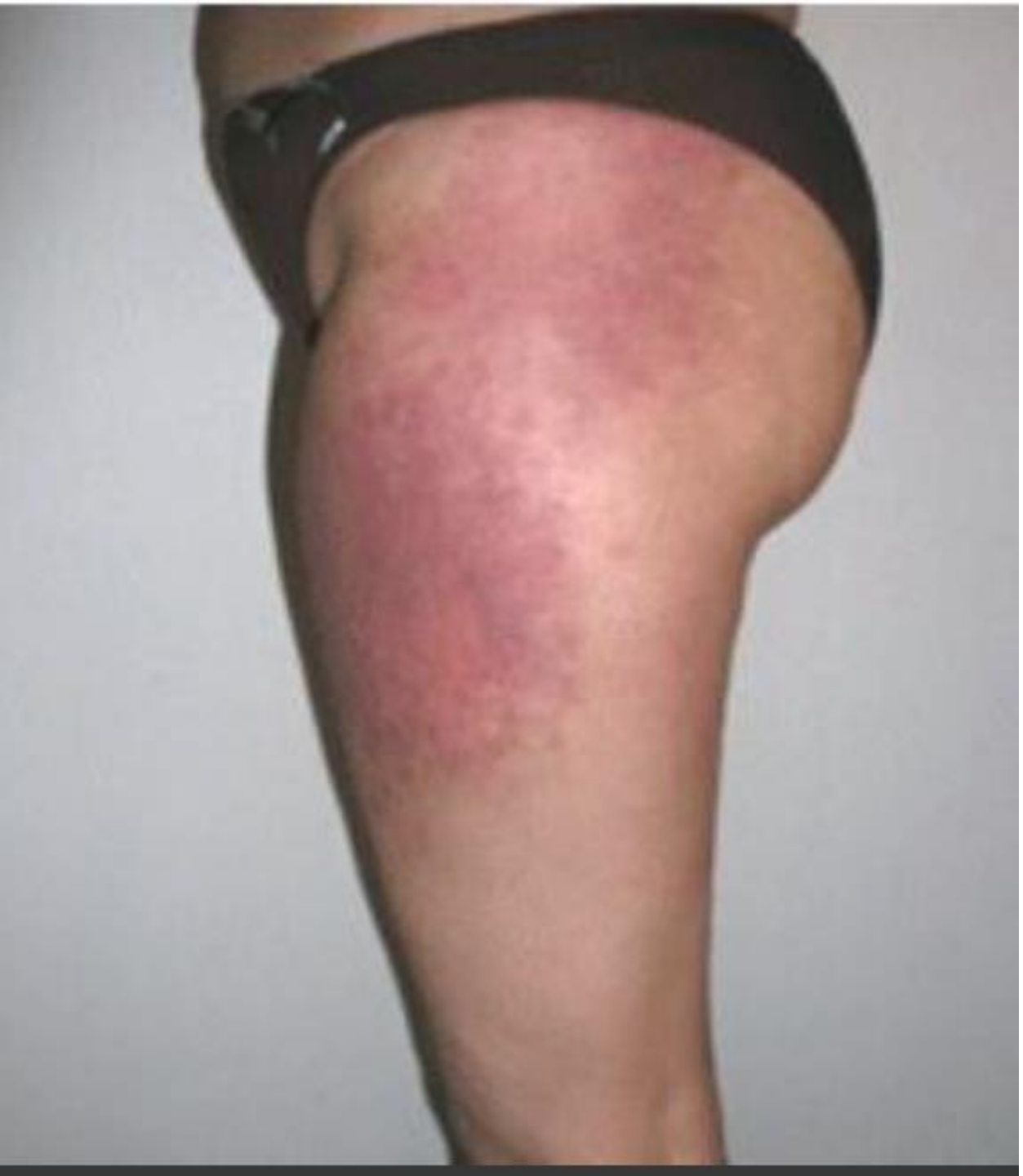


DERMATOMYOSITIS VS LUPUS

- In Lupus (the first picture) we have demarcated malar rash, notice that the nasolabial area is spared.
- While in Dermatomyositis, we have extensive redness with involvement of the Forehead and nasolabial areas.

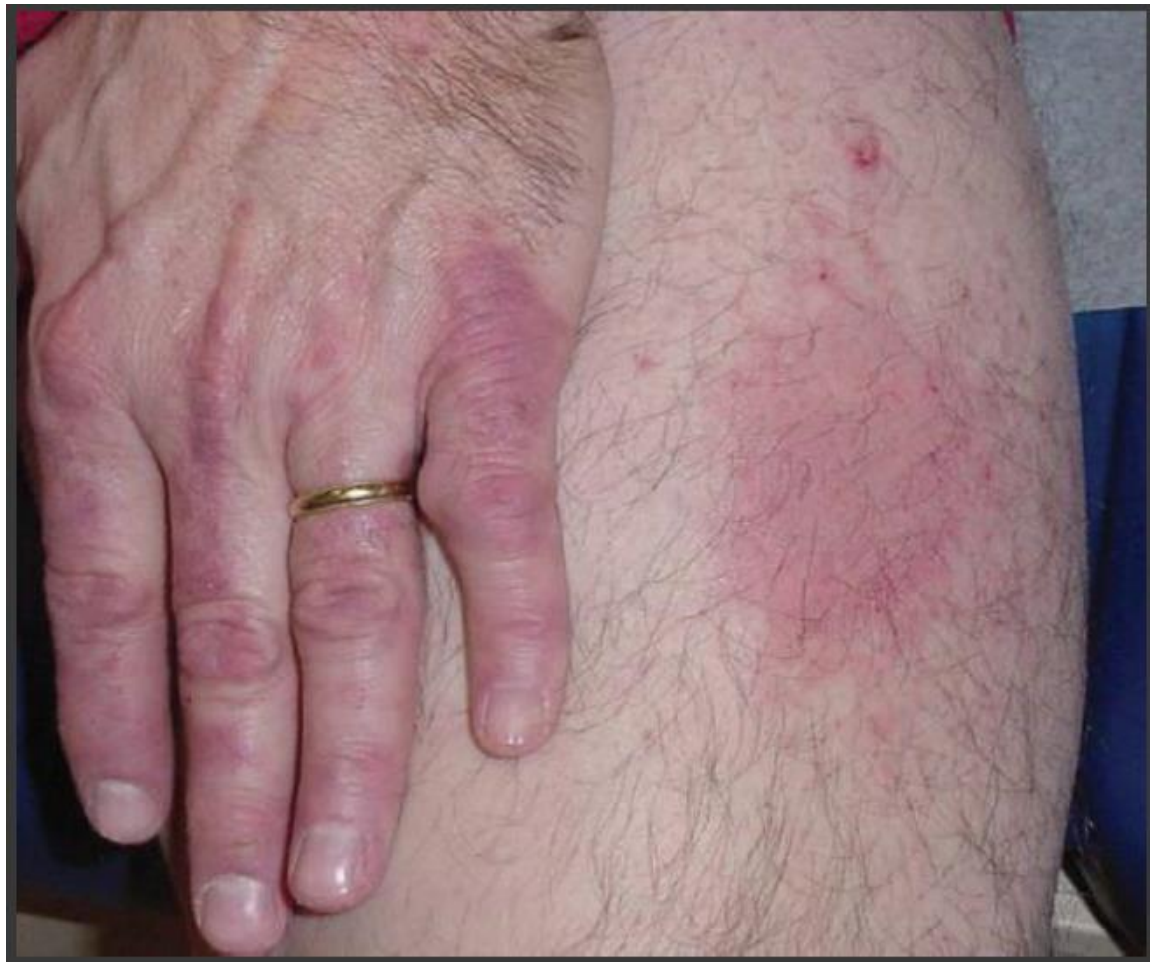




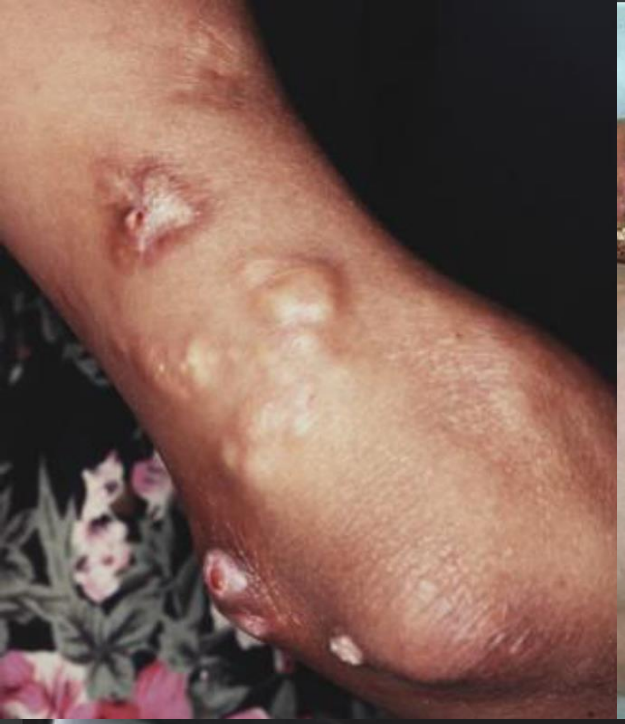


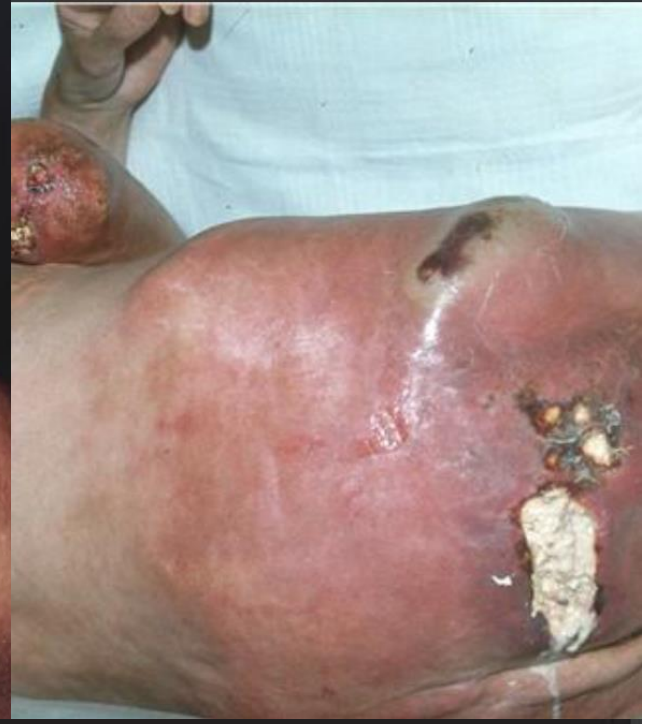
HOLSTER SIGN

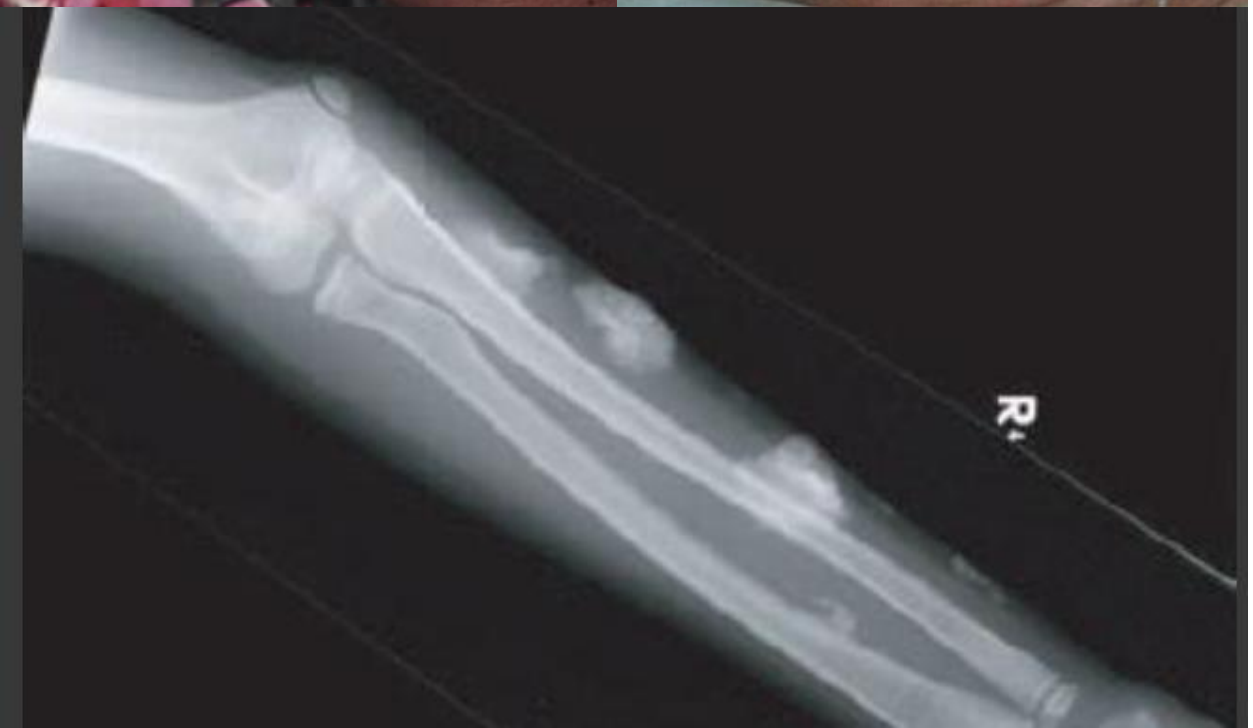
- Redness and photosensitive appearance with puffiness and edema on the lateral surface of the thigh and the hips.
- Seen in Dermatomyositis.



HOLSTER SIGN ERYTHEMA AND GOTTRON ERYTHEMA





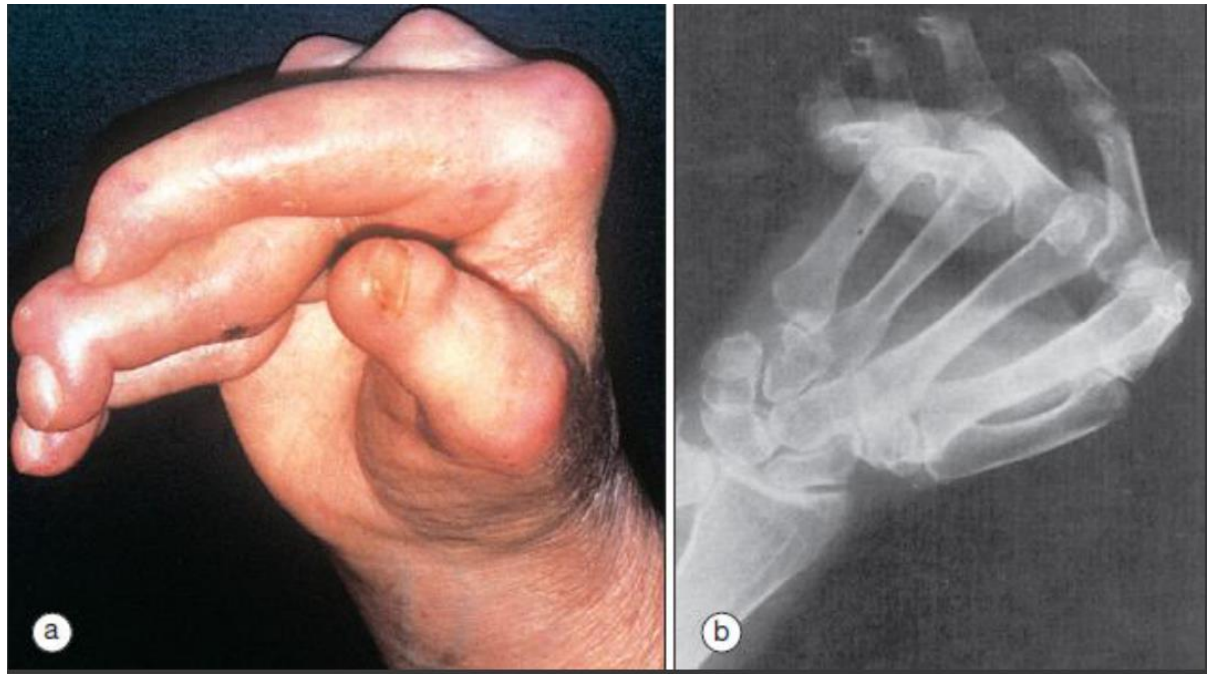


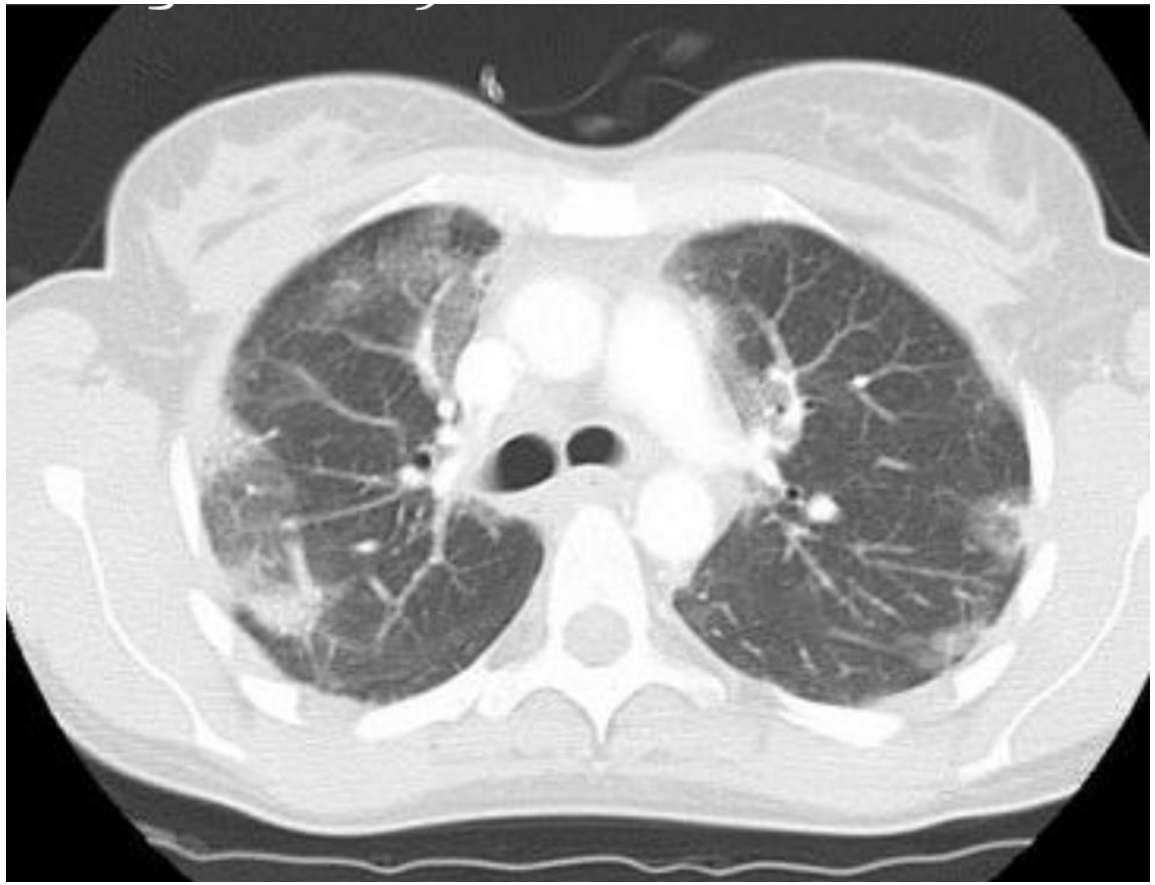
CALCINOSIS

- Soft tissue calcification, which can be disabling and may be disfiguring Cosmetic or Functional wise especially if in the buttock region.
- Seen in Limited Scleroderma and Juvenile Dermatomyositis.

Deforming arthropathy of polymyositis

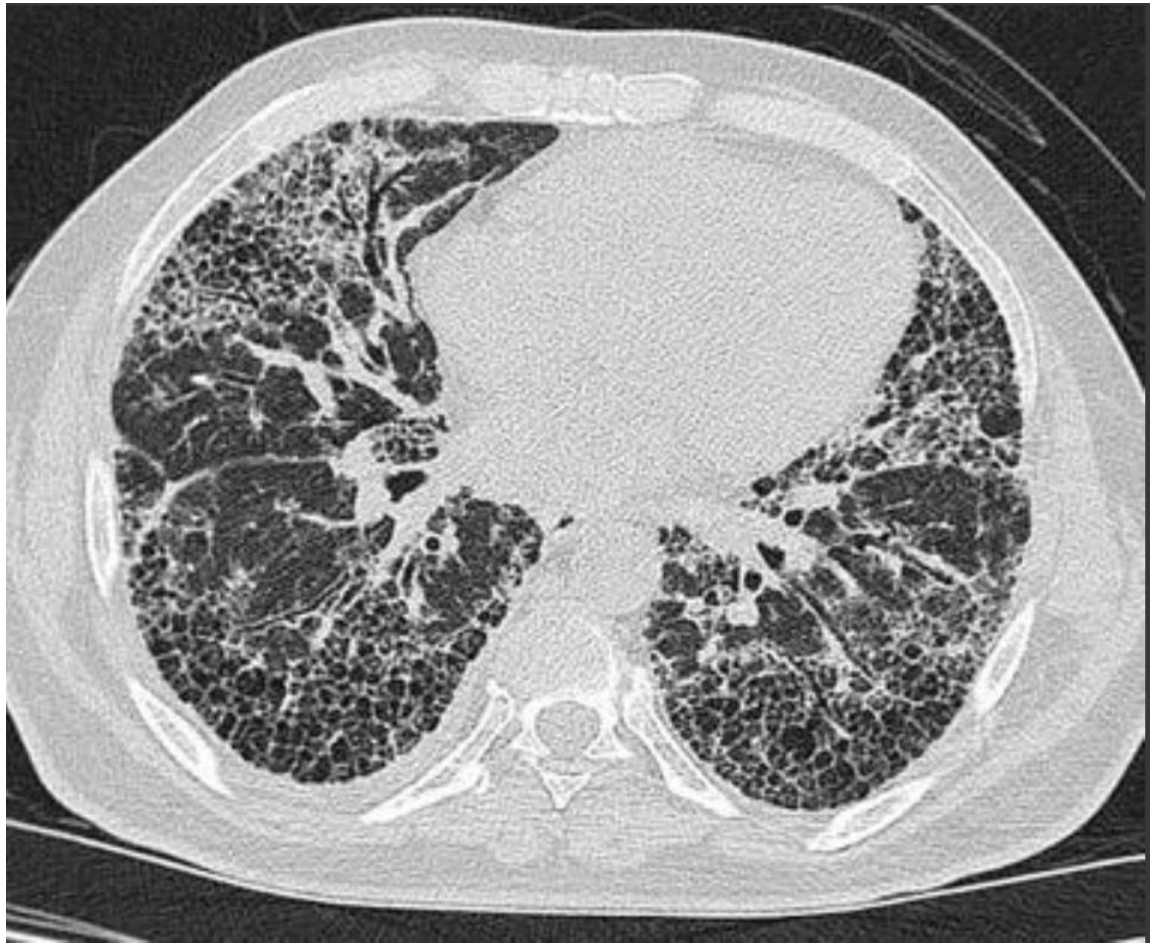
- Picture A: Rheumatoid-like deformity of the hand in a patient with Anti-Jo-1 autoantibody.
- Anti-Jo-1/ Antisynthetase Antibodies: Autoantibodies which are one of the laboratory diagnostic arms of Myositis (Myositis specific Antibodies).
- Anti-Jo-1 causes a syndrome characterized by an abrupt onset of Fever, Cracked hands, Raynaud phenomenon, Interstitial Lung Disease, Fibrosis and Arthritis.
- Picture B: Radiograph hand, showing numerous subluxations but minimal bony erosive changes.





INTERSTITIAL LUNG DISEASE.

- Interstitial Lung Disease showing fibrosis and infiltrate.
- Seen in both Polymyositis and Dermatomyositis + Scleroderma.



ADVANCED LUNG DISEASE IN MYOSITIS

- This CT shows advanced stage with Cystic formation and Honeycombing associated with lung fibrosis.

DIAGNOSIS OF POLYMYOSITIS AND DERMATOMYOSITIS

- Elevated CK levels indicate more inflammation.

Muscle enzymes

- CK, AST, ALT, LDH, aldolase
- There is a correlation between CK level and disease activity
- There is correlation between anti-Jo-1 titre and disease activity
- ESR & CRP do not correlate with disease activity or response to treatment

Causes of raised CK

- **1.** Strenuous exercise
- **2.** Muscle trauma
  - **(a)** Injury
  - **(b)** EMG
  - **(c)** Surgery
- **3.** Diseases affecting muscle
  - **(a)** Myositis
  - **(b)** Metabolic
  - **(c)** Dystrophies
  - **(d)** Myocardial infarction
  - **(e)** Rhabdomyolysis
- **4.** Drugs
  - colchicine, steroids , statins
- **5.** Endocrine and metabolic abnormalities
  - **(a)** Hypothyroidism
  - **(b)** Hypokalaemia
- **6.** Normal
  - **(a)** Ethnic group
  - **(b)** Increased muscle mass
  - **(c)** Technical artefact

Autoantibodies

–Myositis-specific antibodies :

- Antisynthetase
  - –Jo-1: Histidyl-tRNA synthetase
- SRP: Signal recognition particle
- Mi-2: Nucleosome remodelling complex

- If the lab results of those antibodies came negative that doesn't rule out Myositis.

MYOSITIS SPECIFIC ANTIBODIES

Anti-synthetase syndrome

- 25% of PM and DM patients have antibodies to an aminoacyl-tRNA synthetase (JO-1)
- **Clinical features:**
  - PM/DM
  - ILD
  - Arthritis
  - Raynaud's phenomenon
  - Fever
  - mechanic's hands.

Anti-SRP

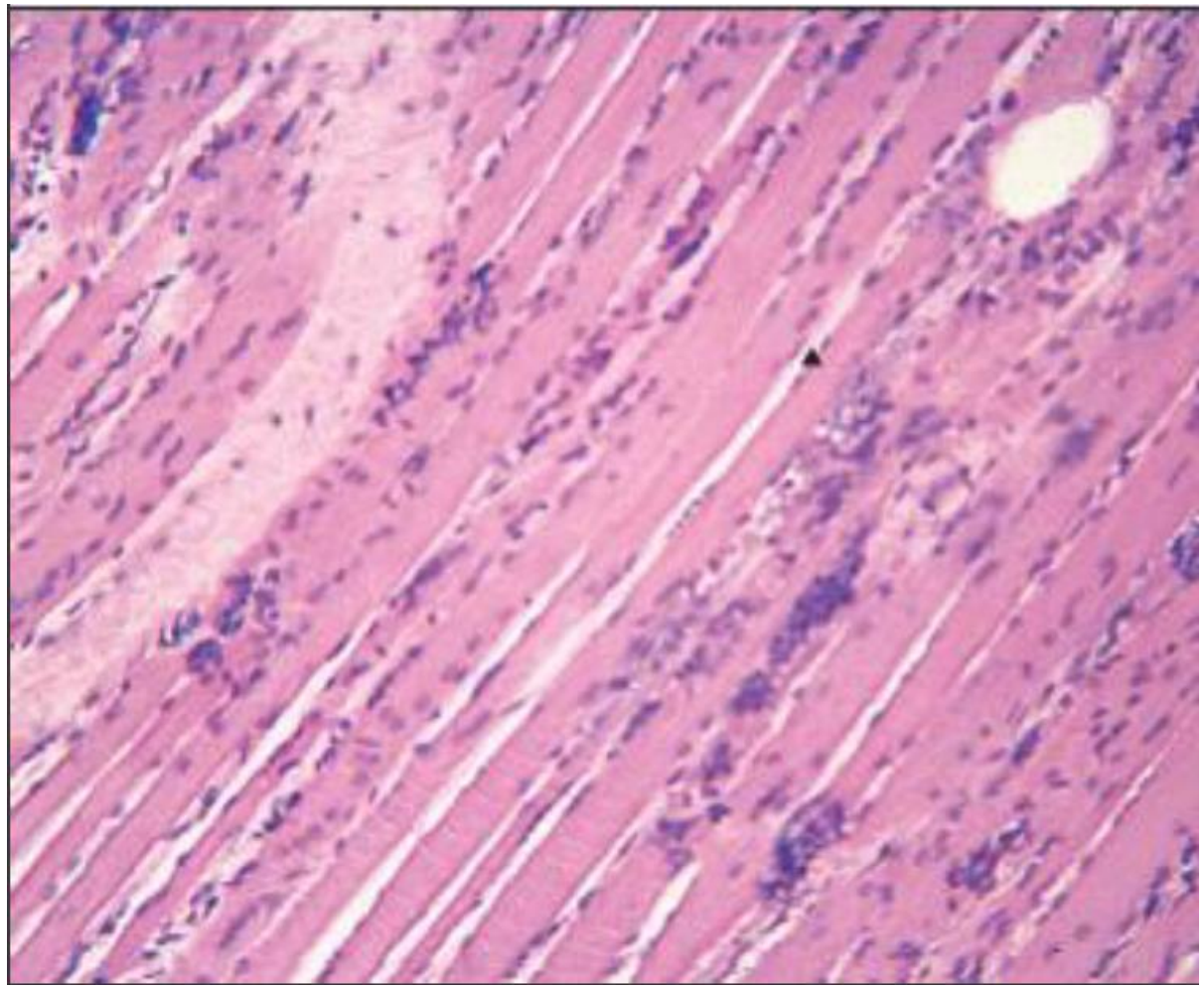
- Polymyositis
- cardiac involvement
- resistance to treatment.

Anti-Mi-2

- DM with V sign or shawl sign.
- Good prognosis.

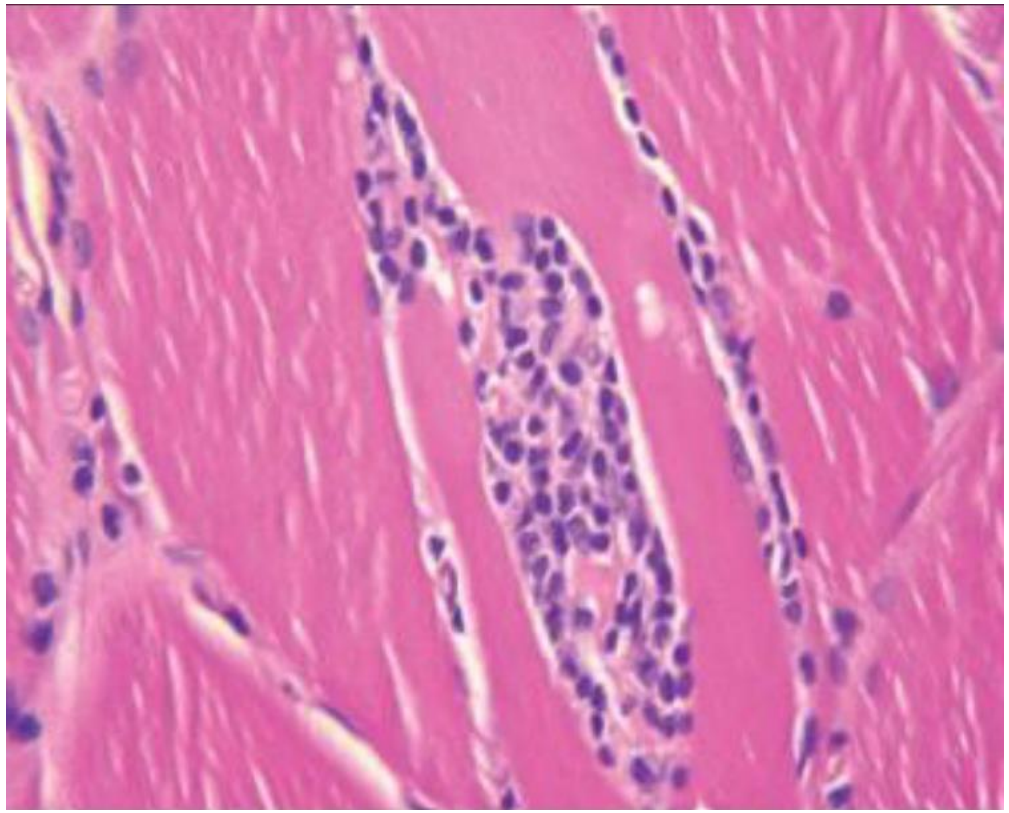
Histological Section of Polymyositis

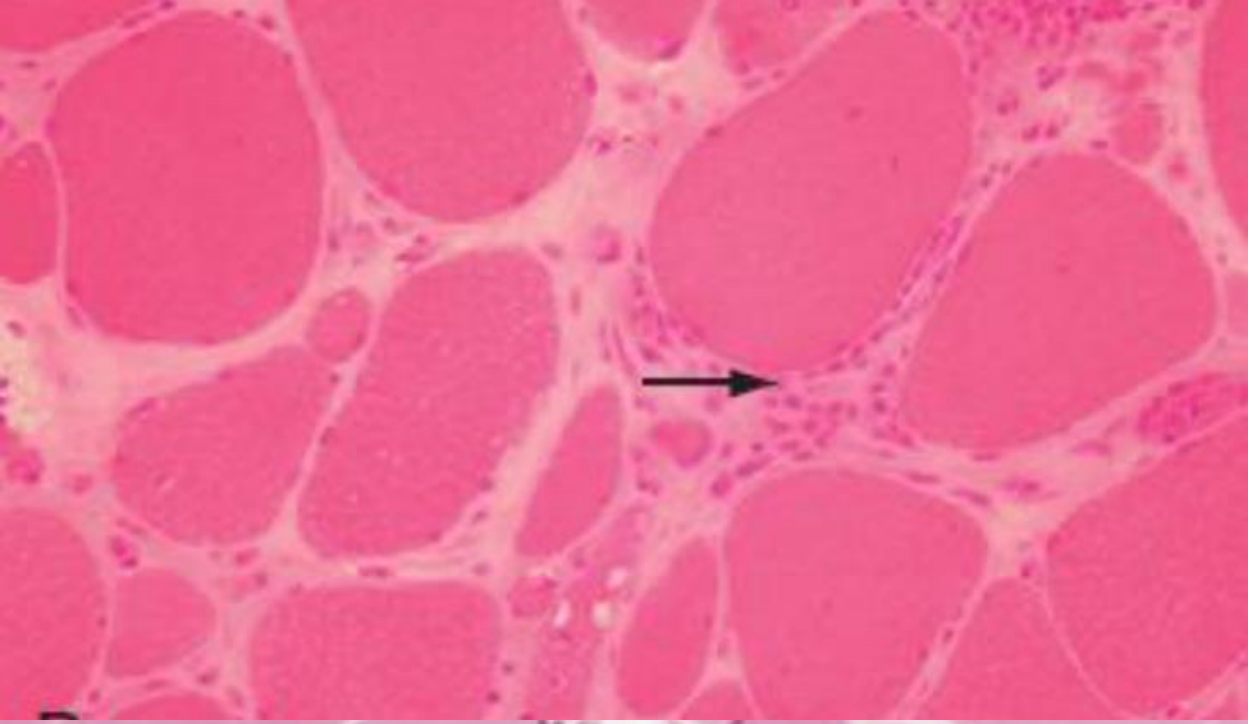
- Keep in mind that Polymyositis is Cell-mediated process (cellular immue attack on muscle fibers).
- CD8+ T-cells are abundant in ENDOMYSIAL areas.
- The arrow indicates an area of degeneration and necrosis of myofibers in association with interstitial lymphocytic and histiocytic cellular infiltrates.

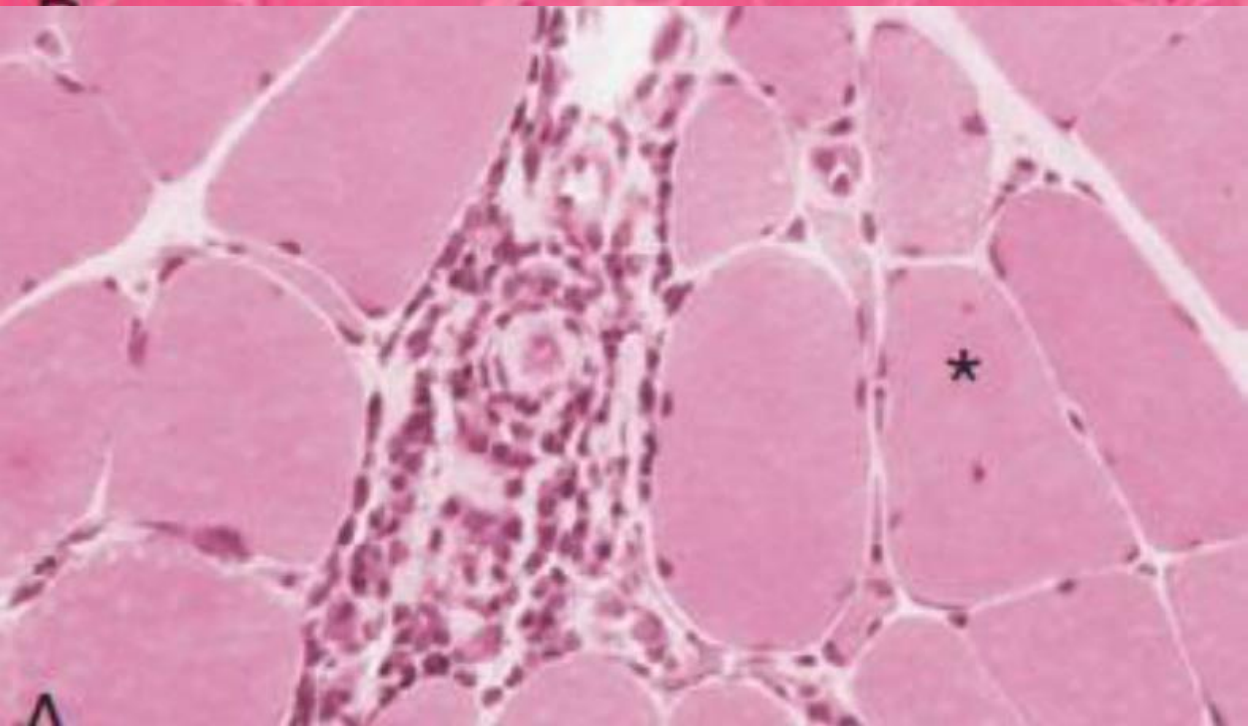


POLYMYOSITIS

- Lymphocytic invasion in non-necrotic myofiber





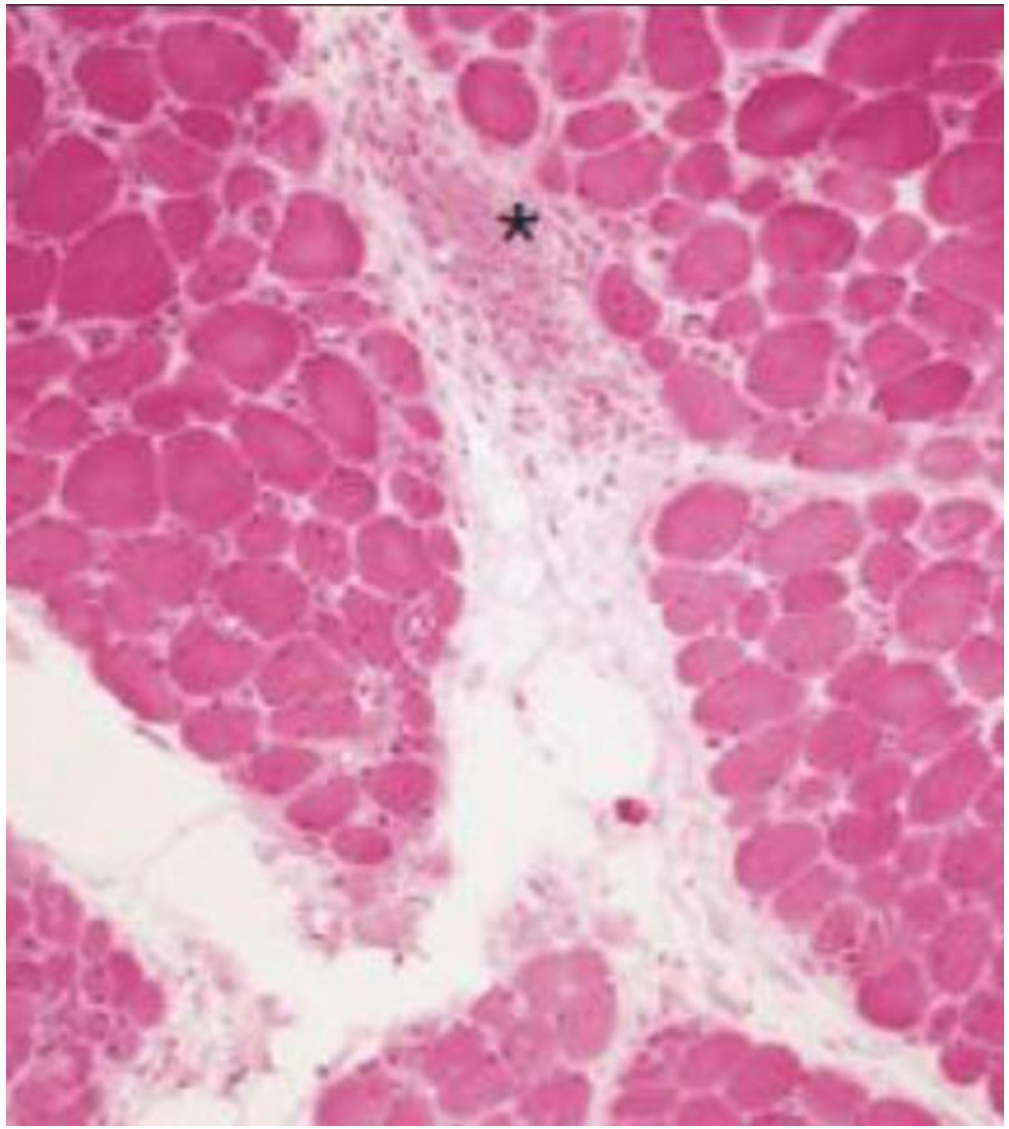


POLYMYOSITIS

- ENDOMYSIAL distribution.
- Inflammatory Cellular infiltrates (CD8+ T-Cells, and Macrophages).

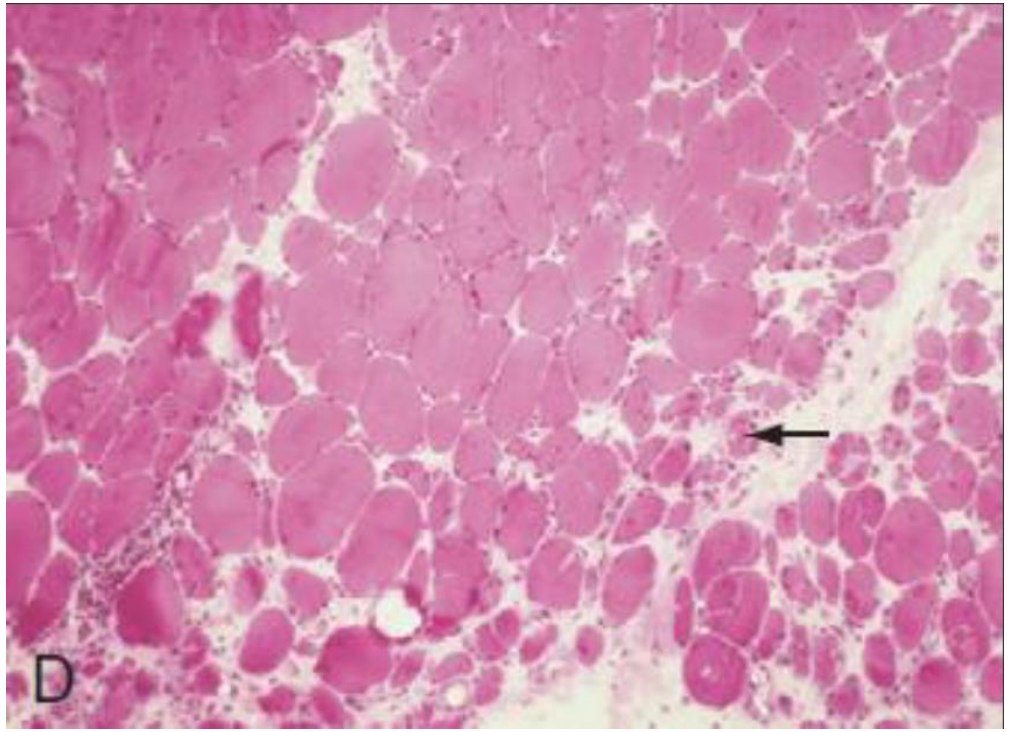
HISTOLOGICAL SECTION OF DERMATOMYOSITIS

- Keep in mind that Dermatomyositis is Humoral mediated process.
- B-cell, CD4+ T-cells infiltrate the PERIVASCULAR area.
- In this section note the PERIMYSIAL involvement + note that it's largely made up of CD4+ T-cells, Macrophages, and Dendritic cells.

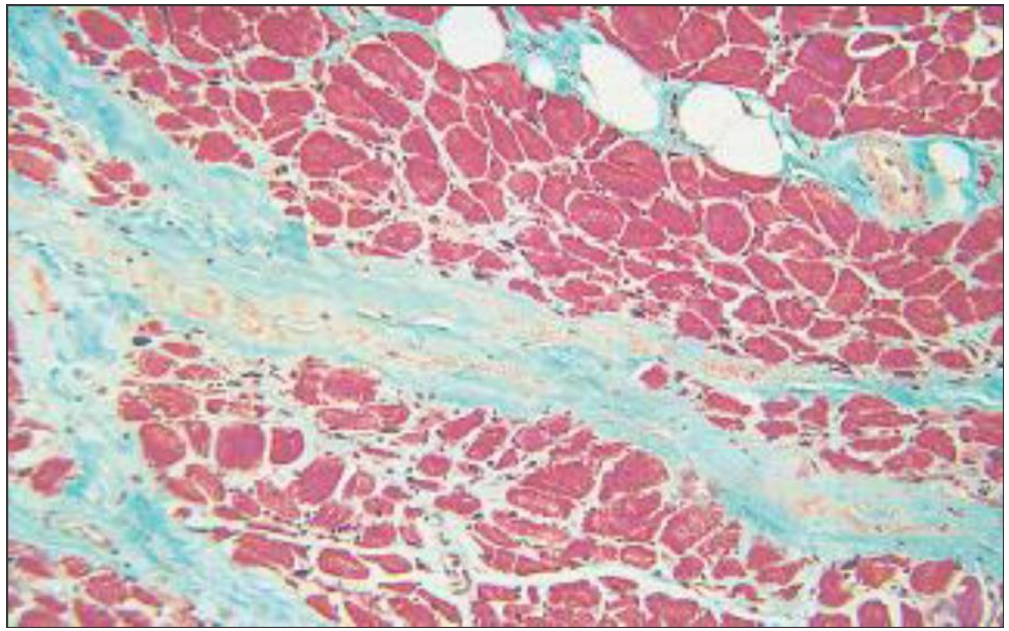


DERMATOMYOSITIS

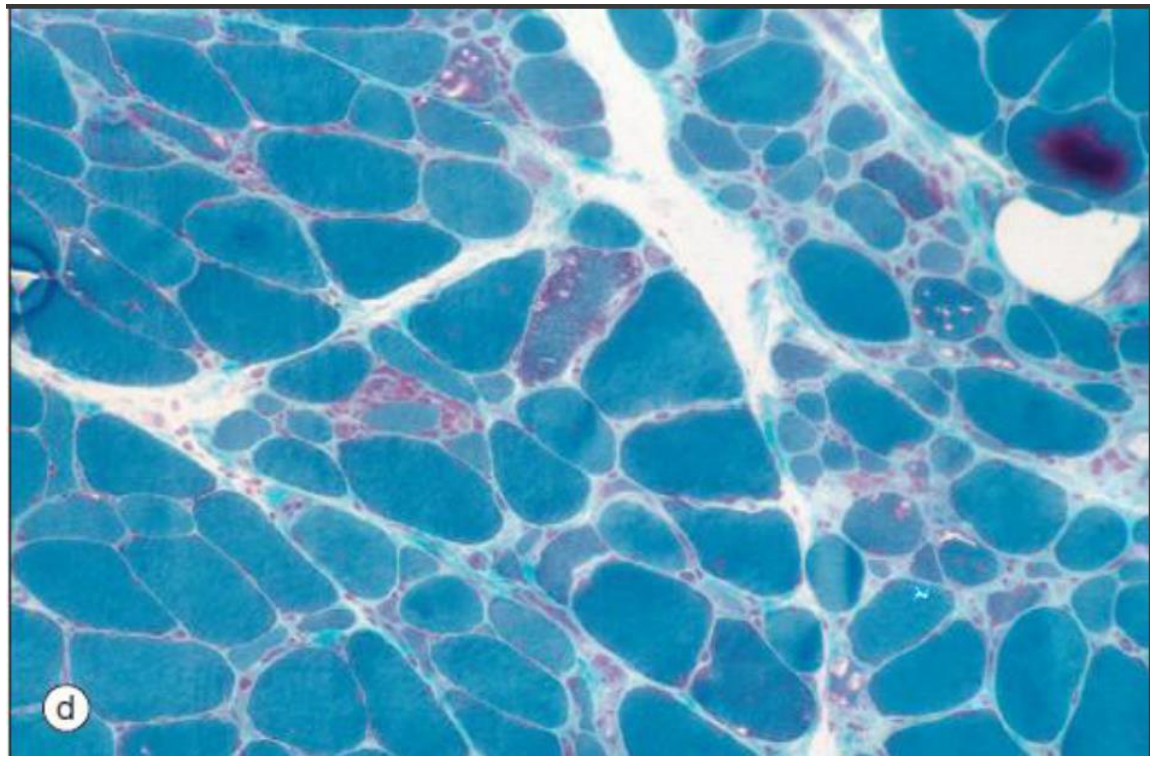
- The arrow shows Perifascicular Atrophy



DERMATOMYOSITIS



- This section shows Atrophic, small fibers in the periphery of the fascicles (Perifascicular Atrophy) and an increase in the fibrous tissue separating bundles of myofibers.

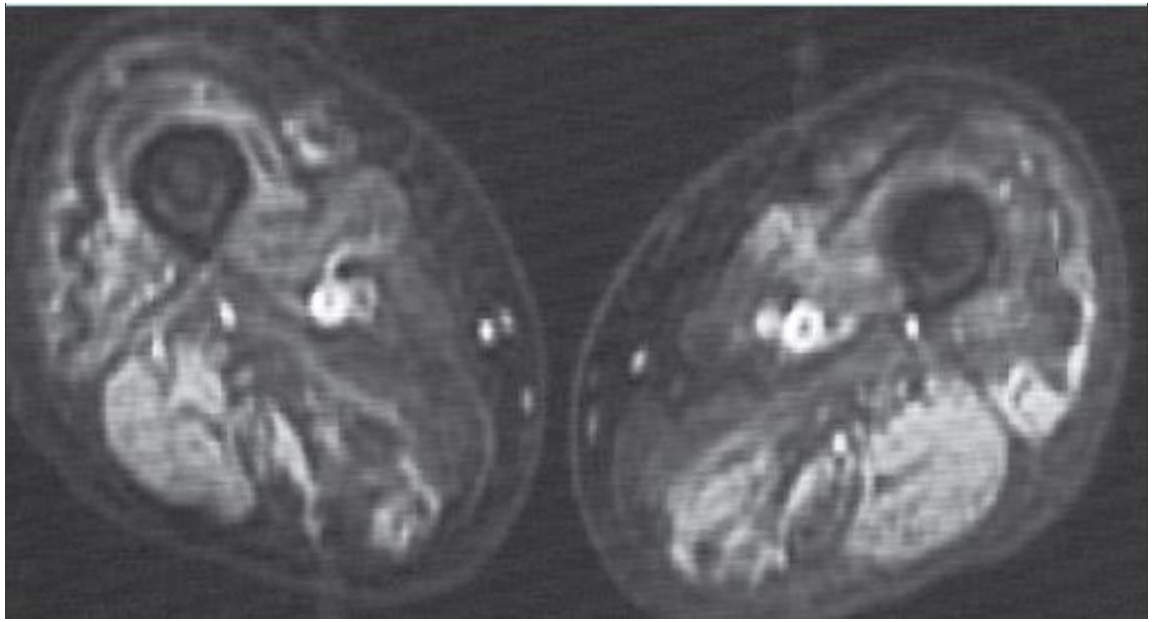


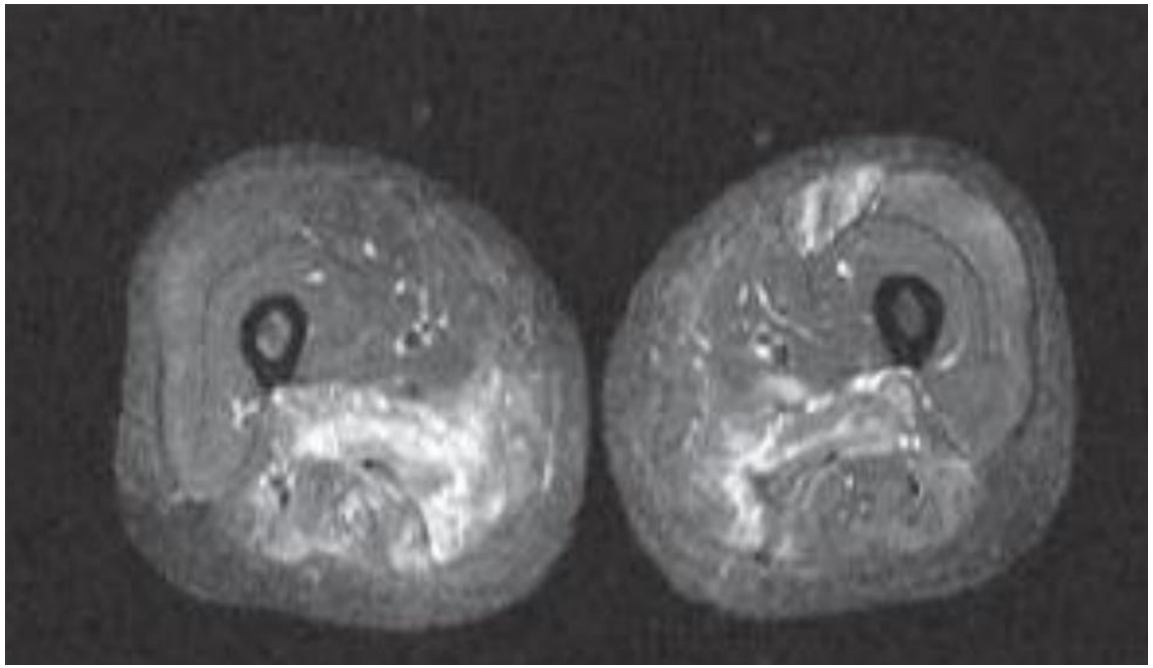
INCLUSION BODY MYOSITIS

- Vacuoles rimmed by basophilic material and small, eosinophilic cytoplasmic and nuclear inclusions.
- Diagnosis confirmed by electron microscopy or Trichrome Stain.
- Note on the section: Red-rimmed Vacuoles (Trichrome Stain),

MRI (STIR TECHNIQUE)

- Inflammation Shows up as bright areas.





TREATMENT OF MYOSITIS

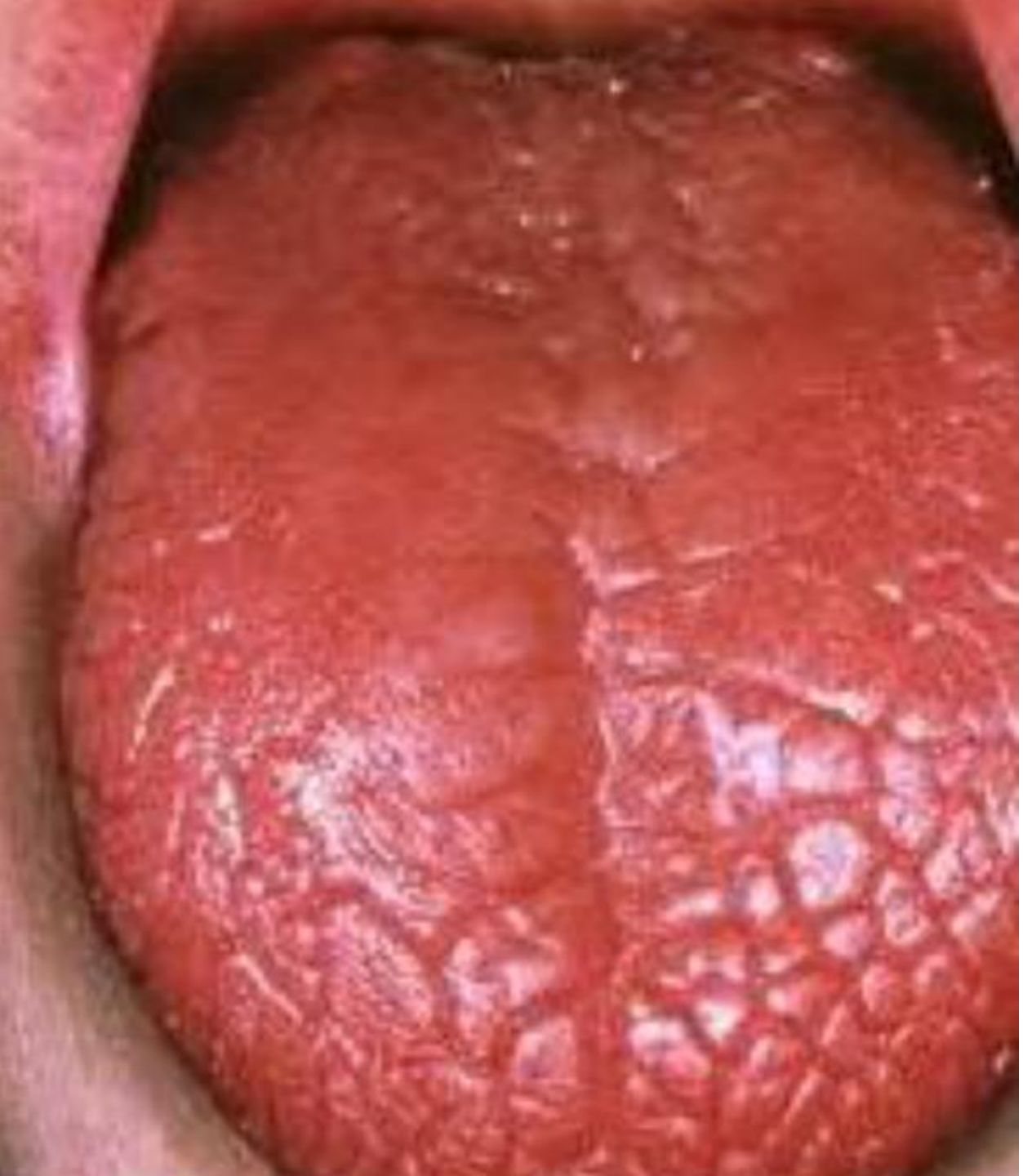
Treatment

- Corticosteroids
- **Indications for immunosuppressive agents:**
  - (i) failure to respond to high-dose steroids
  - (ii) persistent disease activity after prolonged therapy despite initial improvement
  - (iii) inability to taper the steroids without recurrence
  - (iv) severe steroid side-effects.
- MTX and azathioprine are the immunosuppressives used most in myositis.
- Duration of therapy is 18-24 months

Cancer screening

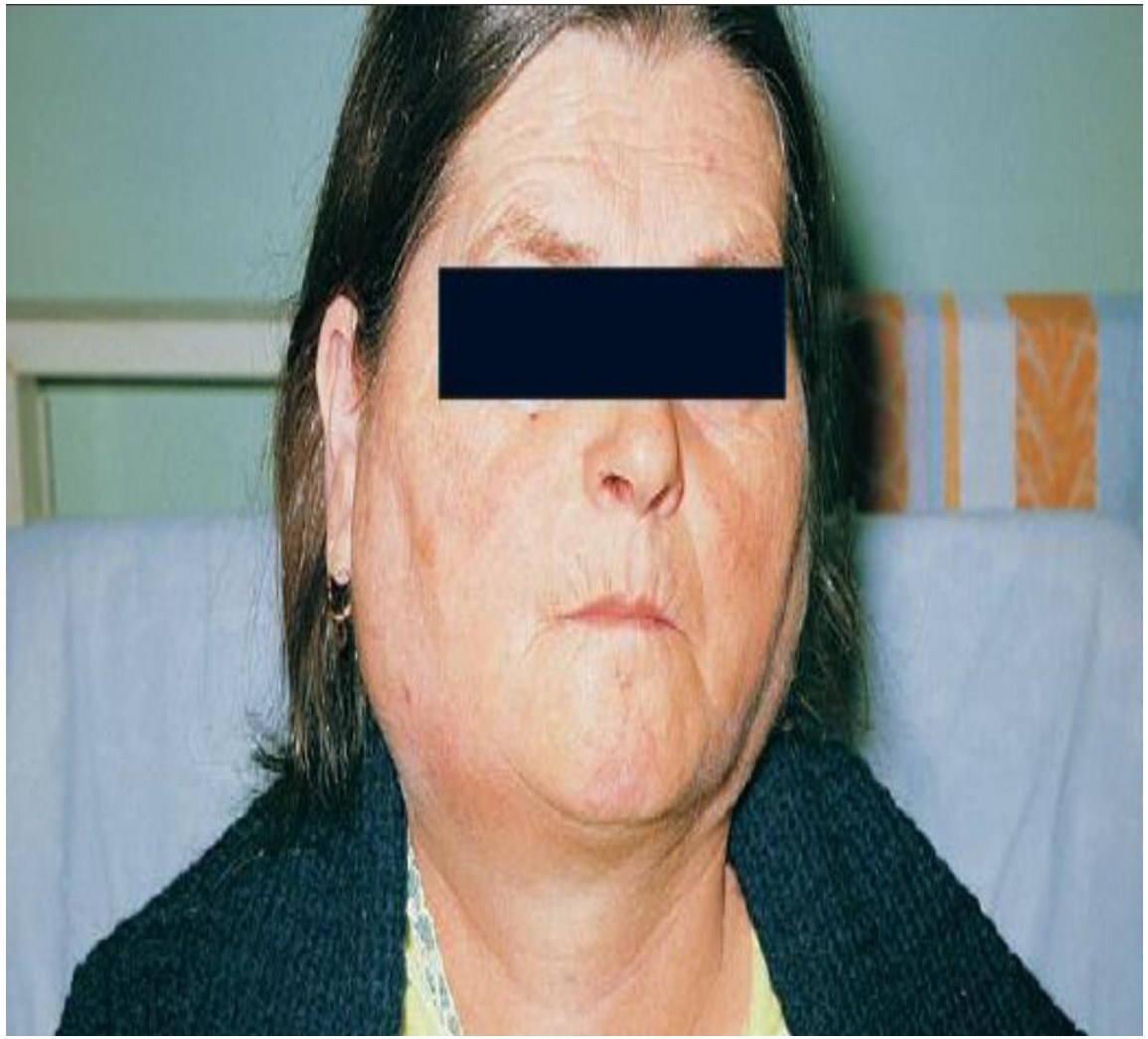
- **All patients >50 years of age should have:**
  - CXR
  - Chest/abdomen/pelvis CT scans
  - Mammography and gynaecological examination (F)
  - Testicular examination in males (M)
  - Faecal occult blood
  - Gastroscopy/colonoscopy

SJOGREN SYNDROME

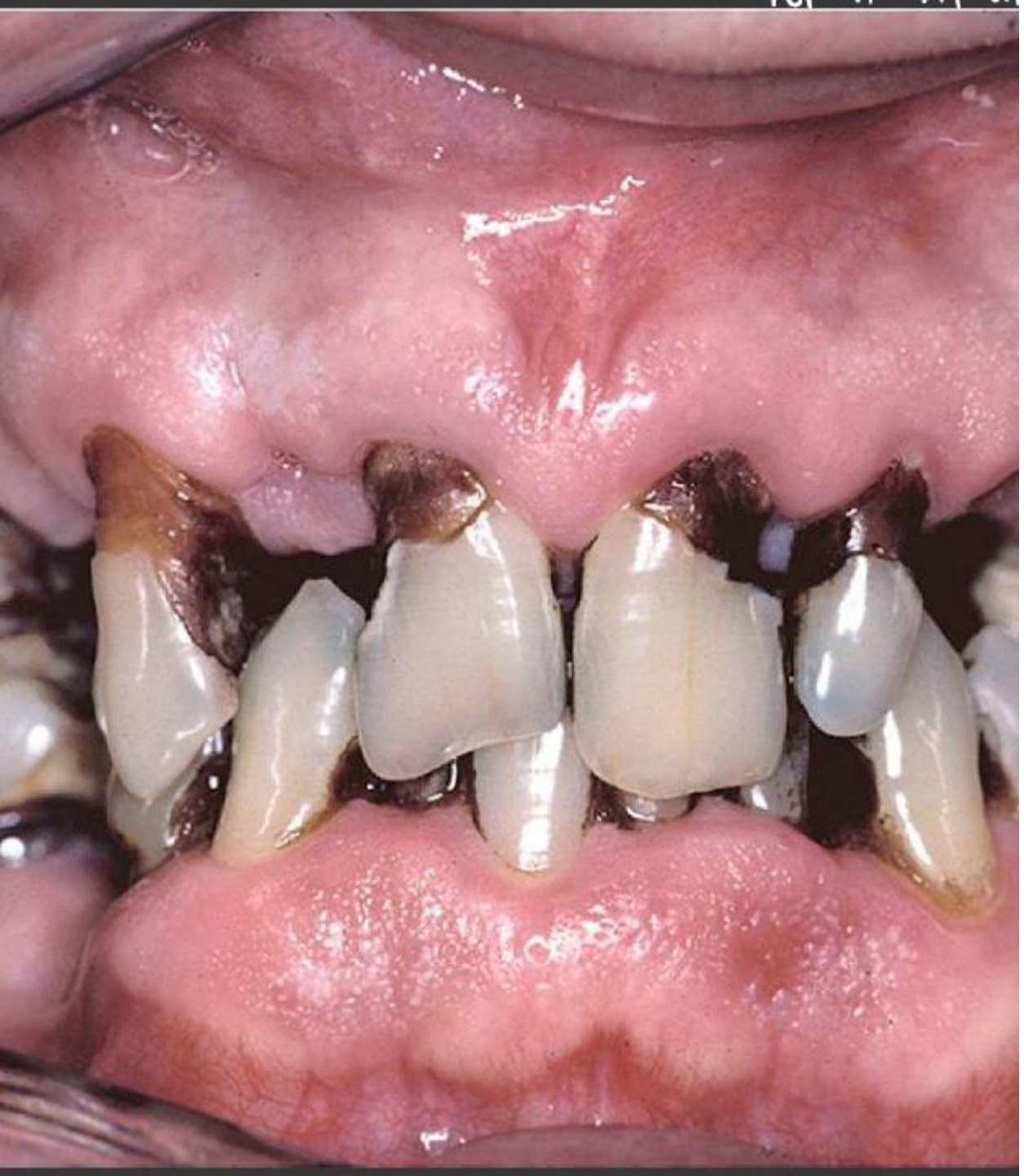


XEROSTOMIA

- Very dry cracked tongue + Dry mouth.
- Seen in Sjogren Syndrome, due to autoimmune lymphocytic infiltrates that replaces functional epithelium, leading to decreased exocrine secretions.
- Associated with Xerophthalmia (Keratoconjunctivitis Sicca) which is dryness of the Conjunctiva and the Cornea



PAROTID GLAND ENLARGEMENT DUE TO CHRONIC PAROTITIS

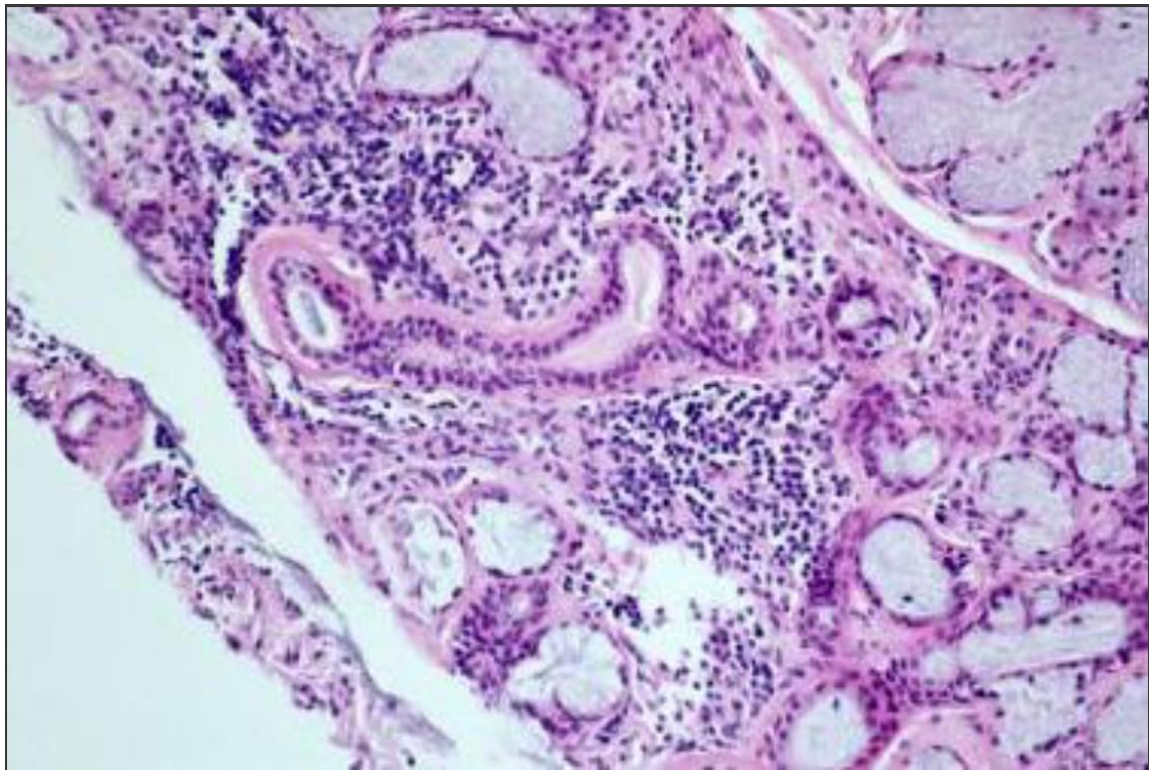


BAD DENTAL HYGIENE SEEN IN SJOGREN

- Indicates very advanced dryness, since saliva is important for health and hygiene.

LIP BIOPSY IN SJOGREN

- It shows dense inflammatory infiltrate around acini.

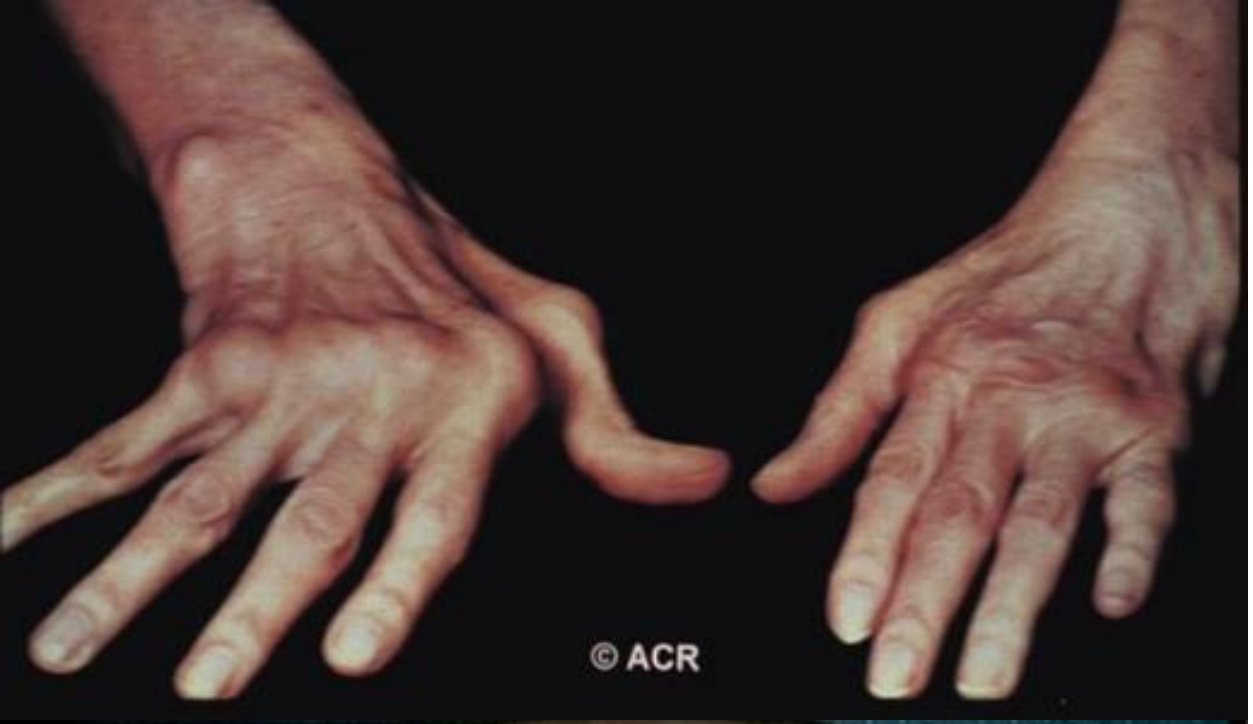


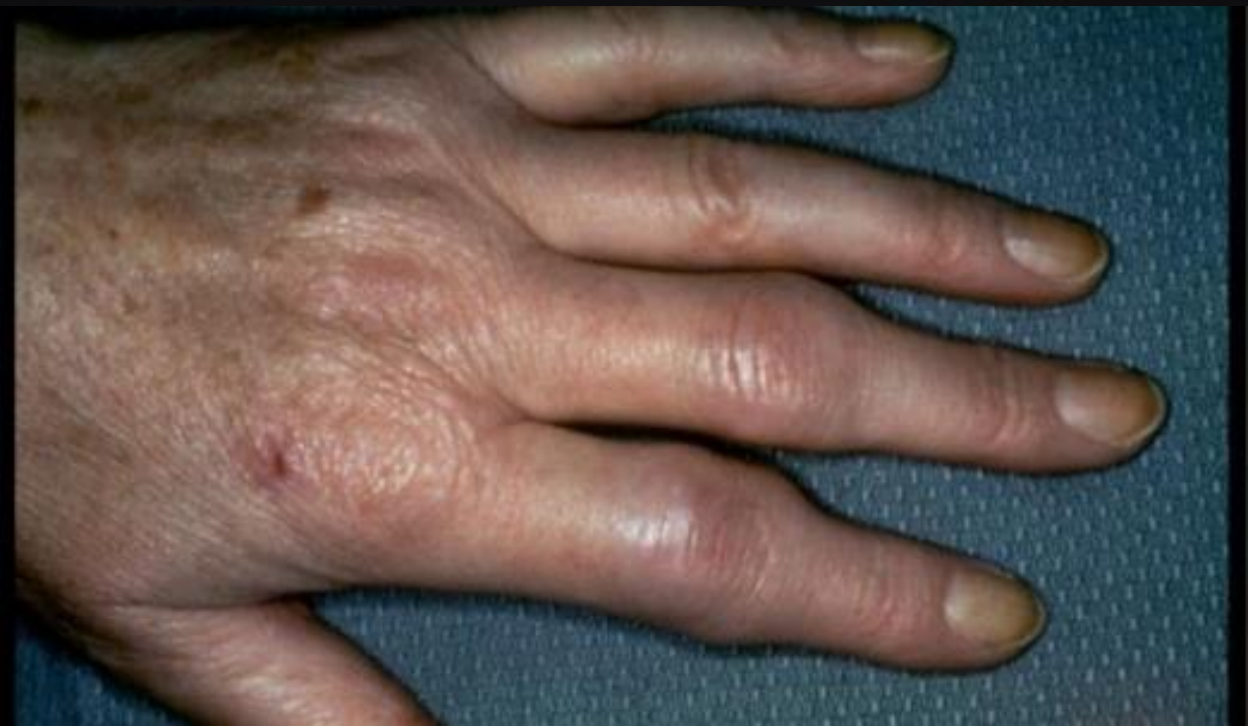
TREATMENT OF SJOGREN SYNDROME

Treatment

- Stimulation of salivary flow by sugar-free flavored lozenges
- dry food, smoking, and drugs with anticholinergic side effects, which further decrease salivary flow, should be avoided
- Adequate oral hygiene after meals to prevent dental disease
- Pilocarpine to increase salivary secretion
- Artificial tears
- Hydroxychloroquine for joint pain

RHEUMATOID ARTHRITIS





HAND DEFORMITIES IN RA

- In the first picture we can see:

1- Ulnar deviation 2- Rt Wrist Inflammation 3- Rt Z thumb deformity

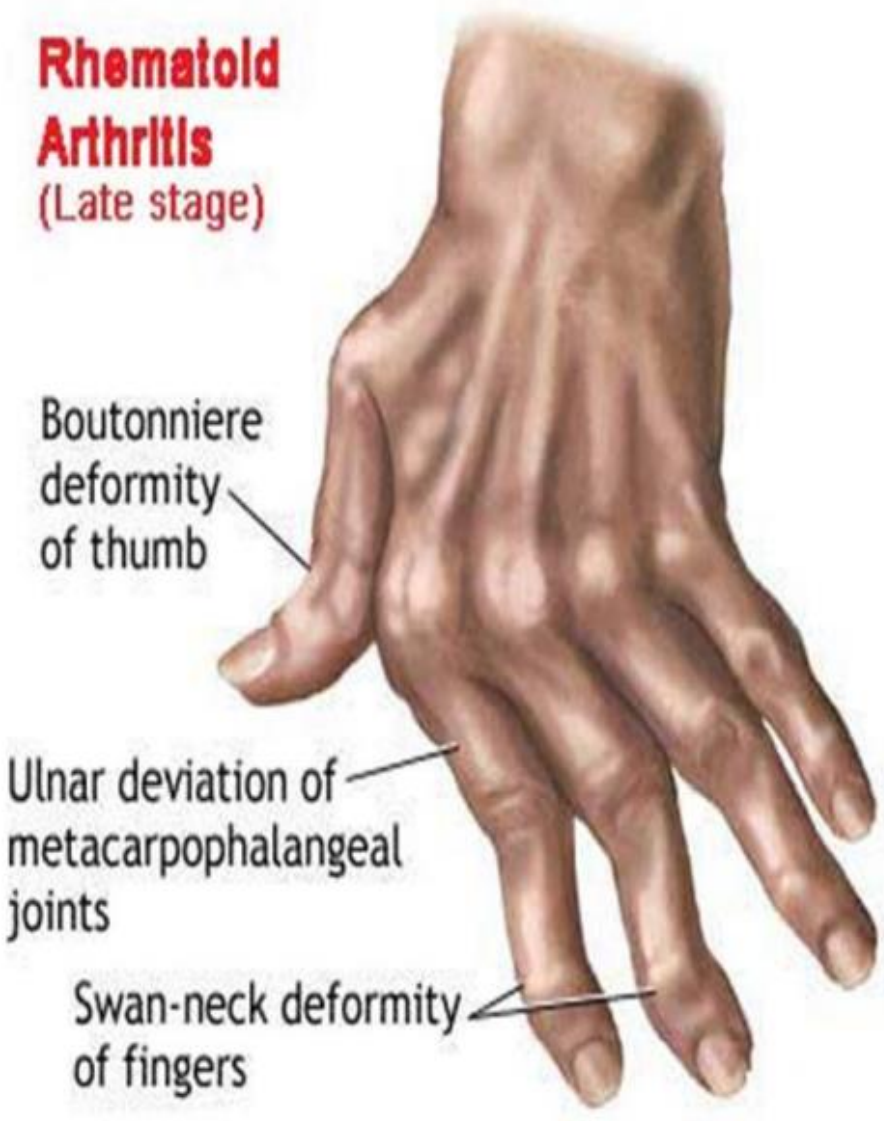
- In the second picture:

1- PIP joints are swollen which indicates SYNOVITIS.

- Synovitis: Inflammation of the synovial tissue (spongy feeling) and is the cardinal sign of RA

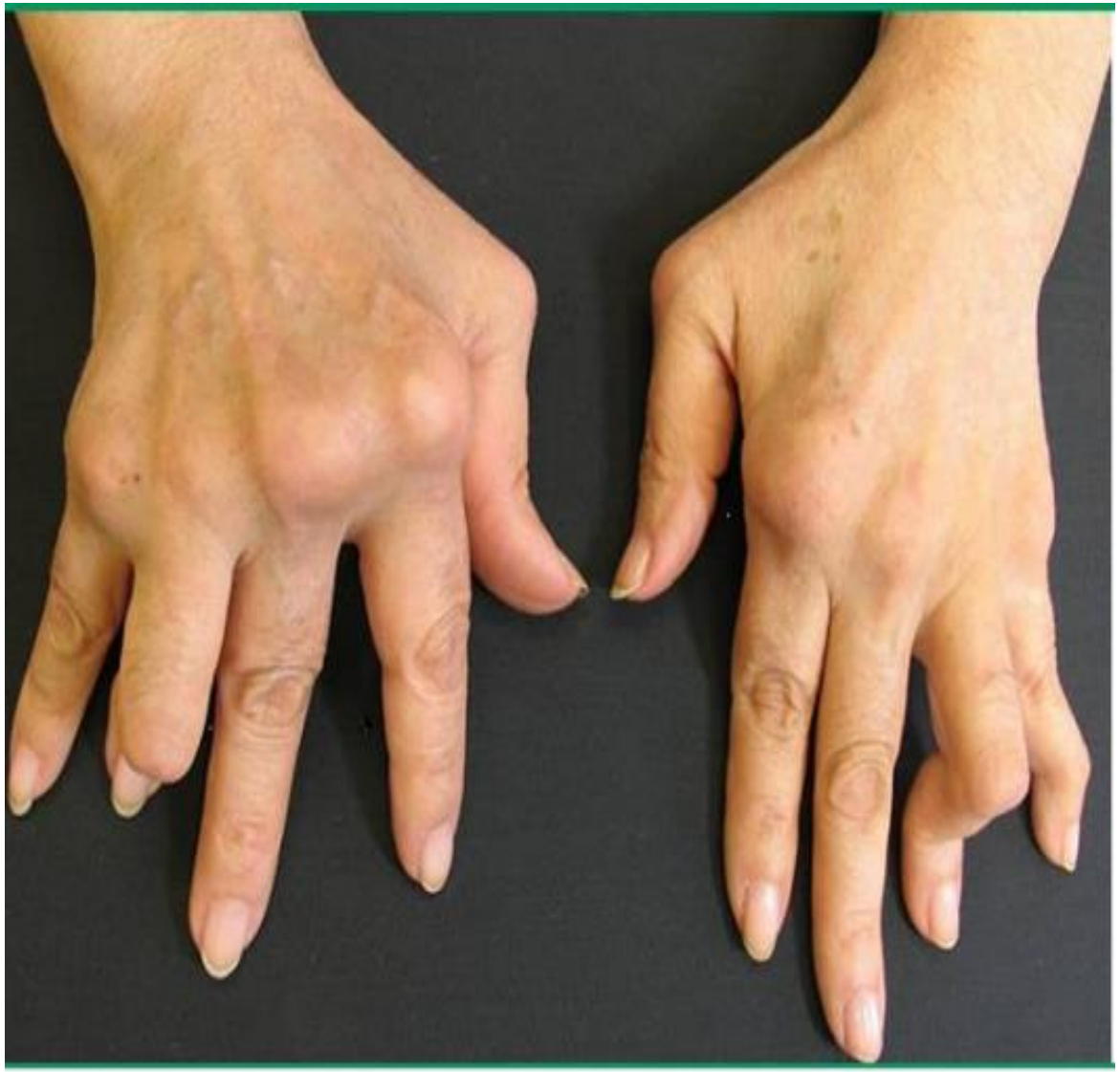
HAND DEFORMITIES IN RA

- Boutonniere Deformity: Hyperflexion of PIP with Hyperextension of DIP.
- Swan-neck Deformity: Hyperextension of PIP with Hyperflexion of DIP.

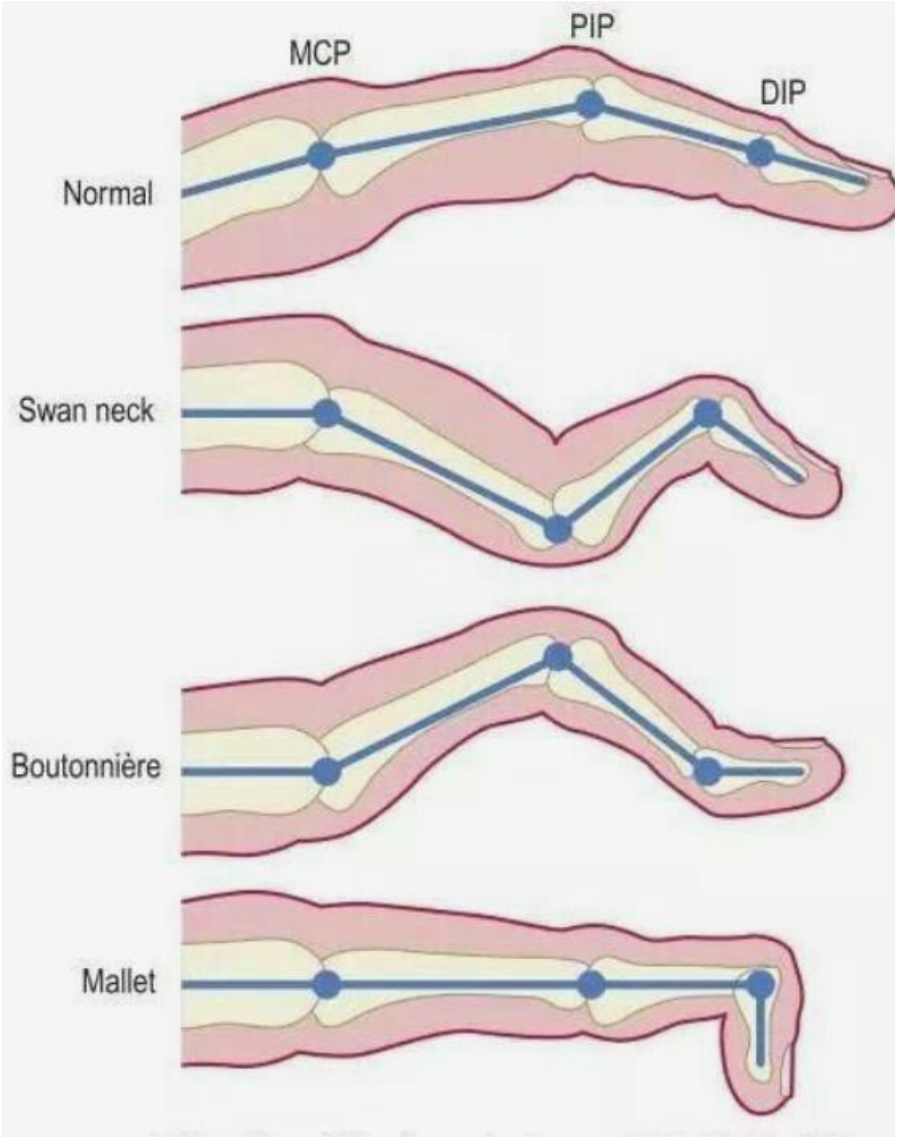


RA HAND DEFORMITIES

1- Boutonniere deformity of both ring fingers.
2- Swan-neck of the Lt little finger.
3- Synovitis and Swelling of MCPs.
4- Ulnar Deviation.
5- Z deformity of the Rt thumb.

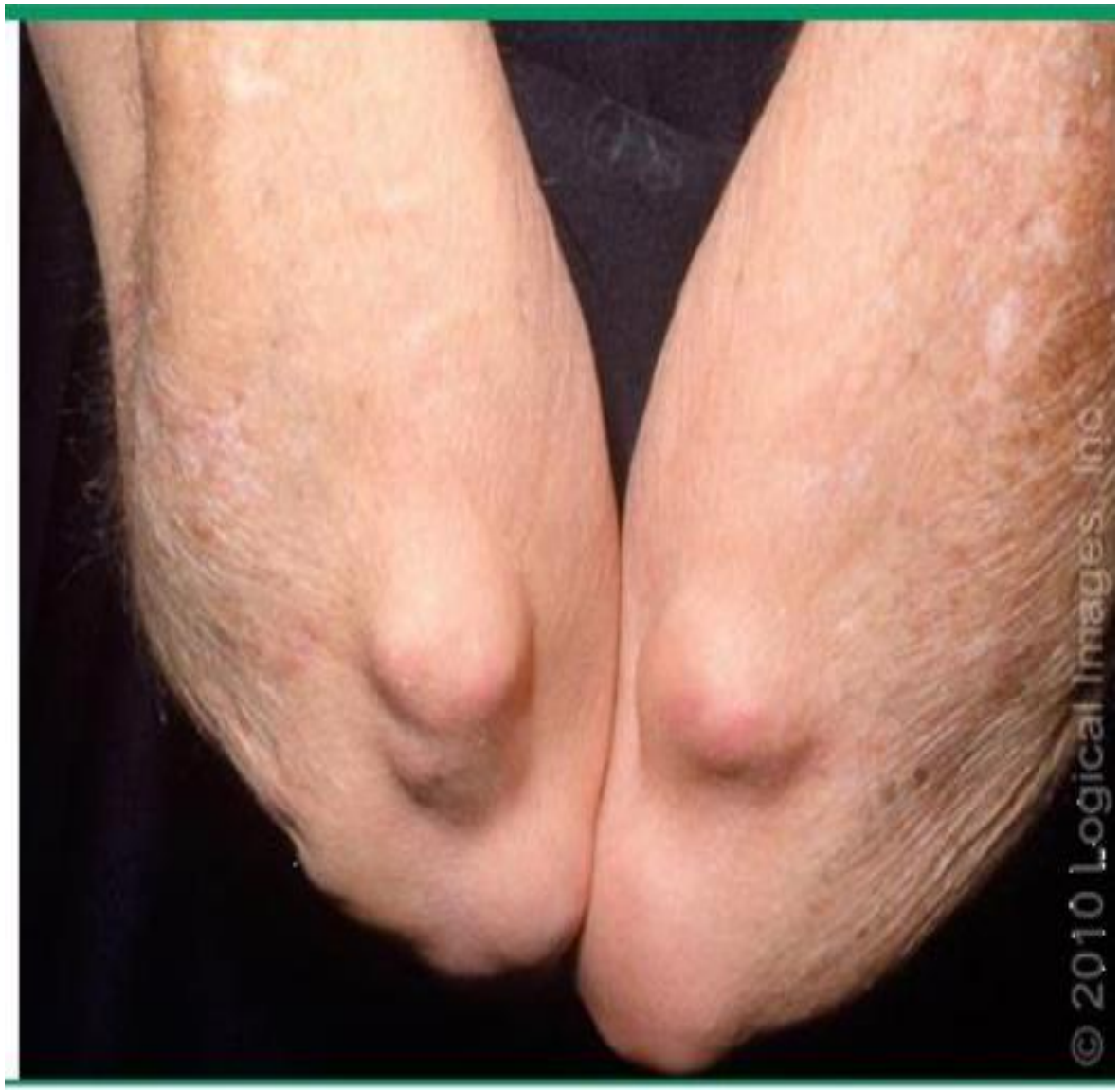


FINGER DEFORMITIES IN RA



RHEUMATOID NODULES

- They are firm, non-tender lesions that typically occur in areas of trauma in individuals with RA.
- The most common extra-articular manifestation of RA.
- Caused by inflammation of the subcutaneous tissue.
- Harder than Gout nodules but softer than Scleroderma calcinosis.
- Found on the extensor surfaces of the arm, but can be found inside the body like in the lungs,



LAB FINDINGS IN RA

Laboratory findings

CBC:

Anemia: Most RA patients are anemic (anemia of chronic disease, NSIADs induced anemia of blood loss ..etc)

Leucopenia: Felty's syndrome (splenomegaly and neutorpenia in long standing RA) or medications- induced

Thrombocytosis (inflammation) or **thrombocytopenia**(Felty's or medications)

KFT/LFT : usually normal (but needed as baseline prior to initiation of medications)

ESR: elevated

CRP: elevated

RA markers

Rheumatoid factor

Antibodies(Mostly IgM) against the Fc portion of IgG.

Found in 75% of RA pts: some pts are negative in the first 6 months of the illness but later seroconvert to positive.

66% sensitive and 82 % specific to RA

High titer is indicative of more aggressive and erosive disease and extraarticular manifestations.

Differential of positive RF beside RA (usually low titer) : bacterial endocarditis, HCV with cryoglobulinemia, aging and primary billiary cirrhosis.

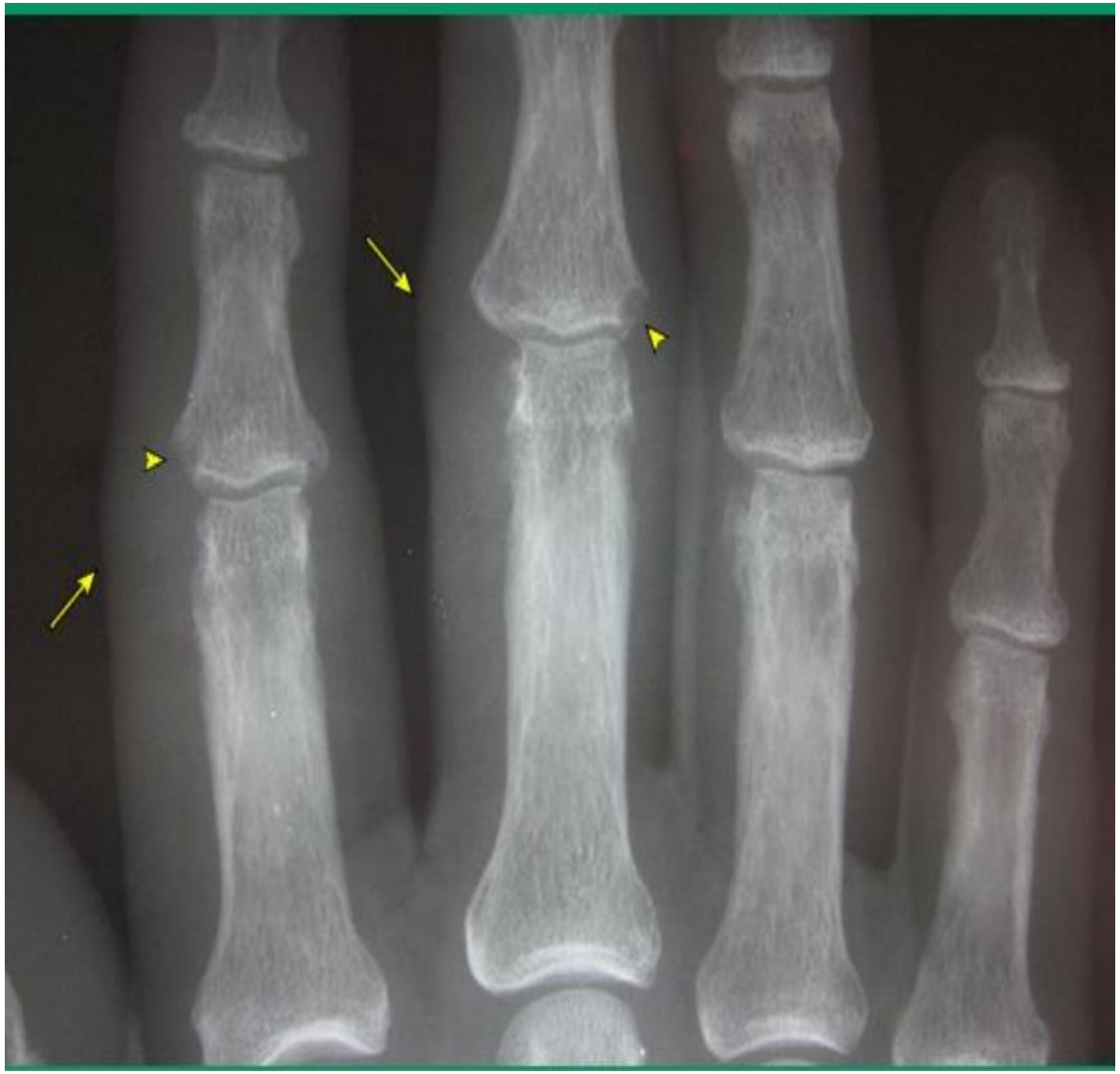
Other laboratory investigations

Synovial fluid: WBC elevated , mostly neutrophils

Pleural fluid: exudative: low to mildly elevated WBC, low glucose, high LDH, and high protein.

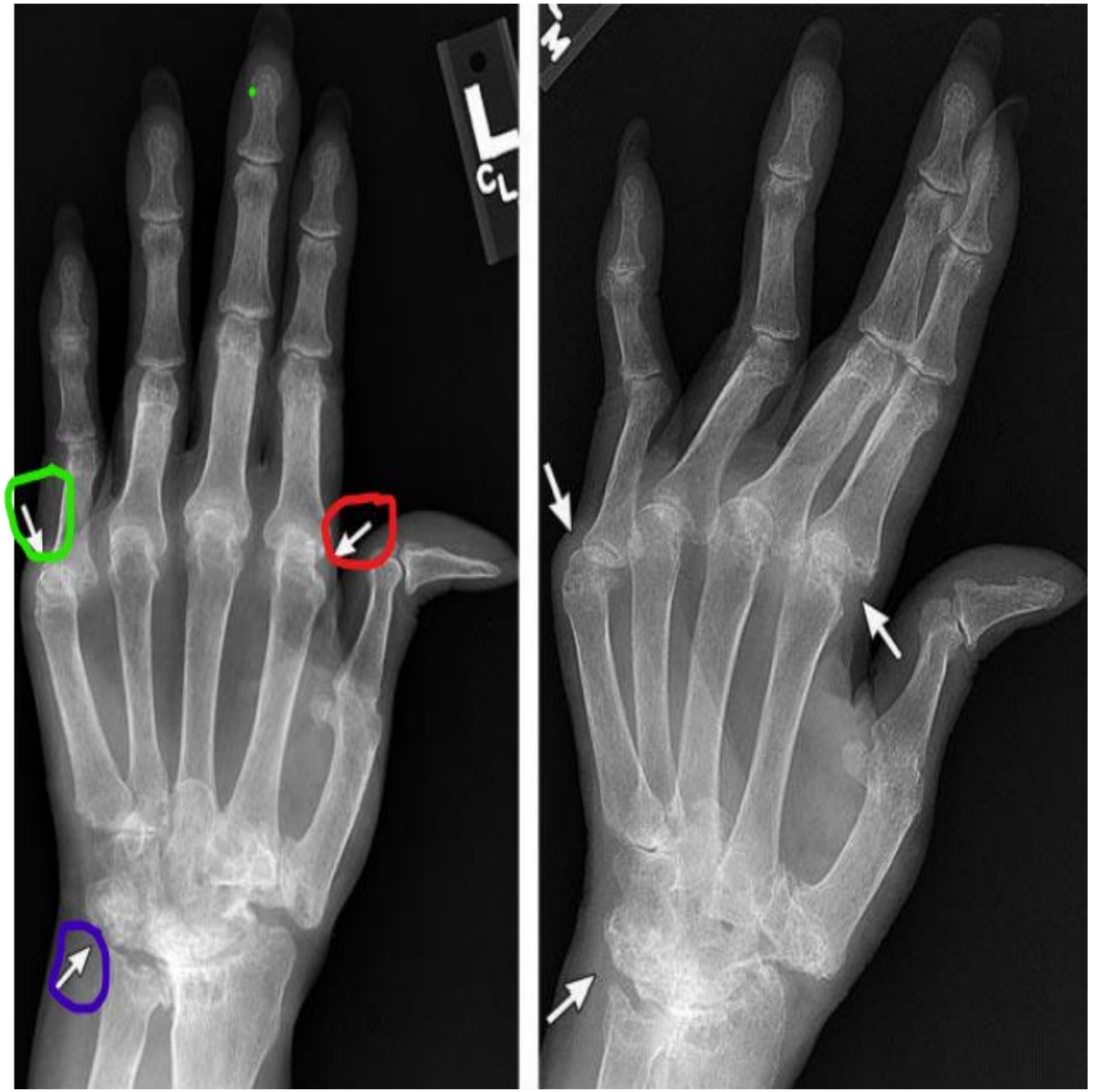
HAND X-RAY OF RA PATIENT

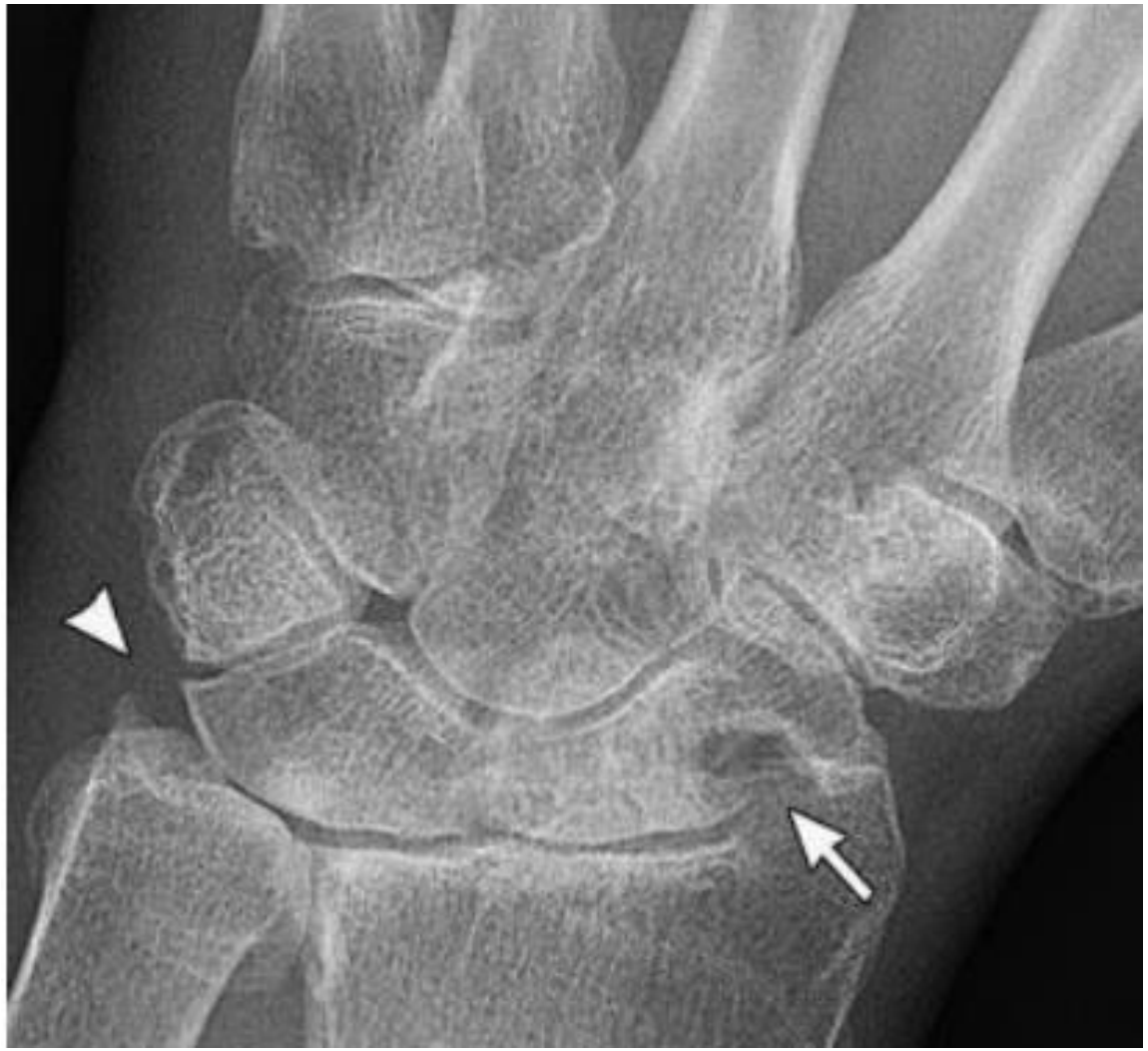
- The X-ray shows soft tissue swelling at the PIP joints (indicated by the arrows) and mild erosive changes (shown by the arrowheads).
- Erosions mean Discontinuity of the cortex.



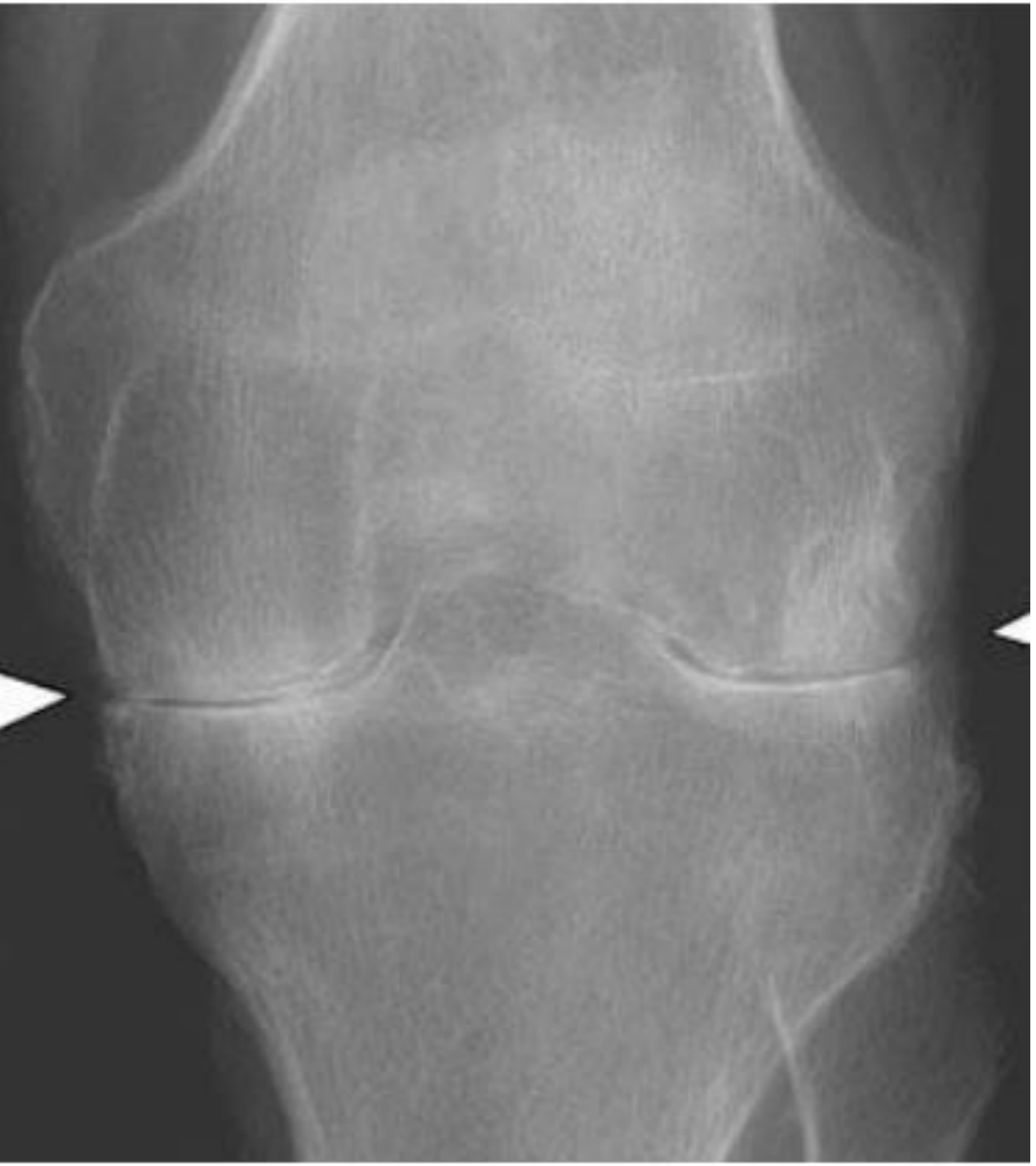
SIGNIFICANT OSTEOPENIA IN RA

- Red arrow shows Erosions.
- Green arrow shows Subluxations.
- Blue arrow shows inflammatory process in the wrist joint.



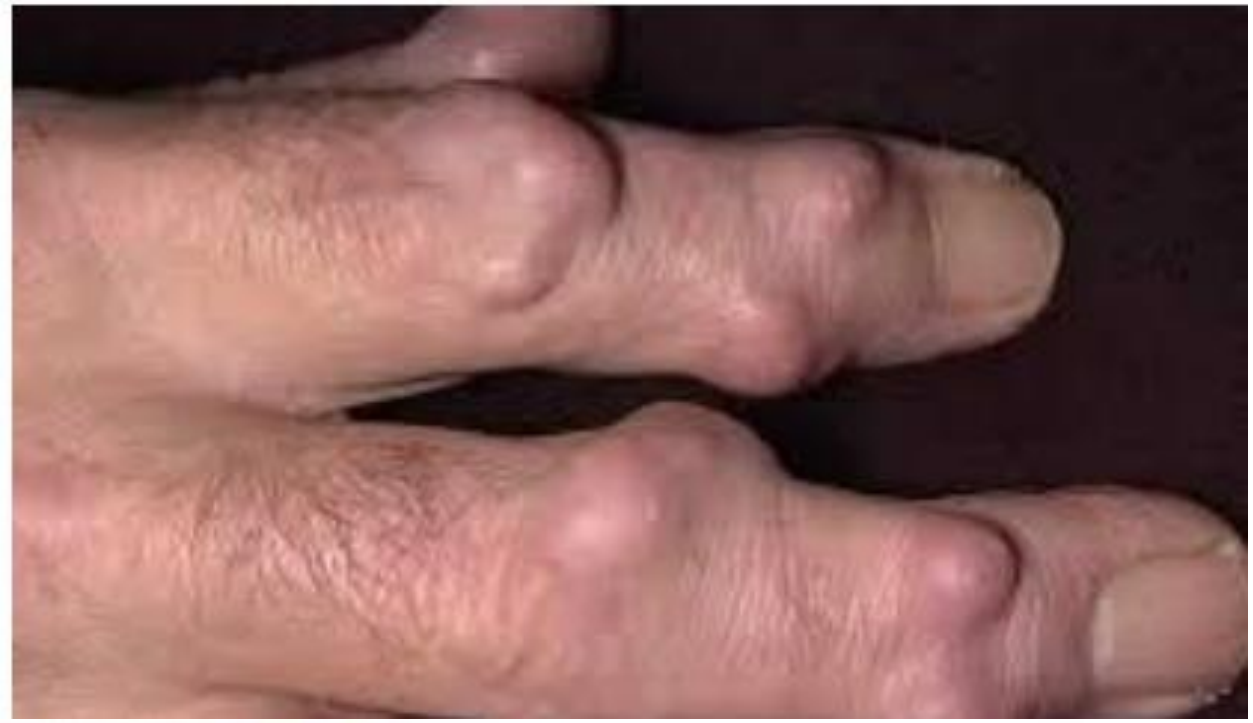


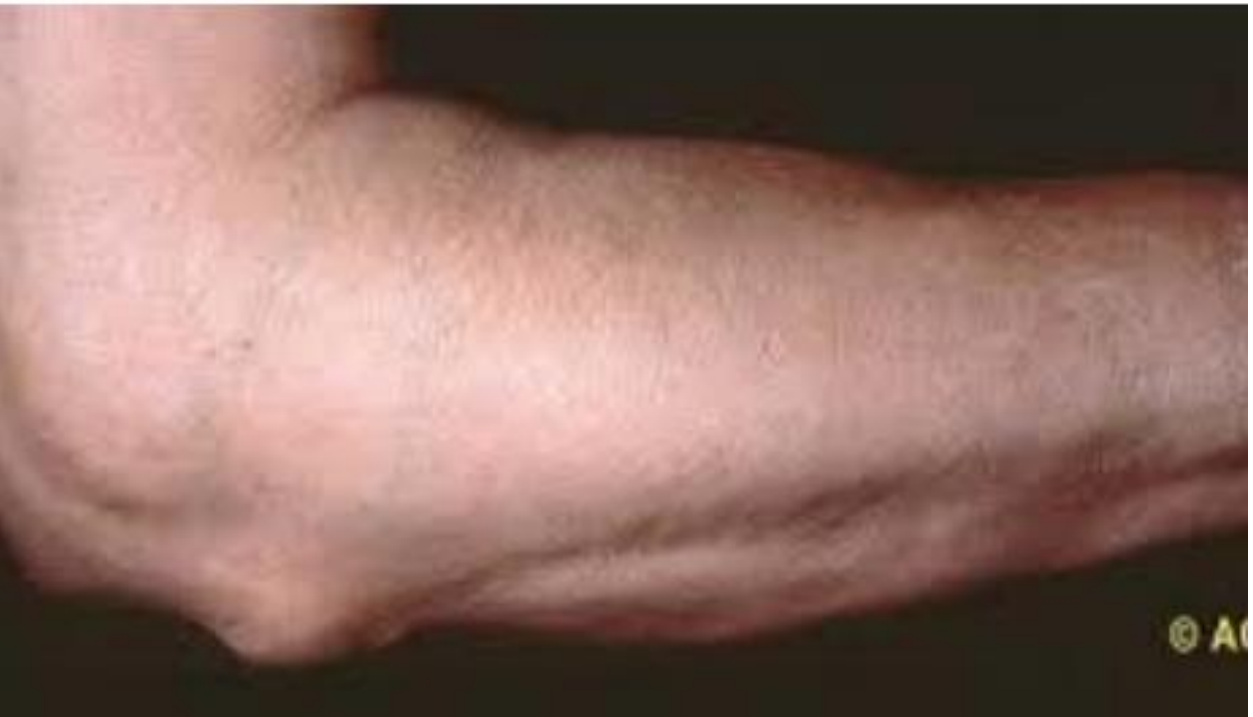
EROSIONS IN RA



KNEE JOINT INVOLVEMENT IN RA

- Notice that there is symmetrical involvement of the medial and lateral sides of the knee joint.
- Osteoarthritis affects the medial compartment and spares the lateral compartment.



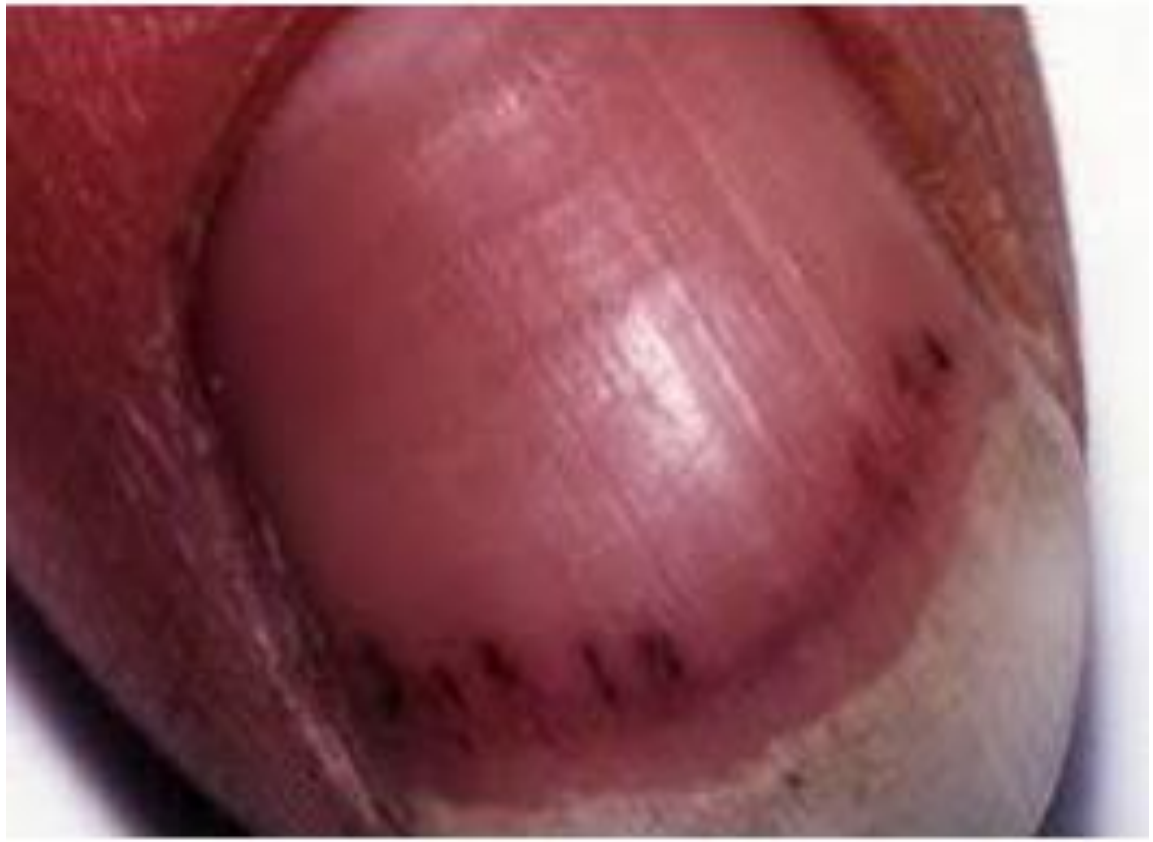


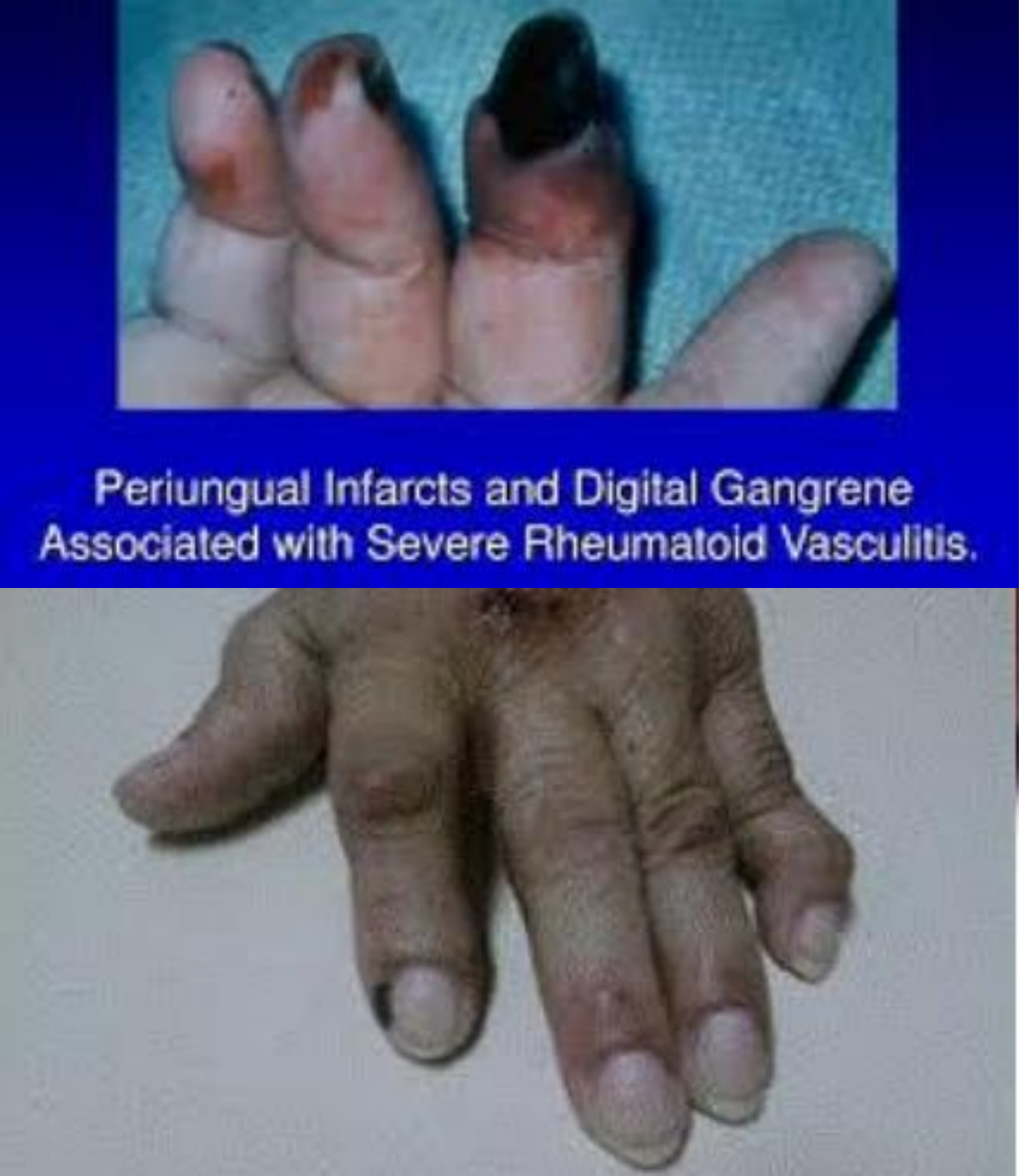
RHEUMATOID NODULES

- The most common extra-articular manifestation in RA.
- Occurs mainly in Seropositive RA.
- Histologically focal central fibrinoid necrosis with surrounding fibroblasts.
- Etiology: as a result of Small vessel vasculitis.

SPLINTER HEMORRHAGES

- One of the cutaneous manifestations of RA.
- Also seen in Infective Endocarditis or in association with trauma.



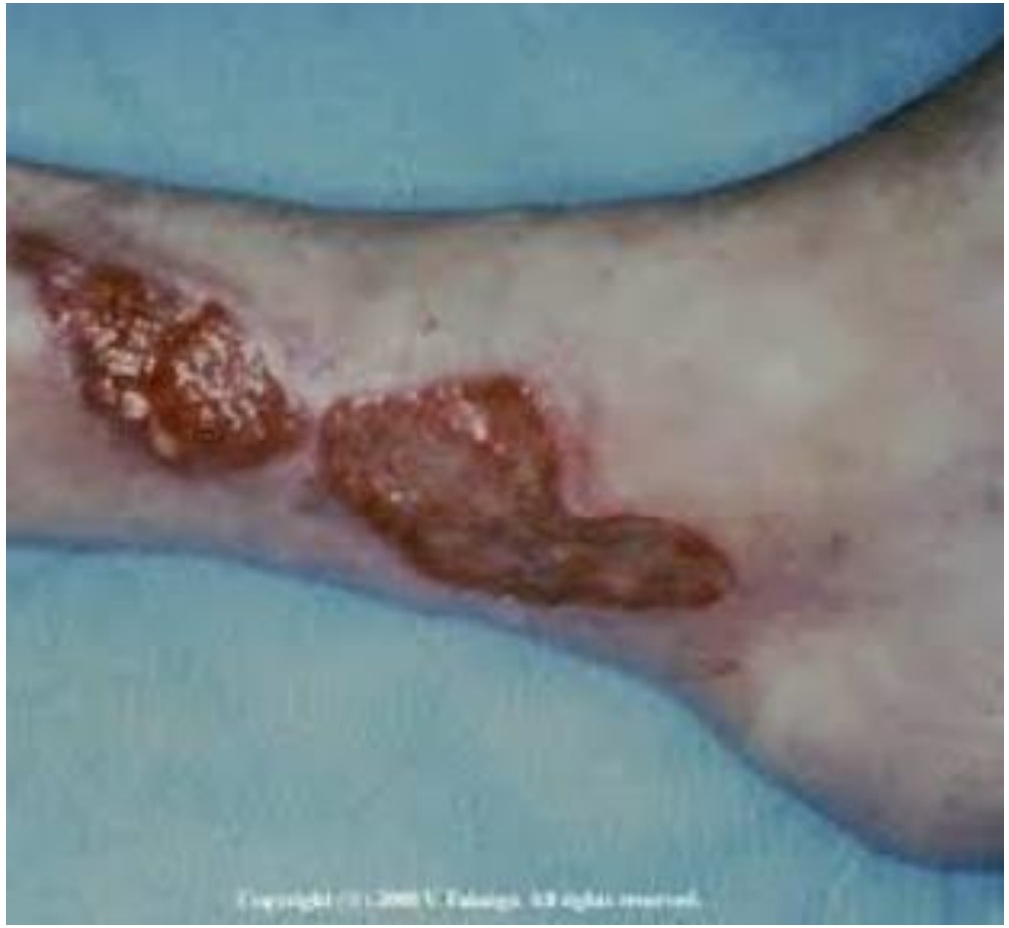


PERIUNGUAL INFARCTS WITH DIGITAL GANGRENES

- One of the cutaneous manifestations of RA.
- They are associated with severe Rheumatoid Vasculitis.

LEG ULCERS

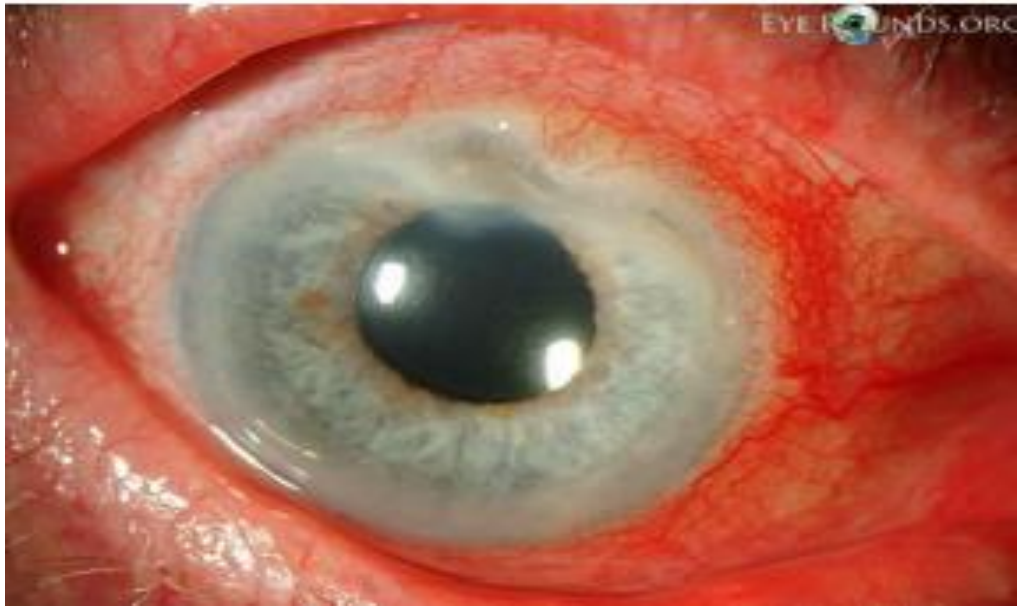
- One of the cutaneous manifestations of RA.
- The cutaneous manifestations of RA are seen mostly in the lower extremities where the skin is exposed to pressure + they indicate more severe disease.



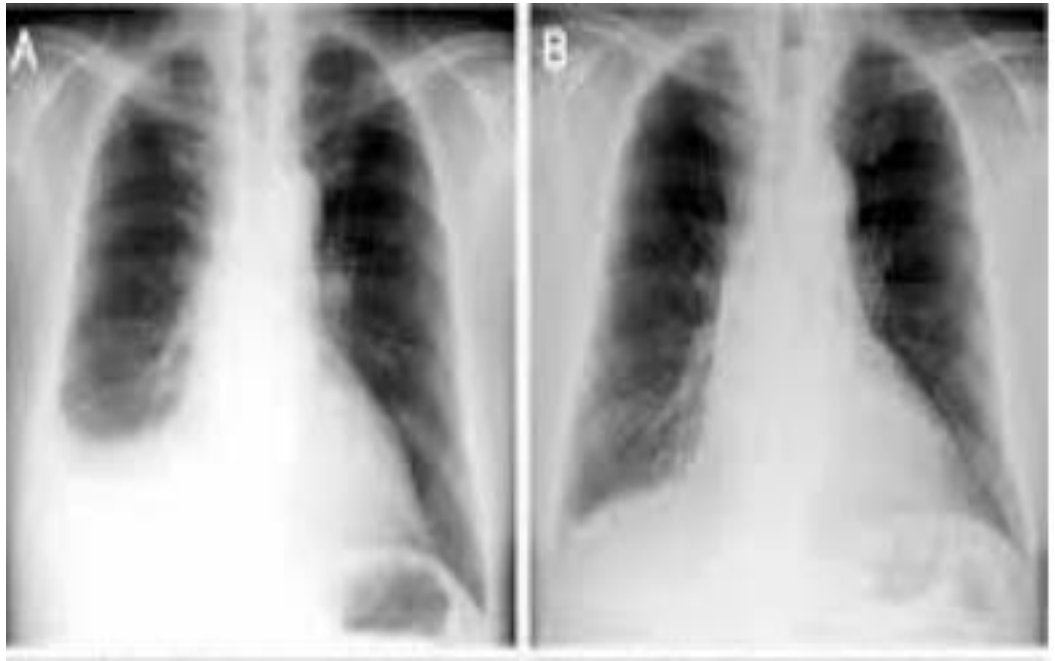
EPISCLERITIS

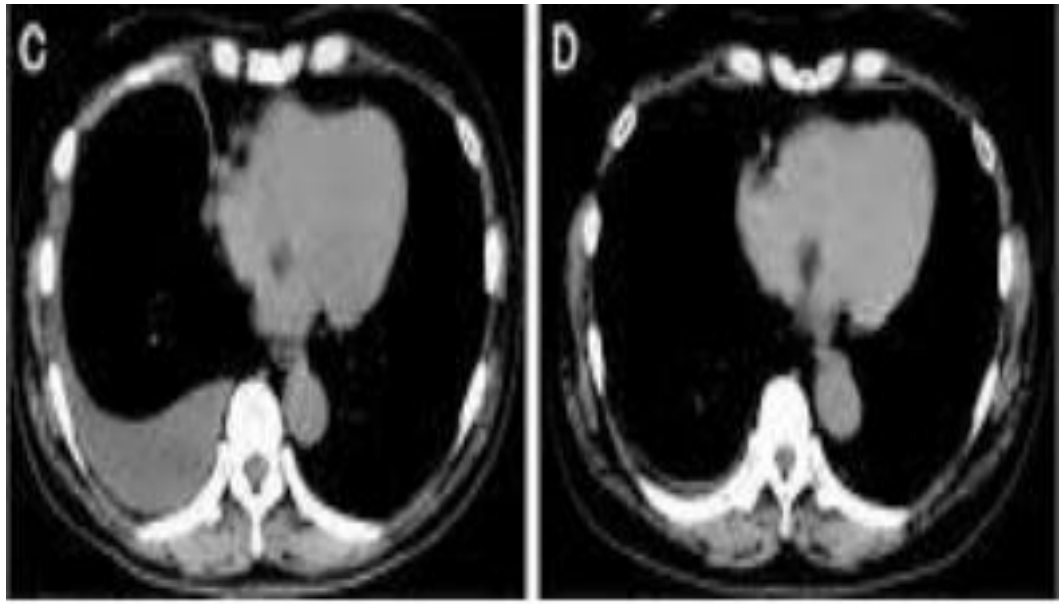
- One of the ocular manifestations of RA.
- Inflammation of the layer superficial to the Sclera (self-limiting).

Scleritis



- One of the ocular manifestation of RA.
- Aggressive process, painful inflammation of the sclera itself.
- If left untreated it will cause Corneal Melt which is an emergency which sometimes requires the use of chemotherapy to stop inflammation and possible vision loss.
- It may also be associated with Keratoconjunctivitis sicca (Sjogren syndrome) and Peripheral ulcerative keratitis which is involvement of the peripheral cornea and can lead to corneal melt.



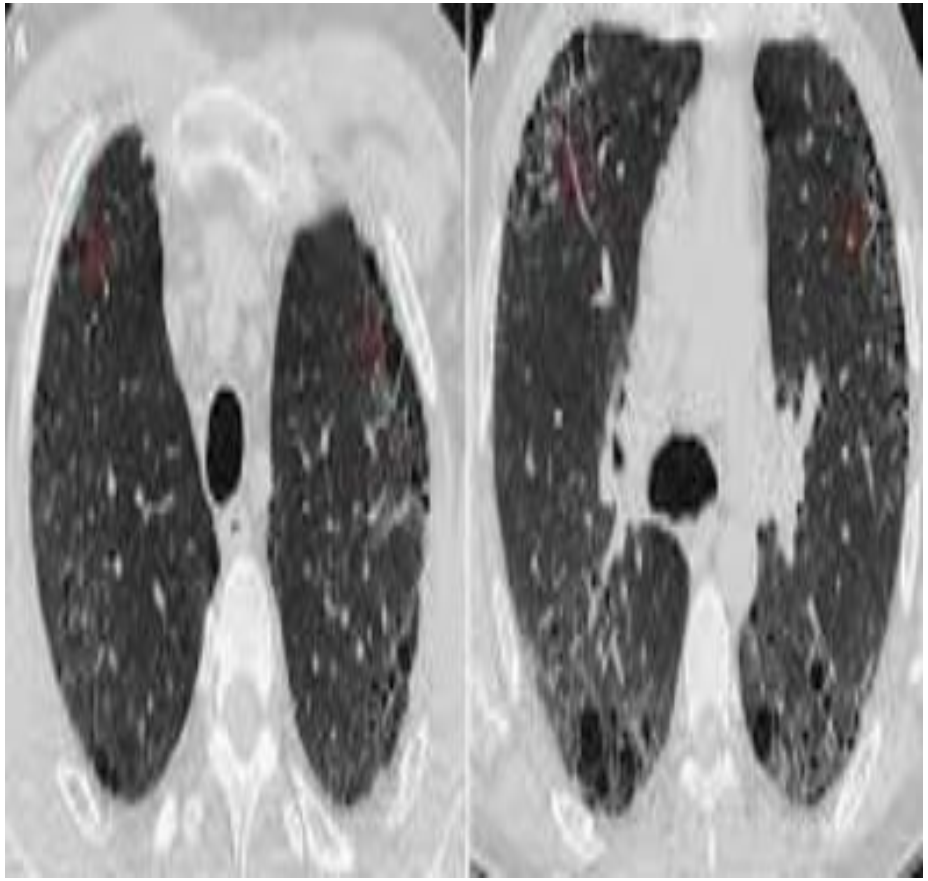


PLEURAL EFFUSIONS

- One of the pulmonary manifestations of RA.
- Those effusions are EXUDATIVE

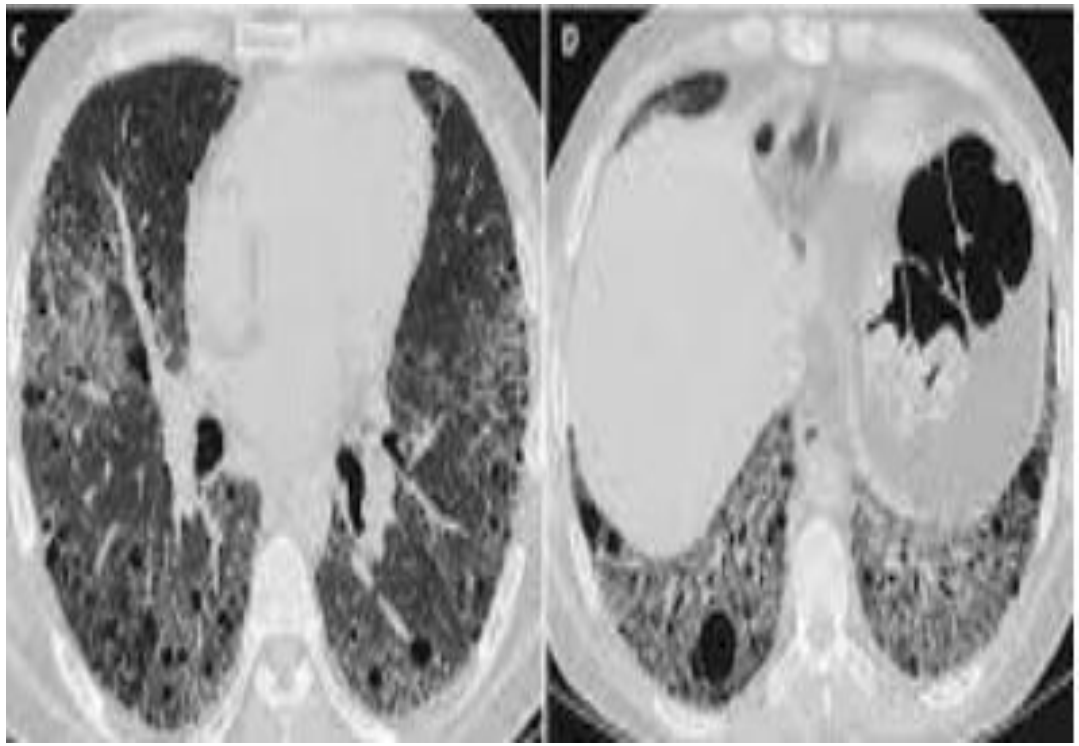
Parenchymal Pulmonary Nodules

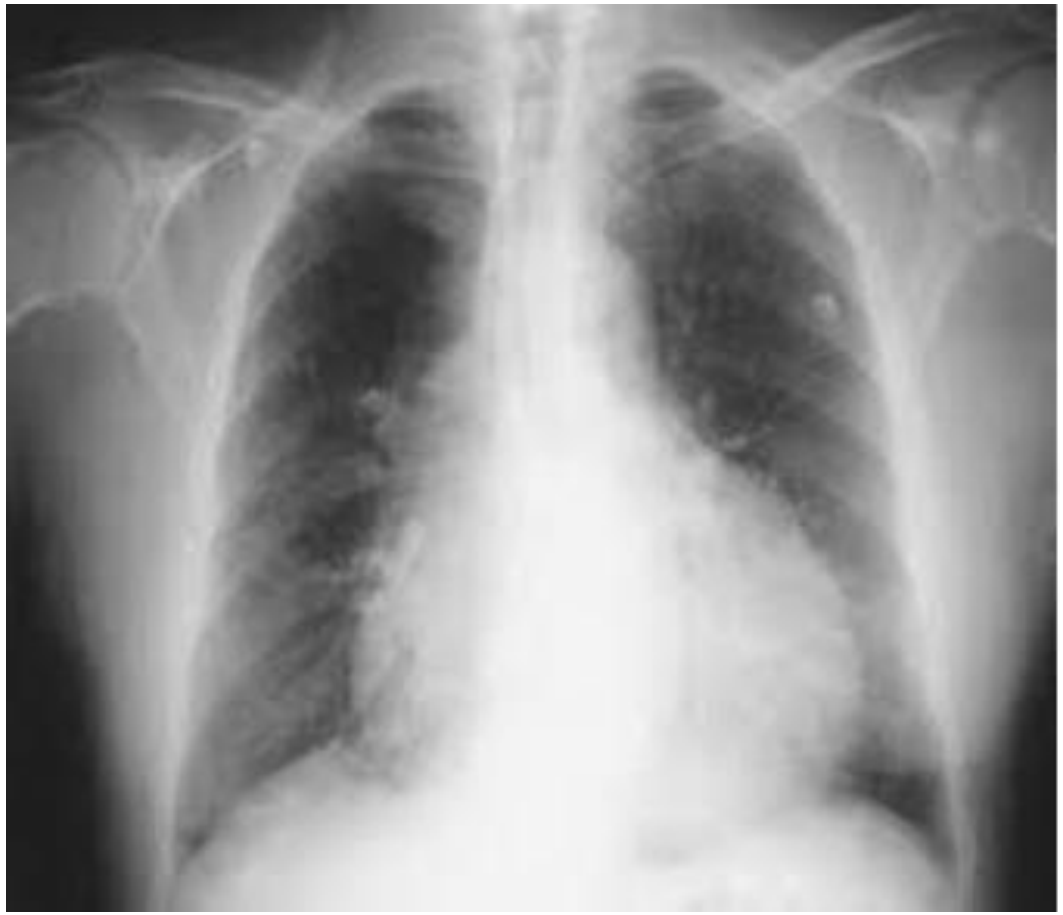
- One of the pulmonary manifestations of RA.
- Asymptomatic
- Found mainly in Seropositive RA with nodules everywhere.



Diffuse Interstitial Pulmonary Fibrosis

- One of the pulmonary manifestations of RA.
- More often in Seropositive RA male patients.
- Indicates longstanding nodular disease.





PERICARDIAL EFFUSION

- One of the cardiac manifestations of RA.
- Can be silent.
- May be associated with Accelerated Atherosclerosis.
- Eventually patients may have Heart Failure due to Diastolic Dysfunction.

TREATMENT OF RA

Treatment of RA oral DMARDs

- Hydroxychloroquine : Mild disease, pregnancy
- Sulfasalazine: mild-moderate disease
- **Methotrexate:** gold standard for moderate to severe RA; Improves overall and cardiovascular survival

- Azathiorpine
- Leflunomide
- Cyclosporine
- Minocycline

Combination therapy

Mono, double or triple therapy

MTX+ SSZ+ HCQ:OK

Avoid combining AZA plus MTX

SSZ+ AZA+ HCQ :OK

Triple plus biologic: anti TNF or non TNF inhibitors.

Other treatments

Glucocorticoids:

- Have both anti-inflammatory and immunoregulatory activity.

✓ can be given orally, intravenously, intramuscularly or can be injected directly into the joint.

✓ useful in early disease as temporary adjunctive therapy while waiting for DMARDs to exert their anti-inflammatory effects.

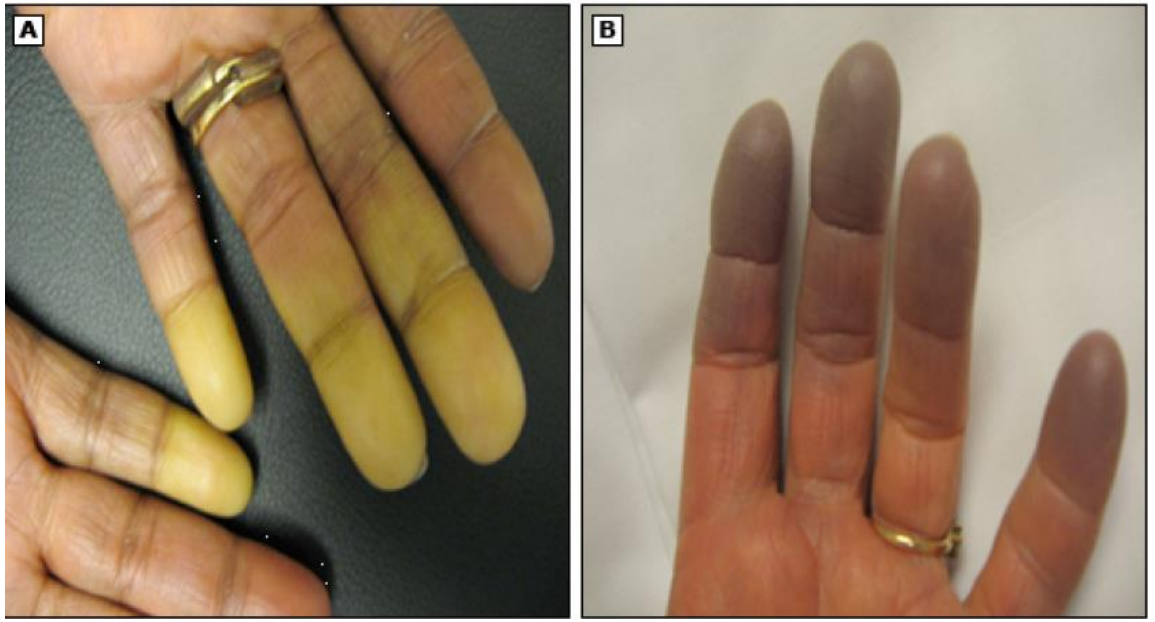
✓ Corticosteroids are also useful as chronic adjunctive therapy in patients with severe disease that is not well controlled on NSAIDs and DMARDs.

✓ The usual dose of prednisone is 5 to 10mg daily.

SLE

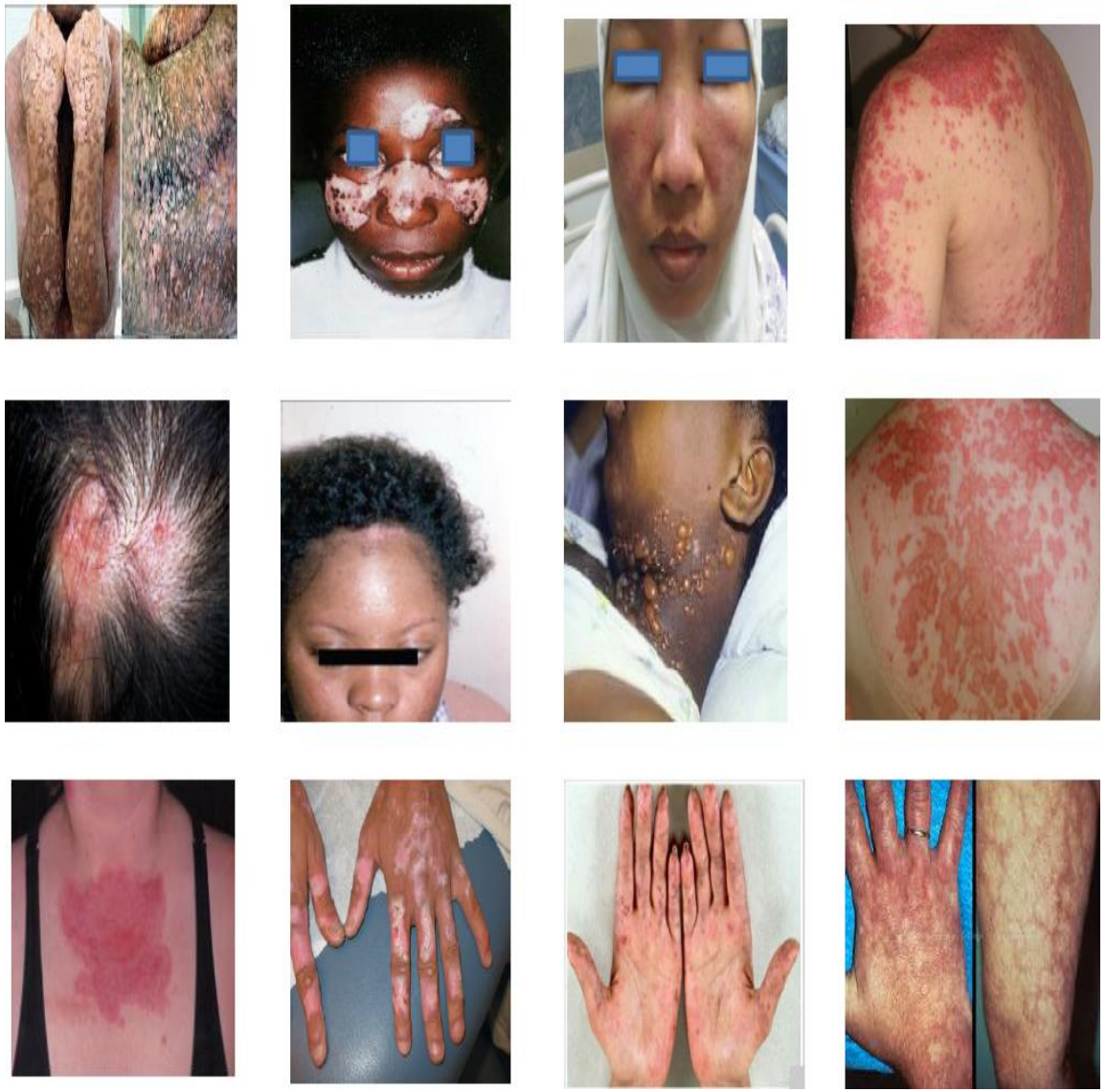
RAYNAUD PHENOMENON

- Vasospasm in peripheral small vessels upon cold exposure, stress or certain medications.
- 3 stages : 1- Pallor 2- Cyanosis 3- Redness
- Common in SLE + Scleroderma

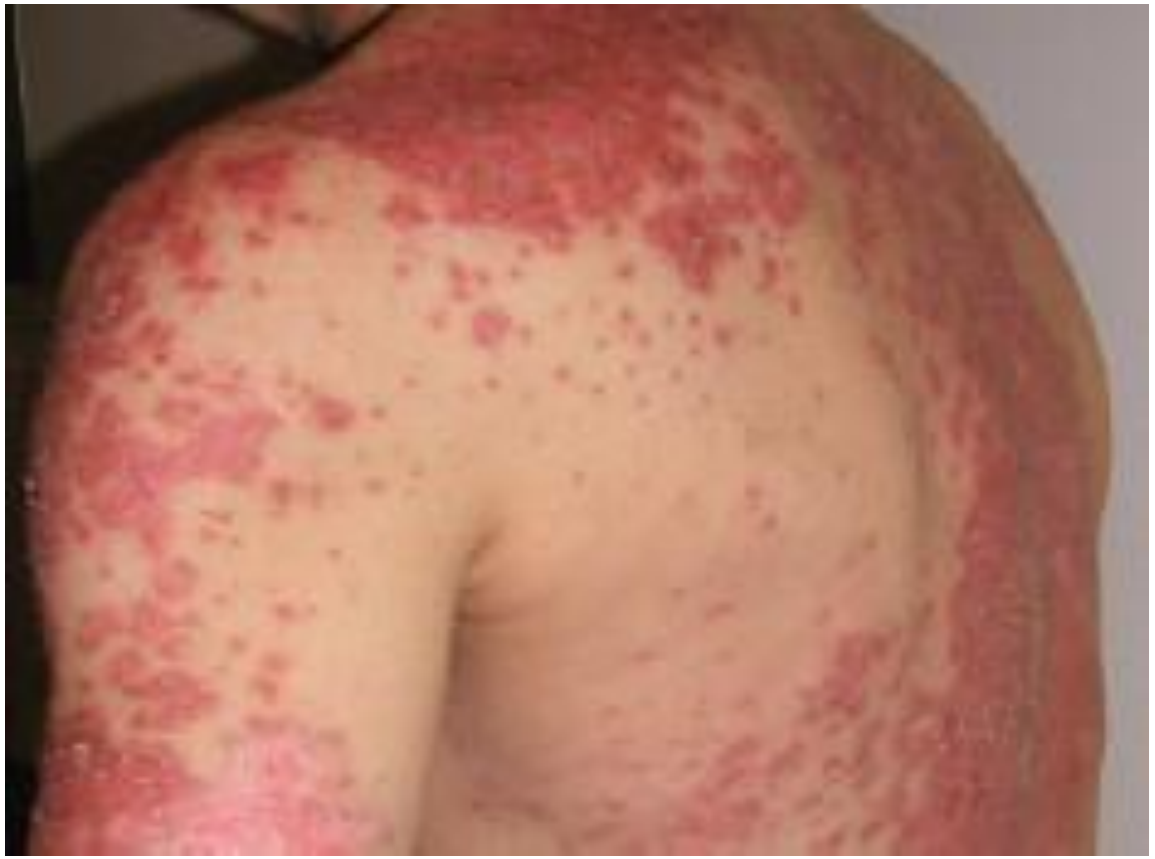


SLE CUTANEOUS MANIFESTATIONS

- Keep in mind that malar rash never keeps a scar.

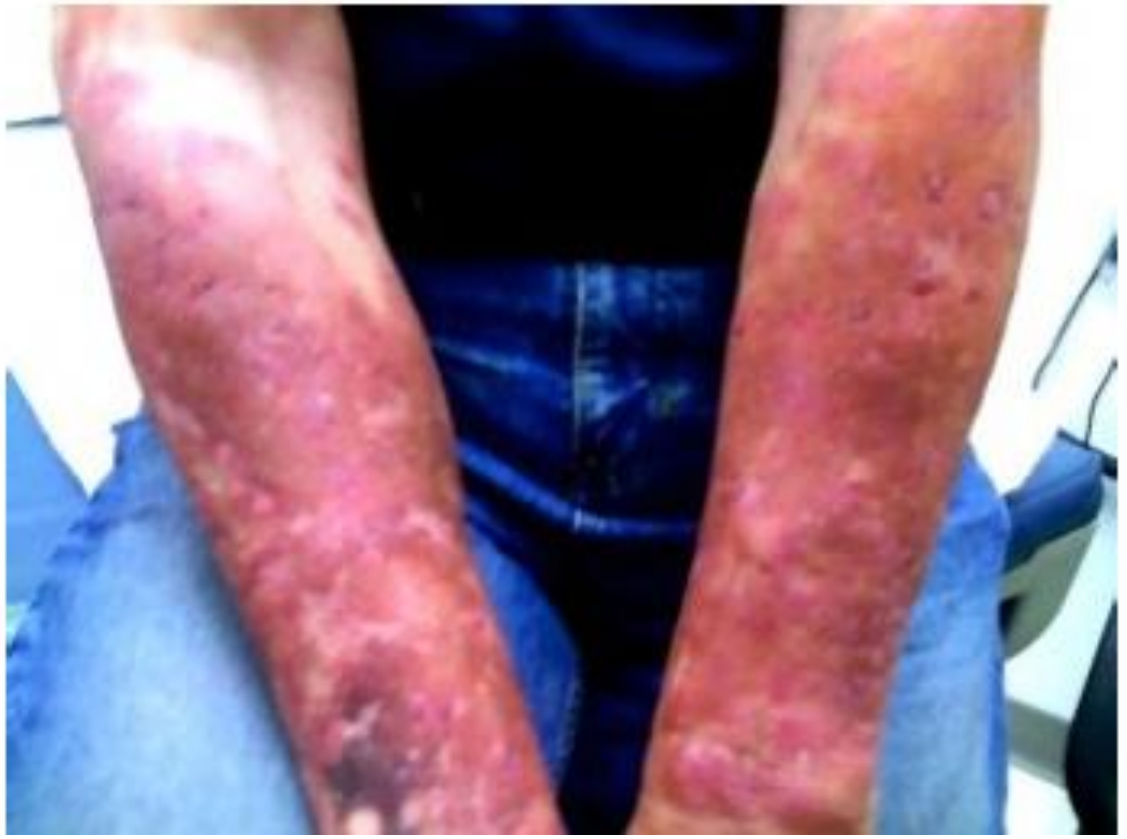


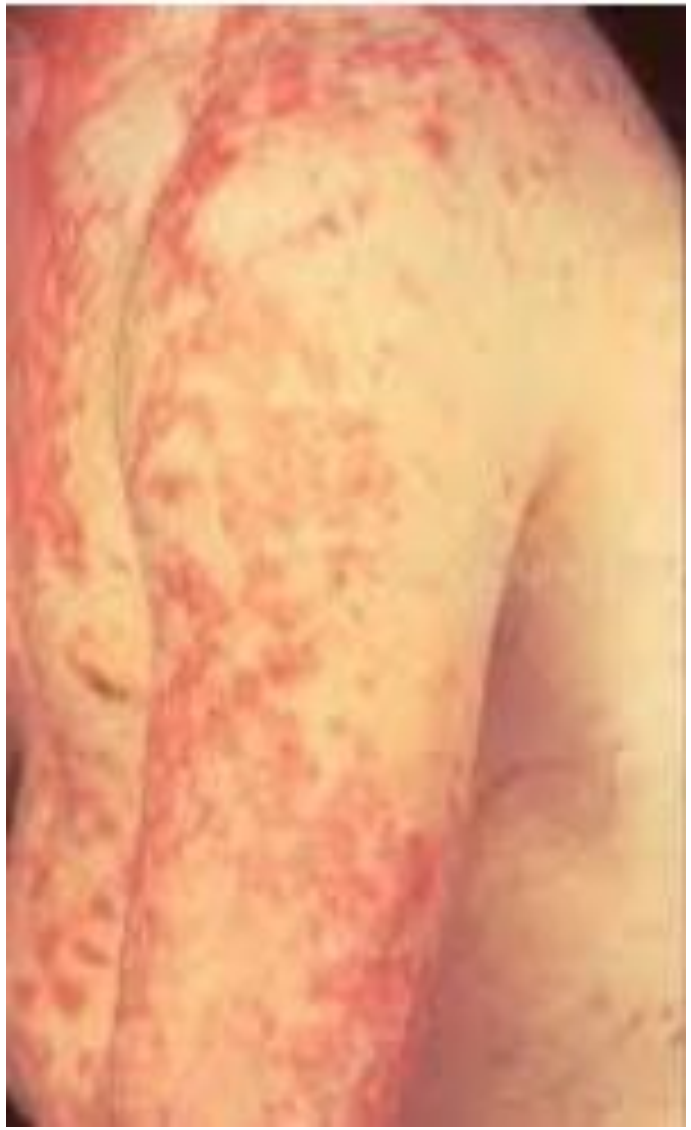
SUBACUTE CUTANEOUS LUPUS



BULLOUS LUPUS

- Seen in Acute / Subacute cutaneous lupus.



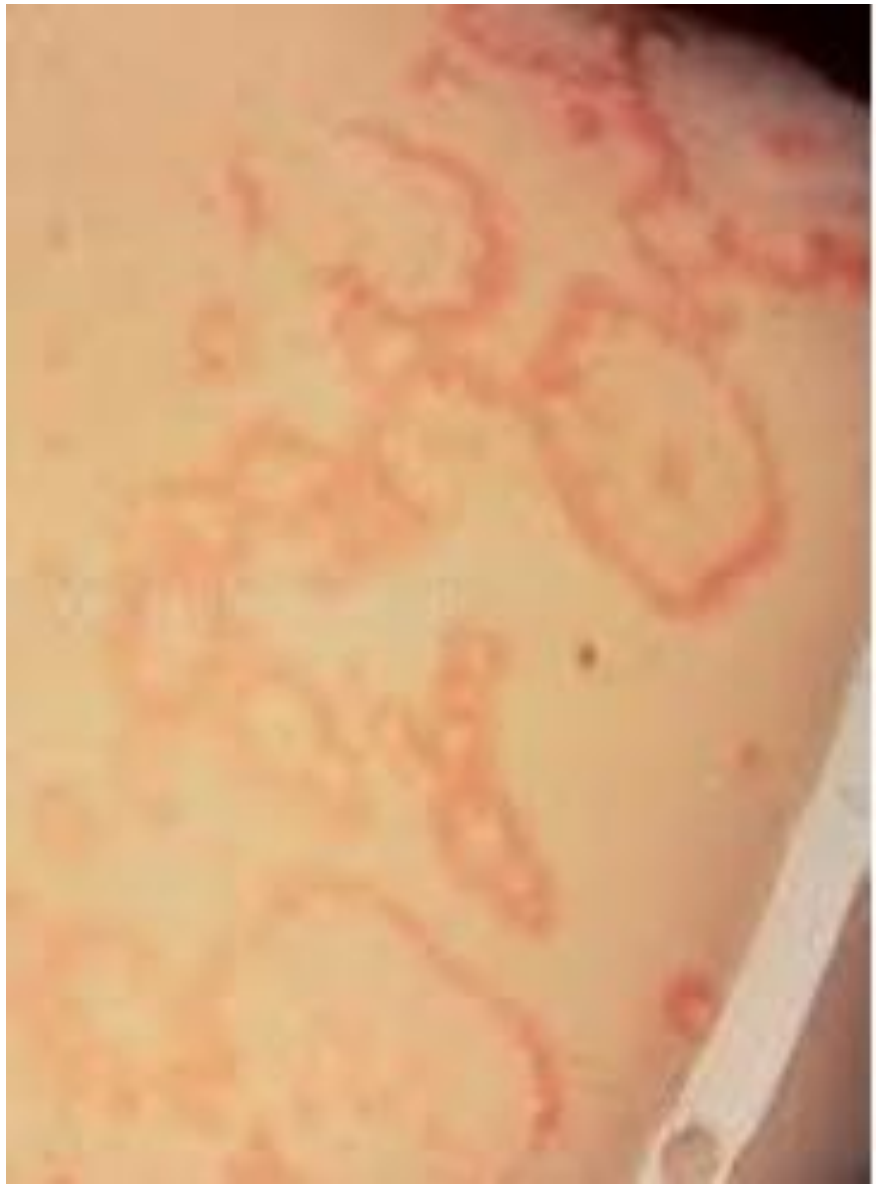


MACULOPAPULAR LUPUS RASH

- Seen in Acute / Subacute Cutaneous Lupus

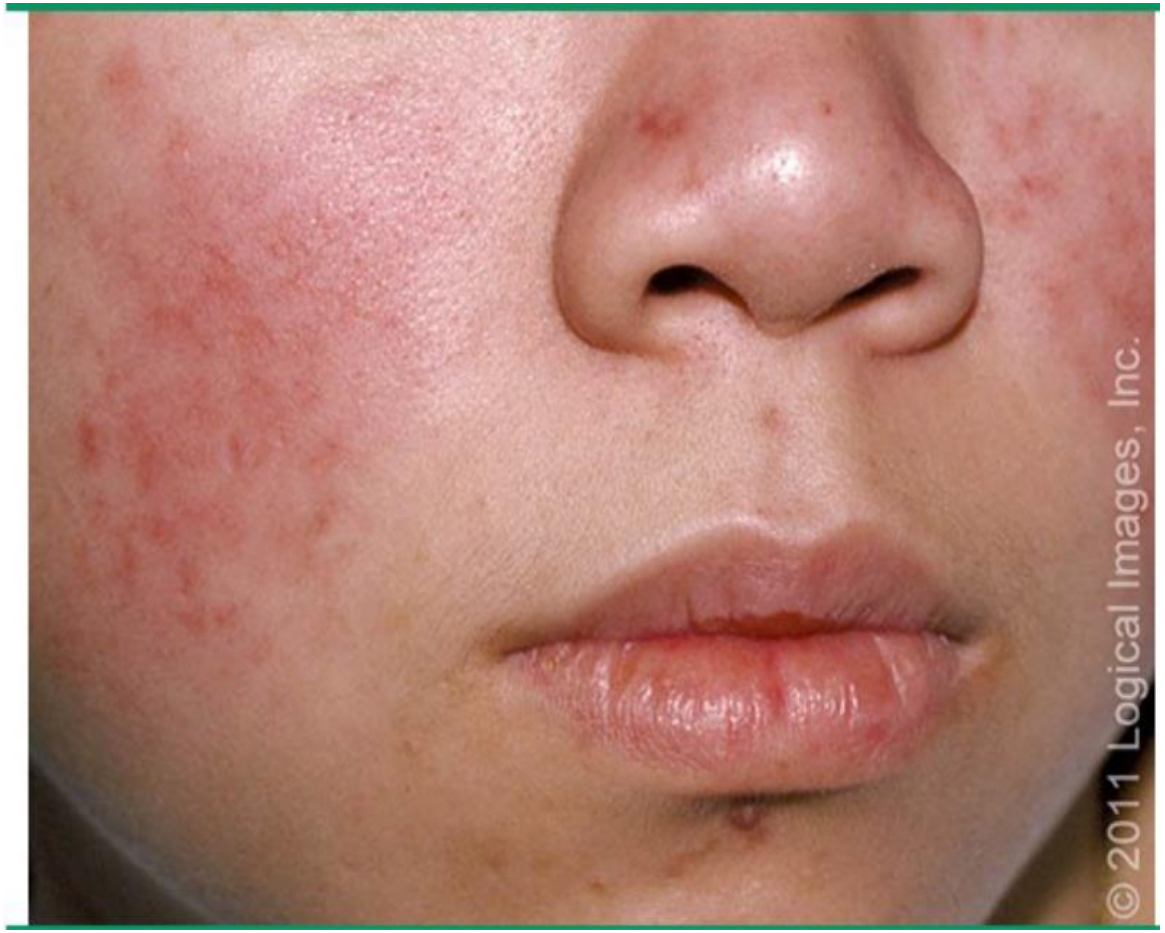
ANNULAR POLYCYCLIC RASH

- Seen in Acute / Subacute Cutaneous Lupus.
- Other cutaneous manifestations of lupus include: Malar Rash , Toxic Epidermal Necrolysis , Photosensitive Lupus Rash, and Nonindurated Psoriasiform.



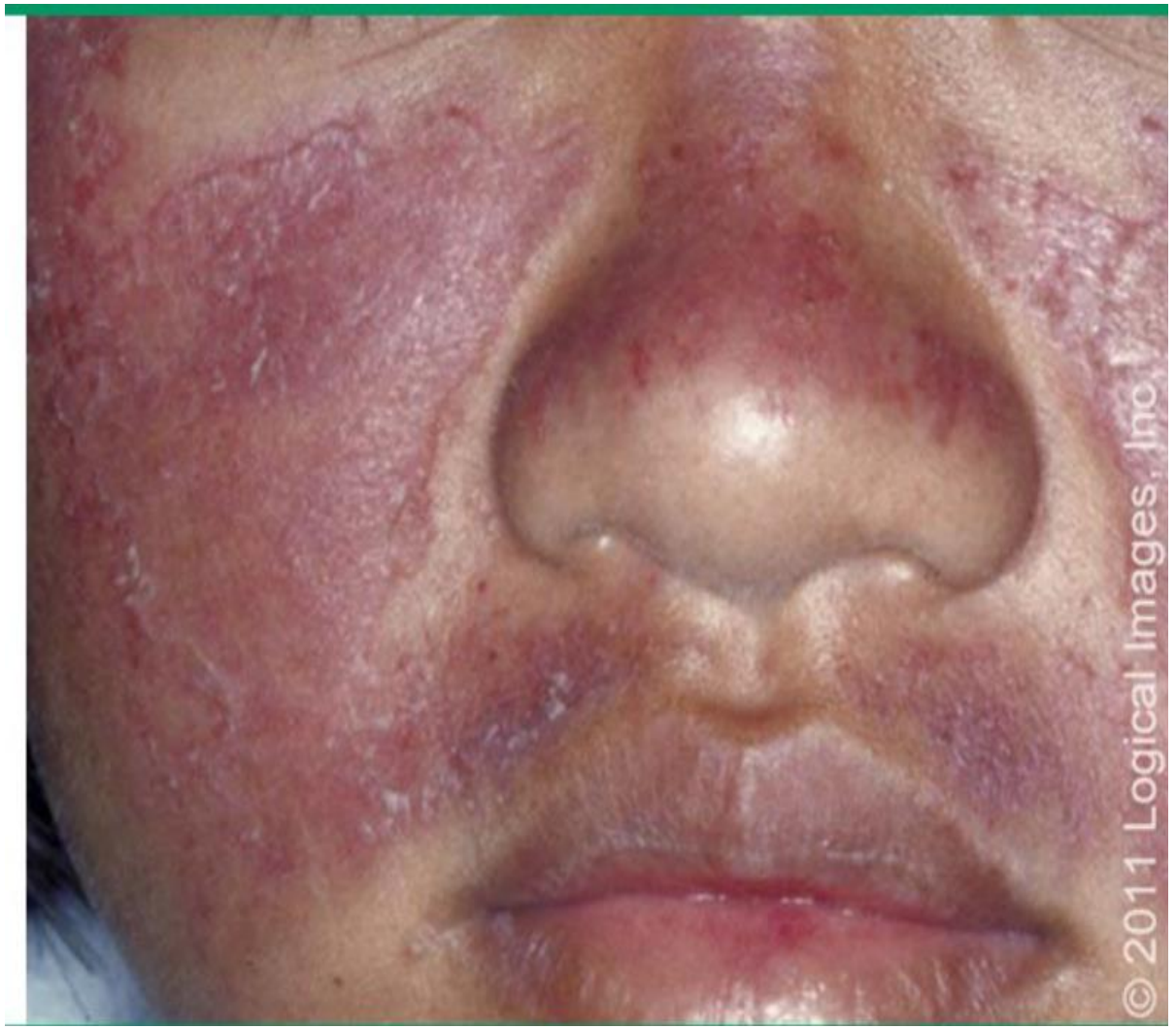
ACUTE CUTANEOUS LUPUS ERYTHEMATOSUS

- Malar Erythema and Subtle Edema are seen on the face of this patient with SLE.



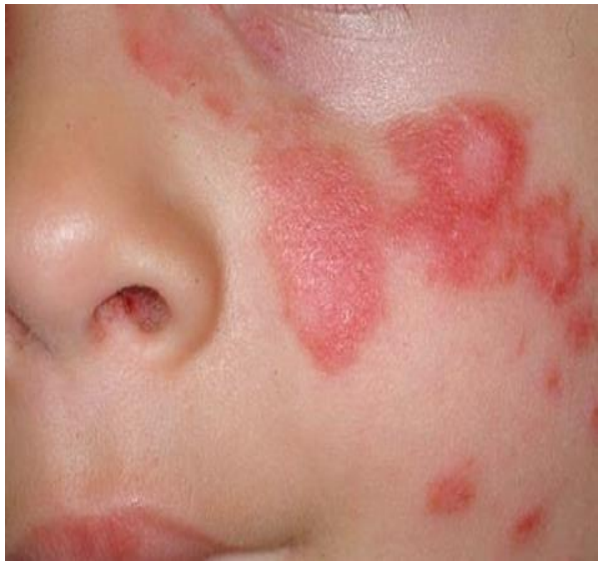
ACUTE CUTANEOUS LUPUS ERYTHEMATOSUS

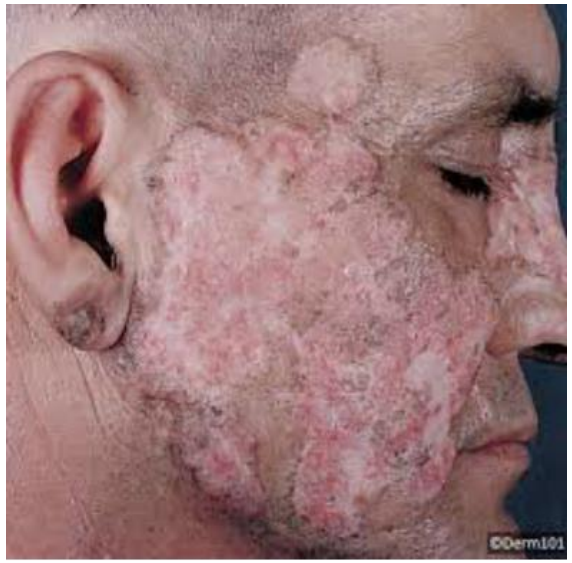
- An erythematous, edematous eruption is found on the malar area.
- Note the sparing of the nasolabial area which distinguishes malar rash in SLE from Dermatomyositis.

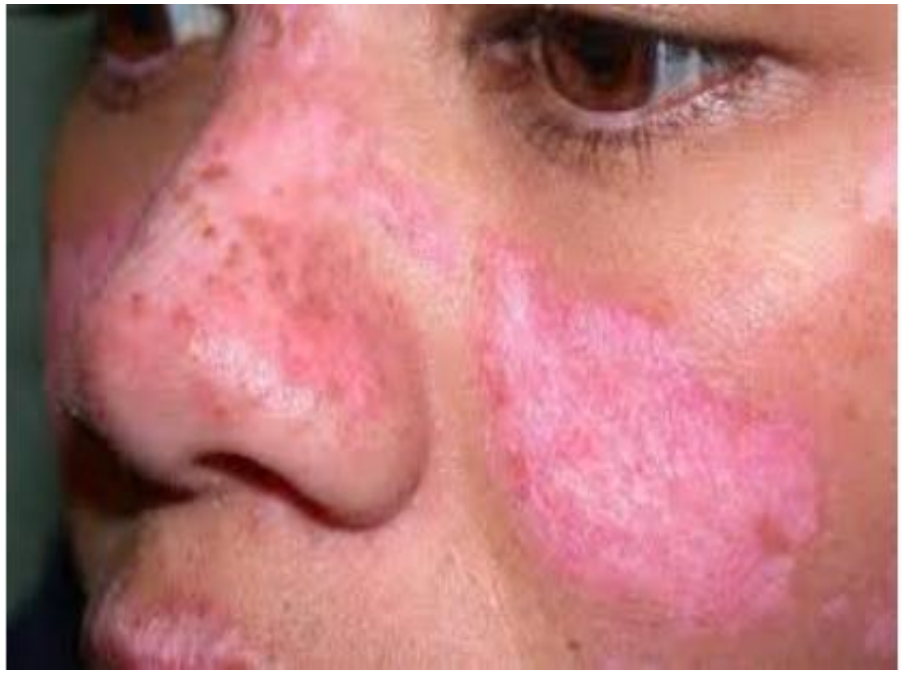


DISCOID LUPUS

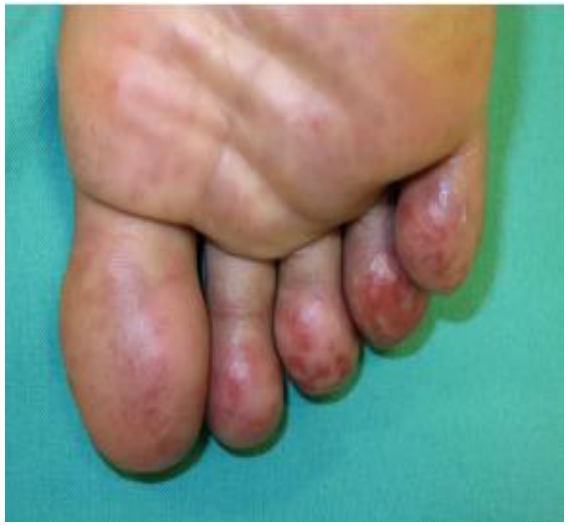
- Seen in Chronic Cutaneous Lupus.
- Can happen in Sun exposed or non-exposed areas and cause scars (distinguishing feature from the typical malar rash which doesn't cause scars).
- Can be disfiguring.

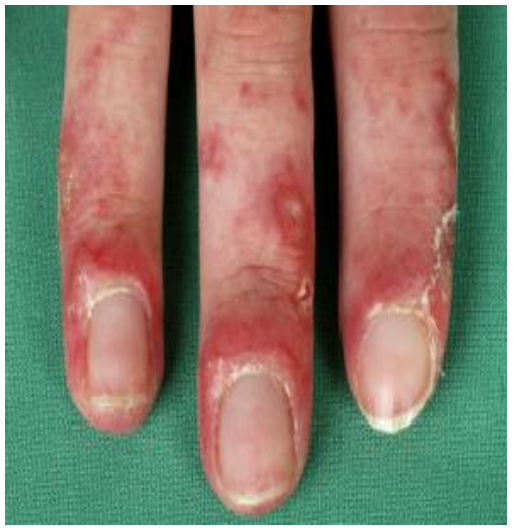


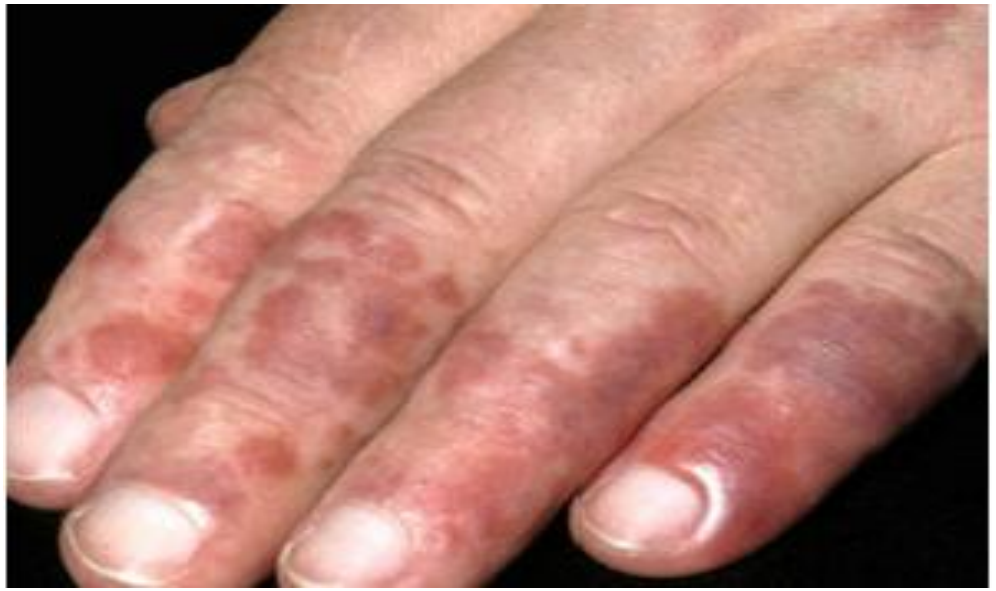




CHILBLAIN LUPUS ERYTHEMATOSUS



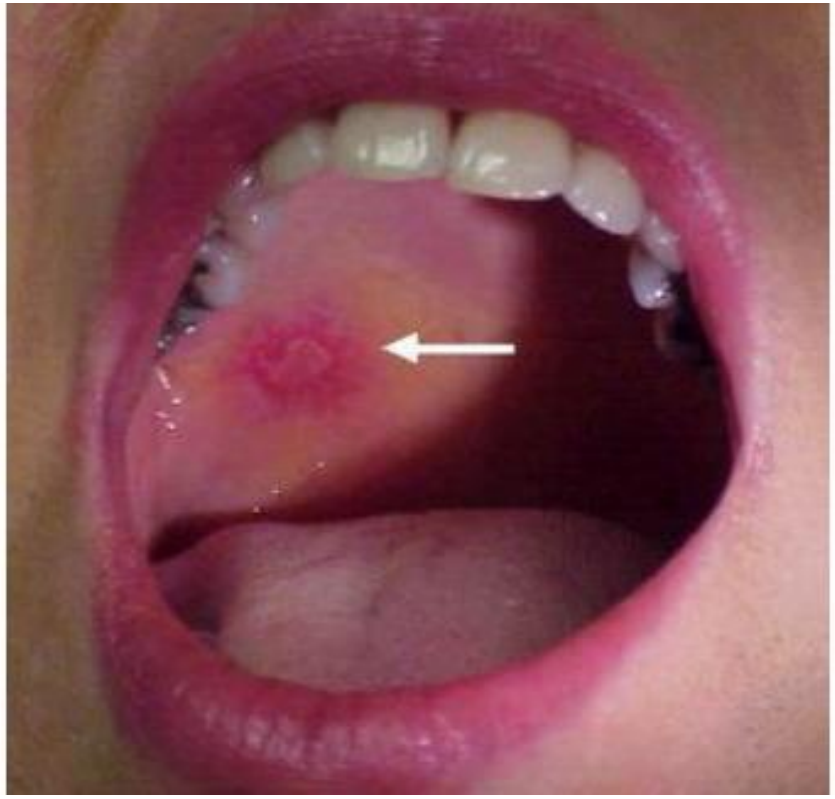




- Pruritic and painful red or dusky purple patches, papules and plaques that are initiated or exacerbated by exposure to cold and moisture in cool climate.
- Found on the Fingers, Toes, Heels, and Soles.
- Seen in Chronic Cutaneous Lupus.

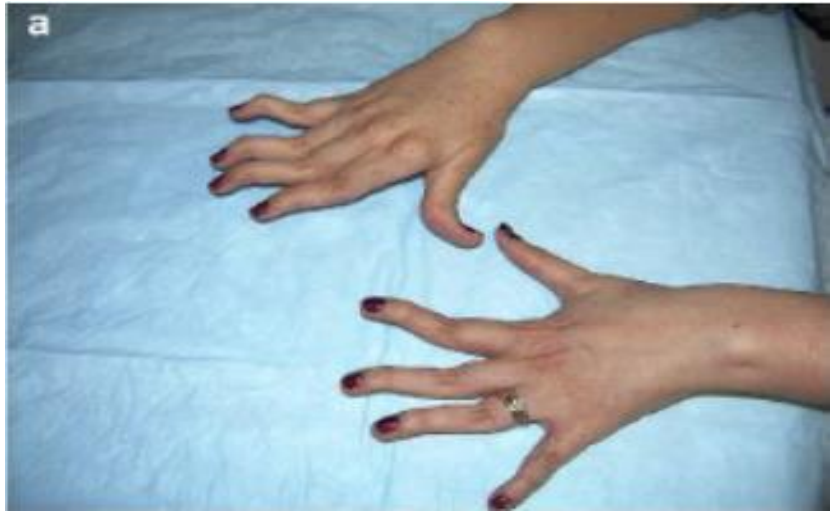
ORAL ULCERS

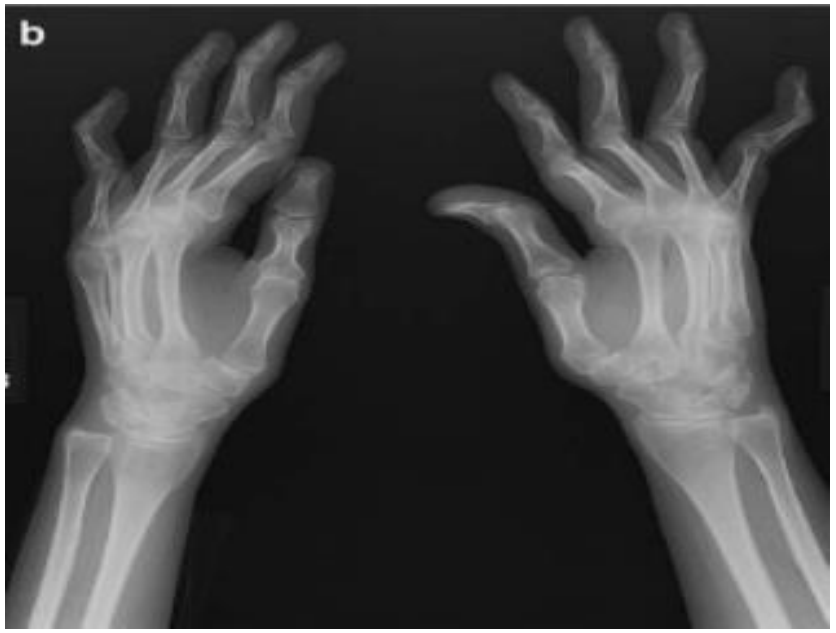
- Seen in chronic lupus erythematosus.
- The patients may have Nasal Ulcers as well.



JACCOUD'S ARTHROPATHY

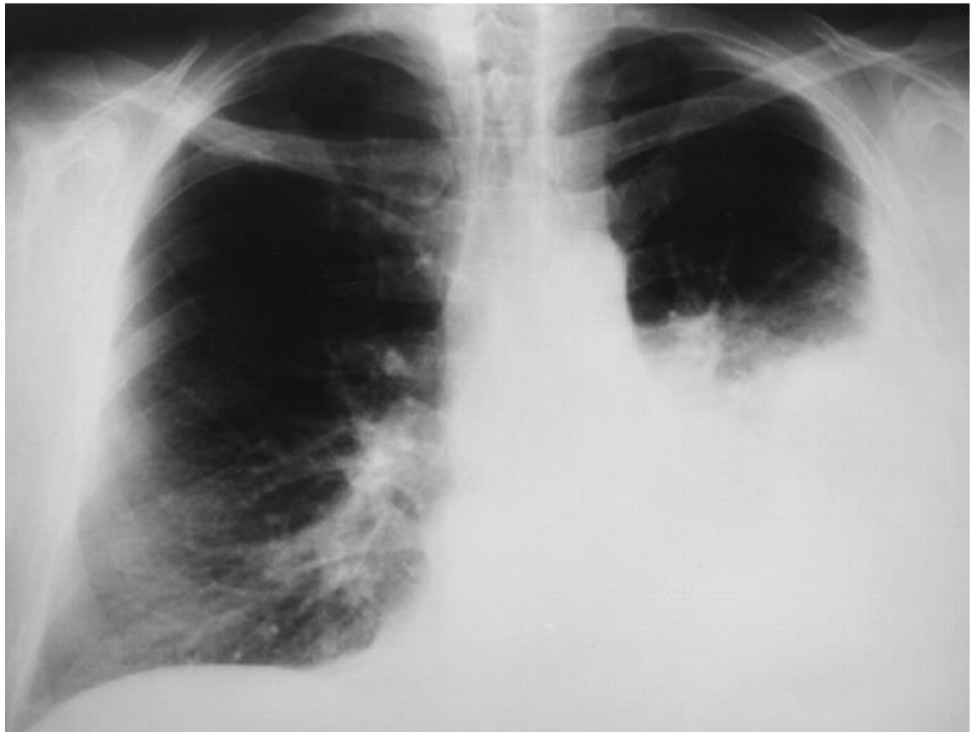
- One of the arthritic changes seen in lupus.
- It is a variant of Lupus Arthritis resulting from ligament laxity and Joint Subluxation.
- Reversible
- It's not a true deformity (you can straighten your finger).





LUPUS PNEUMONITIS

- One of the pulmonary manifestations seen in SLE.
- The most common pulmonary manifestation seen in lupus is Pleuritis / Pleural effusion as seen in this CXR.
- Patients may also have Cavitating pulmonary nodules, Pulmonary hypertension, Pulmonary vasculitis, Pulmonary embolism, Alveolar hemorrhage, Chronic interstitial pneumonitis, and Bronchiolitis obliterans.



LAP TESTS FOR SLE

LABORATORY TESTING:

The ANA test is positive in all patients with SLE at some time in the course of their disease

If the ANA is positive:test for other specific antibodies such as dsDNA, anti-Sm, Ro/SSA, La/SSB, and U1 ribonucleoprotein (RNP).

If the initial ANA test is negative, but the clinical suspicion of SLE is high, then additional antibody testing may still be appropriate. This is partly related to the differences in the sensitivity and specificity among the methods used to detect ANA.

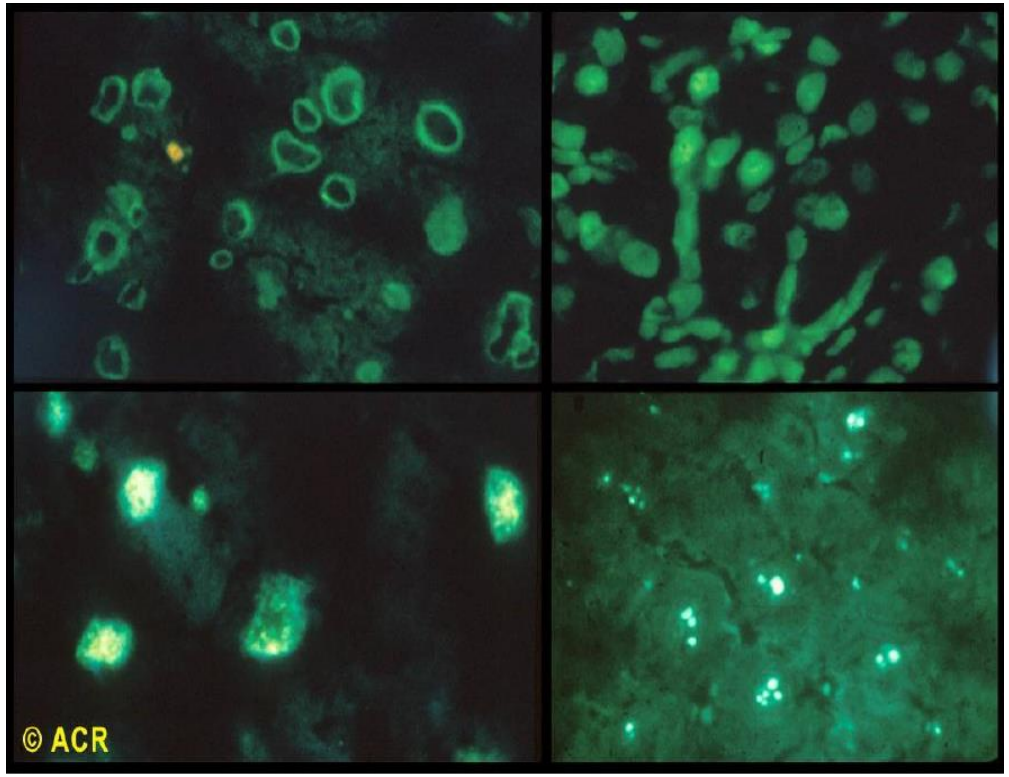
Approach to SLE diagnosis

LABORATORY TESTING:

- Complete blood count and differential may reveal leukopenia, mild anemia, and/or thrombocytopenia
- Elevated serum creatinine may be suggestive of renal dysfunction
- Urinalysis with urine sediment may reveal hematuria, pyuria, proteinuria, and/or cellular casts
- ANA
- Antiphospholipid antibodies (lupus anticoagulant [LA], IgG and IgM anticardiolipin [aCL] antibodies; and IgG and IgM anti-beta2-glycoprotein [GP]
- C3 and C4 or CH50 complement levels
- Erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) levels
- Urine protein-to-creatinine ratio

ANA STAINING PATTERN IN IMMUNOFLUORESCENCE

- ANA is an autoantibody that bind to contents of cell nucleus.
- Most ANAs are directed against nucleic acids or proteins associated with nucleic acids.
- In SLE the most predominant antigen is the Nucleosome.



TREATMENT OF SLE

Treatment of SLE

- No permanent cure for SLE: treatment relieves symptoms

❖ **NSAIDs** (nonsteroidal anti-inflammatory drugs): Reduce inflammation and pain

❖ **Corticosteroids**
- Reduce inflammation
- Used after significant organ damage

❖ **Antimalarial Drugs**
- Hydroxychloroquine (Plaquenil), chloroquinone (Aralen)
- Reduces inflammation, protects against organ damage
- Used for skin symptoms, joint pain

❖ **DMARDs (disease-modifying antirhematic drugs)**
- Belimumab (Benlysta), rituximab (Rituxan)
- Methotrexate, azathioprine and mycophenelate mofetil

Hydroxychloroquine

- Reduction in flares
- Reduction in lipids
- Reduction in thrombosis
- Reduction in organ damage
- Improved survival
- Triples mycophenolate response
- Prevents seizure
- Reduction in CHB in neonatal lupus

Vitamin D

Improved vitamin D level positively affects:

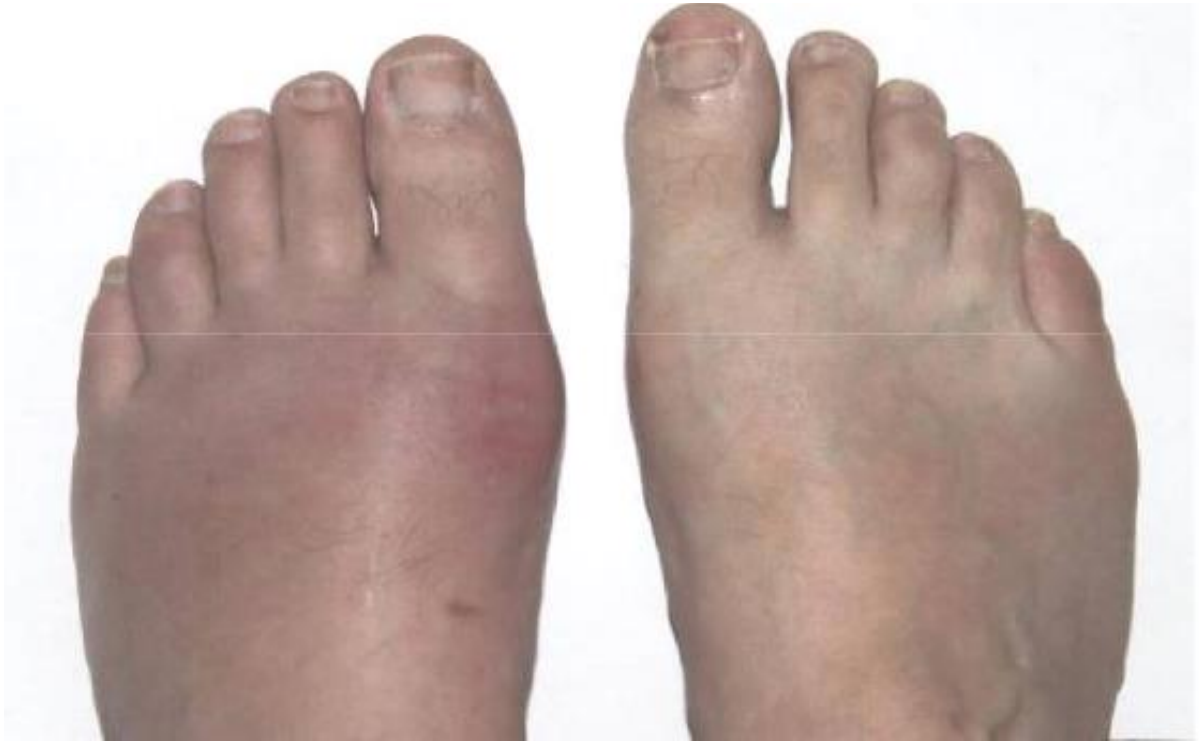
- Disease activity
- Urine protein/Cr
- Systolic blood pressure

Low vitamin D is associated with venous thrombosis

GOUT AND OSTEOARTHRITIS

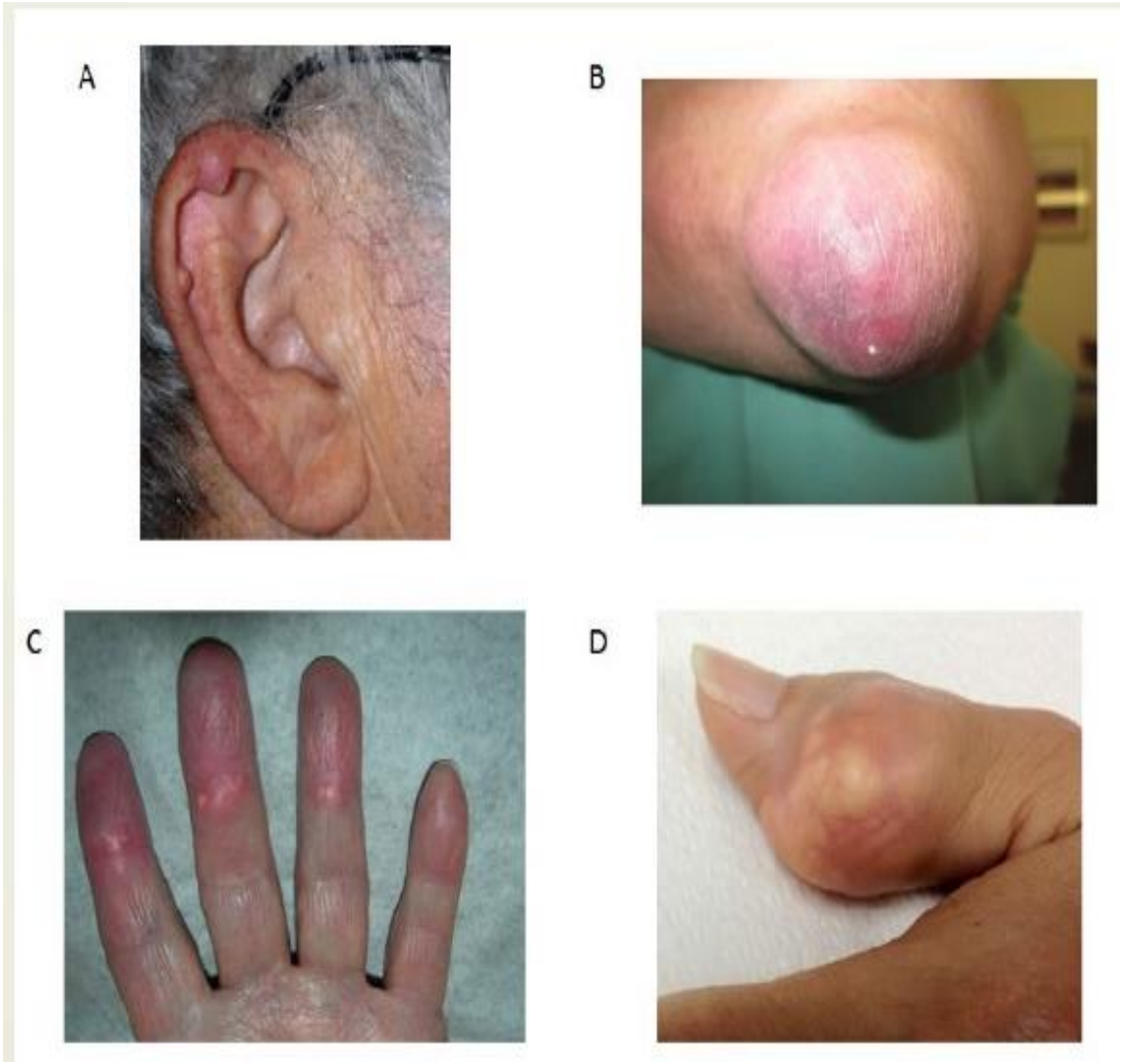
Acute Gout

- Notice the inflammatory process in the left leg (Swollen Lt first Toe).
- It's an acute inflammatory arthritis that may be associated with tenosynovitis, bursitis and/or cellulitis.
- The most common joint to be affected is the 1st metatarsophalangeal joint.
  - Estrogen is a protective factor.
  - Doesn't respond to antibiotics.



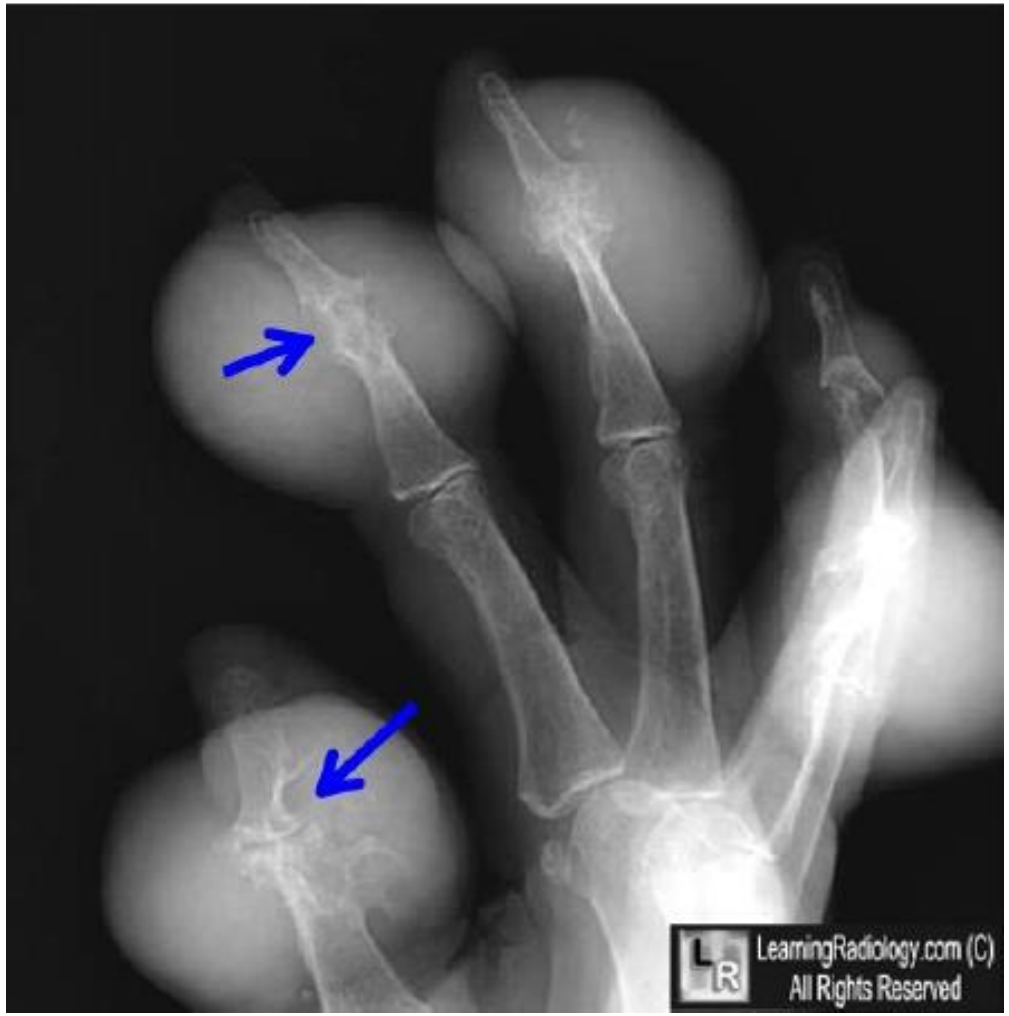
TOPHUS

- Draining or Chalk-like subcutaneous nodule under transparent skin with overlying vascularity (Soft, white material)
- Seen typically on the cold parts of the body, that is the Ears, Olecranon bursa, Finger pads, Tendons (especially Achilles' tendon).
- Seen in Patients with Chronic Gout due to deposition of Uric acid in these locations.



TOPHACEOUS GOUT

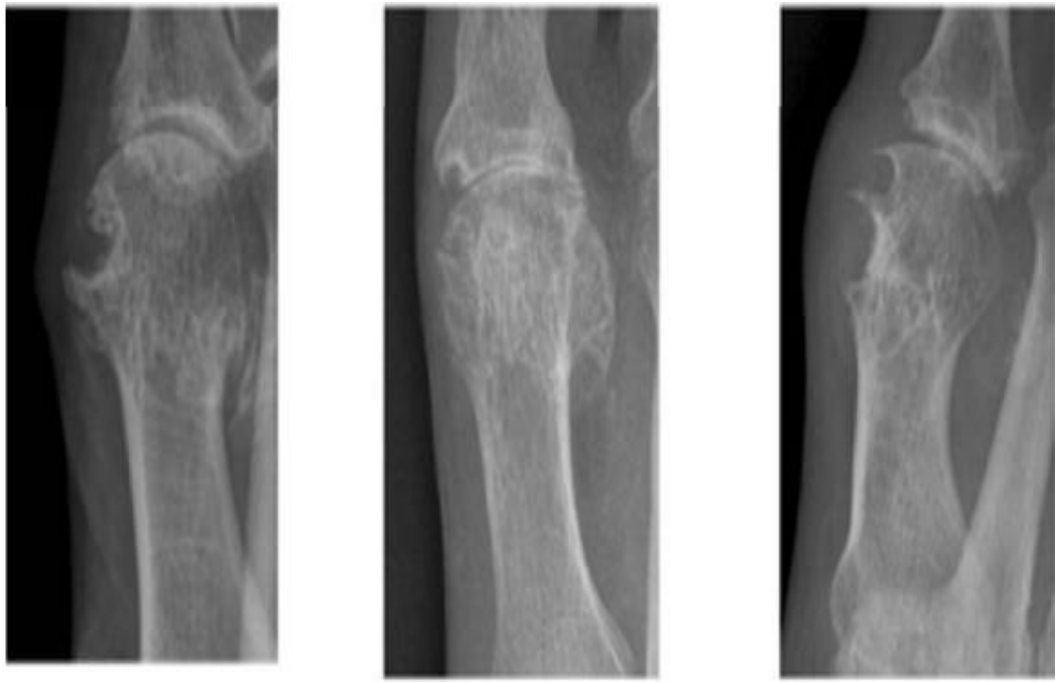
- A chronic erosive deforming arthritis associated with peri-articular and subcutaneous urate deposit (tophi).
- Over long time it destructs bone and cartilage and may cause Dactylitis.
- Note on the X-ray that you have middle phalanx erosions.

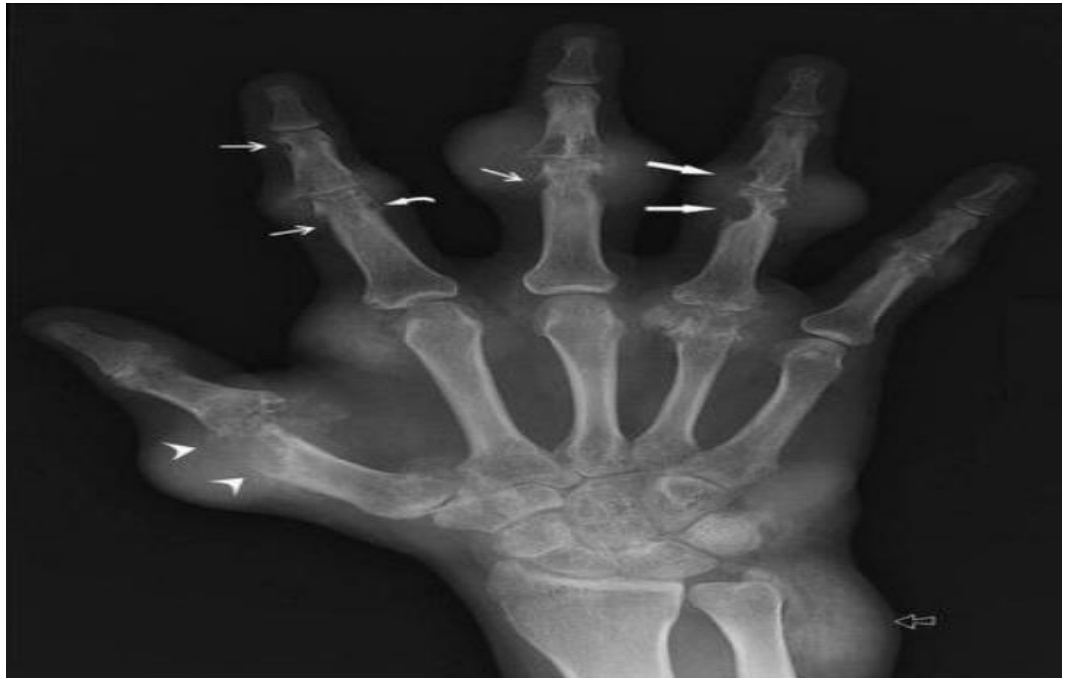


DIAGNOSIS OF GOUT

Diagnosis of gout

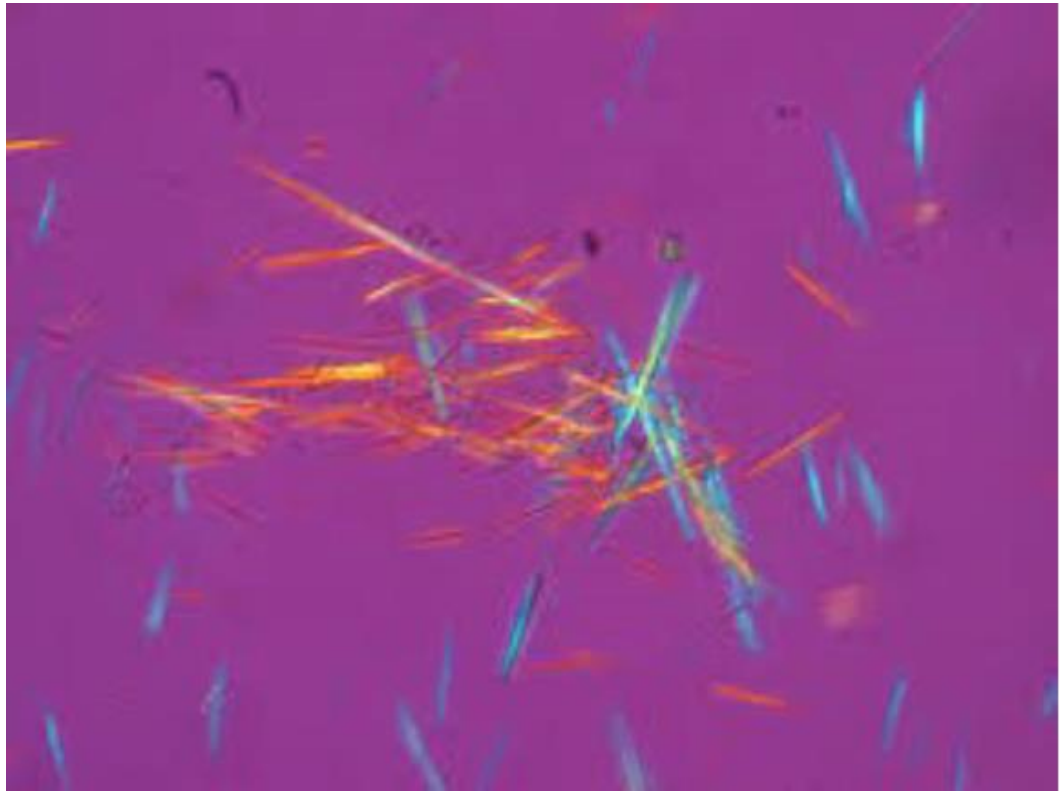
- Crystal identification is the golden standard test
- Serum urate level
- Radiology
- Synovial fluid: MSU crystals
- Histology: MSU crystals





RADIOGRAPHIC CHANGES IN GOUT

- Initially and early in the disease, X-rays are usually normal.
- However, after a few repetitive acute attacks there will be punched out erosions (like a rat bite) with sharp margins and overhanging edges.



CRYSTALS APPEARANCE ON ANISOTROPY

- Anisotropy: we apply a polarizer, then we add a joint sample.
- Yellow needle shaped crystal with polarized direction → Negative gout.
- Blue and in other direction than polarized → Positive Gout.

TREATMENT OF GOUT

Treatment of gout

TREATMENT OF ACUTE ATTACK:

NSAIDs, colchicine and steroids (intra-articular or systemic)

The first line of therapy is to rest the affected joint and to use full doses of a non-steroidal anti-inflammatory drug (NSAID):
indomethacin 50mg 8 hrly (or maximum 50mg
6 hrly); naproxen 500mg 12 hrly; diclofenac 50mg 8 hrly, provided the patient's renal function is normal.

Colchicine can be a useful adjunct to NSAIDs if the acute attack does not settle rapidly.
0.5 mg twice or three times a day

Treatment of gout

- Intra-articular : if NSAID use is contra-indicated and one or at most two joints are inflamed.
- Systemic steroids for polyarticluar disease or if NSAIDs or colchicine contraindicated(CKD, PUD, CHF)
- Allopurinol or uricosuric drugs should not be commenced during an acute attack of gout.

Non-pharmacological treatment

Avoid diuretic therapy; weight gain; alcohol consumption; Aspirin therapy at low doses

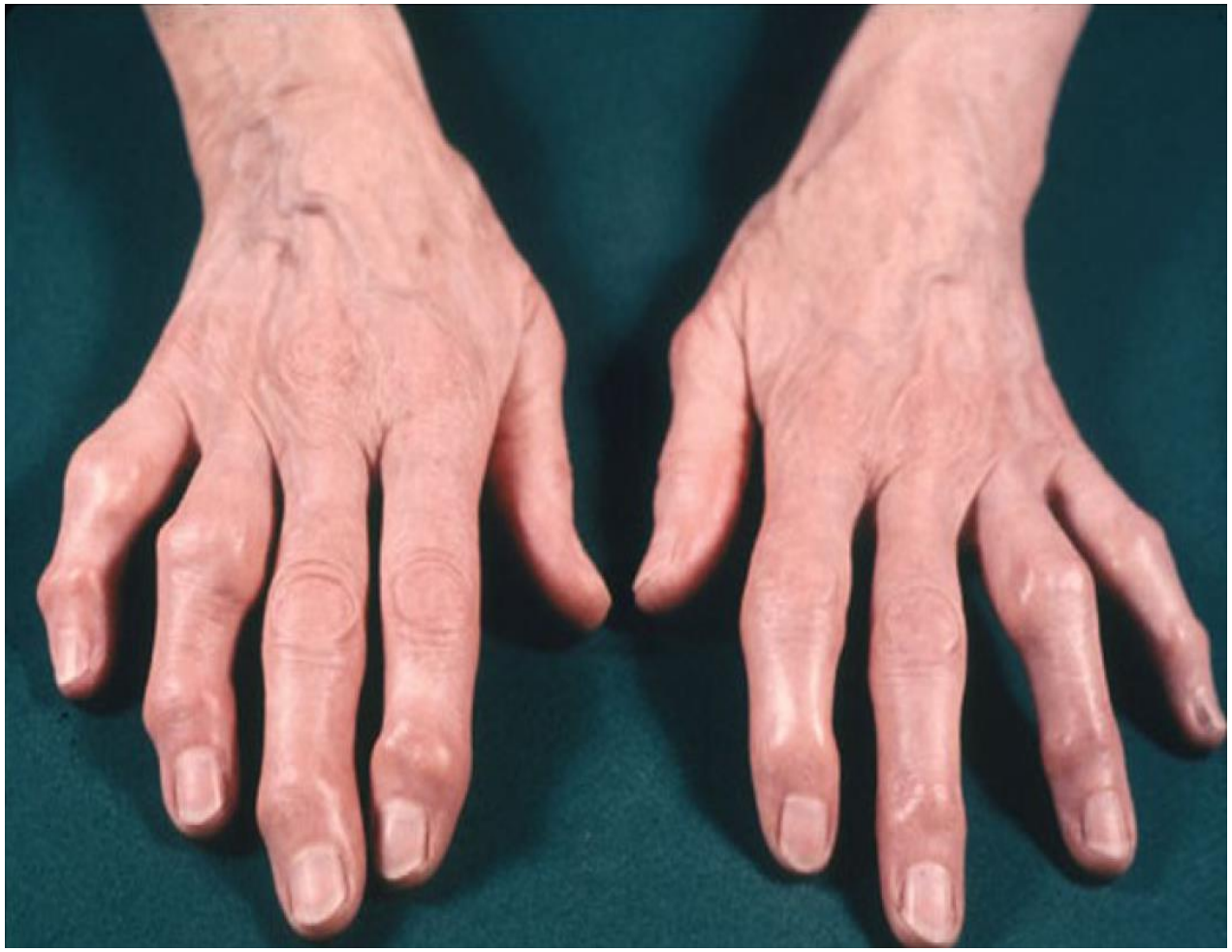
Hand Deformities in Osteoarthritis

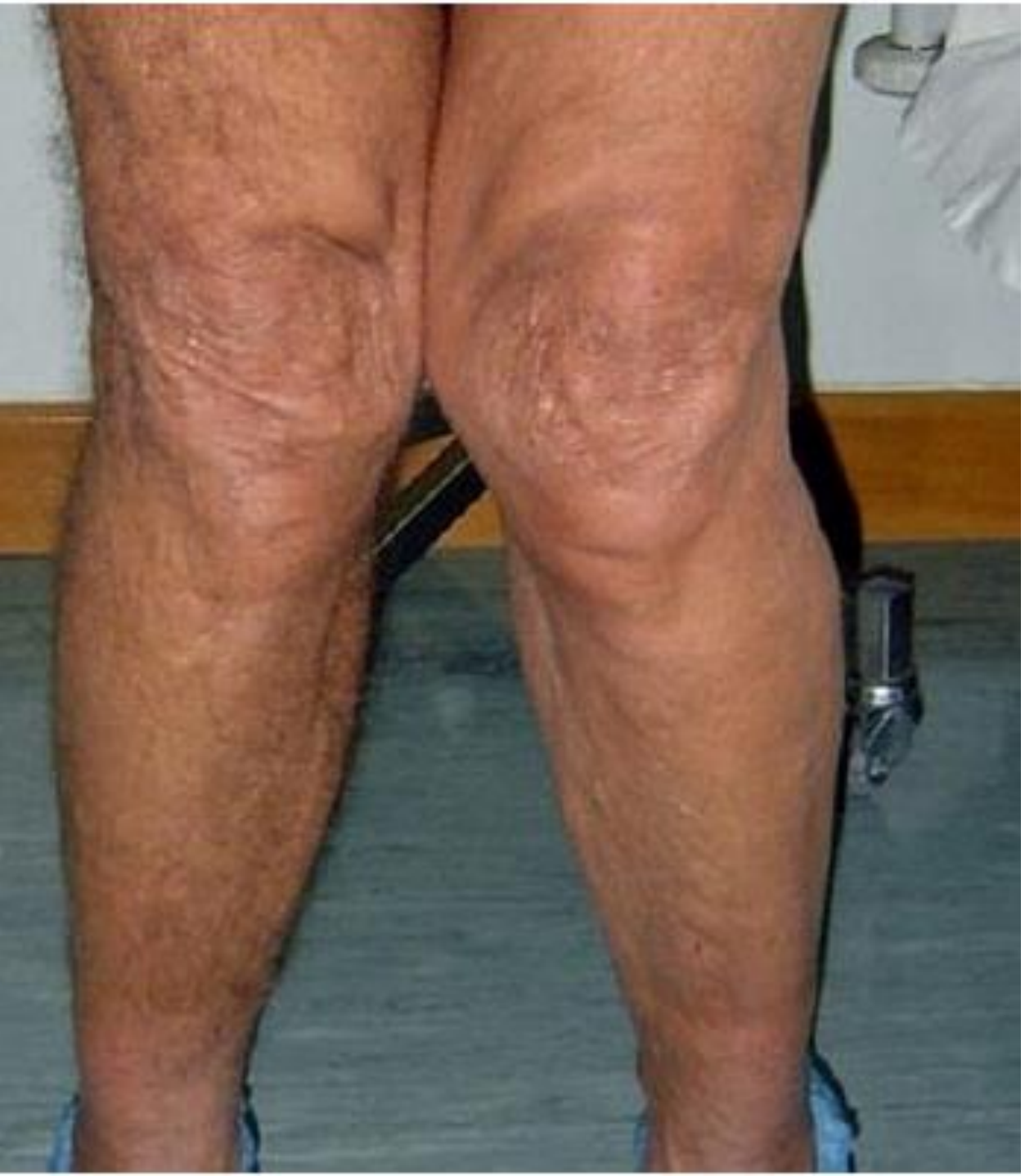
- You can notice swelling with bony deformities and malalignment of the affected joint.
- Those bony deformities are common in the hands and lead to:

  1- Enlargement of PIP (Bouchard nodes)

  2- Enlargement of DIP (Heberden nodes)

  3- Squaring at the base of the thumb (the first carpometacarpal Joint)
- Bouchard nodes: bony bumps on the PIP of the finger.
- Heberden nodes: bony bumps on the DIP of the finger.





KNEE OSTEOARTHRITIS

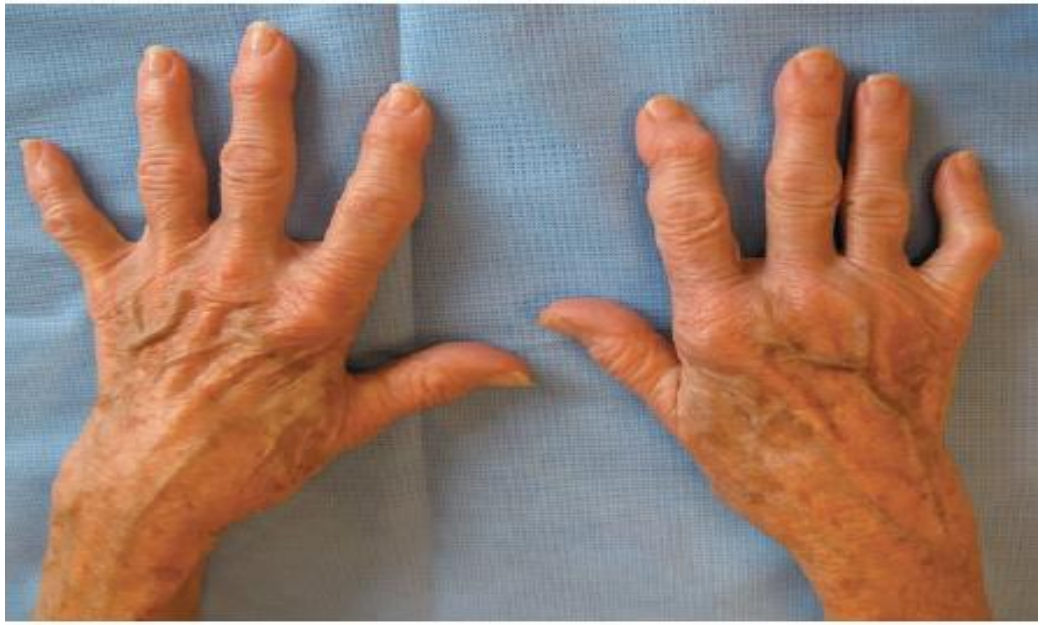
- New bone formation with bony enlargement.
- Those patients present with a limited range of motion, small effusions, joint line tenderness, and an abnormal gait may also be observed.

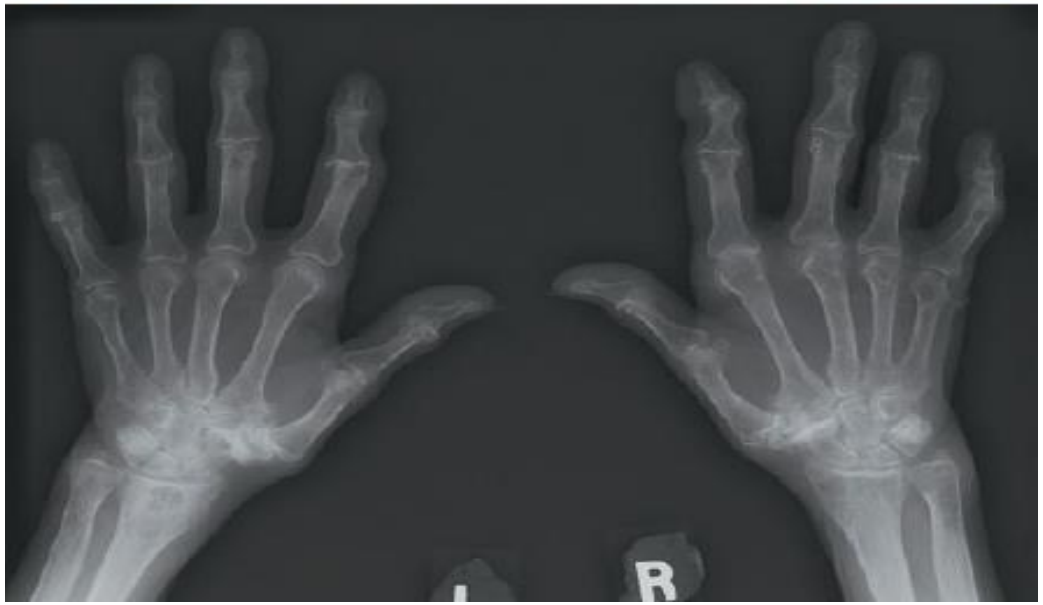
DIAGNOSIS OF OA

Approach to the diagnosis of OA Imaging

- OA is essentially a clinical diagnosis. Plain radiographs may be done in the initial workup to help confirm the diagnosis in moderate to advanced OA, but they are not sensitive in detecting early disease. They may also help rule out less common etiologies for pain, such as a bone tumor, pigmented villonodular synovitis, or avascular necrosis, when suspicion exists.
- They are poorly correlated with the symptoms

- Computed tomography or magnetic resonance imaging, are rarely needed

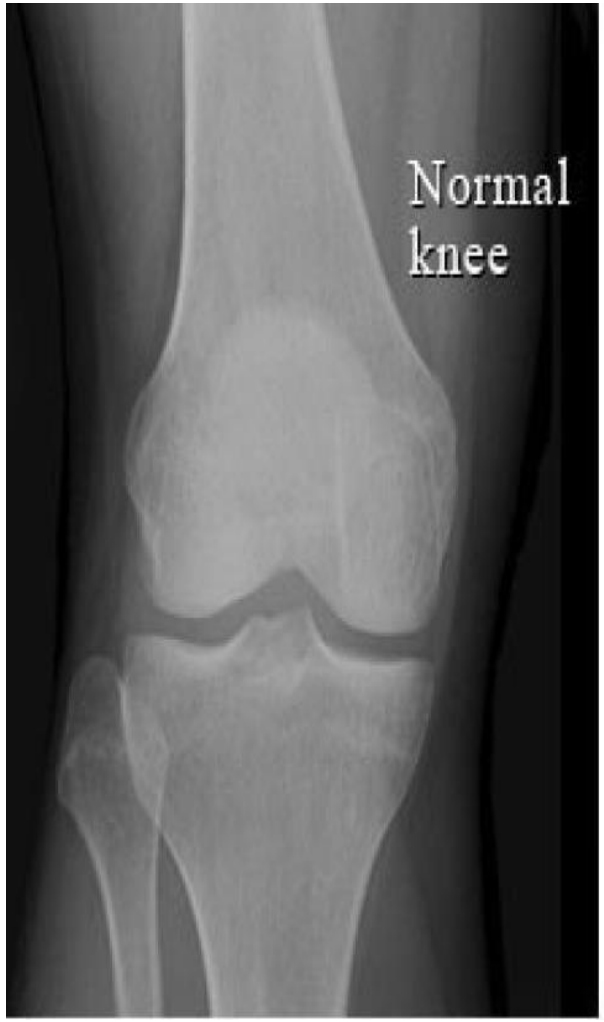


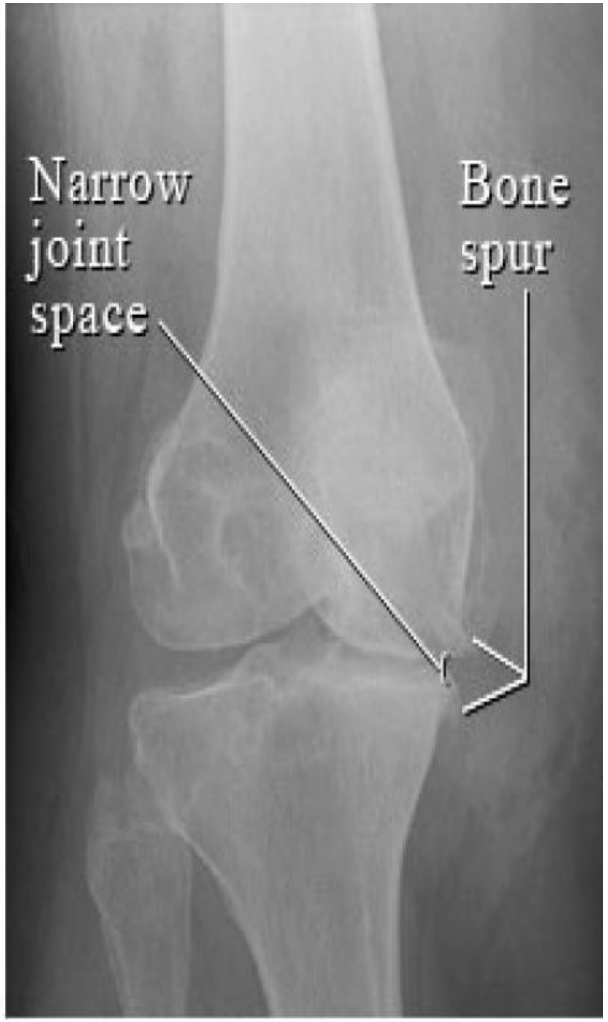


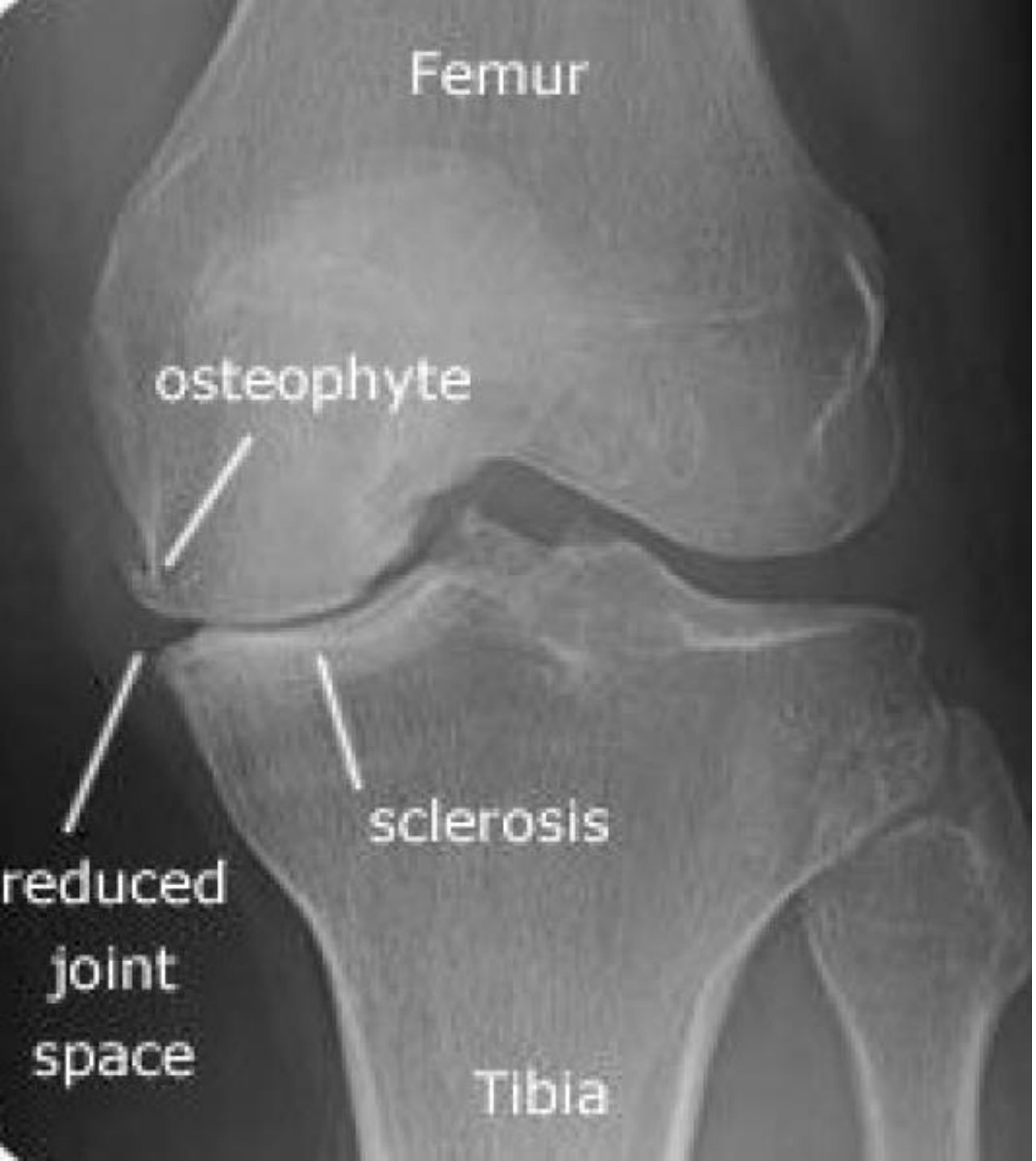
HANDS OF A PATIENT WITH OA

- Note that this patient has Heberden's and Bouchard's nodes of multiple digits.
- On the X-ray, we can see the presence of Osteophytes, with Joint space narrowing and cysts typical of OA.
- Also, there is Gull-wing deformities at the third PIP, suggestive of Erosive Osteoarthritis.

OA CHANGES ON X-RAY

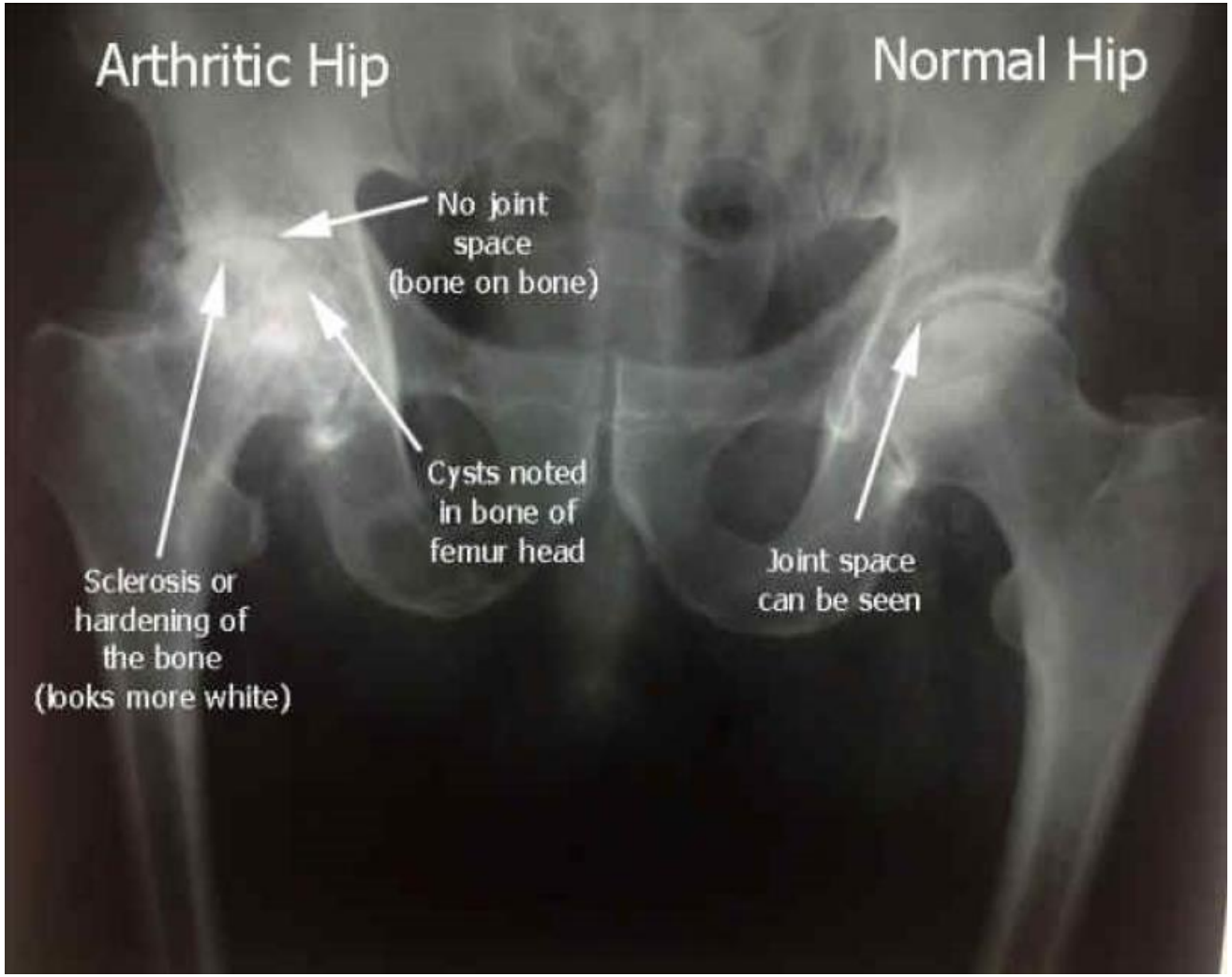






OA CHANGES ON X-RAY

OA CHANGES ON X-RAY



DIAGNOSIS OF OA

Approach to the diagnosis of OA

Labs

- Laboratory testing usually is not required to make the diagnosis

- Inflammatory markers (CRP, ESR) should be ordered in the initial workup if inflammatory arthritis, such as rheumatoid arthritis, is a differential diagnosis. These tests are normal in OA.

TREATMENT OF OA

Treatment of Osteoarthritis

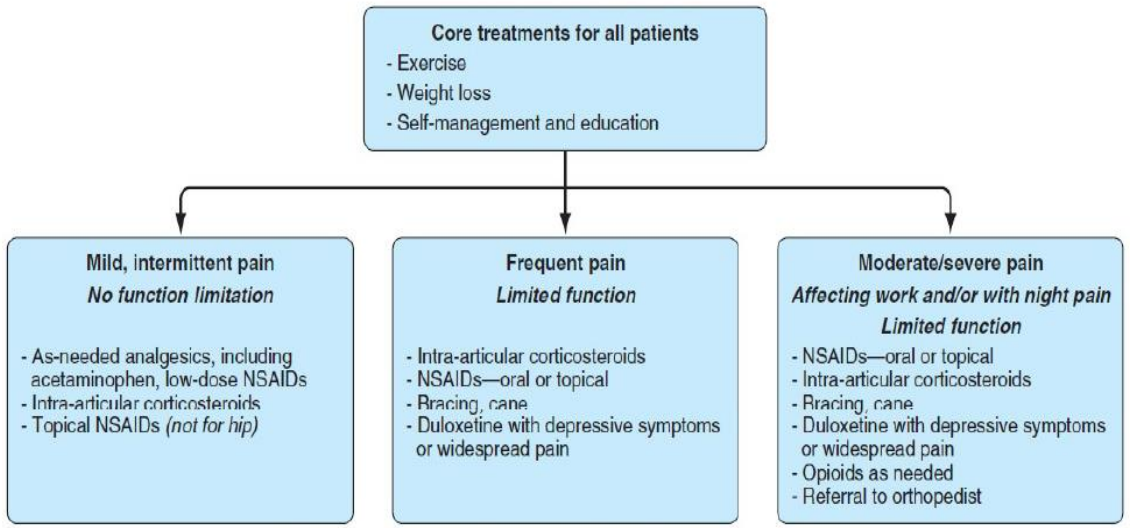
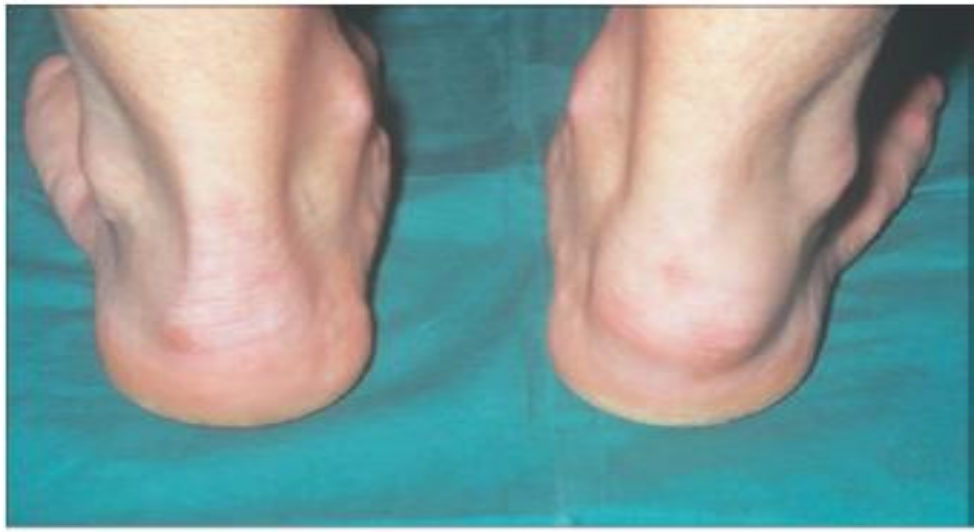


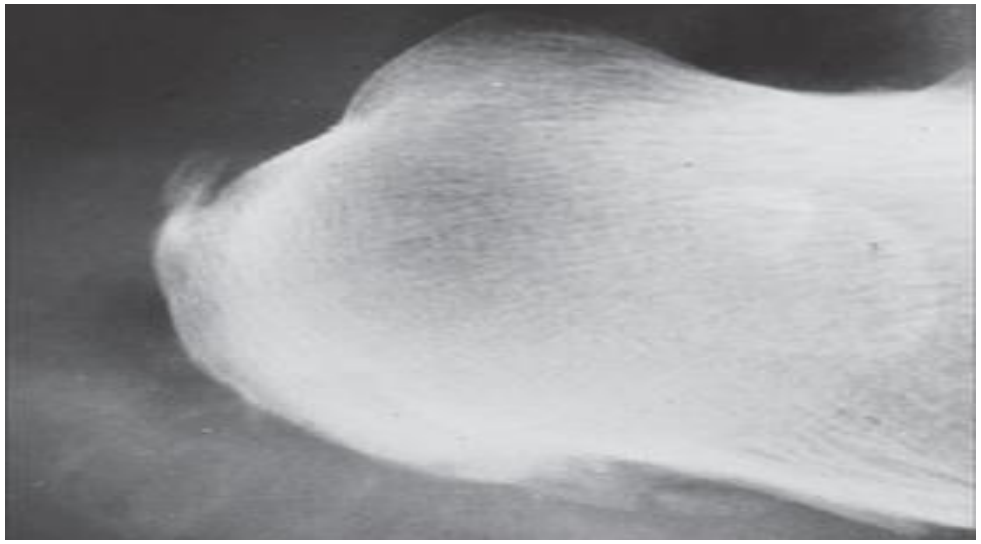
Figure 100-2 Algorithm for management of knee and hip osteoarthritis.

SPONDYLOARTHROPATHIES

ENTHESITIS

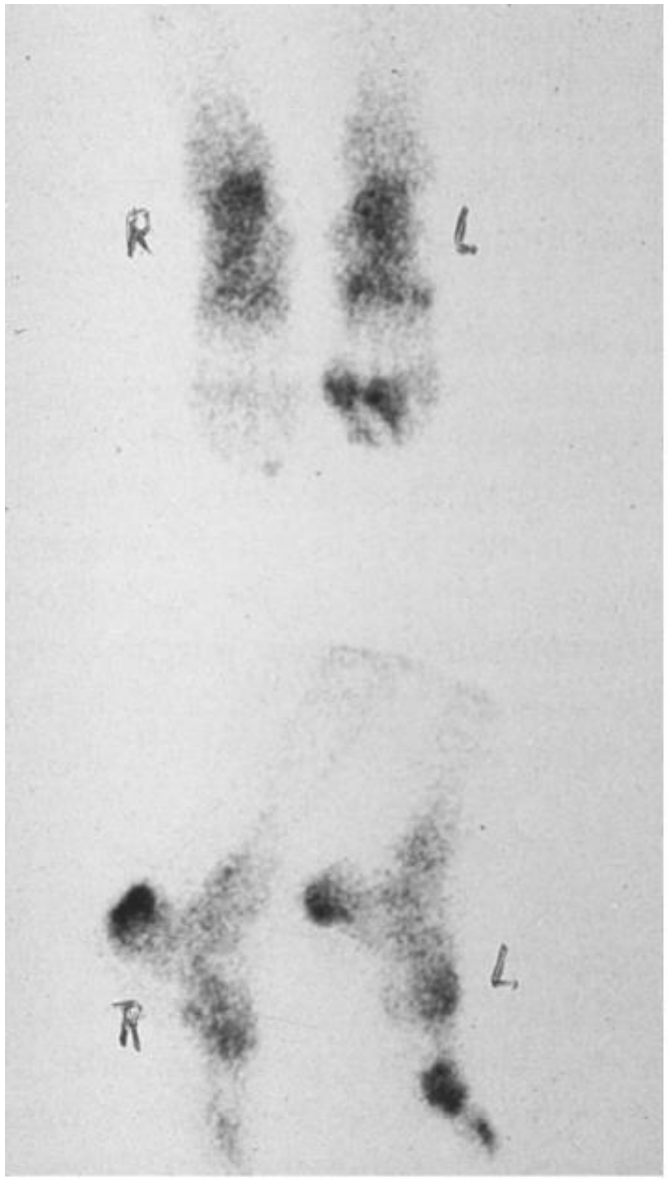
- Seen in Ankylosing Spondylitis.
- The most common is swelling at the heels, at the insertion of Achilles tendon or at the insertion of the Planter fascia ligament into the Calcaneus.
- Other sites: Iliac Crests, Greater Trochanters, Epicondyles at the elbows, Tibial Plateaus, Costochondral Junctions at the sternum, Humeral Tuberosities, Manubrial-sternal joints, Occiput, and Spinous process.

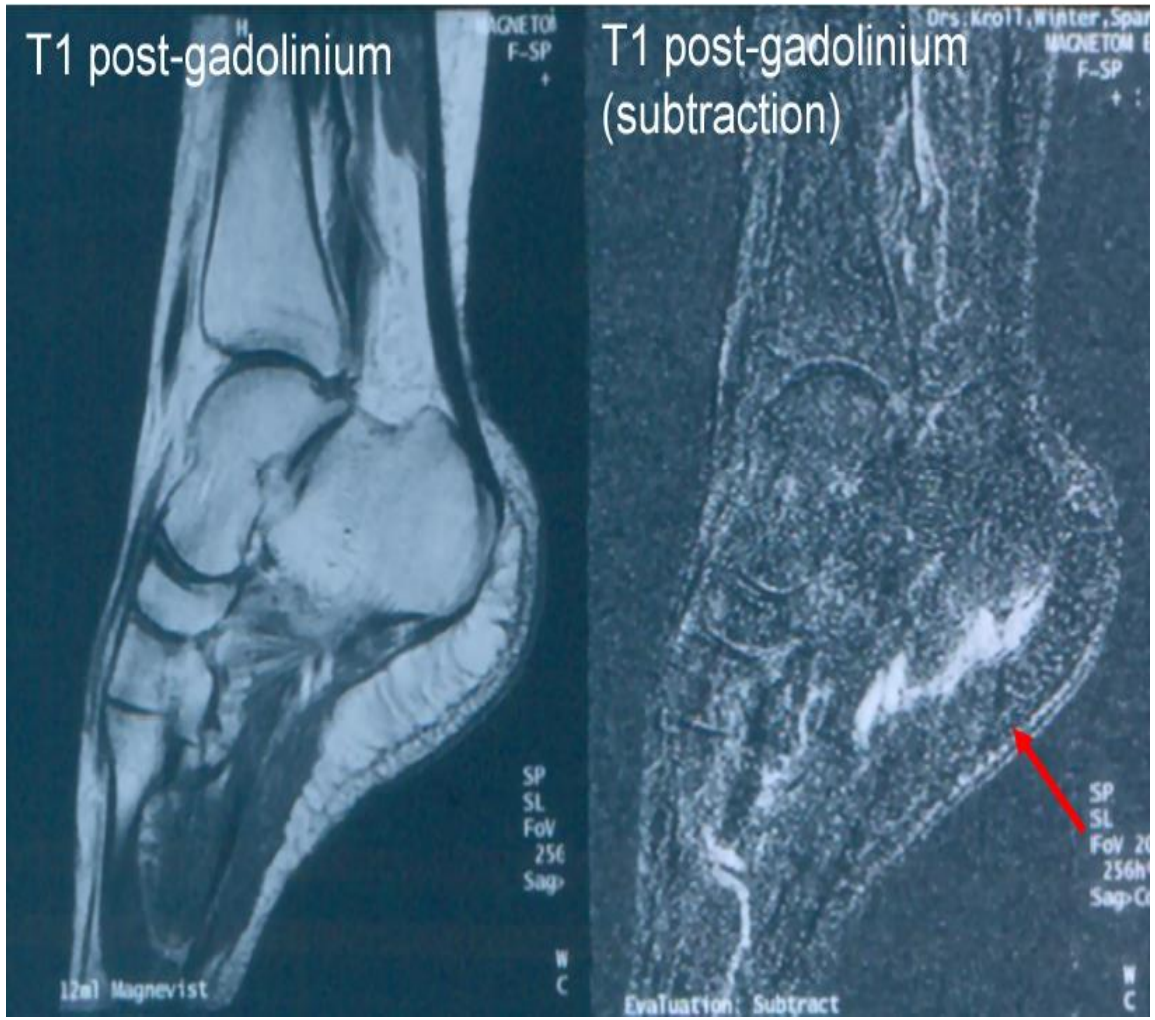




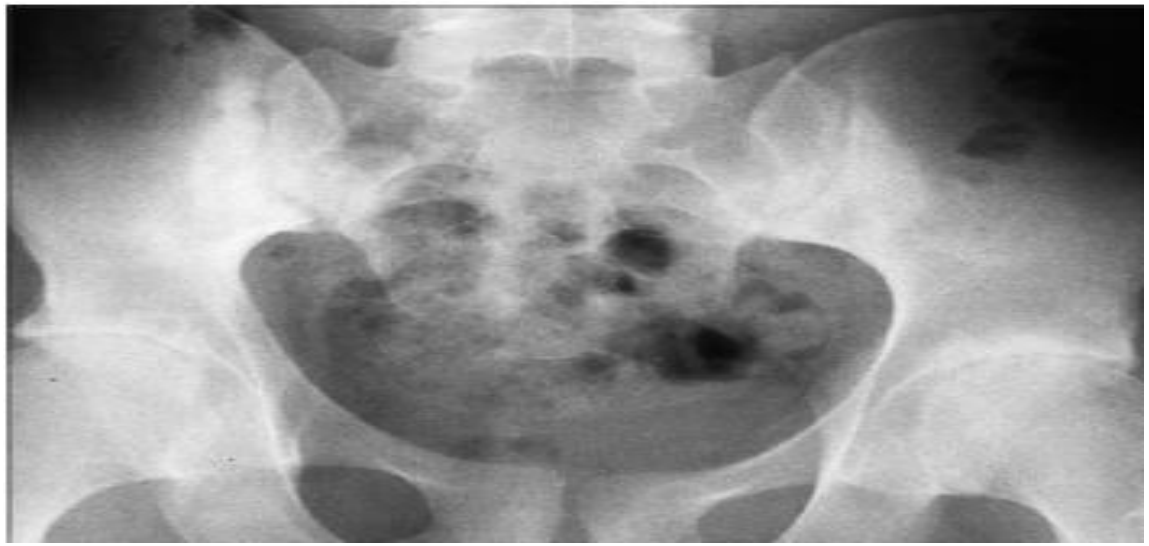
ENTHESITIS AS MANIFESTED BY SCINTIGRAPHY

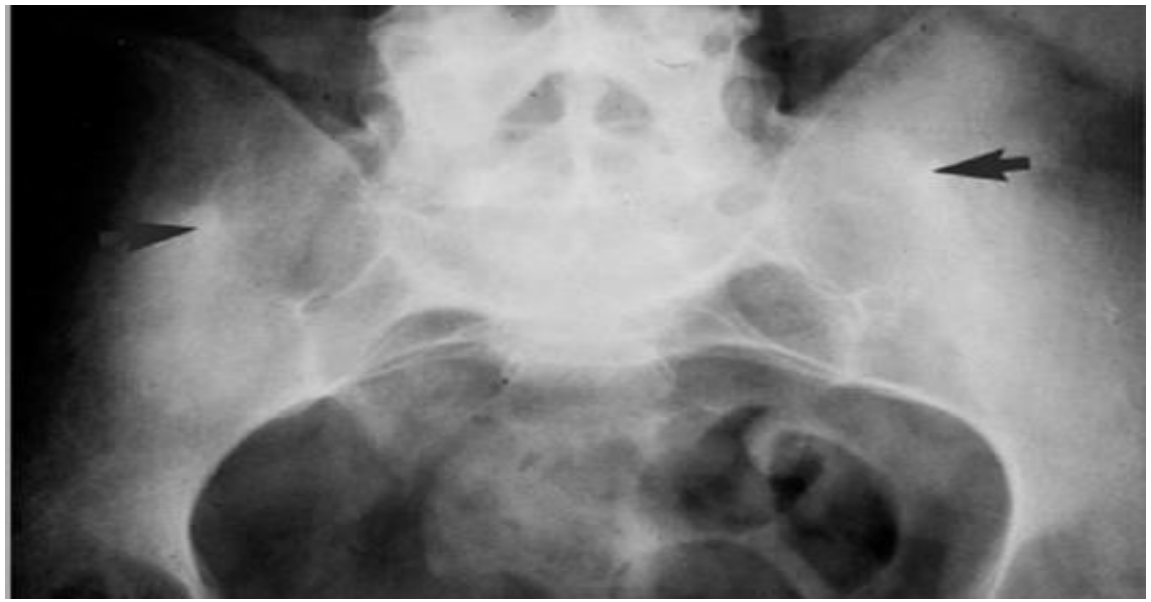
- Again, it's a manifestation of Spondylarthritis.
- In the picture above we can see acute inflammation of both heels and of the MTP joints of the 1st and 2nd toes of the Lt foot.
- In the second picture there is Achilles tendon enthesitis in the Rt heel, and Fascia Plantaris enthesitis in the Lt heel.





ENTHESITIS OF THE PLANTER FASCIA BY MRI

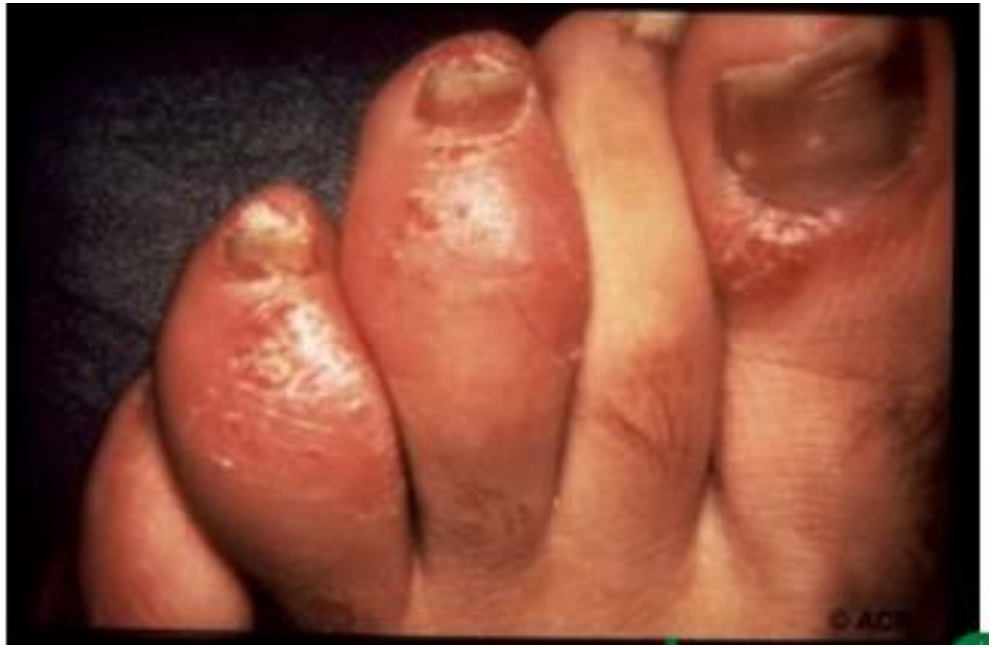




Sacroilitis

- CD8+ T-cells invade the subchondral area at the junction of the bones and the cartilage (An enthesis).
- Cartilage on Iliac side is replaced by bone, obliterating the joint space and hardening the joint.
- So basically, what happens is that there will be bone formation at the joints and in end-stage disease there will be fusion of the spine.

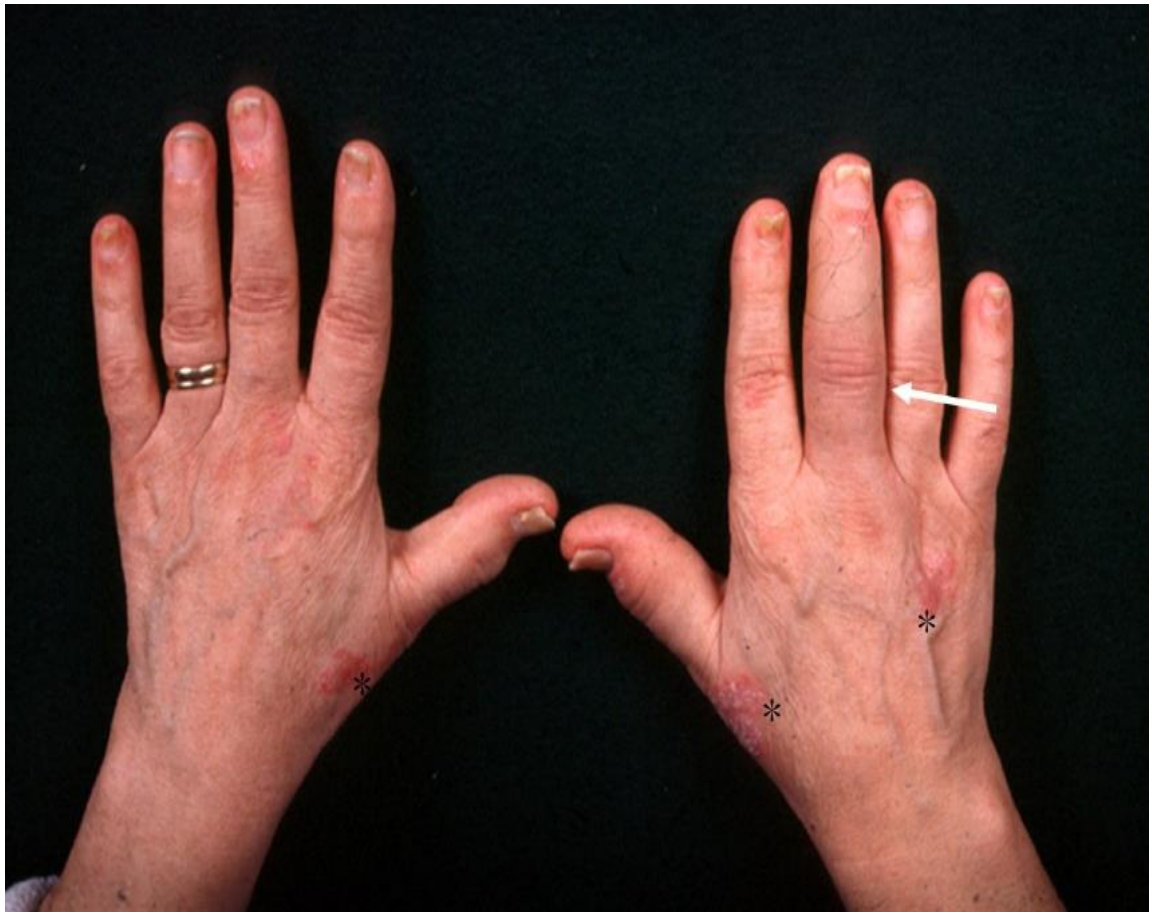
DACTYLITIS (SAUSAGE DIGITS)



- Characteristic of Spondyloarthropathy.
- The entire digit is swollen related to inflammation in the flexor tendon, sheath and marked adjacent soft tissue involvement.
- So, the Tendon Sheath is inflamed not the Joint.
- There may be a little pain or tenderness.
- Other DDx for Dactylitis:

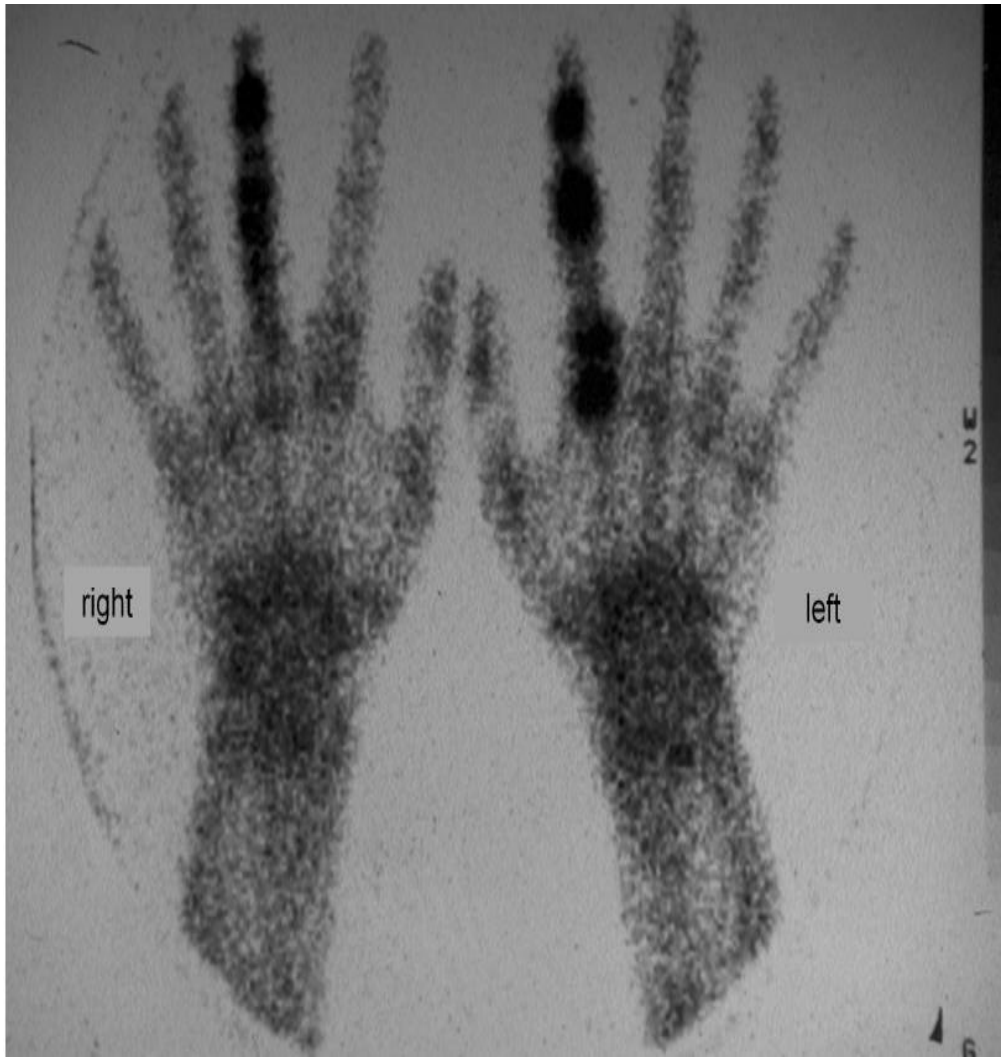
Tb, Syphilis, Sarcoidosis, Sickle cell disease, and Tophaceous Gout.

DACTYLITIS



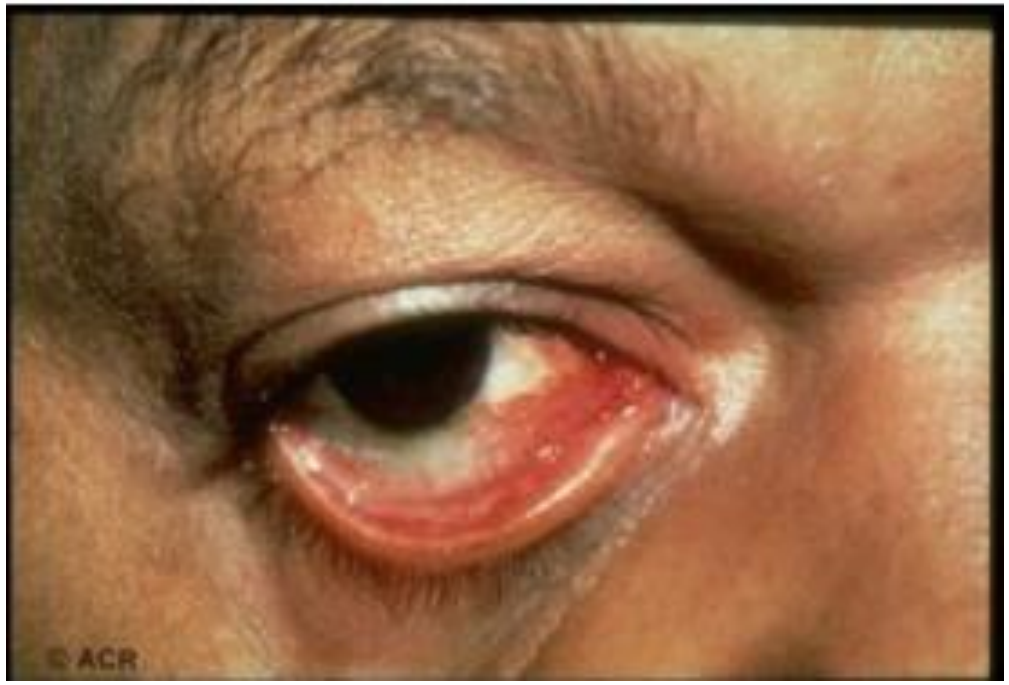
ARTHRITIS OF SEVERAL JOINTS AS SEEN BY SCINTIGRAPHY

- Typical for Psoriatic Arthritis.
- Notice the uptake in flexor tendon sheath in the middle finger of the Rt hand, and the index in the Lt hand.

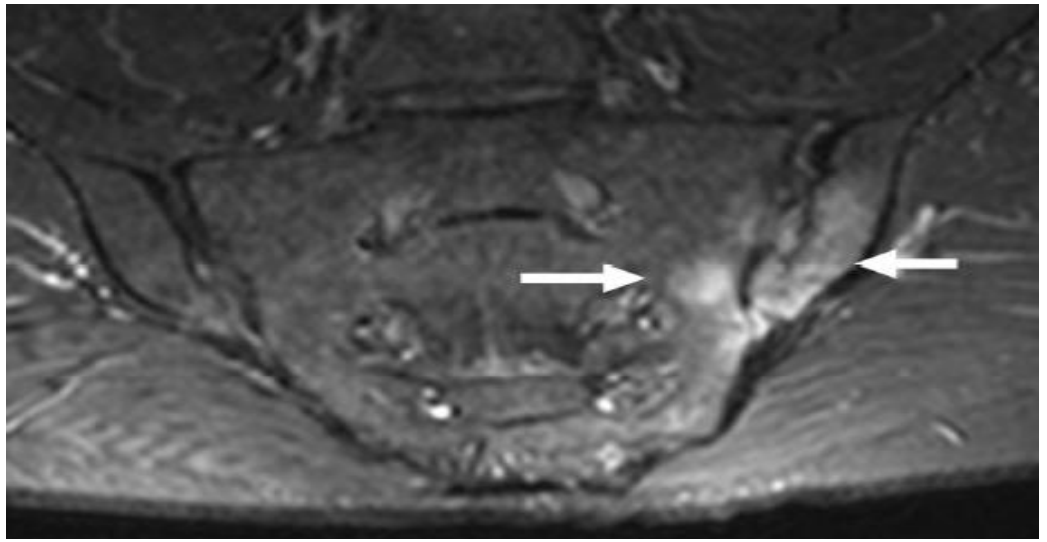


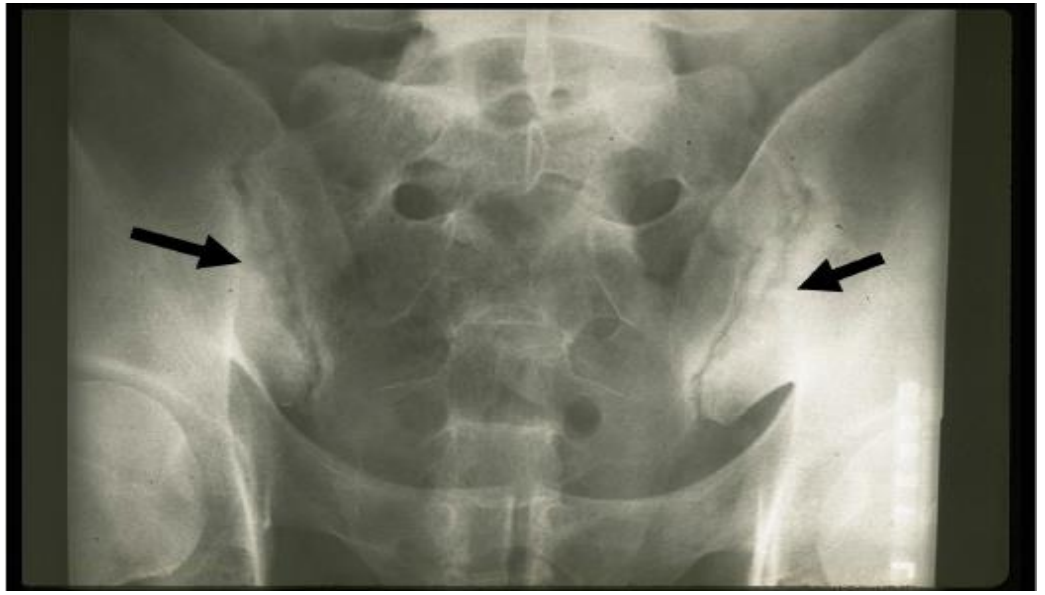
CONJUNCTIVITIS

- Mostly seen with Reactive Arthritis.
- Non-purulent and transient and not associated with vision loss.
- Anterior Uveitis: Acute onset of unilateral redness, pain, photophobia, and excessive lacrimation, most seen with Spondylarthritis.



SACROILIITIS BY MRI AND X-RAY

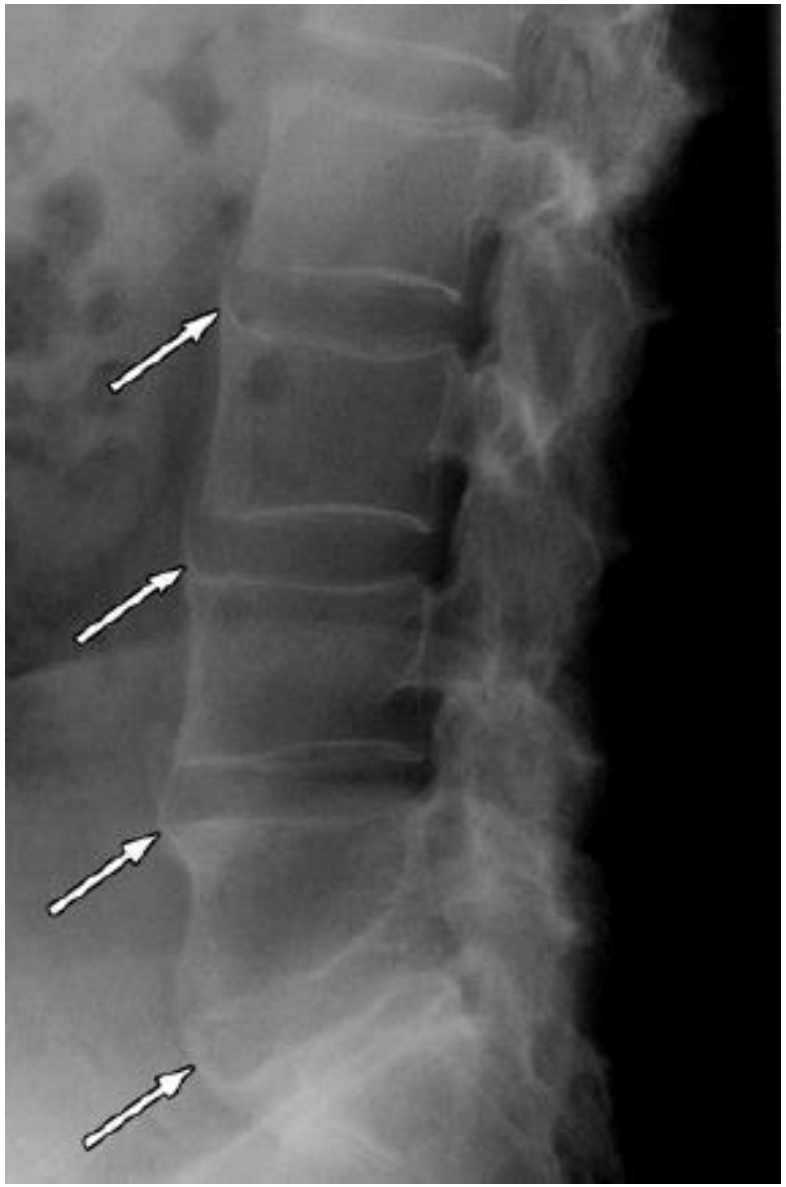




- Typical for patients with Axial Spondylarthritis.
- In the MRI we have Active inflammatory Sacroiliitis without bony changes (the arrows are pointing towards Sclerosis on the Ileal side of the Sacroiliac joint).
- In the X-ray we have Sacroiliitis with bony changes (grade II), (the arrows are pointing towards Sclerosis with irregularity).

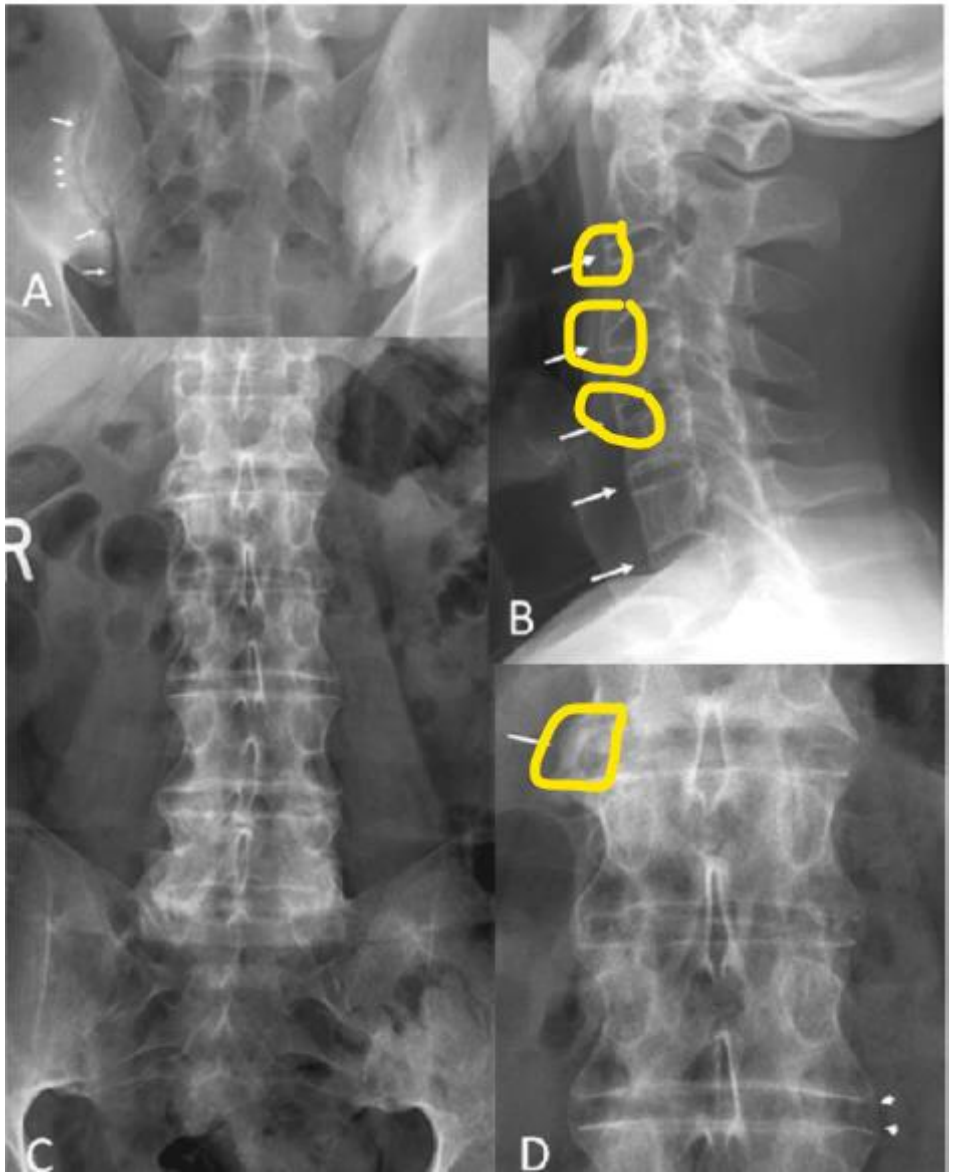
RADIOGRAPHIC FEATURES IN ANKYLOSING SPONDYLITIS

- This X-ray shows an early changes which are Erosions.
- Early Spondylitis is characterized by Small Erosions at the corners of the Vertebral bodies with Reactive Sclerosis (Called Romanus Lesions and Shiny corner sign).
- So, it begins with Erosions then it progresses into Bony Formation (Syndesmophytes) and if left untreated there will be Anterior Spinal ligament Fusion (Bamboo Spine).



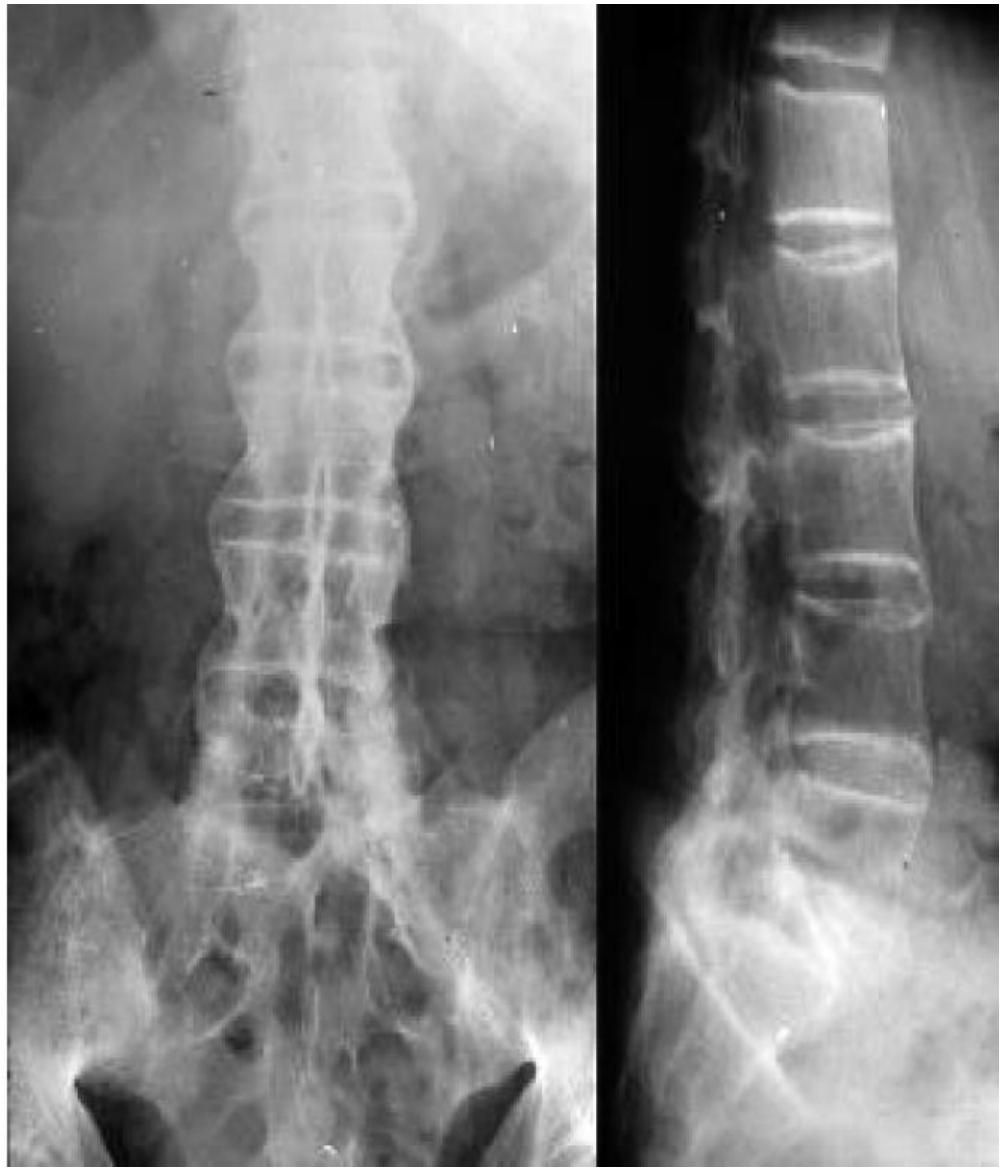
ANKYLOSING SPONDYLITIS

- The most important view is the Lateral View on X-ray (picture B).
- In picture C, notice that the Sacroiliac joint is deformed and not clear on imaging.
- Picture D, is an anterior view and it shows the bony growth or Syndesmophytes.



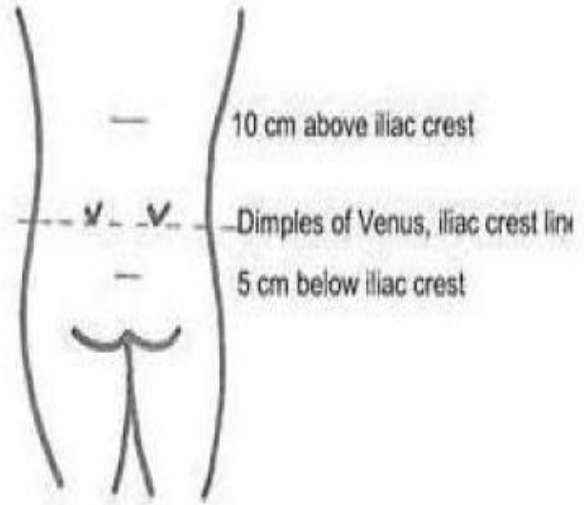
BAMBOO SPINE IN ANKYLOSING SPONDYLITIS

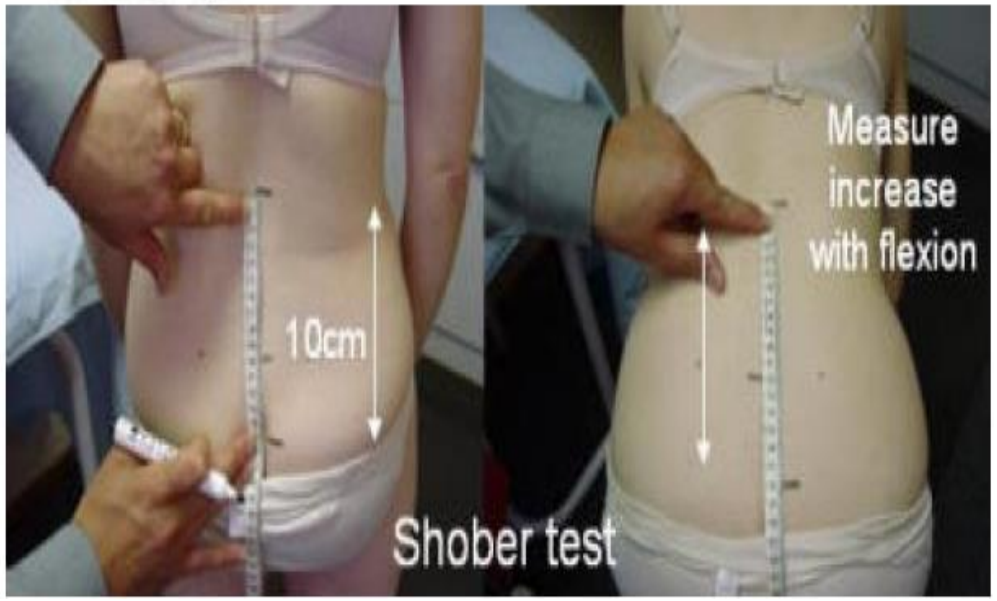
- Again, Lateral view is the most important to show the fusion.



SHOBER'S TEST

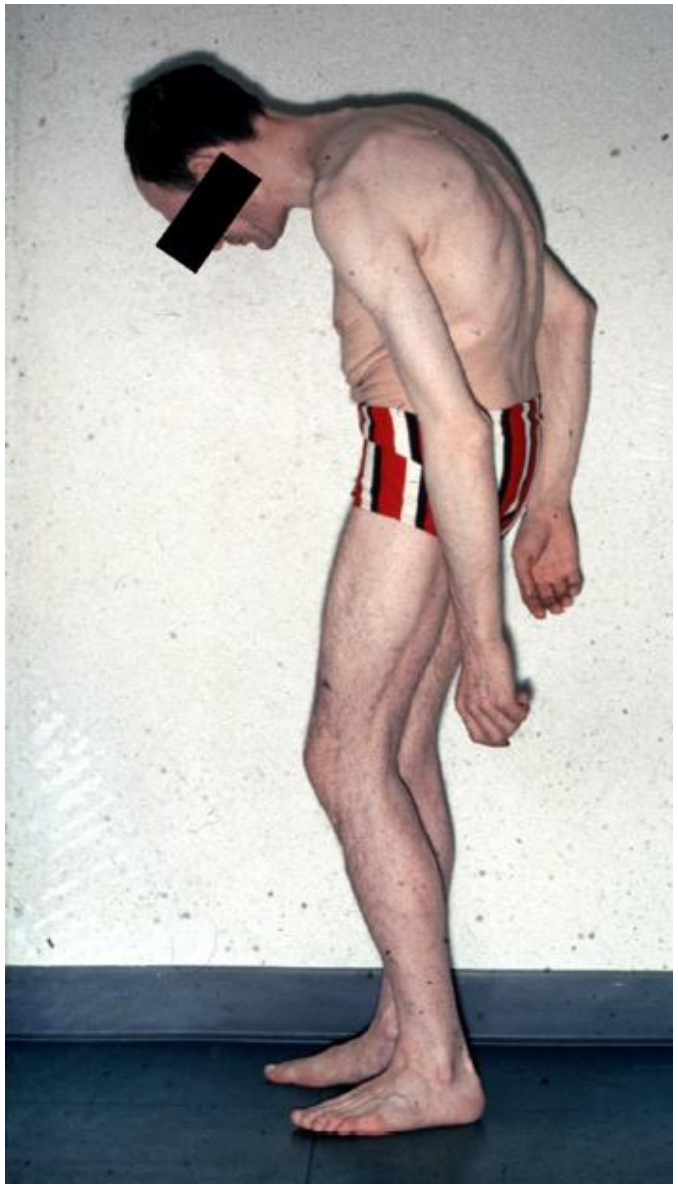
- This test is used to assess the range of motion and the mobility of the spine.
- If the test result was <5 cm → then this is abnormal, and it indicates loss of range of motion from fused spine.





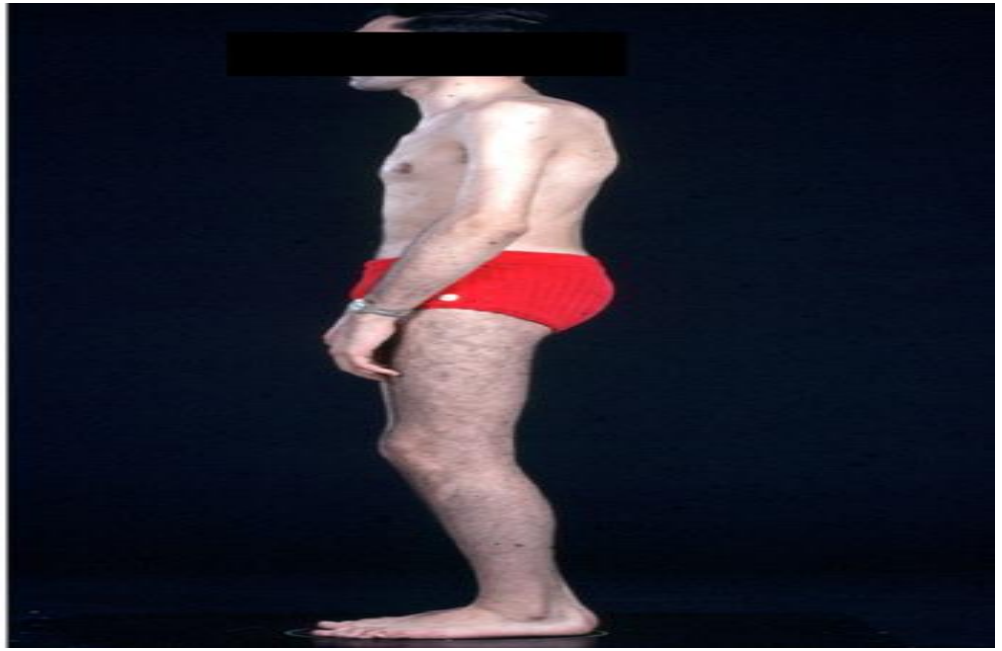
SEVERE KYPHOSIS OF THE THORACIC AND CERVICAL SPINE

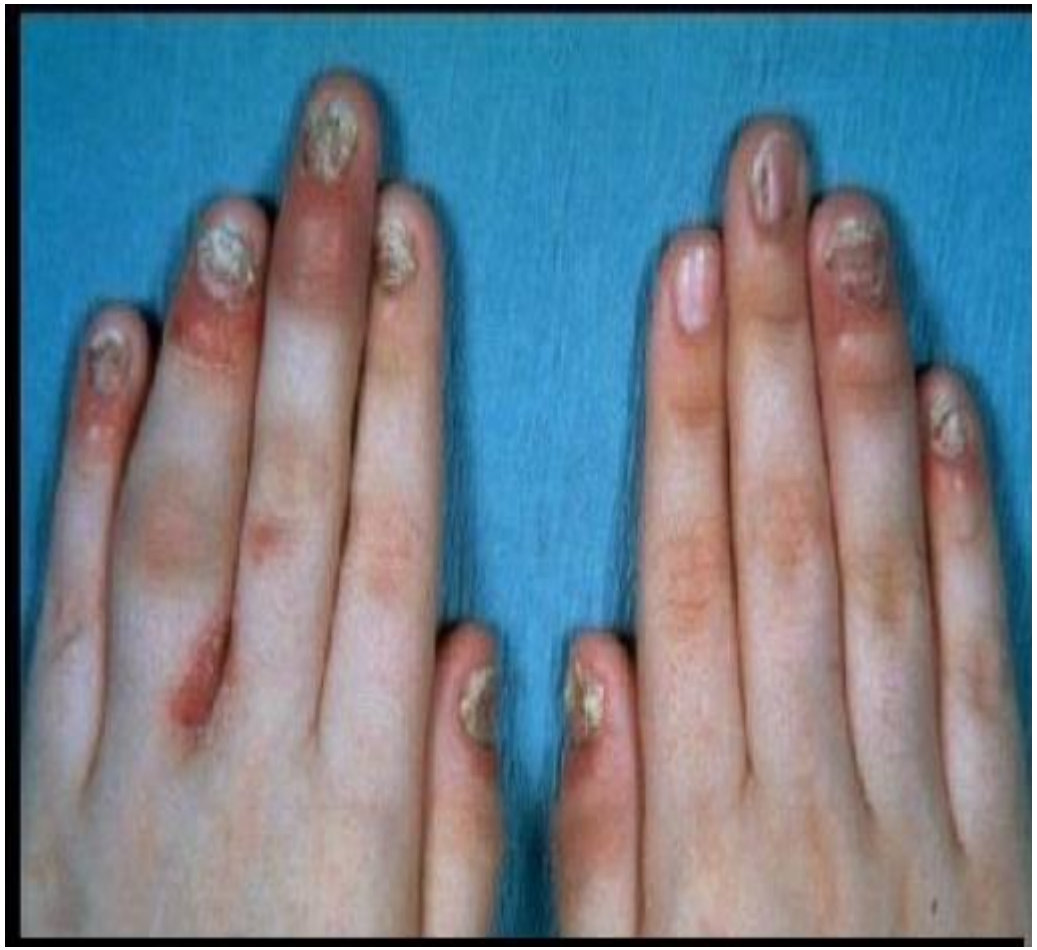
- It indicates Final Stage of AS.
- Those patients are unable to look ahead when walking, they can't raise their back "can't see the sun".



LOSS OF LORDOSIS (FLAT BACK)

- Seen in Ankylosing Spondylitis.
- There's no Flexibility of the lumber spine on Bending Forward.



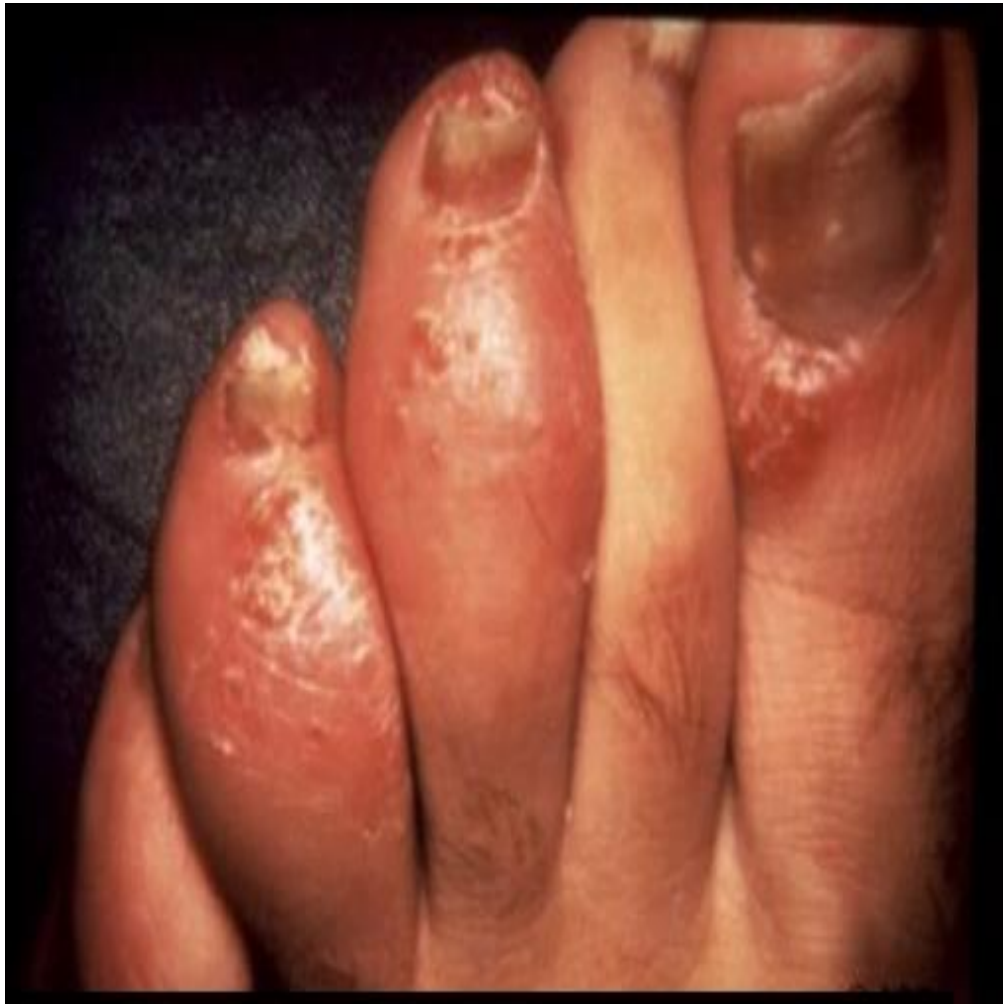


PSORIATIC ARTHRITIS

- Inflammation without bony formation.

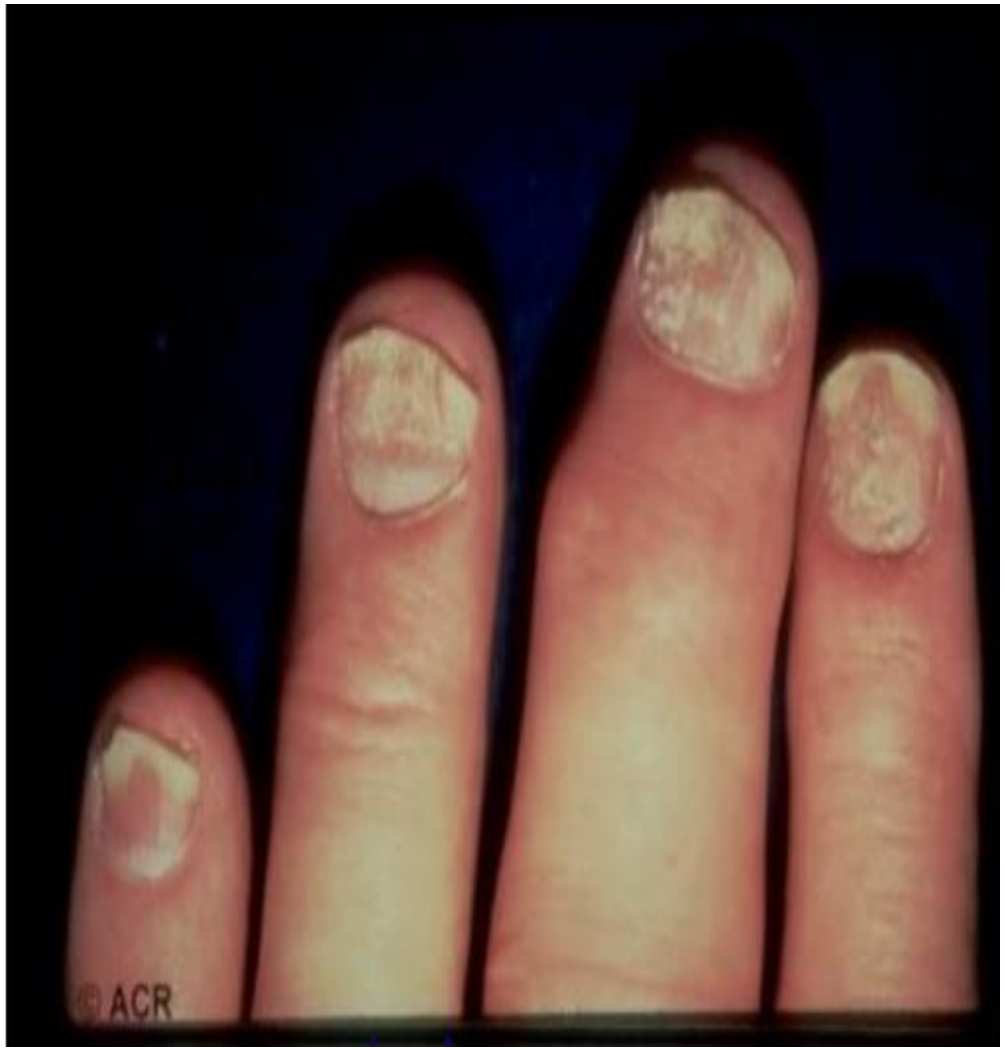
DACTYLITIS

- Seen in Psoriatic Arthritis and Reactive Arthritis.



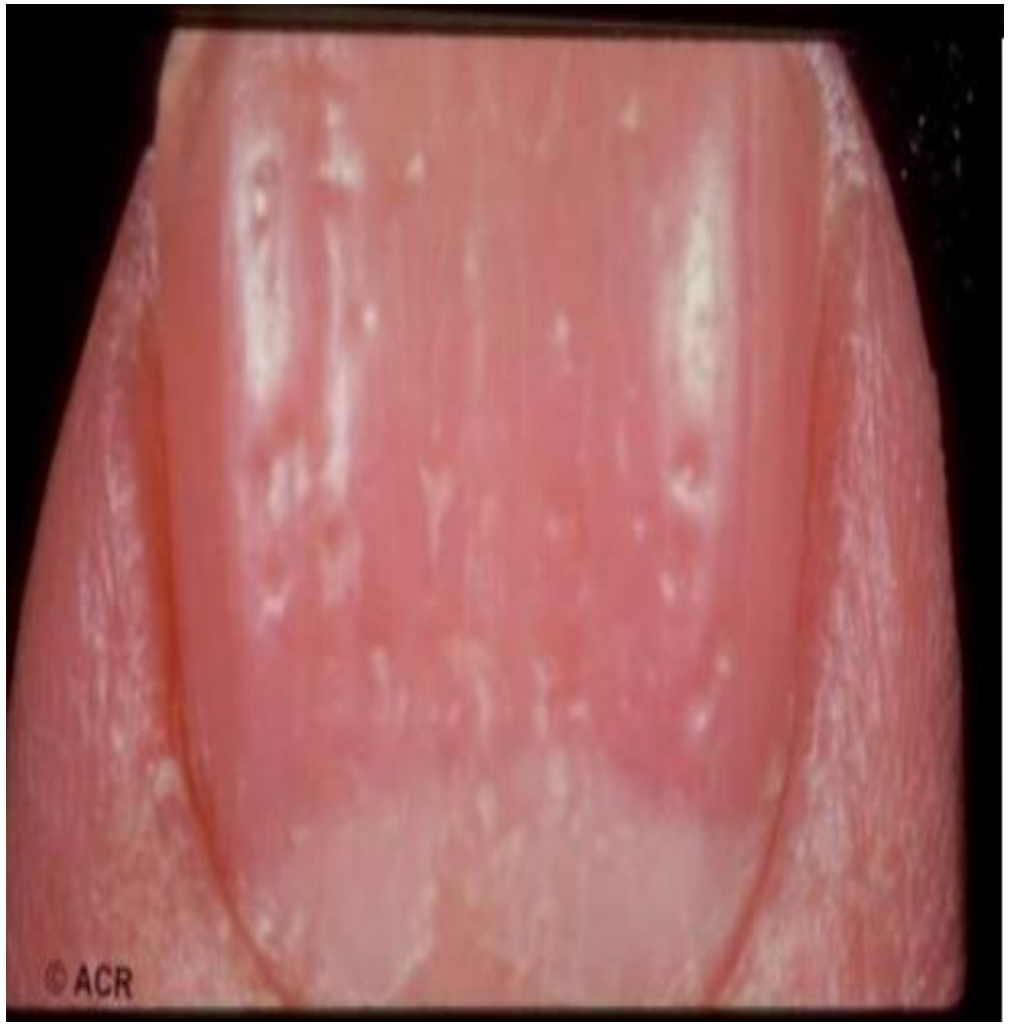
ONCHYLOSIS

- Seen in Psoriatic Arthritis.



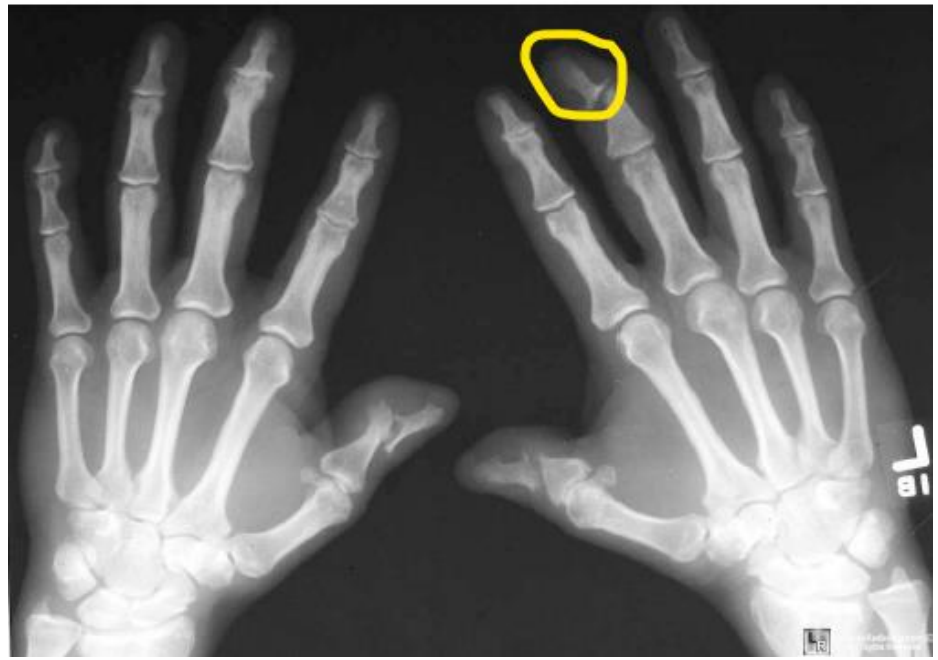
NAIL PITTING

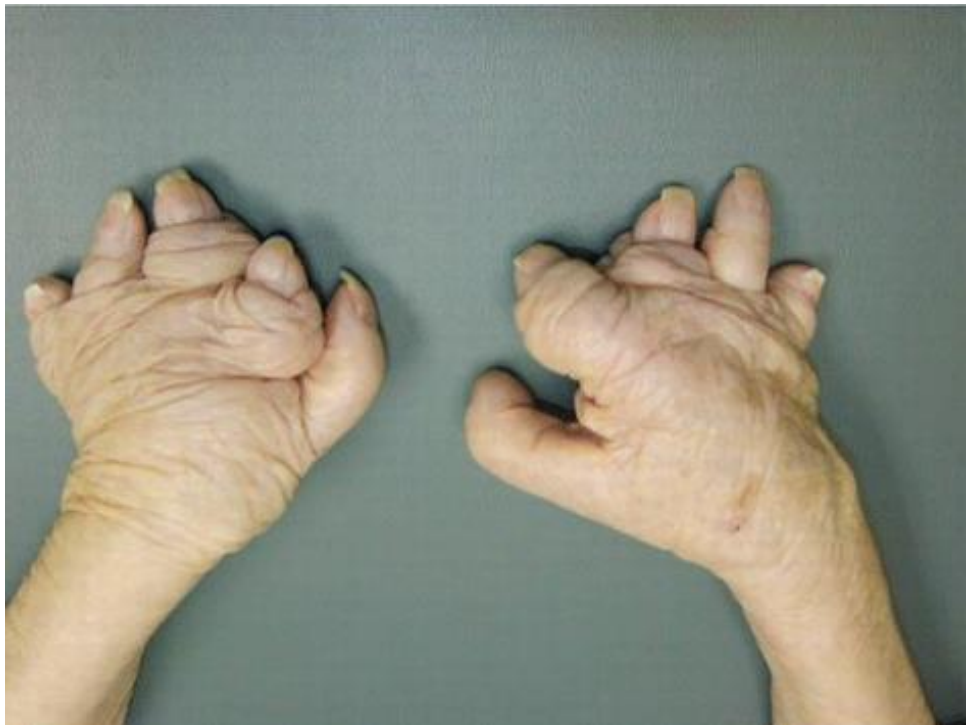
- Seen in Psoriatic Arthritis.

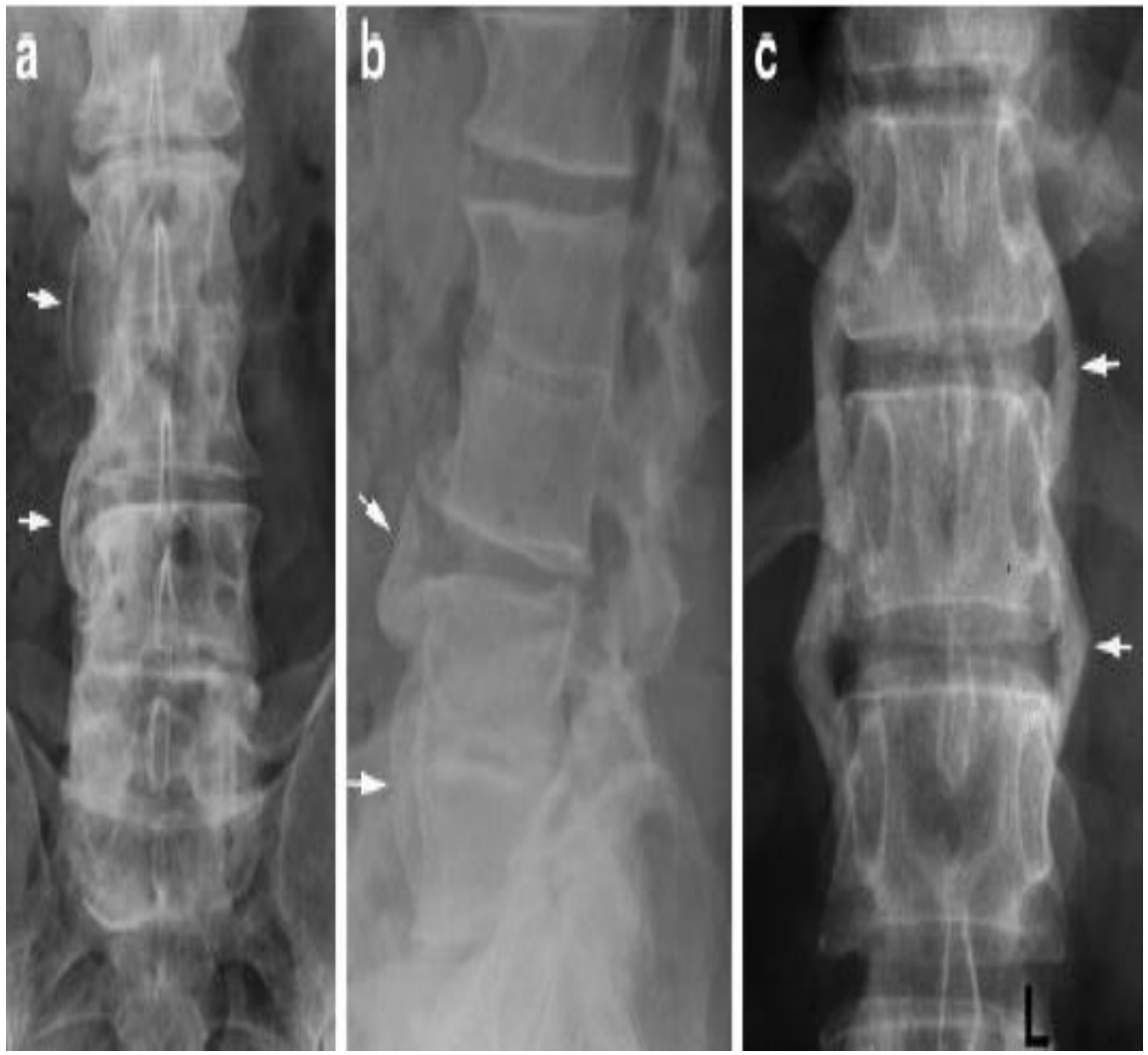


ARTHRITIS MUTILANS

- Distal phalanx dissolves and only the skin remains.
- On the X-ray note the Pencil-in-cup deformity due to bony erosions.
- The finding in the second picture is called Telescoping fingers, due to long standing inflammation in the digits.

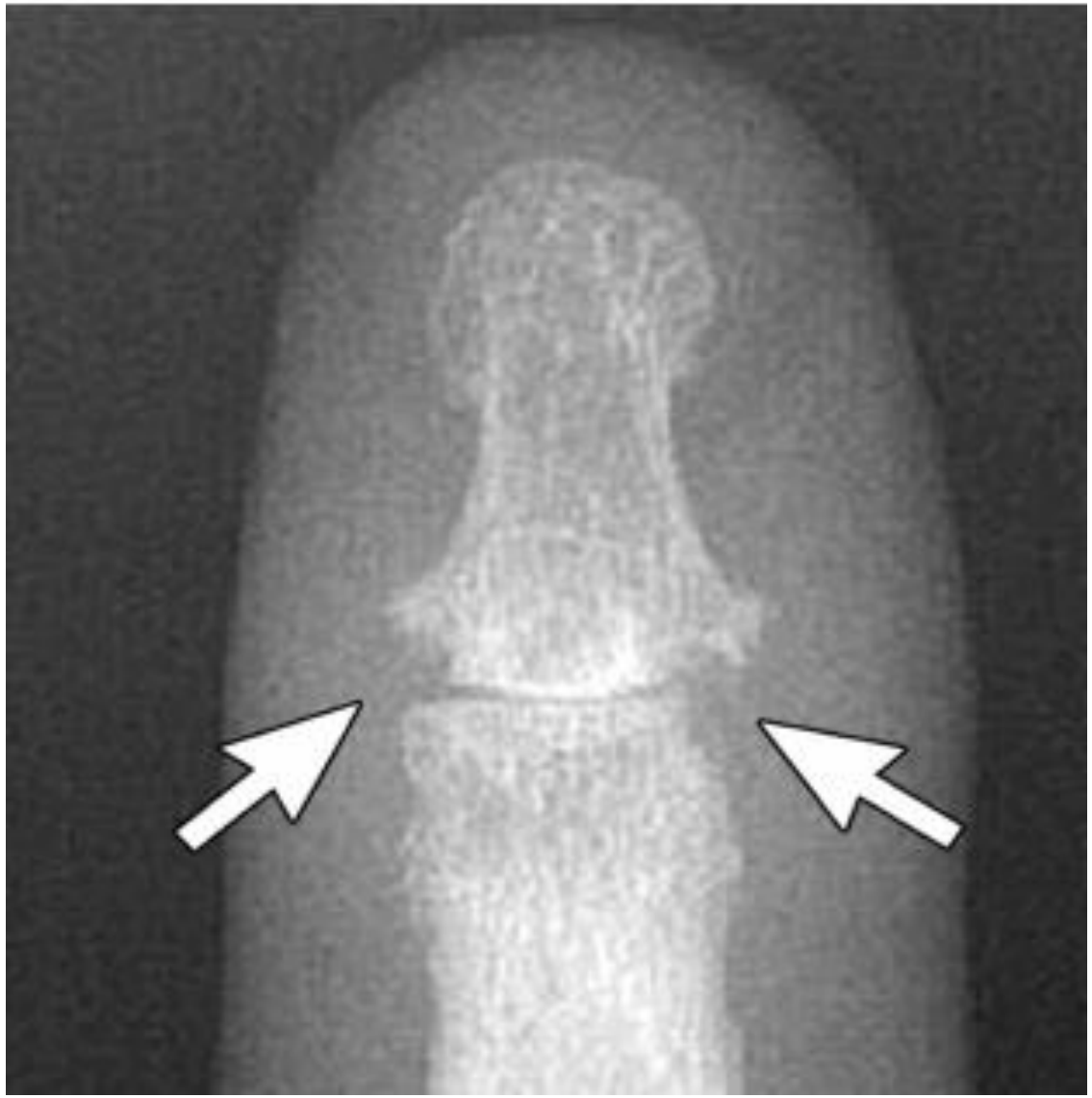






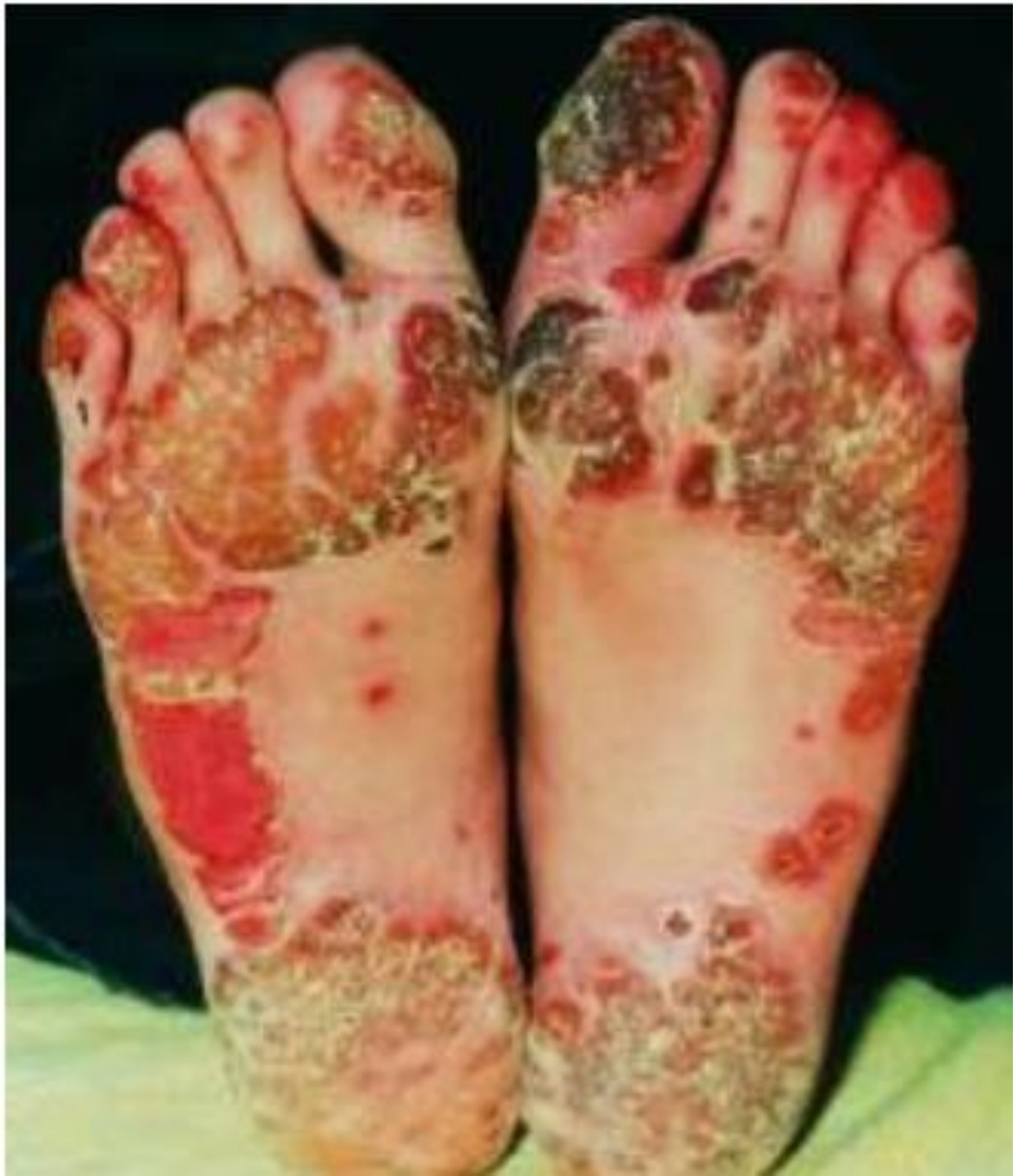
PSORIATIC ARTHRITIS

- This is Psoriatic not Ankylosing, as there is no Syndesmophytes (they appear bulky and interrupted on X-ray).



PSORIATIC ARTHRITIS

- Fluffy bony erosion + Bone Formation
- Fluffy appearance.



KERATODERMA BLENORRHAGICA

- Important hallmark seen in REACTIVE ARTHRITIS.
- It's a papulosquamous skin rash, it comprises vesicles that become hyperkeratotic, forming crusts before disappearing.
- Seen on the Palms / Soles and Penis (causing Circinate Balanitis).
- Other manifestations of Reactive Arthritis:

Painless Oral Ulcers, Inflammatory Back Pain, Enthesitis, Dactylitis, Anterior Uveitis.

Treatment of SPA

- Axial Vs peripheral disease
- Physical therapy: improves function, flexibility and disease activity
- NSAIDs: first line therapy. Less progression.? DMARD?
- Glucocorticoids not recommended in AS.
- DMARDs: sulfasalazine, methotrexate: peripheral arthritis only not in axial disease.

Treatment of spondyloarthropathies

Nonsteroidal antiinflammatory agents
Naproxen sodium, indomethacin, meloxicam, diclofenac sodium ,,etc

Disease modifying anti-rheumatic drugs (DMARDs)
Sulfasalazine
Methotrexate

Tumor necrosis factor antagonists
Infliximab
Etanercept
Adalimumab
Certolizumab pegol
Golimumab

IL-17 antagonist:
secukinumab

For axial arthritis, exercises to maintain posture and flexibility

TREATMENT OF SPONDYLOARTHROPATHIES

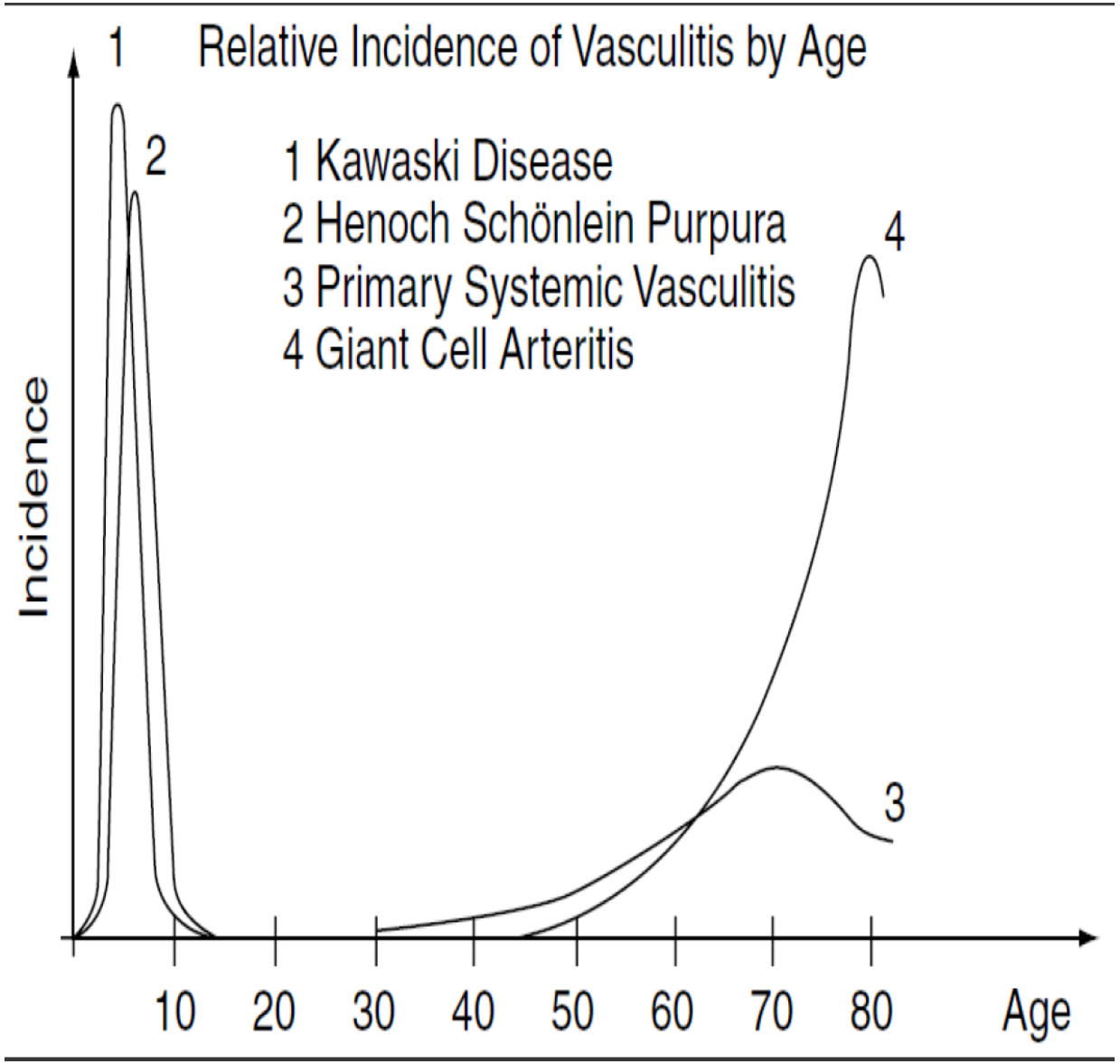
VASCULITIS

Dominant vessel involved	Primary	Secondary
Large arteries	Giant cell arteritis (GCA) Takayasu arteritis (TA)	Aortitis associated with RA Infection (e.g., syphilis, tuberculosis)
Medium arteries	Classical PAN Kawasaki disease	Hepatitis B virus associated PAN
Small vessels and medium arteries	Wegener's granulomatosis (WG)[a] Churg–Strauss syndrome (CSS)[a] Microscopic polyangiitis[a]	Vasculitis secondary to RA, SLE Sjögren's syndrome Drugs[b] Infection (e.g., HIV)
Small vessels (leukocytoclastic)	Henoch–Schönlein purpura (HSP) Cutaneous leukocytoclastic angiitis	Drugs[c] Infection Hepatitis C virus induced cryoglobulinemia

PRIMARY AND SECONDARY CAUSES OF DIFFERENT FORMS OF VASCULITIS

RELATIVE INCIDENCE OF VASCULITIS BY AGE

- Kawasaki and Henoch Schonlein Purpura are seen mainly in Children.
- Primary systemic vasculitis is seen in Middle Age.
- Giant Cell Arteritis is Seen in Elderly.



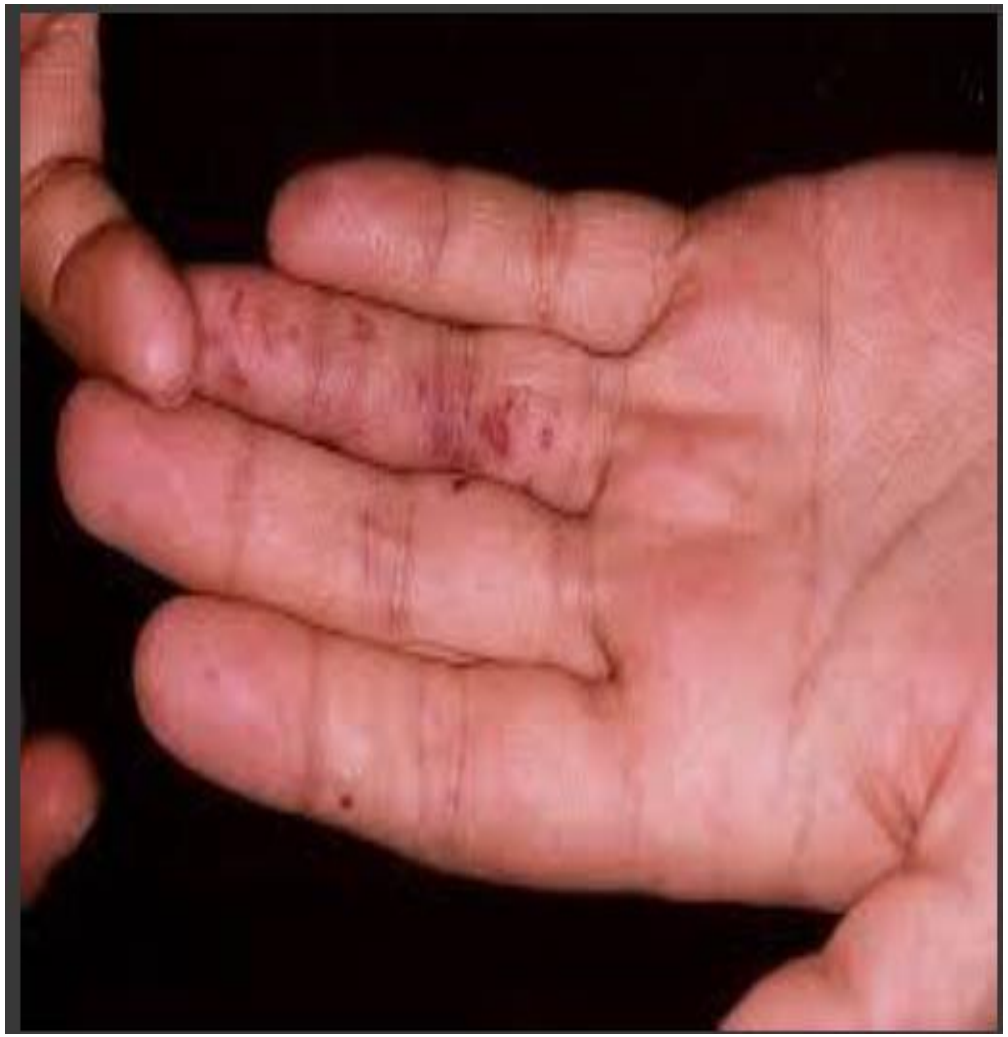
TYPICAL CLINICAL MANIFESTATIONS OF LARGE, MEDIUM AND SMALL VESSEL VASCULITIS

Large	Medium	Small
Headache	Cutaneous nodules	Purpura
Limb claudication	Ulcers	Vesiculobullous lesions
Asymmetric blood pressures	abdominal pain	Urticaria
Absence of pulses	Livedo reticularis	Glomerulonephritis
Bruits	Digital gangrene	Alveolar hemorrhage
Aortic dilatation	Mononeuritis multiple	Cutaneous extravascular necrotizing granulomas
	Microaneurysms	Splinter hemorrhages
		Scleritis/episcleritis/uveitis

- In Large Vessel Vasculitis, patients will have ischemia like symptoms + systemic symptoms.
- Regarding Asymmetric blood pressure, the vessel with vasculitis will be slightly hypertensive.
- In Medium vessel vasculitis, Abdominal pain is mainly related to Mesenteric Vasculitis.
- Purpura is non-blanchable skin rash on dependable part of the body, due to extravasation of RBCs at inflammation site.

VASCULITIC RASH

- One of the clinical manifestations of Vasculitis.

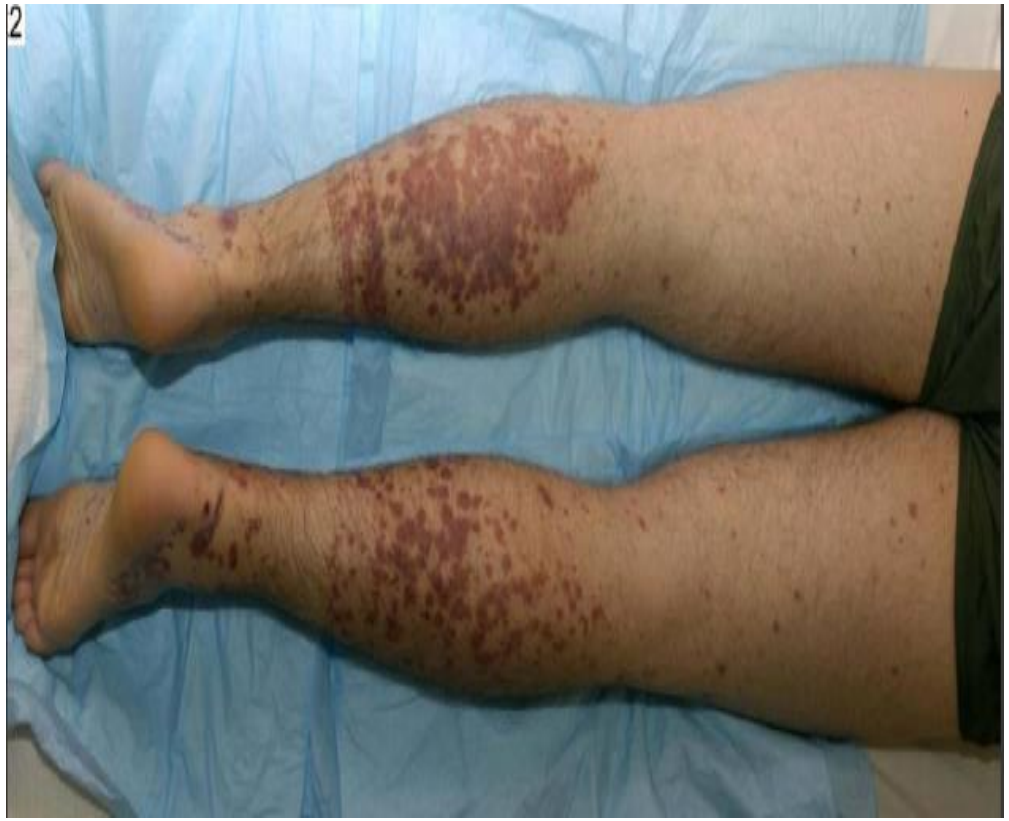


NAIL FOLD INFARCTION

- Seen in Vasculitis and Rheumatoid arthritis.

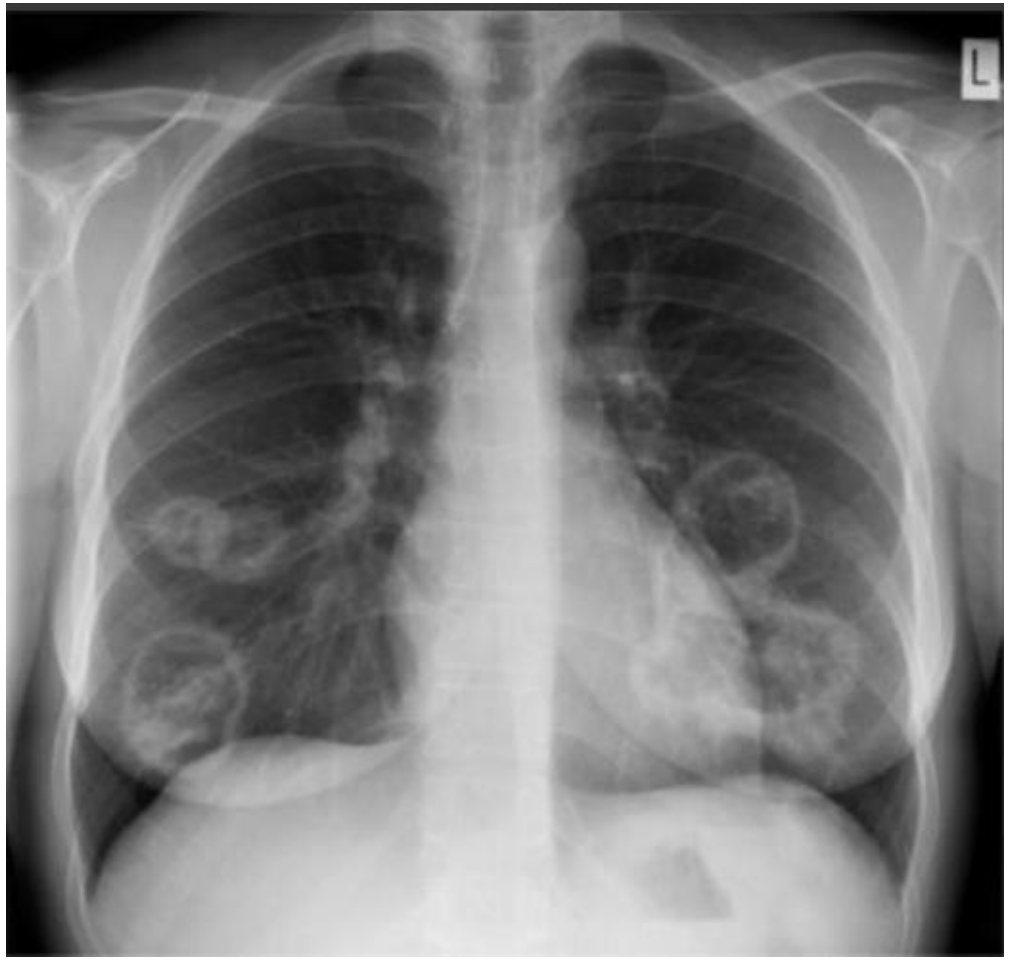
PURPURA

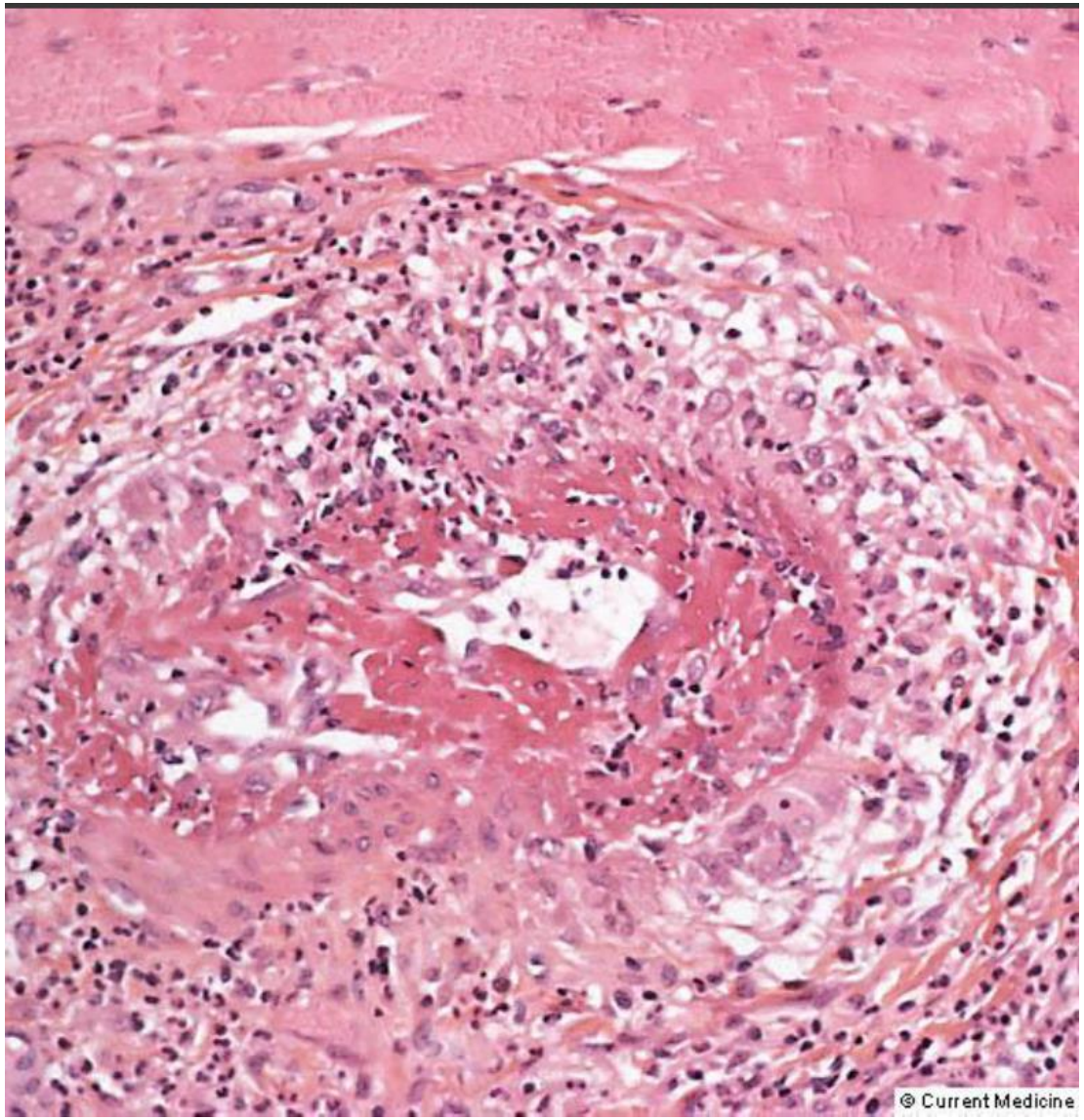
- Seen in Small Vessel Vasculitis (Hypersensitivity Vasculitis).



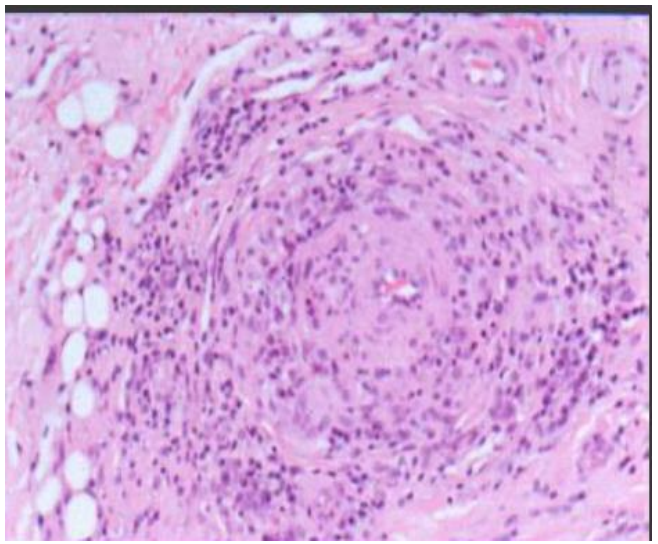
CAVITARY LUNG LESION

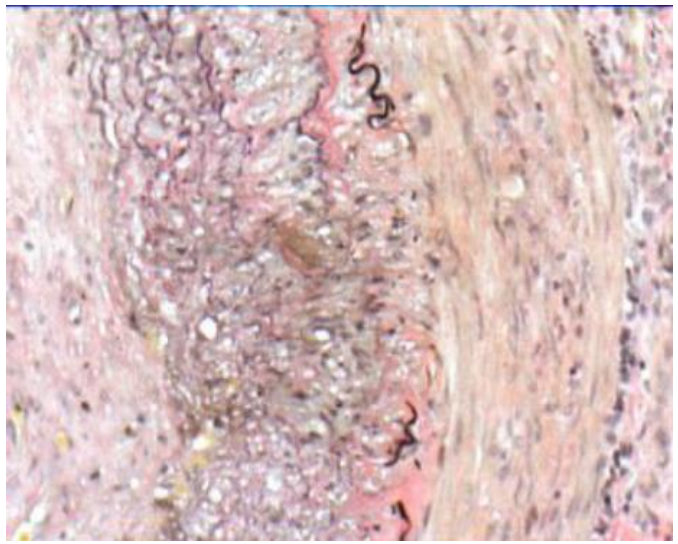
- Seen in Vasculitis.

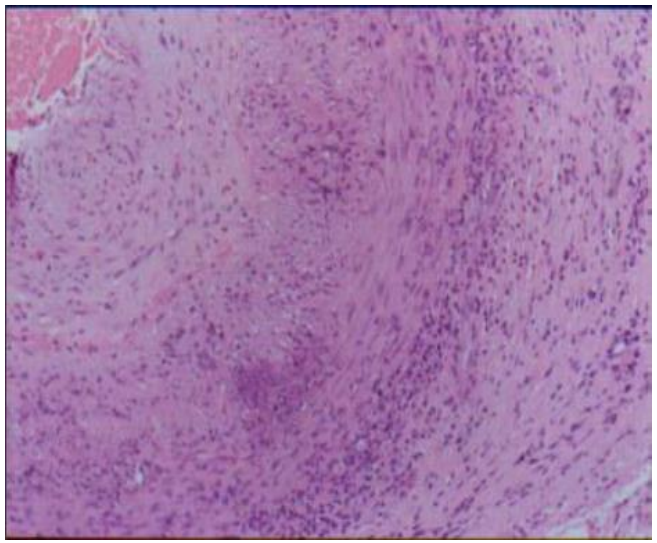


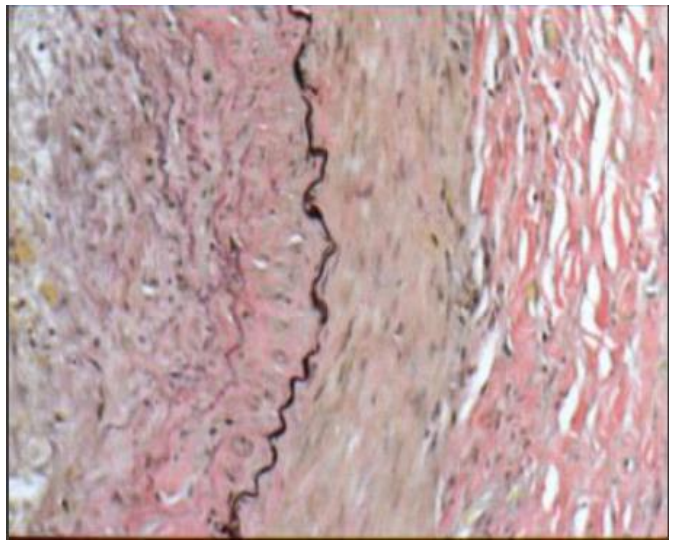


SKIN BIOPSY SHOWING LEUKOCYTOCLASTIC VASCULITIS.



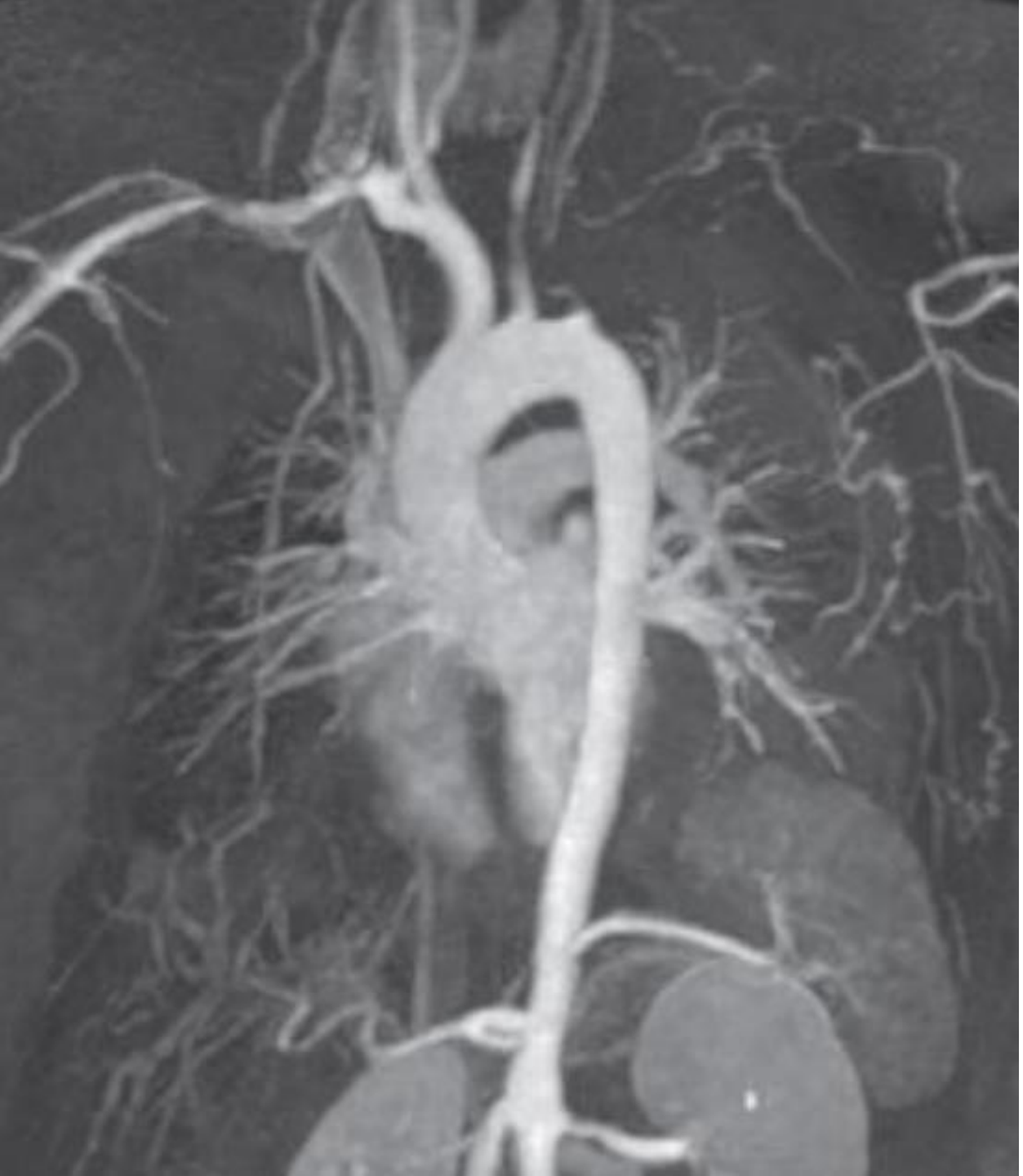






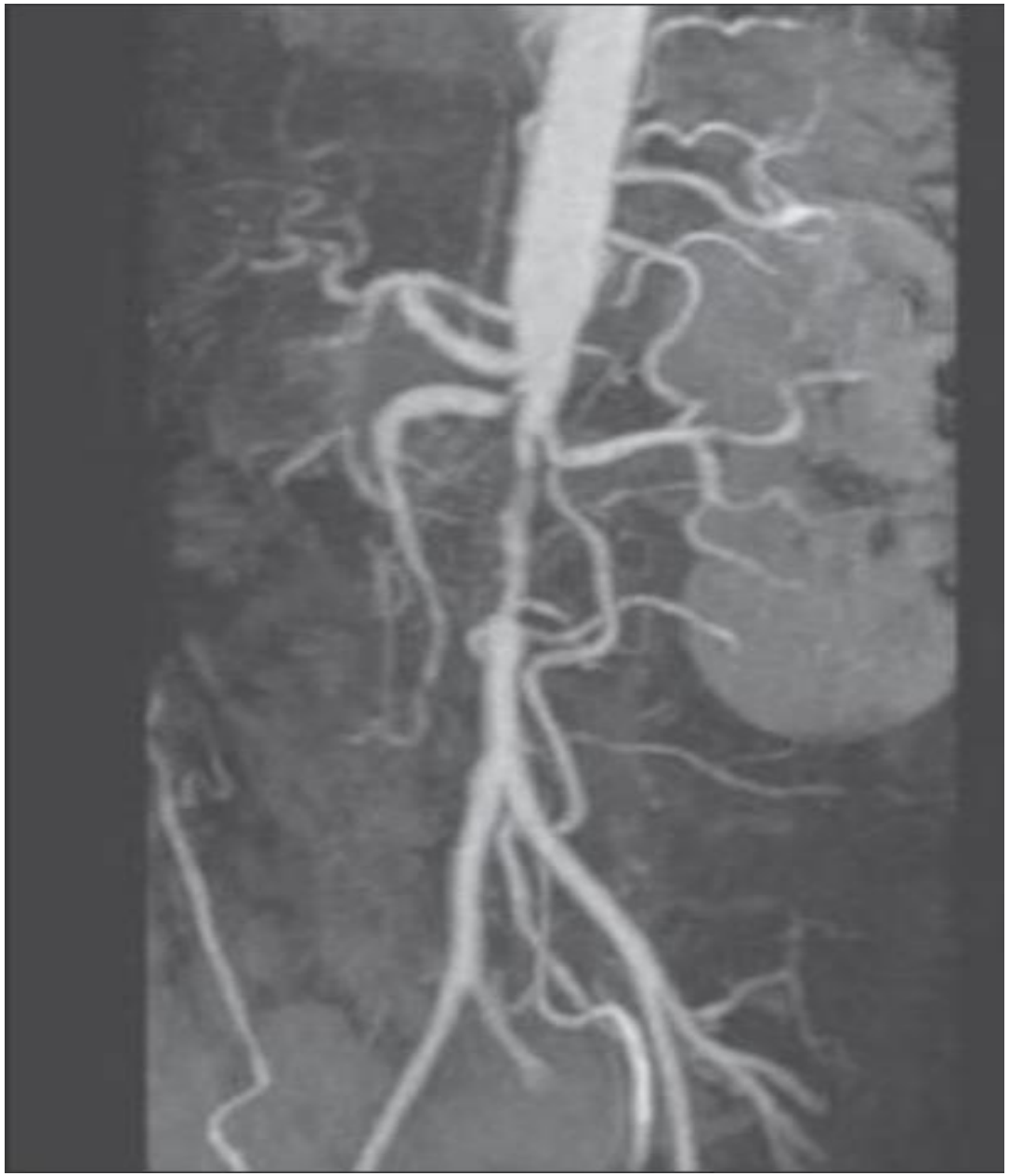
HISTOLOGICAL SECTIONS OF GIANT CELL ARTERITIS

- Temporal Artery Biopsy.
- Skip lesions are common.
- A Negative biopsy result doesn't rule out GCA.
- Note the Granuloma in the first picture.



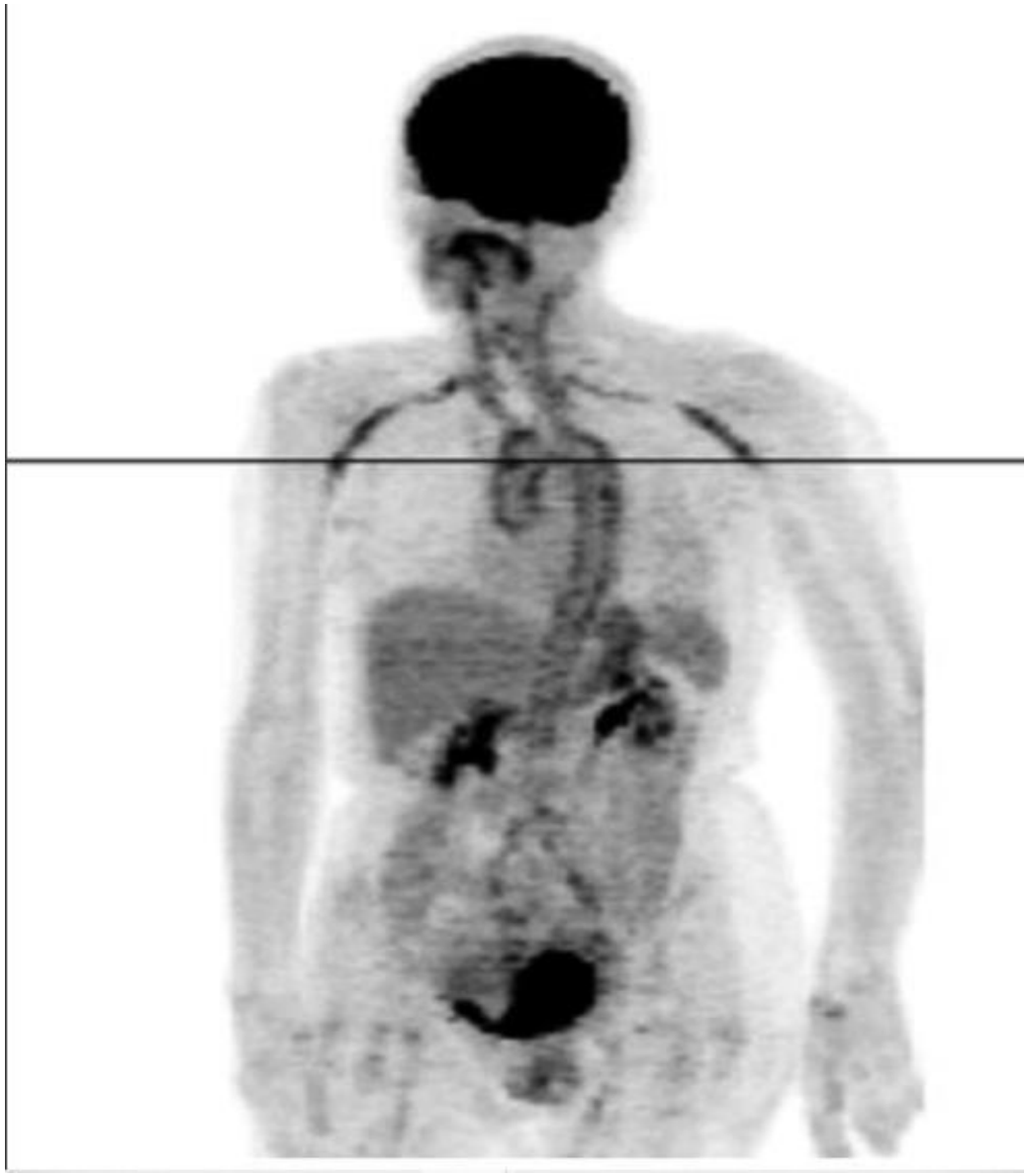
TAKAYASU'S ARTERITIS RADIOLOGY

- There is loss of Opacification in the common carotid artery.



TAKAYASU'S ARTERITIS RADIOLOGY

- Infrarenal Aortic narrowing.



18F-FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY (18F-FDG-PET)

- PET CT scan: more advanced imaging (nuclear CT), it looks at the function and the anatomy.
- 18F-FDG is taken up by metabolically active cells including at sites of inflammation.
- Uptake can be visualized in the walls of inflamed large vessels.
- If all vessels are showing, then all of them are inflamed.

Takayasu's Arteritis: Treatment

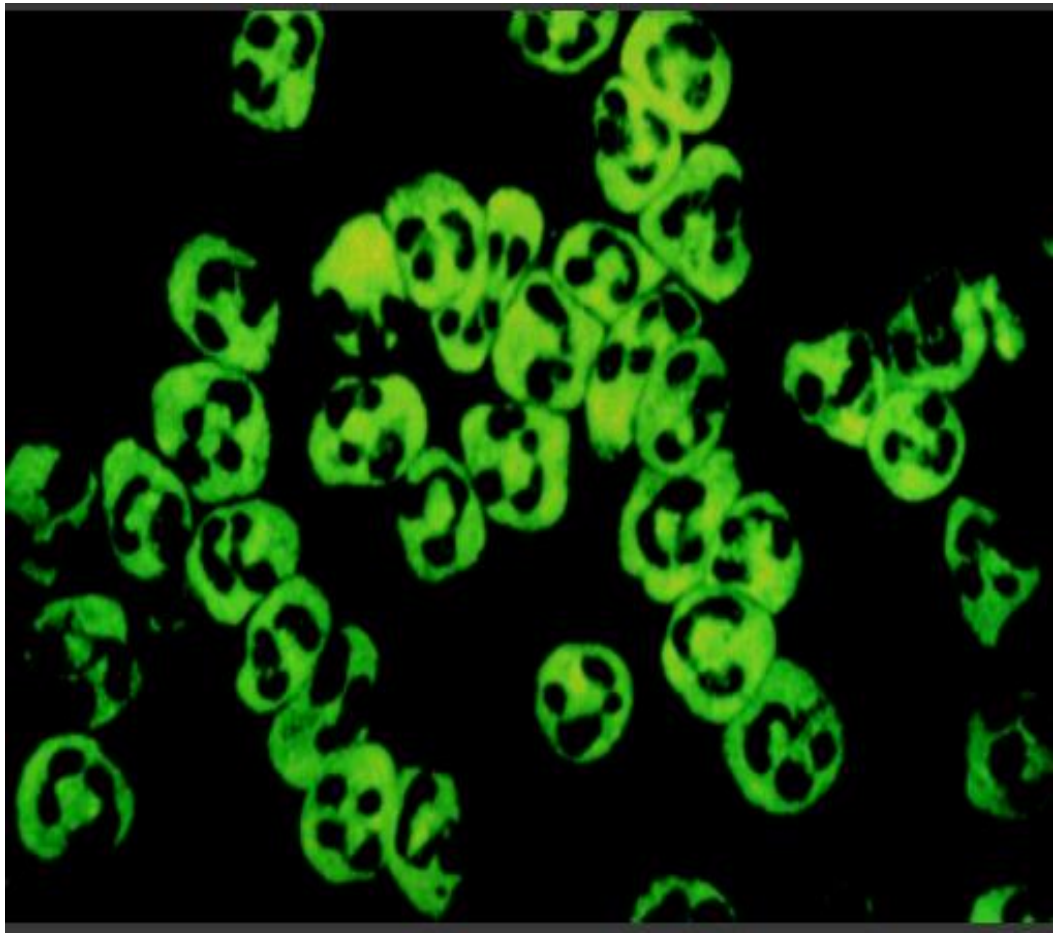
- High-dose oral prednisolone at 0.5–1 mg/kg
- Steroid-sparing agents: Azathioprine, methotrexate
- Surgery

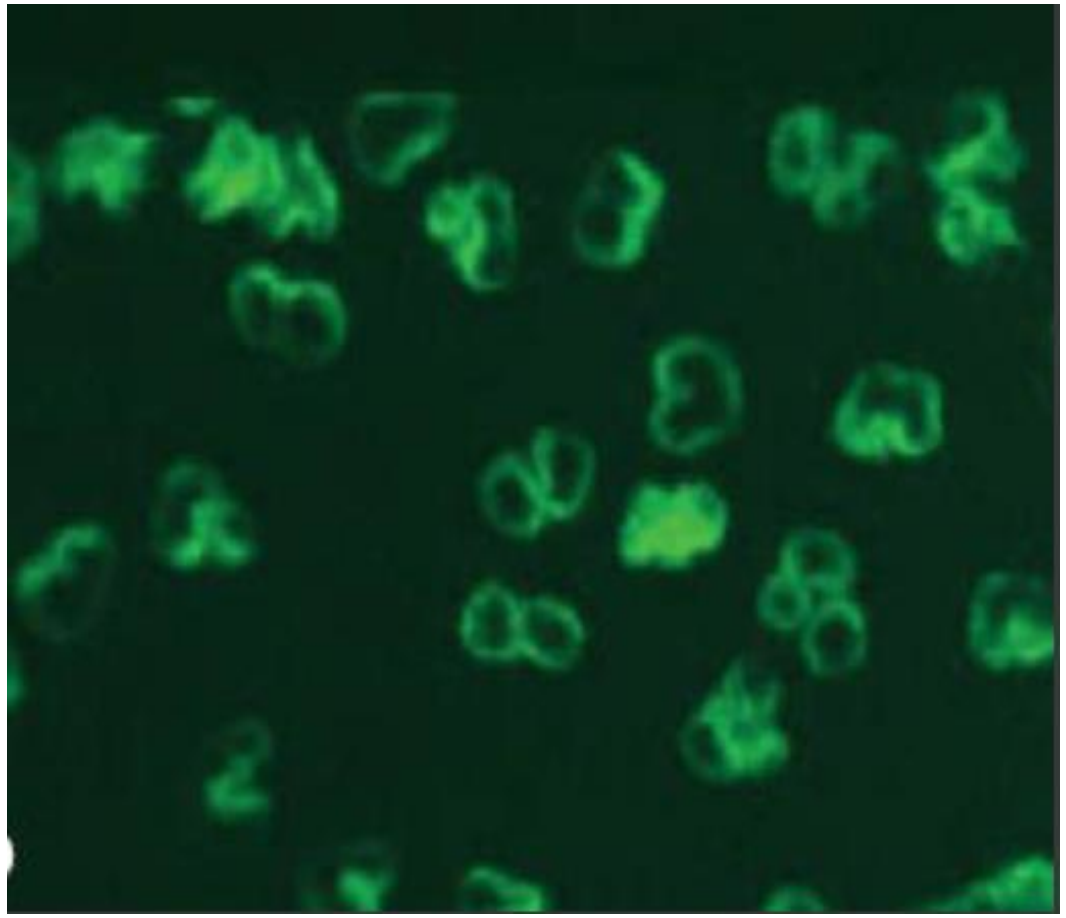
TREATMENT OF TAKAYASU'S ARTERITIS

- Surgery is indicated if there's significant stenosis and revascularization is needed.

C-ANCA

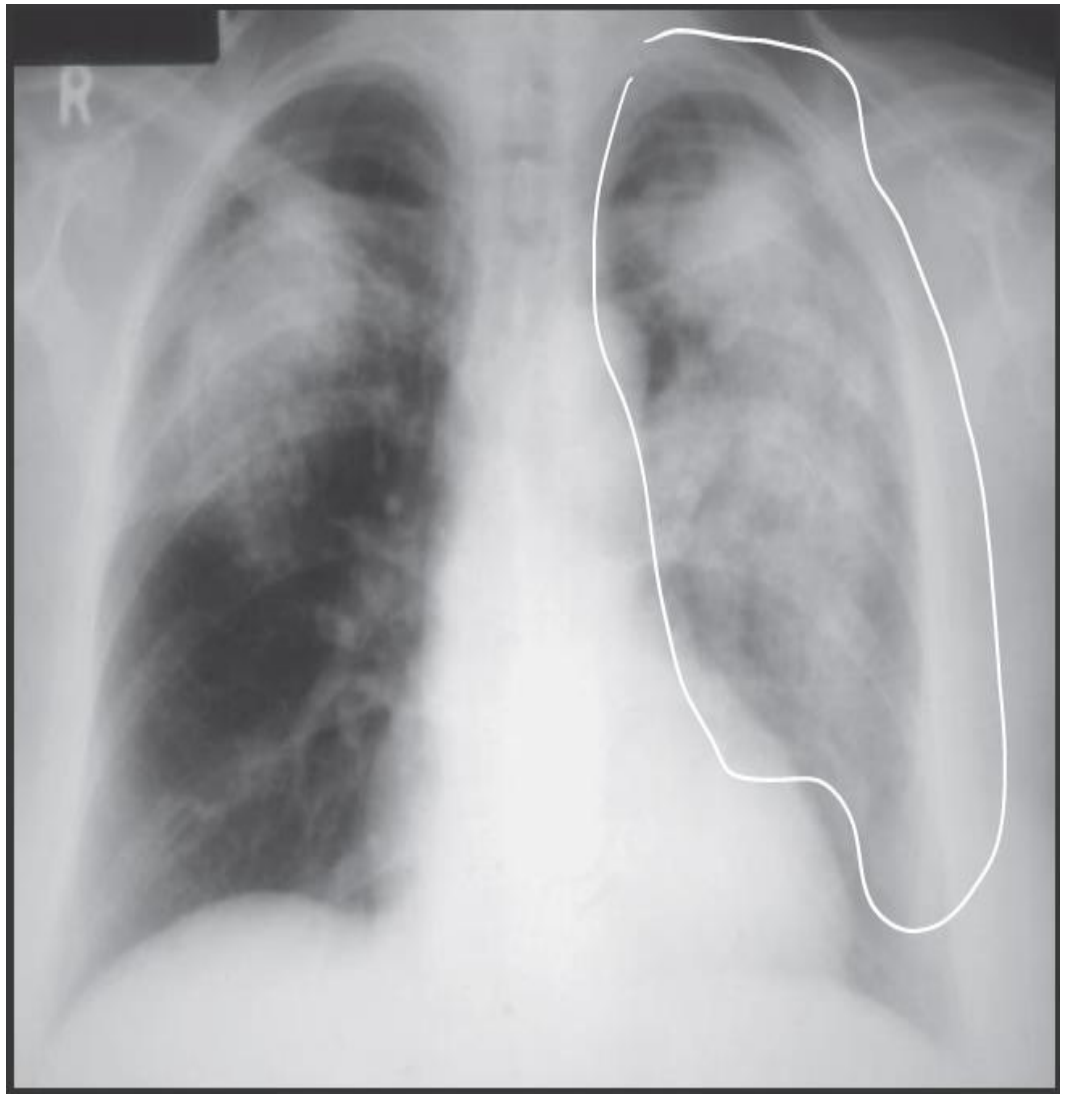
- Antibody against Azurophilic granules in Neutrophils.
- Seen in ANCA associated vasculitis.
- Cytoplasmic C-ANCA: against Proteinase 3 , Specific for Wegener Granulomatosis.





P-ANCA

- Antibody against Azurophilic granules in Neutrophils.
- Seen in ANCA associated vasculitis.
- Perinuclear P-ANCA: Against Myeloperoxidase, occur in Churg-Strauss Syndrome and Microscopic Polyangiitis.
- P-ANCA in diseases other than Primary vasculitis is directed against other antigens like Elastase, Lactoferrin, and Cathepsin G.

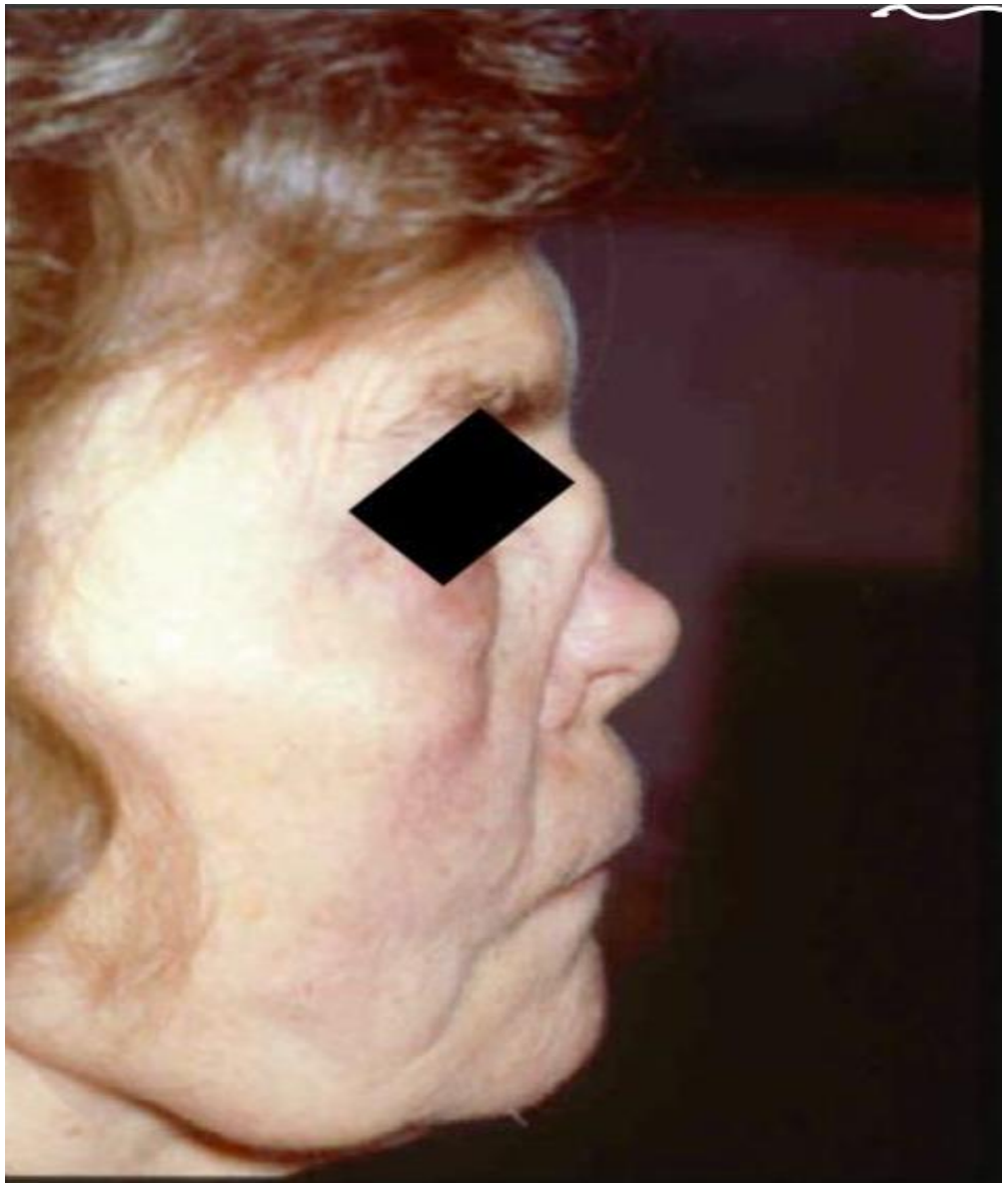


PULMONARY HEMORRHAGE IN MICROSCOPIC POLYANGIITIS

- Diffuse Alveolar Hemorrhage
- P-ANCA associated.

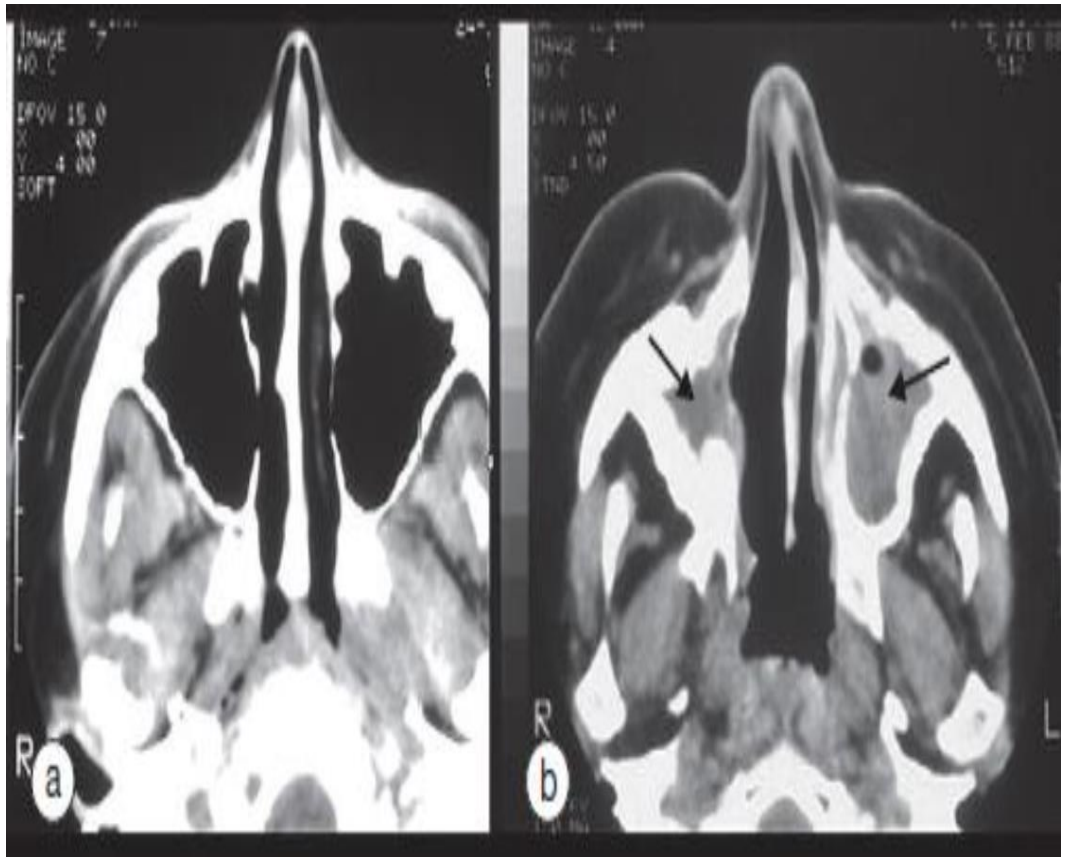
SADDLE NOSE DEFORMITY IN WEGENER GRANULOMATOSIS

- Another name of the disease is: Granulomatosis with Polyangiitis.
- C-ANCA associated.
- The nose consists of 2 parts: Bony and Cartilaginous, in this disease the inflammation is in the Cartilaginous part.



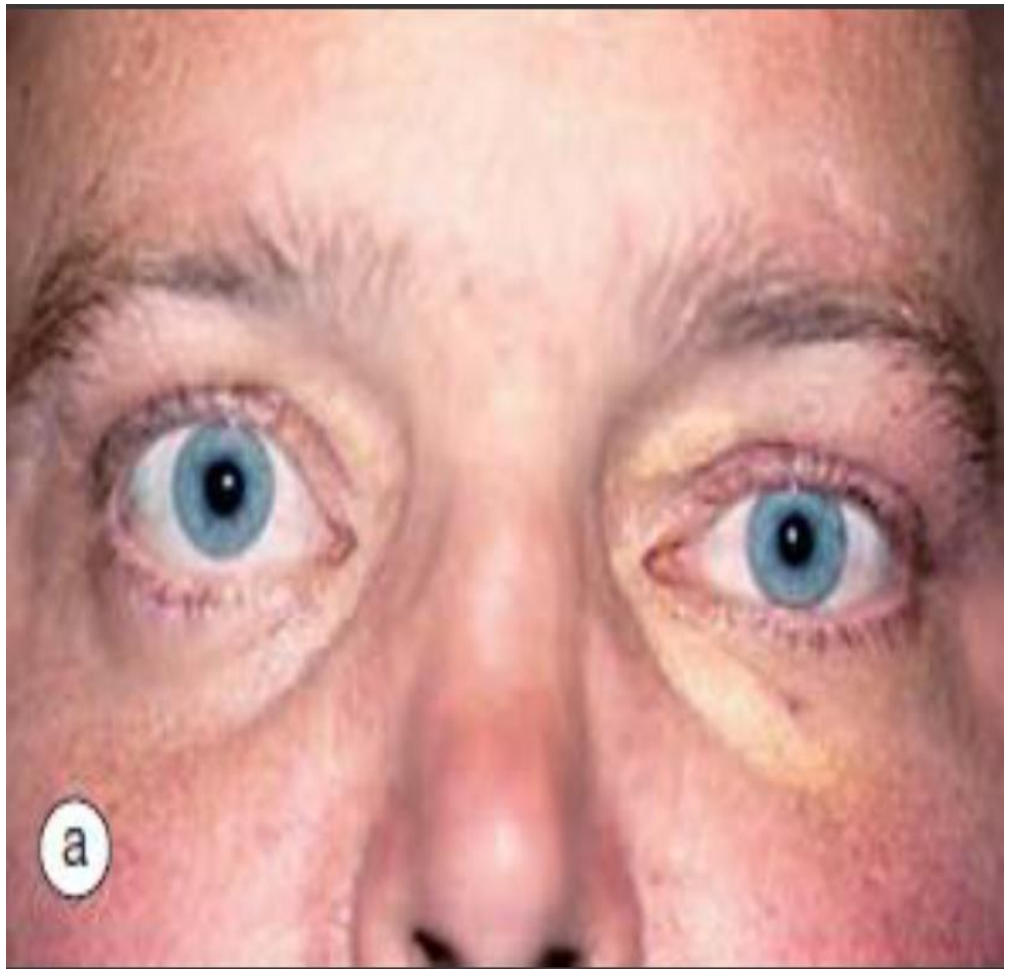
COMPARISON BETWEEN NORMAL CT SCAN AND A CT SCAN OF A PATIENT WITH WEGENER GRANULOMATOSIS

- Notice that in the abnormal CT (on the right) we have chronic Sinusitis in the Maxillary Sinus.



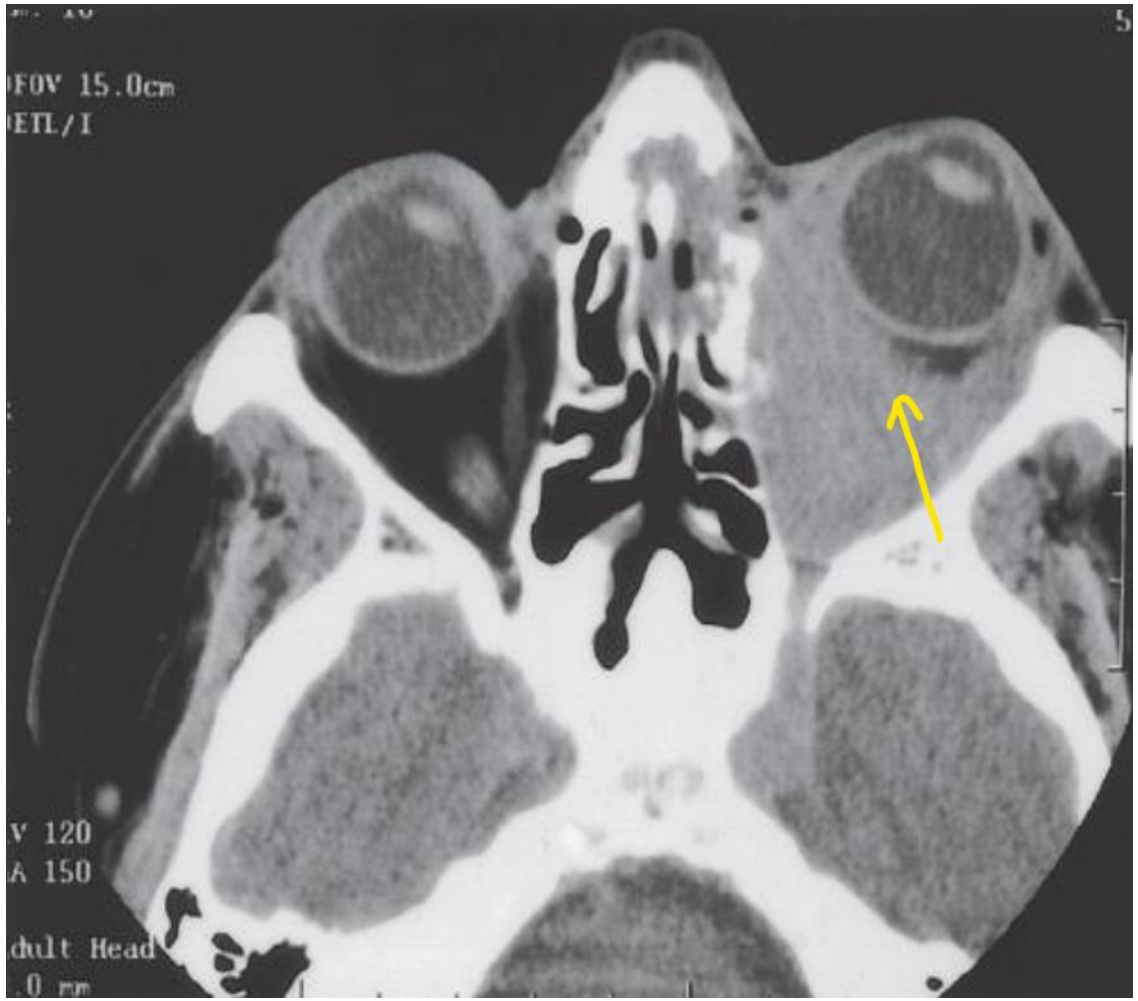
EXOPHTHALMOS DUE TO ORBITAL PSEUDOTUMOR.

- Seen in Wegener Granulomatosis.
- It is a proptosis in the eye due to retro-orbital mass.
- Associated with intractable pain and loss of vision.
- Refractory to therapy.



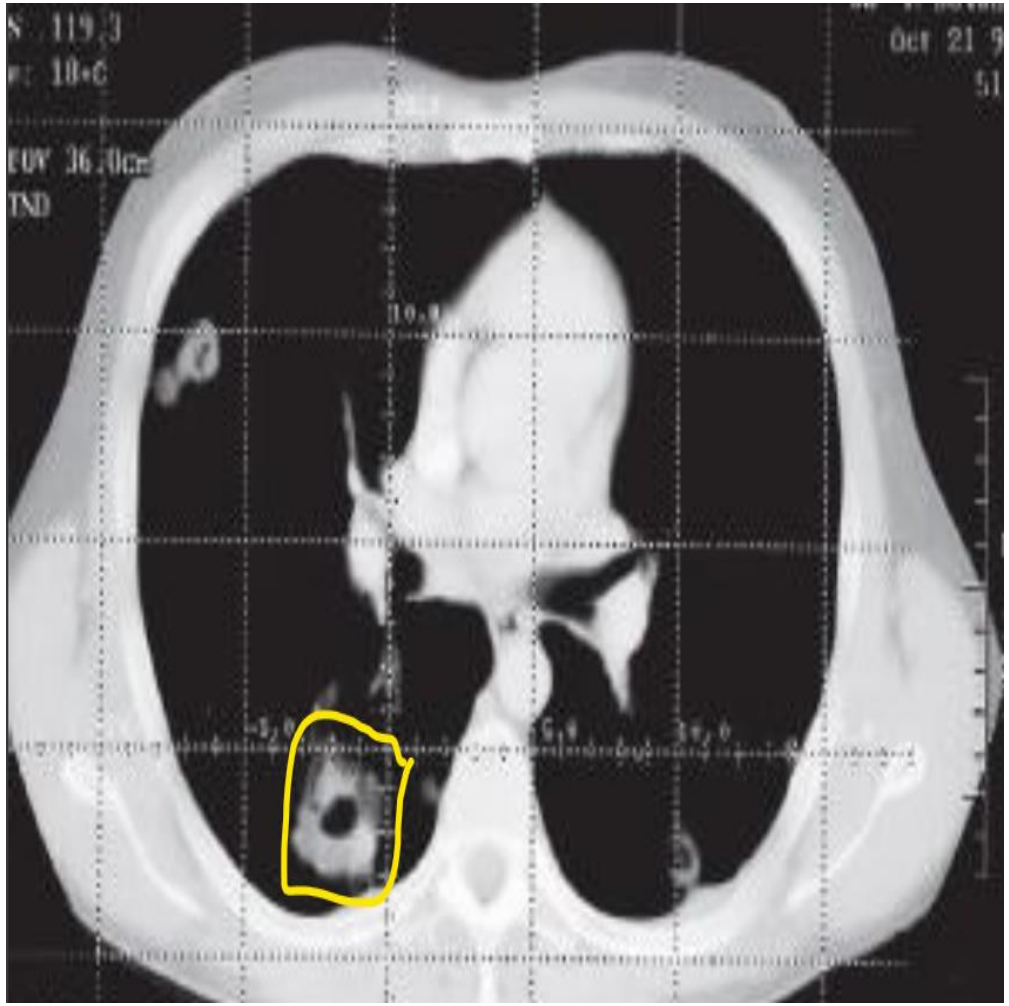
WEGENER GRANULOMATOSIS

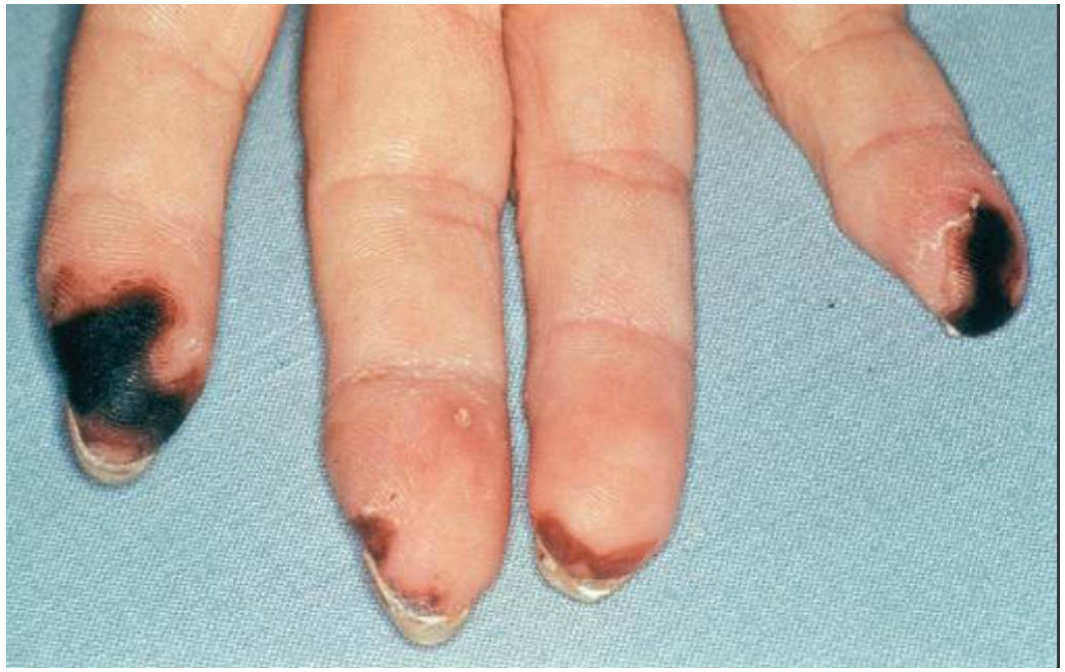
- Lt orbital mass causing proptosis and visual loss through compression of the optic nerve + Orbital infiltration by inflammatory cells.



WEGENER GRANULOMATOSIS

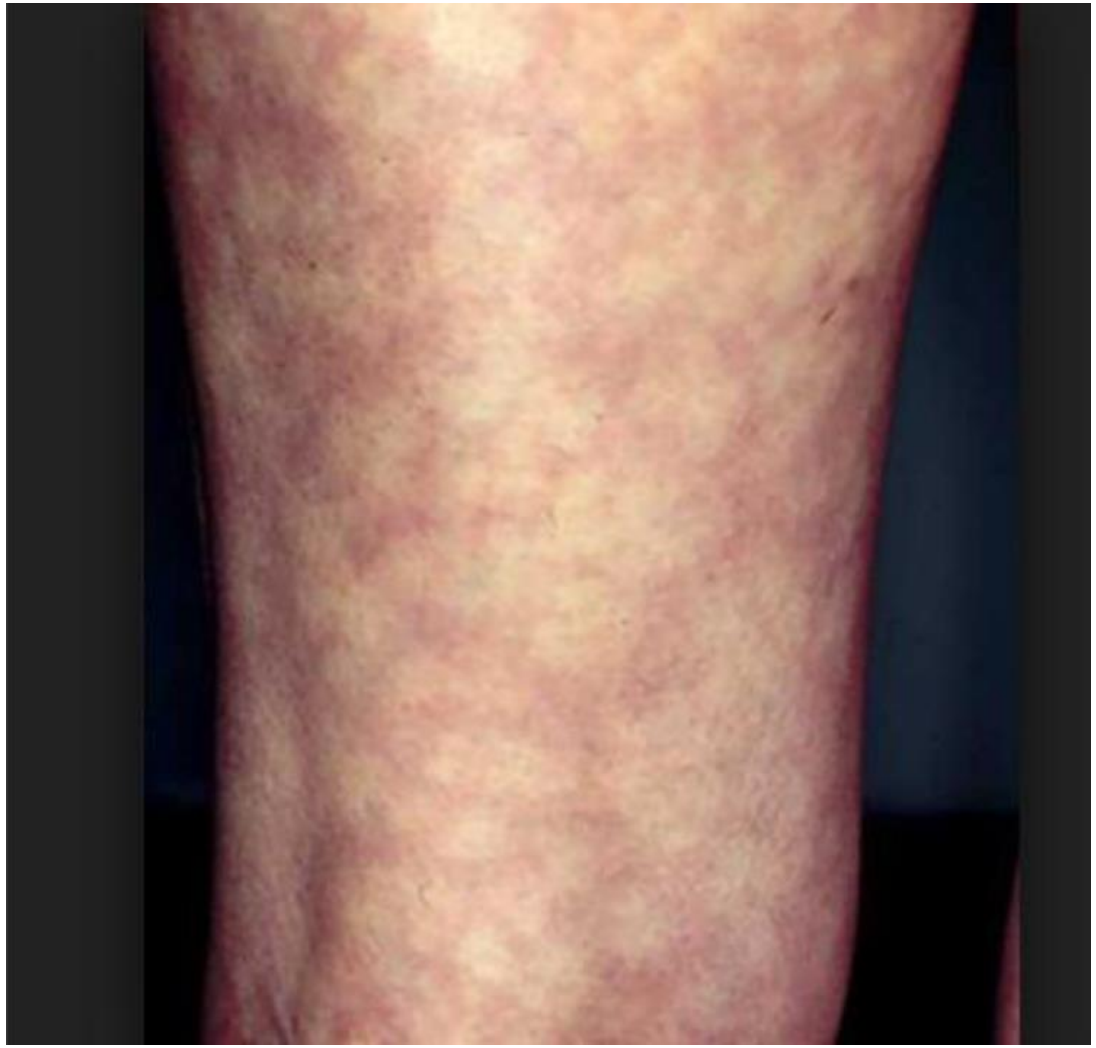
- Multiple bilateral pulmonary nodules, many of which have cavitated.
- Notice the cavitary lesion in the lung (inside the yellow circle).





DIGITAL TIP INFARCTION IN POLYARTERITIS NODOSA

- Infarction in the index and little finger.
- Vasculitic Rash in the middle and ring fingers.
- No ANCA association in Polyarteritis nodosa.



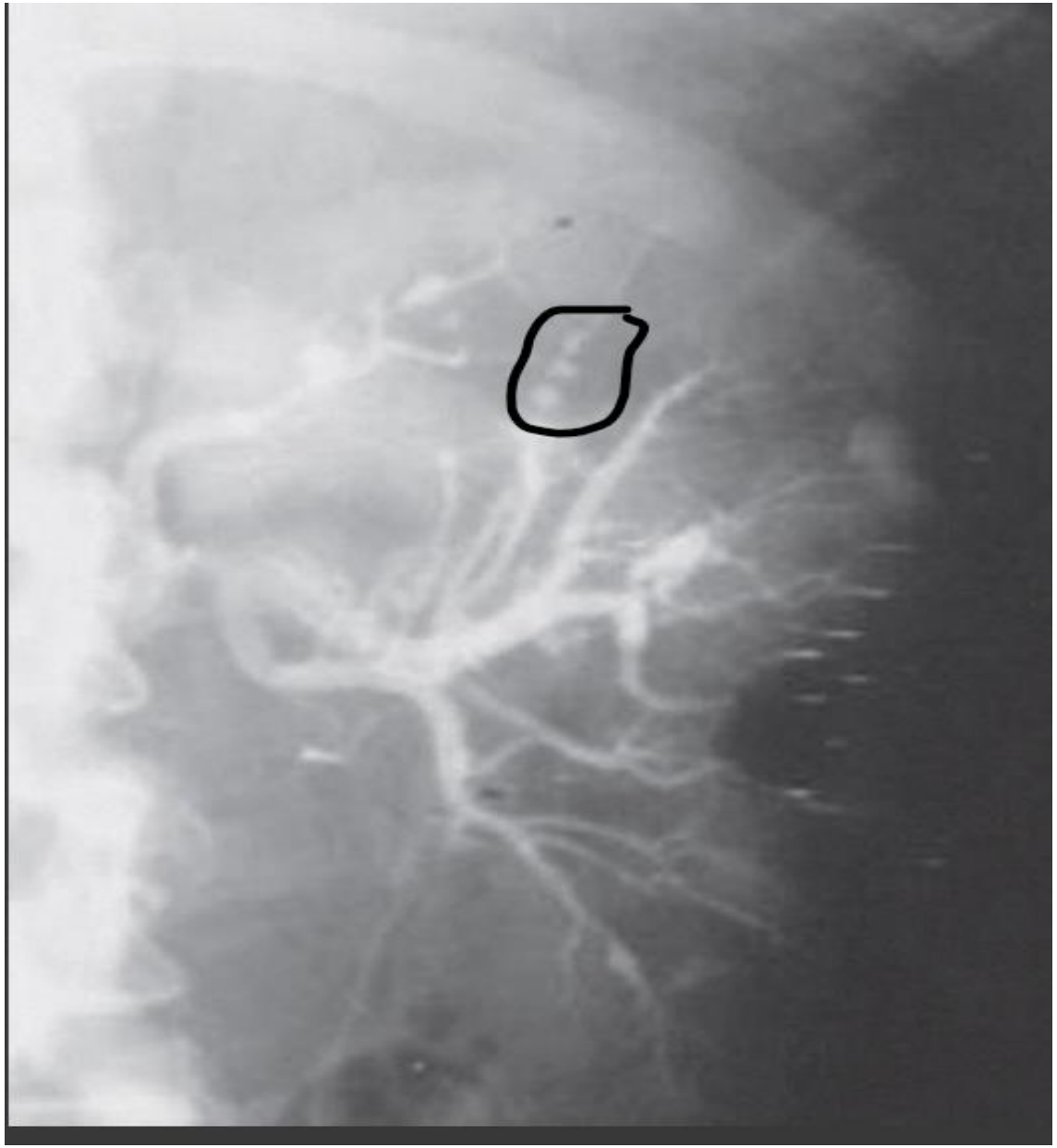
LIVEDO RETICULARIS

- Lacy (web-like) appearance on the skin, arms hands, and legs.
- Caused by stasis of the blood in superficial vessels leading to slow blood flow.
- Seen in Polyarteritis nodosa.
- Other DDx :

1- Antiphospholipid syndrome 2- Lupus

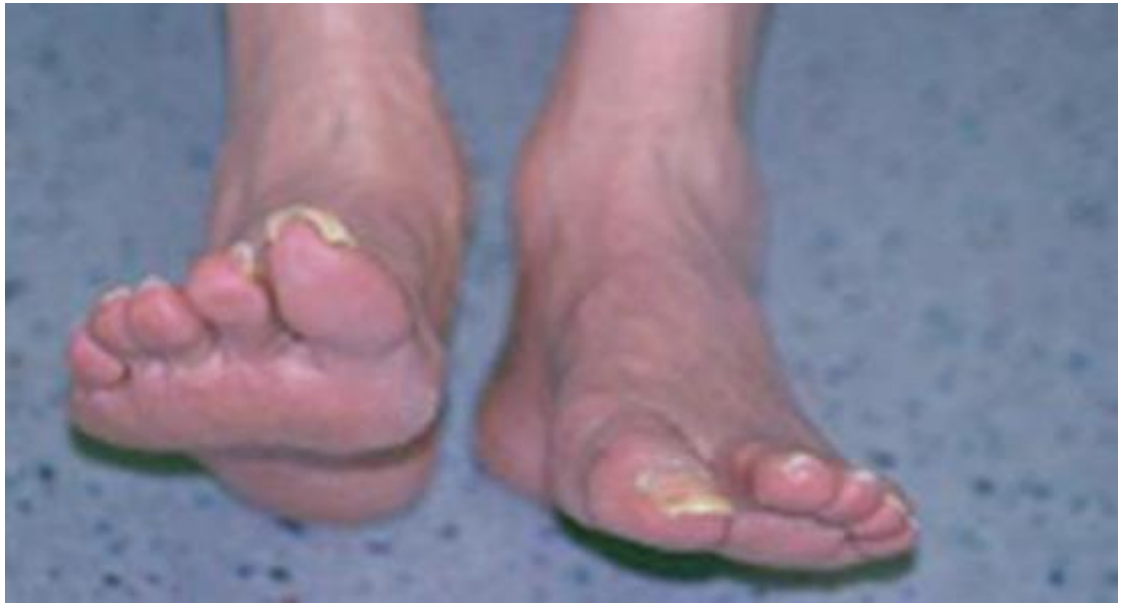
ANGIOGRAM SHOWING MICROANEURYSMS IN POLYARTERITIS NODOSA

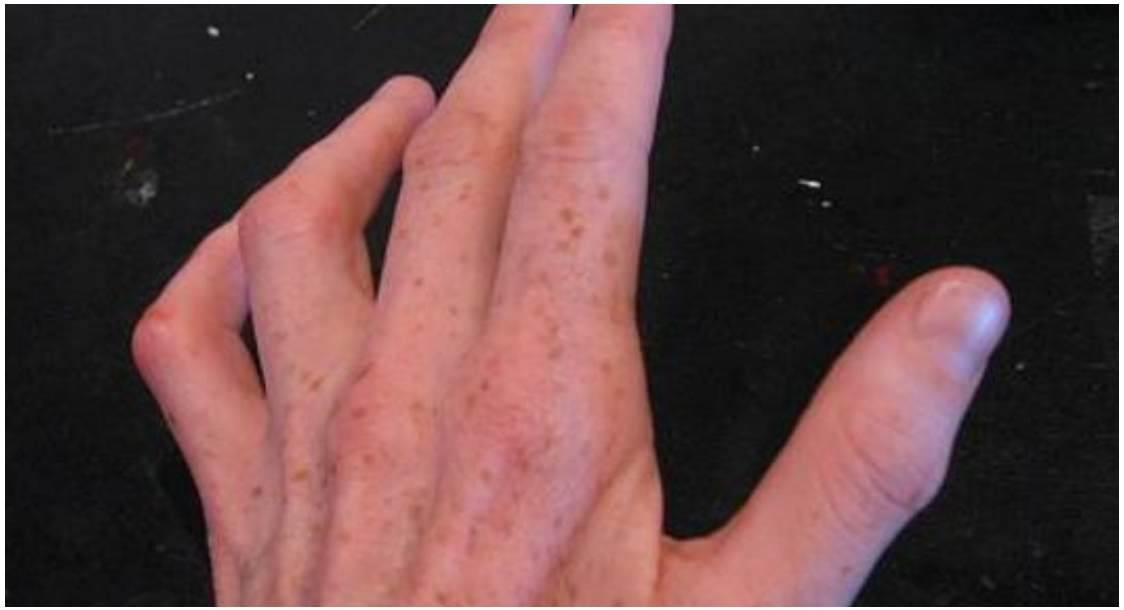
- This angiogram is from the kidney.
- Notice the small, rounded dilations in the branch → Microaneurysms.
- It indicated Polyarteritis nodosa (Diagnostic).
- There's nothing to biopsy here, so we need an angiogram, it's invasive and requires large amount of contrast but is able to show the aneurysms.



MONONEURITIS MULTIPLEX

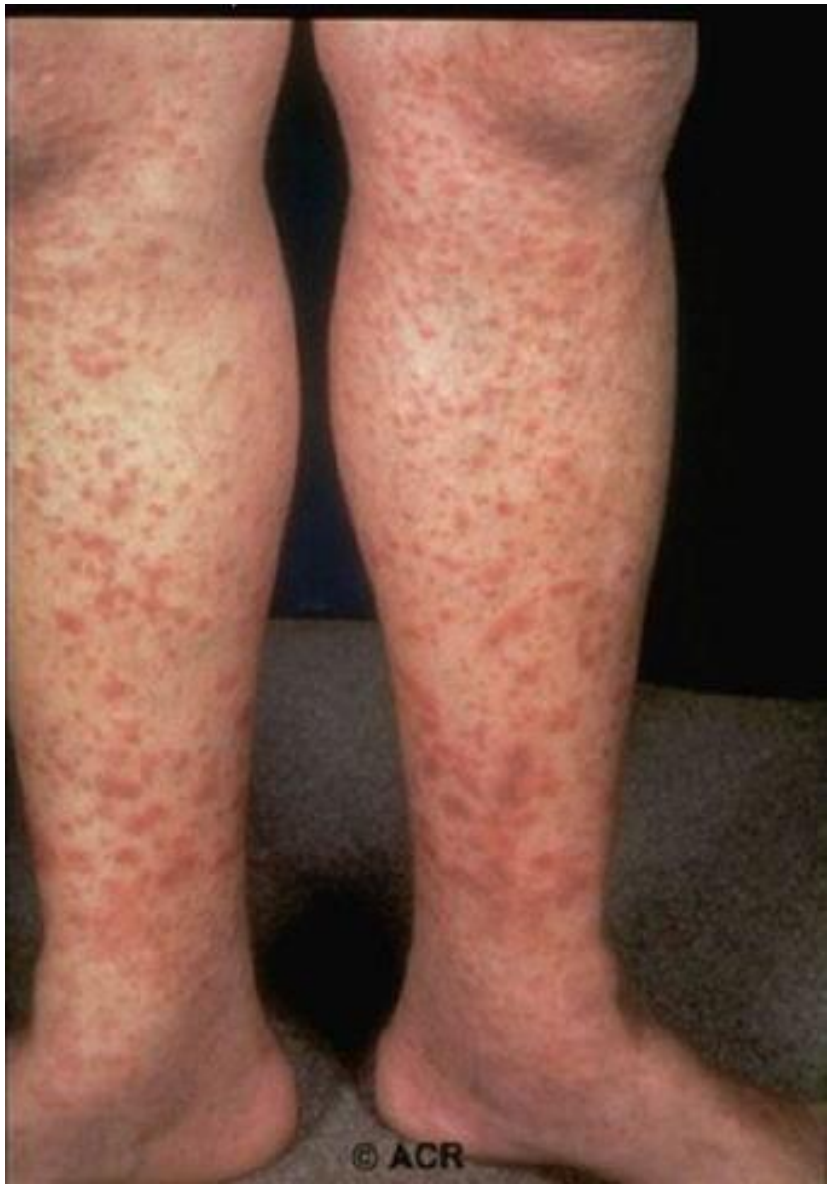
- A sign of Vasculitic Neuritis.
- Sudden Foot Drop
- Telangiectasia





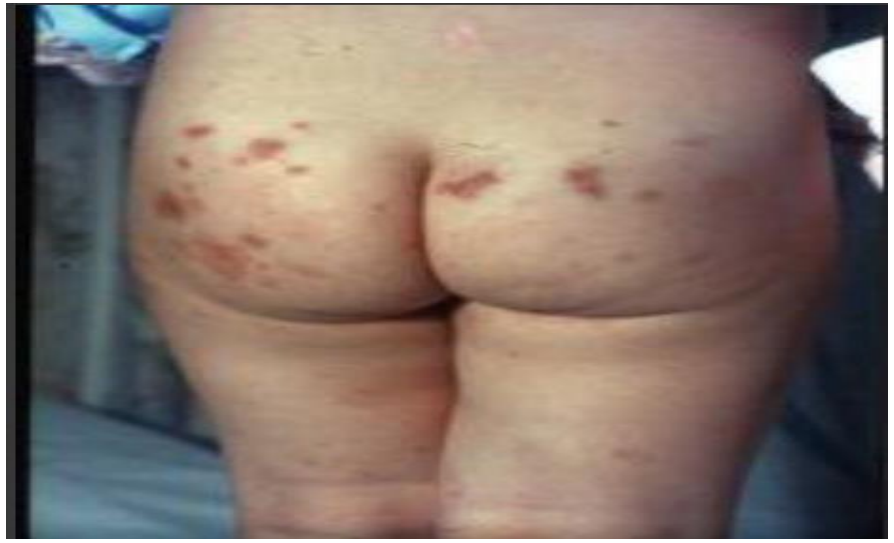
PURPURA

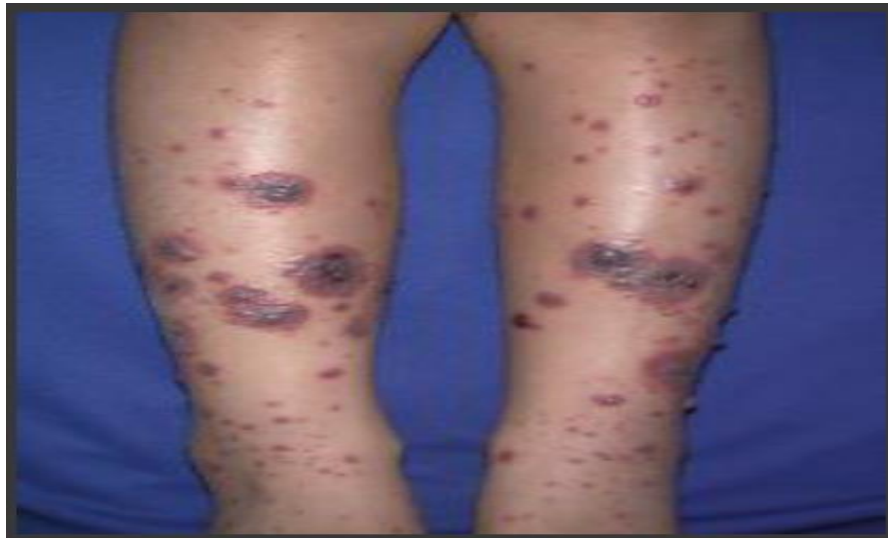
- A sign of Hypersensitivity Vasculitis (Small Vessel Vasculitis).
- Associated with IgA dominant immune deposits.
- Follows Upper Respiratory Tract Infection.

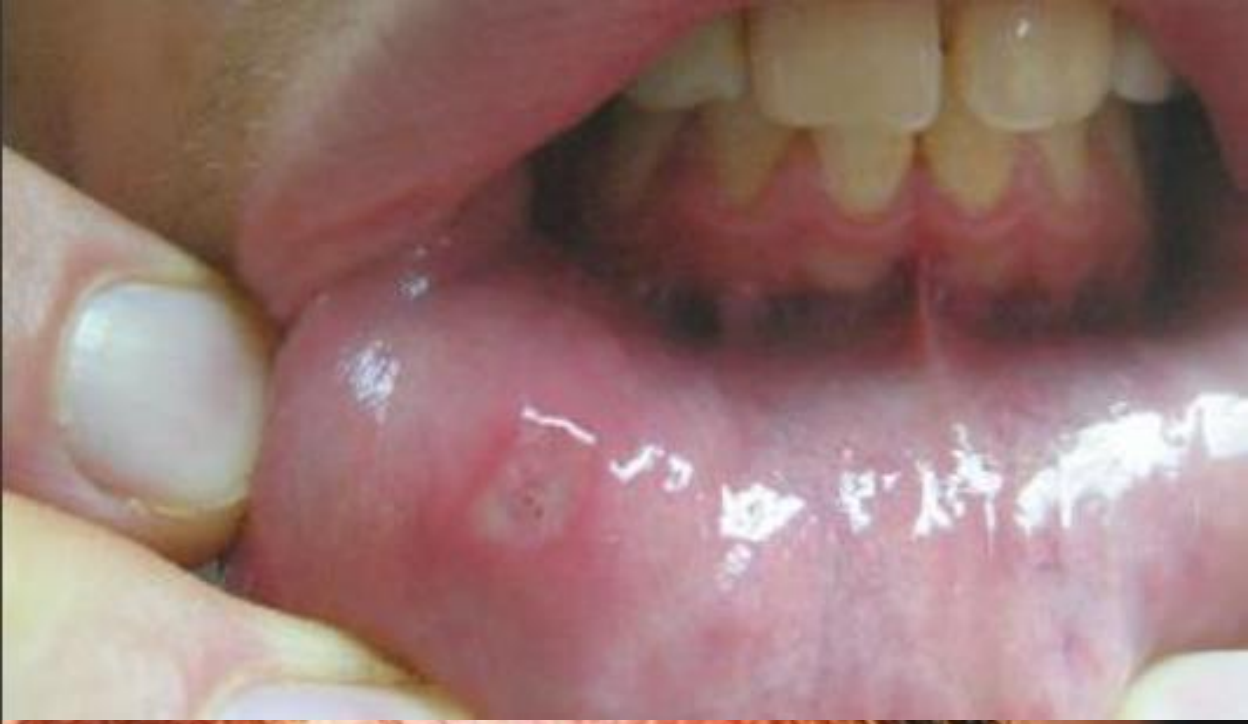


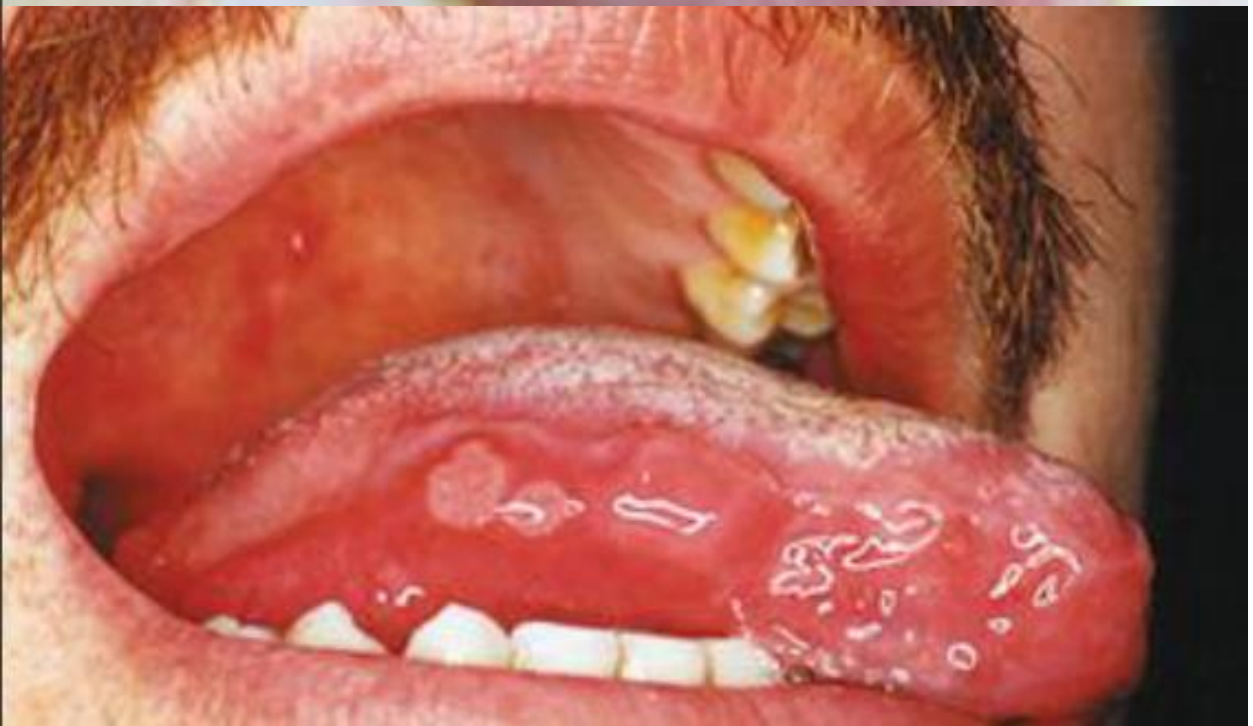
HENOCH-SCHONLEIN PURPURA

- On dependent parts.
- As the size of the purpura increases, the severity increases.



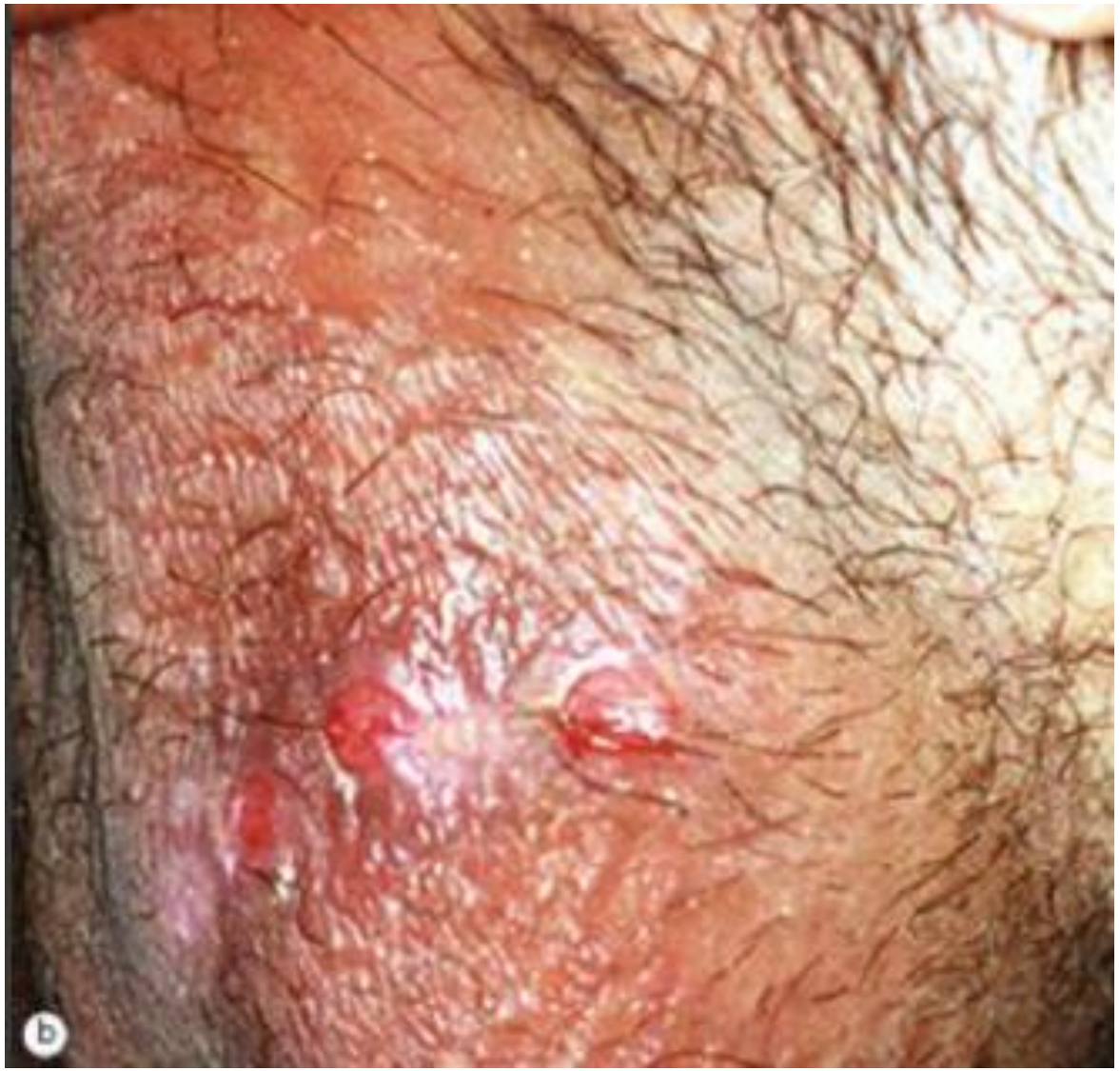






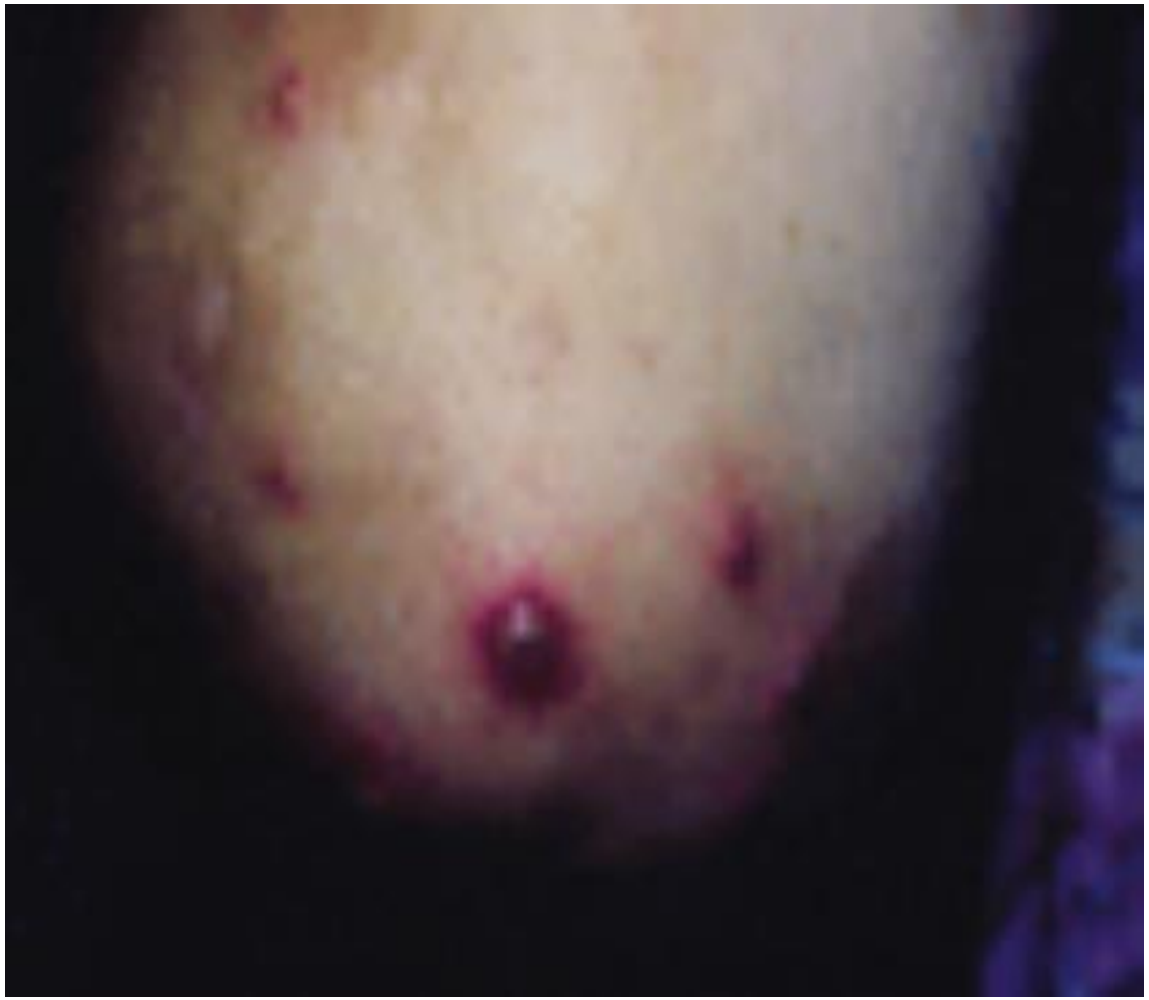
BEHCET ORAL ULCERS

- Aphthous ulcers.
- Recurrent with depressed base and white membrane.



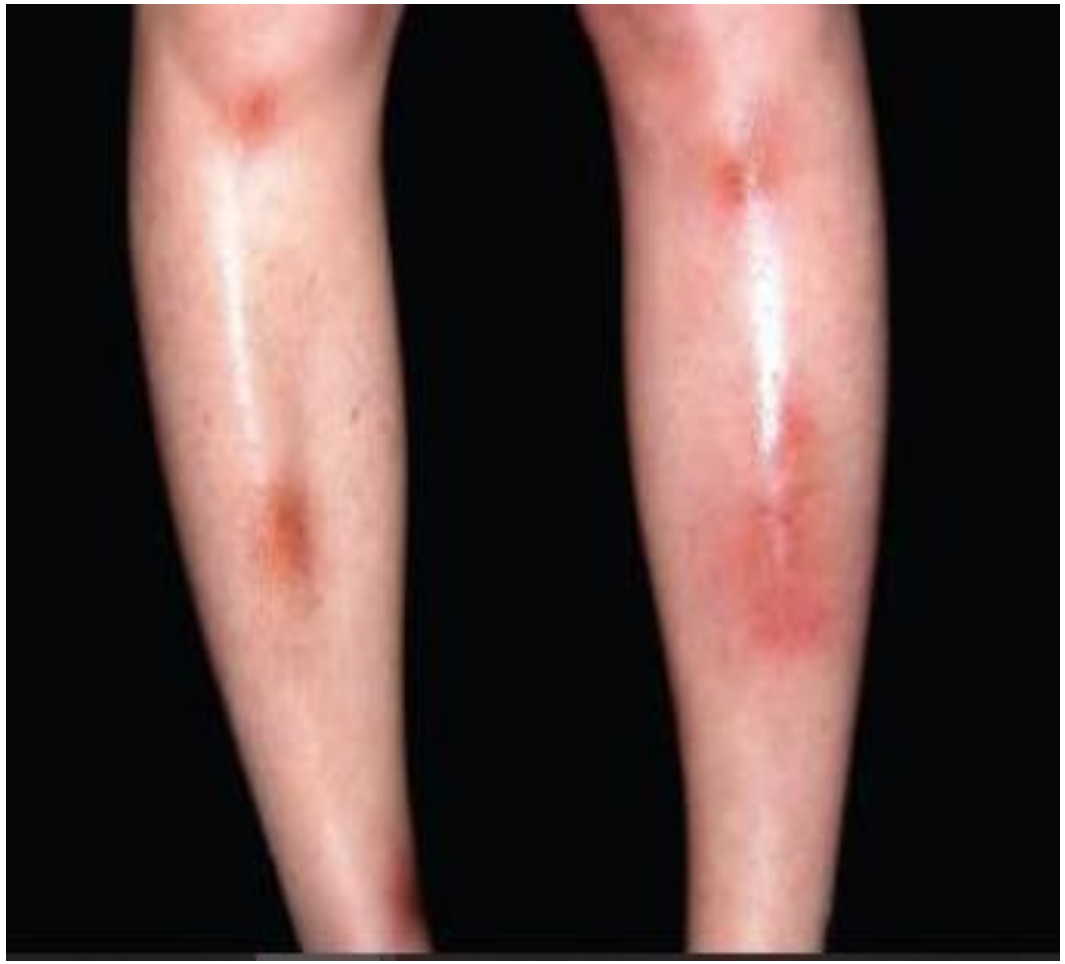
BEHCET GENITAL ULCERS

- They leave a scar.



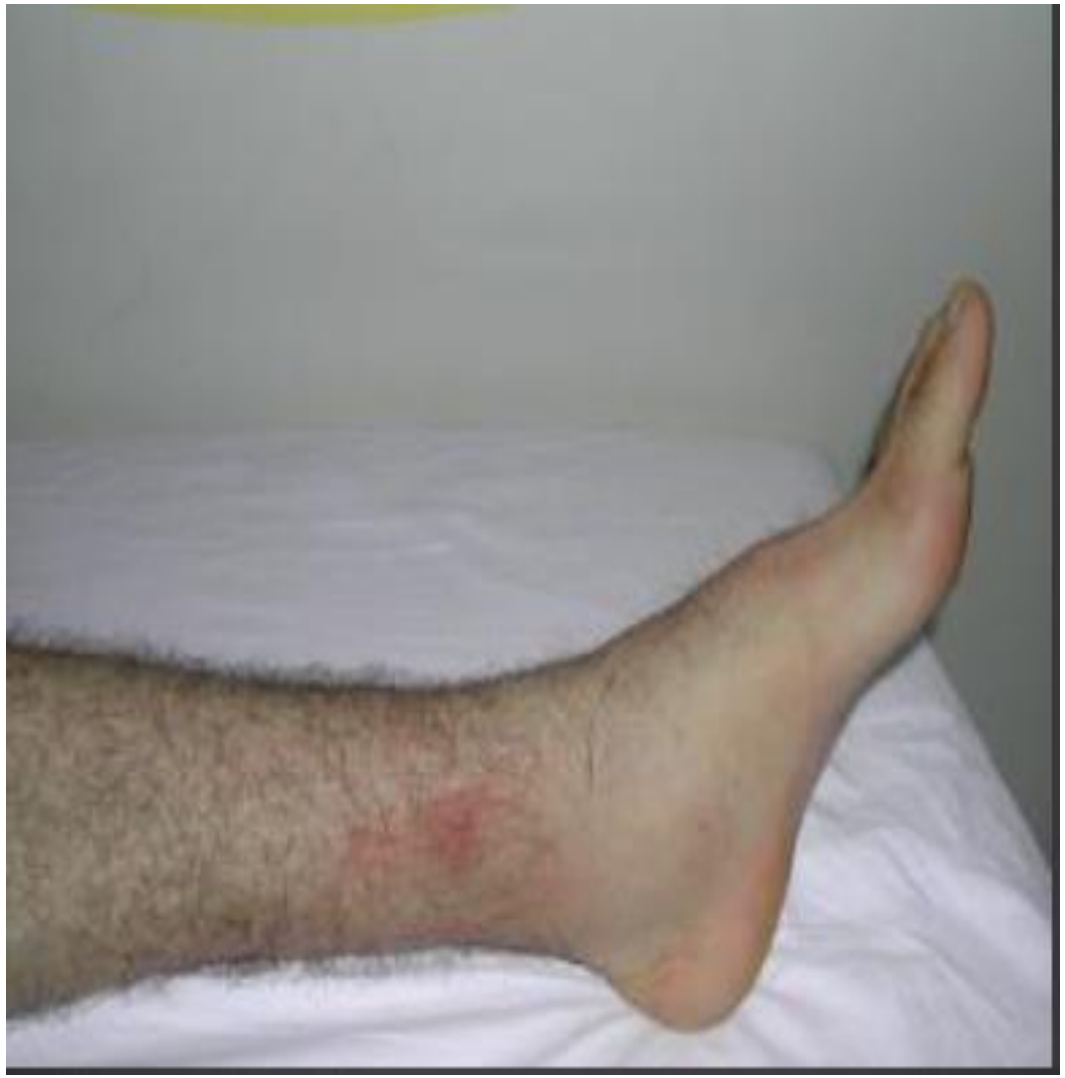
ACNEIFORM LESIONS

- Seen in Behcet disease.
- Acne-like lesions (the patient denies having such lesions before).



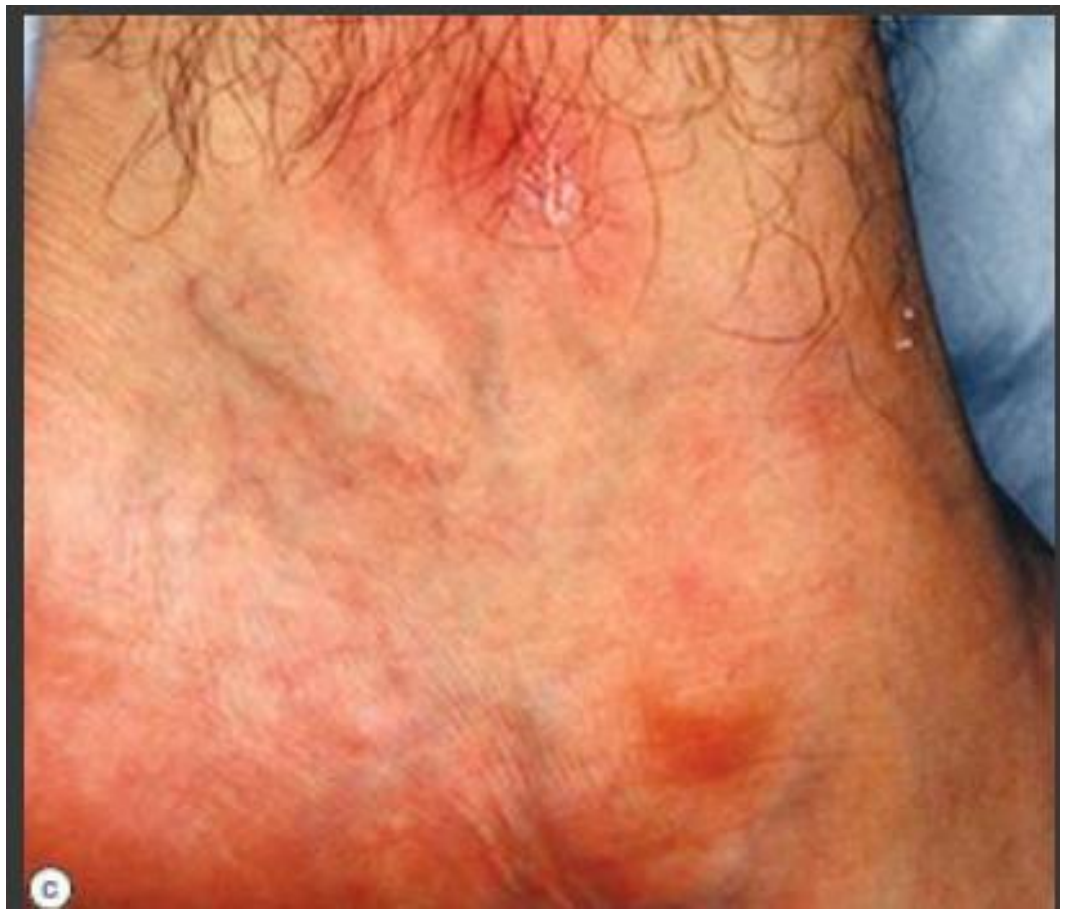
ERYTHEMA NODOSUM-LIKE LESIONS

- A sign of Behcet disease.
- Classically found on the shins of the legs and are very Tender.



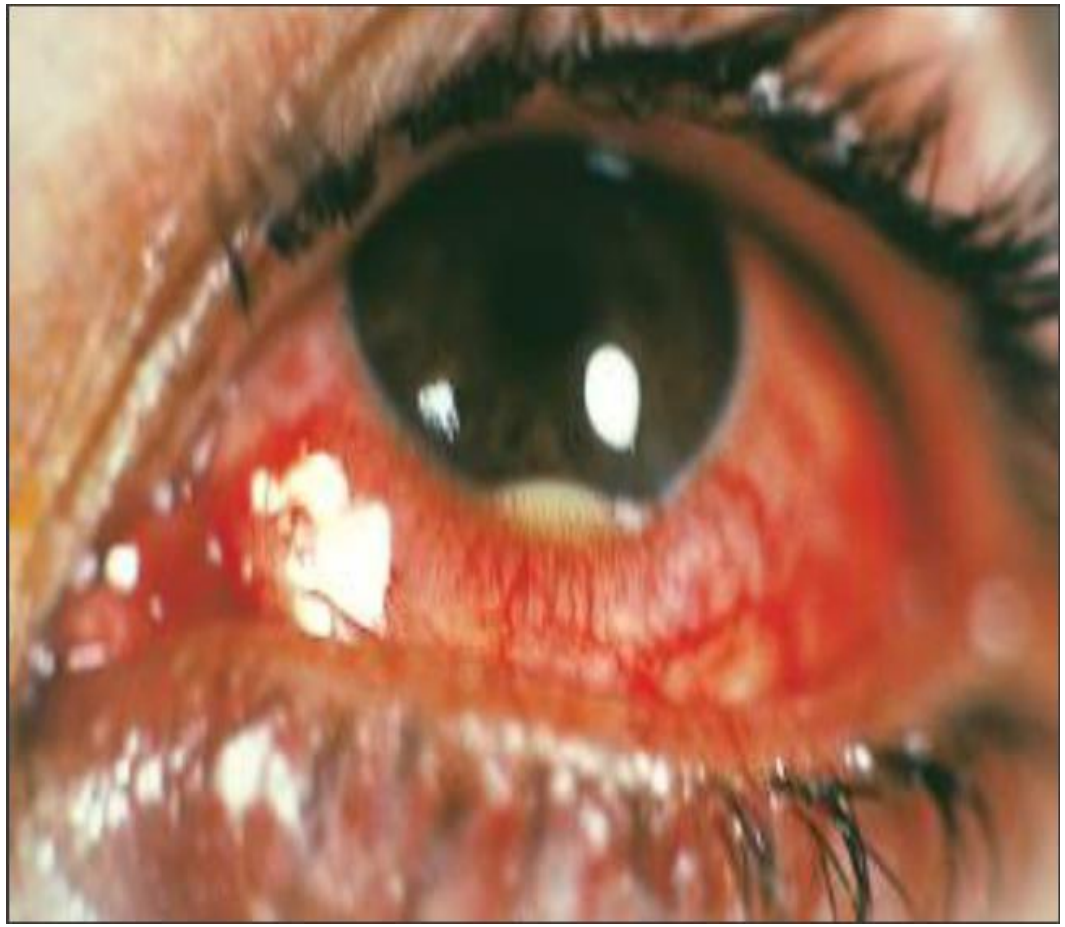
SUPERFICIAL THROMBOPHLEBITIS

- A sign of Behcet disease.
- Painful and described as a Cord-like Structure.



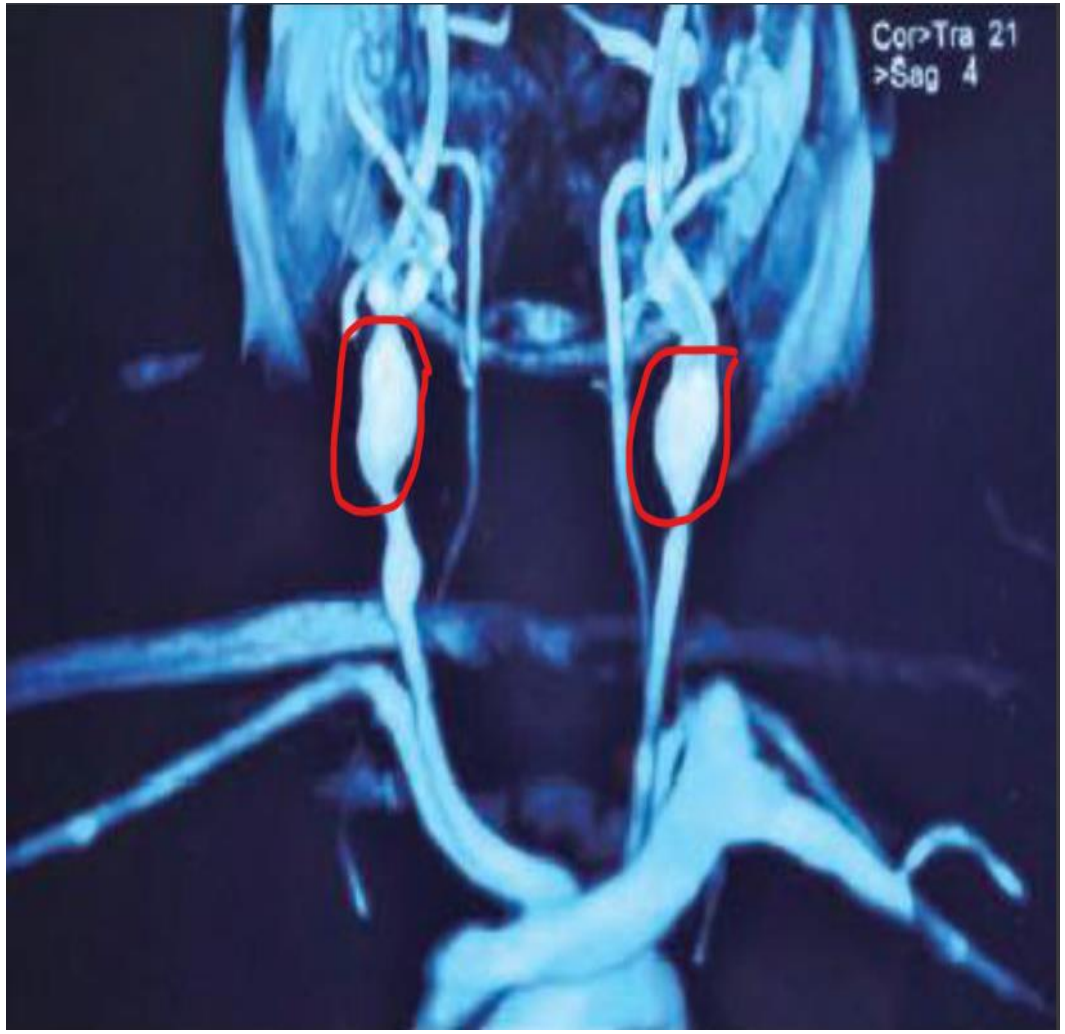
PATHERGY TEST

- A sign of Behcet disease.
- Needle at the site of subdermal penetration of the skin.
- It forms pustule that wasn't there before penetration.
- It indicates activation of neutrophils.
- Along with other symptoms it indicates Behcet disease, but it's not specific.

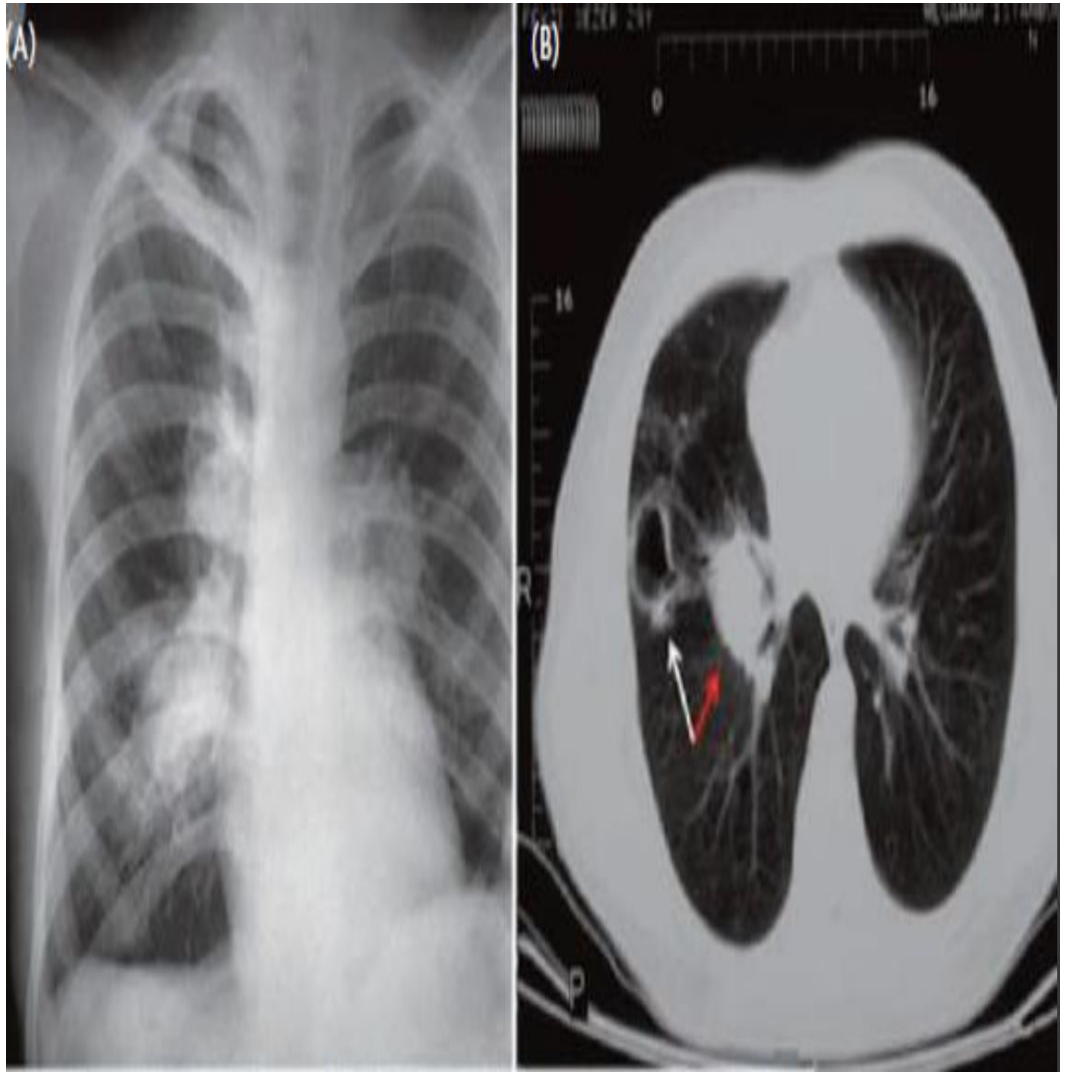


BEHCET EYE LESIONS

- Anterior uveitis and hypopyon.



CAROTID ANEURYSMS IN BEHCET DISEASE



PULMONARY ARTERY ANEURYSM IN BEHCET DISEASE

- More common in males.
- If not treated properly, it may lead to death.

TREATMENT OF BEHCET DISEASE

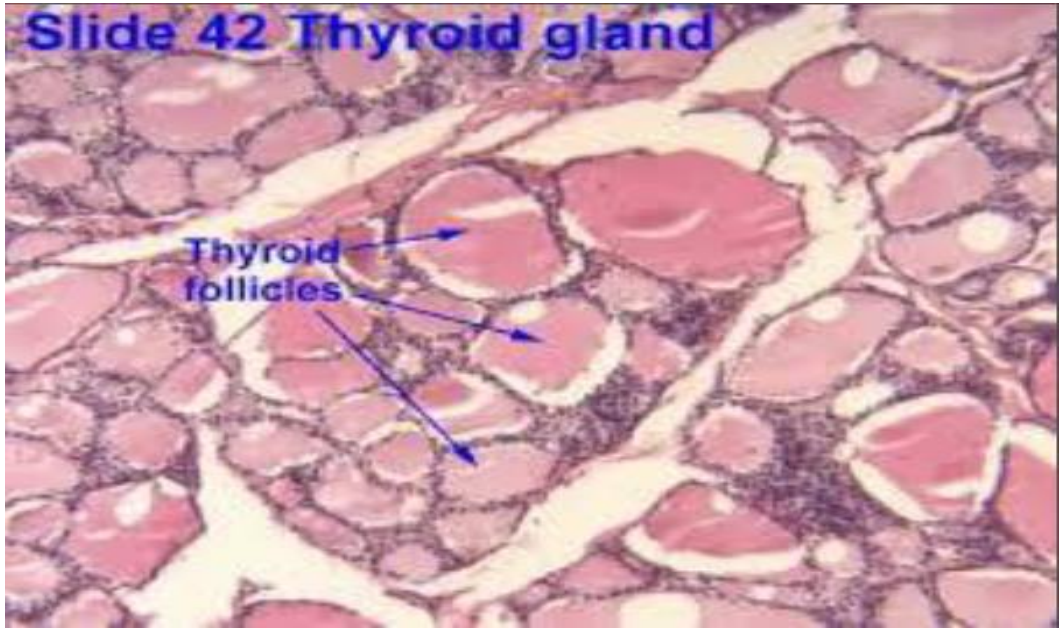
Behcet's Treatment

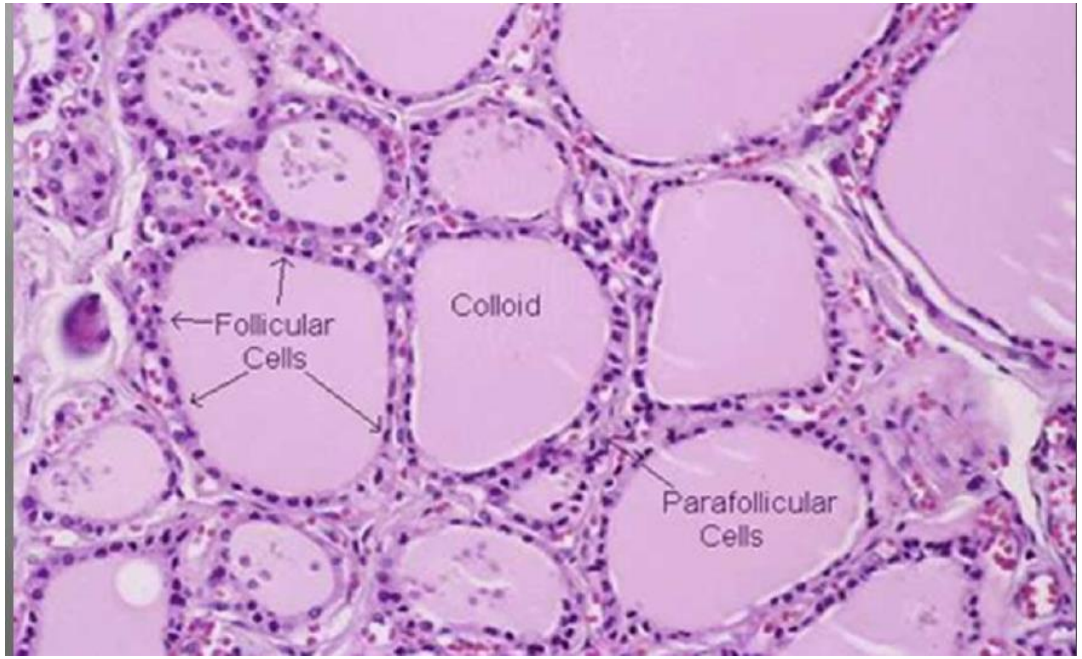
Depends on manifestations

- **Oral lesions:**
  - Colchicine
  - Azathioprine
  - Thalidomide
- **Arthritis**:
  - Colchicine
- **Eye**:
  - Steroids
  - Azathioprine
  - Interferon alpha
  - MMF
  - Infliximab
  - Rituximab
- **Vasculopathy**:
  - Steroids & cyclophosphamide
- **Neurological**:
  - Steroids
  - Interferon alpha
  - Anti-TNF

ENDOCRINOLOGY

THYROID DISORDERS





CROSS SECTION OF THE THYROID GLAND

- Thyroid tissue appears as closely packed ring-shaped structures consisting of a single layer of thyroid cells surrounding the lumen.
- The thyroid also contains Parafollicular cells (C cells), which may undergo hyperplasia early in the syndrome of familial medullary carcinoma of the thyroid (MEN2) and give rise to this tumor in both familial and sporadic forms.

THYROID GLAND

- A → Normal Thyroid Gland
- B → Normal Thyroid Follicle
- C → Parafollicular Cells (seen with Calcitonin immunostain).

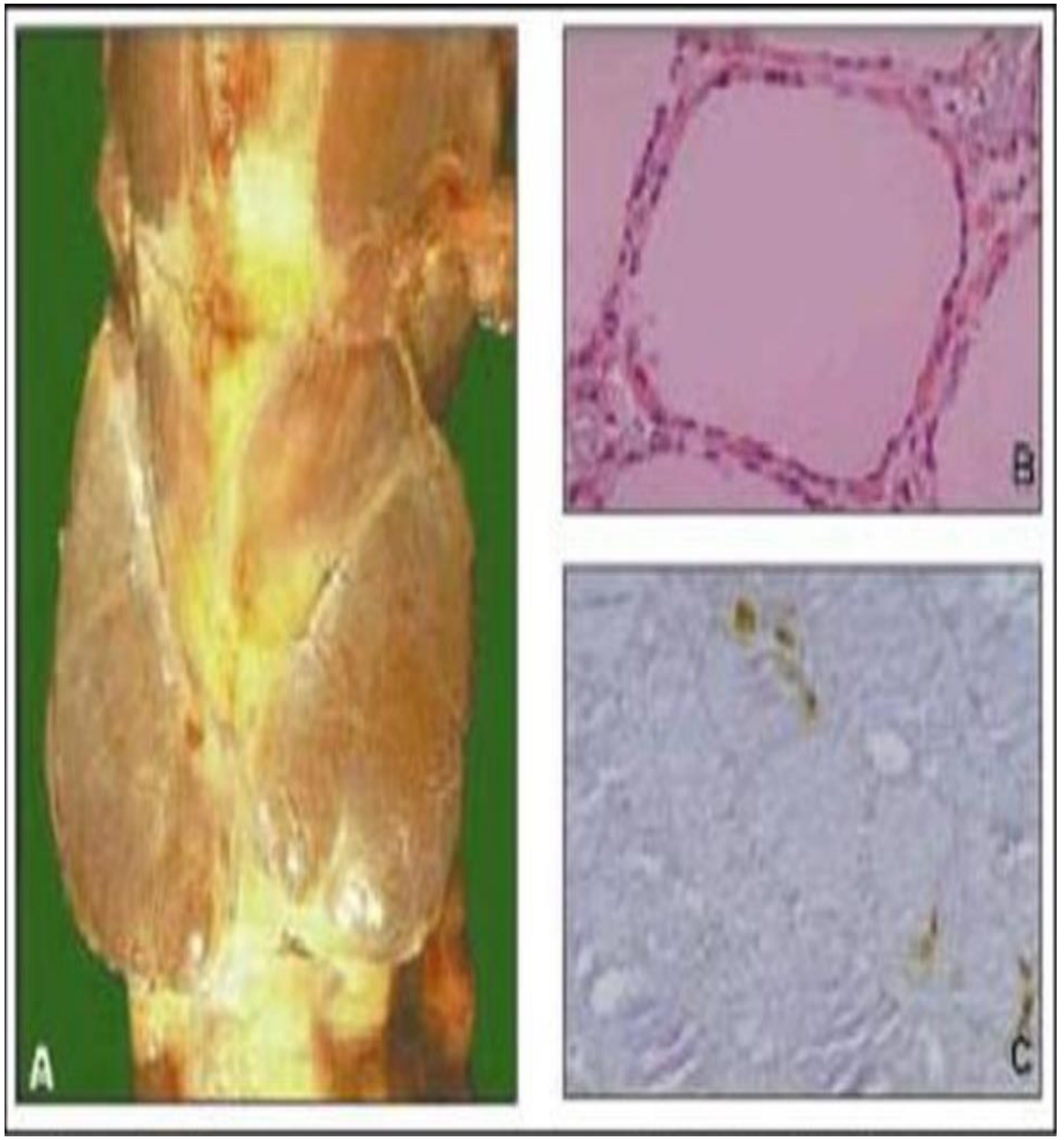
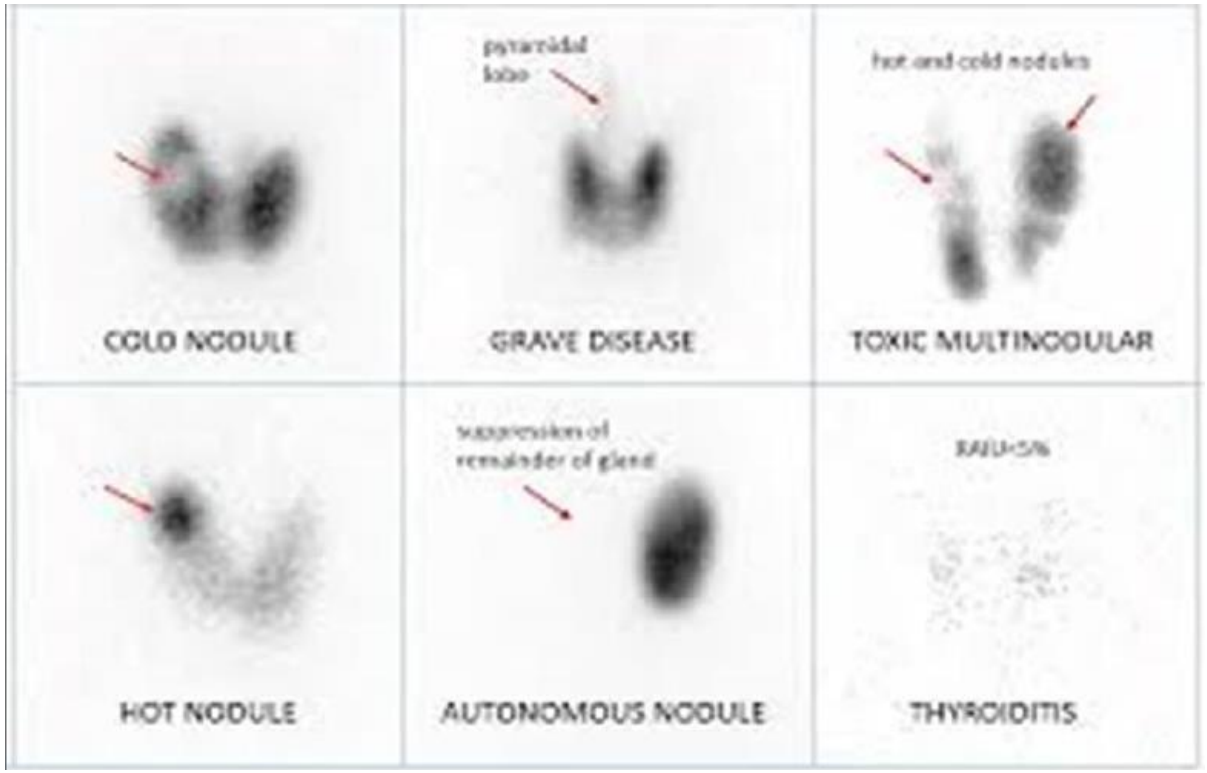


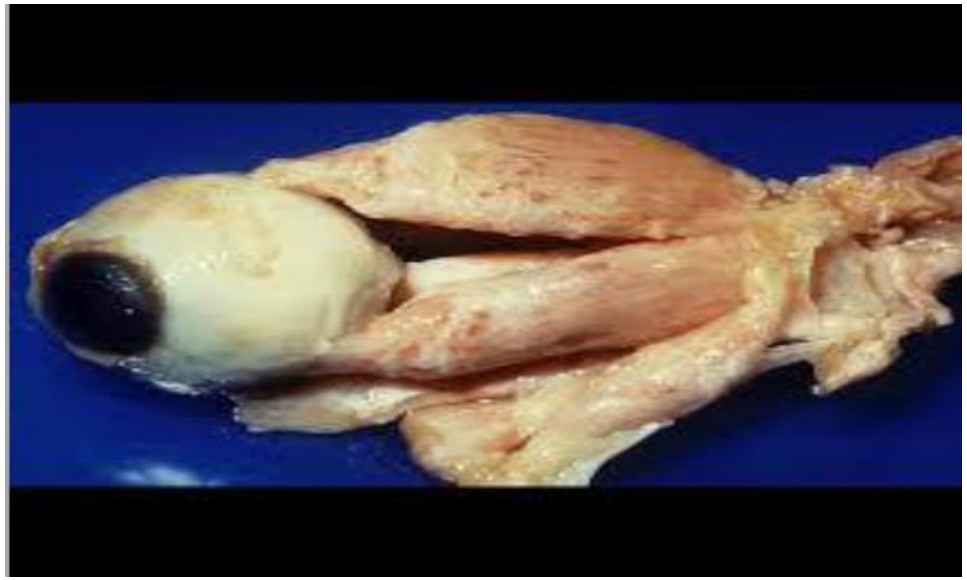
Illustration of the test that provide information about thyroid iodine metabolism

- Cold nodules are 80% benign and 20% malignant.
- In Graves disease there is excess Iodine, and in 60% there is diffuse uptake of iodine.
- Subacute Thyroiditis → Primary Thyrotoxicosis
- In primary thyrotoxicosis we need to test thyroid uptake, if there is low iodine uptake (which is less than 1%) we refer to the best imaging test which is Hot Thyroid Ultrasound.
- The best choice of treatment for Autonomous nodule is Reactive Iodine.
- Autonomous nodules could be Toxic Left Adenoma (Hot nodule) → Treat with Methimazole.
- Total Thyroidectomy is aggressive and not needed.
- The last pattern could be Thyroiditis, or it could be a patient taking Thyroxine or with Destructed Thyroid Gland.



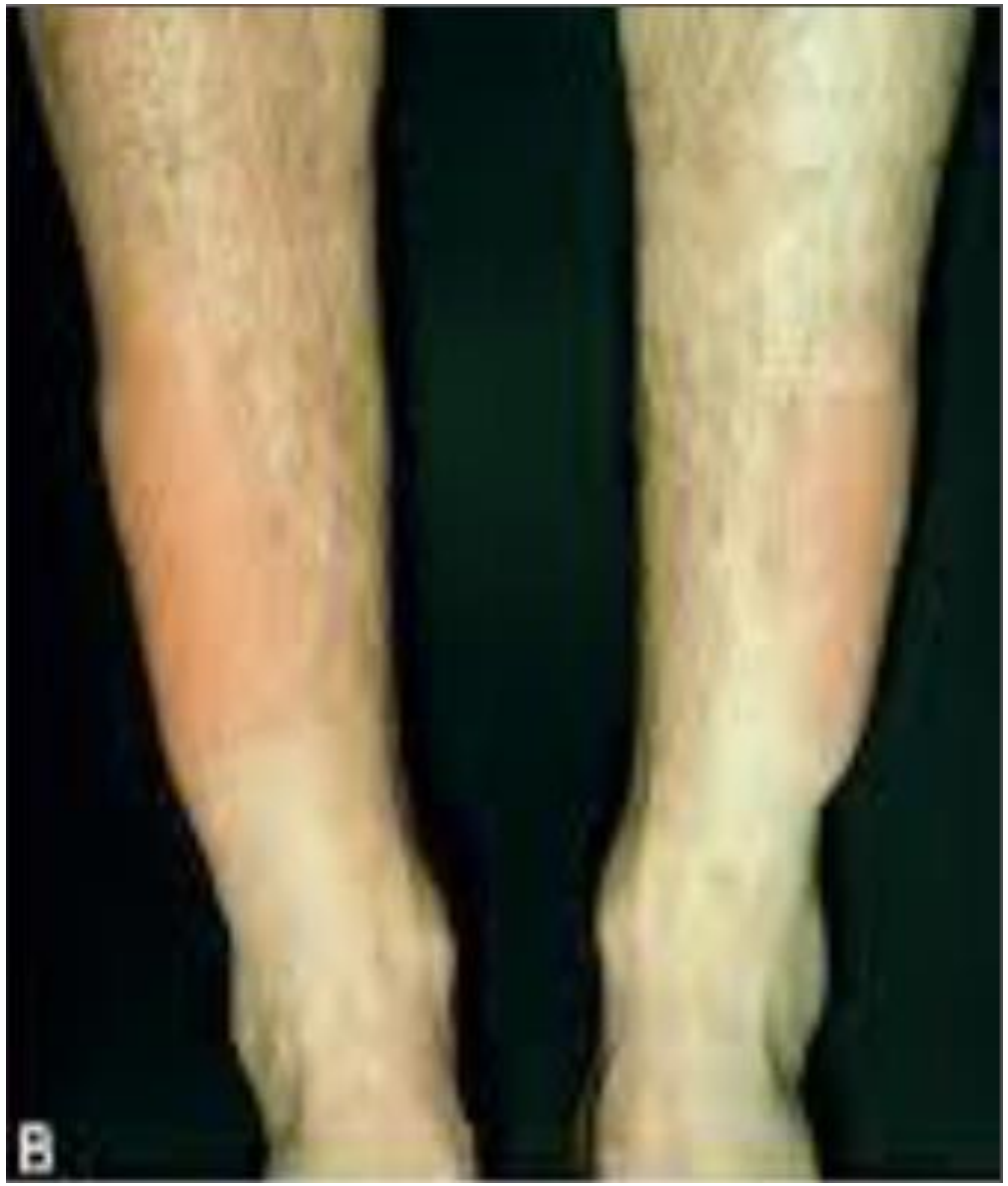
EXOPHTHALMOS / OPHTHALMOPLEGIA

- Specific for Graves Disease.
- Graves Disease is an autoimmune disease caused by Thyroid Stimulating Immunoglobulin which has receptors in the Thyroid Gland, Extraocular muscles, Skin, and Nail Beds.



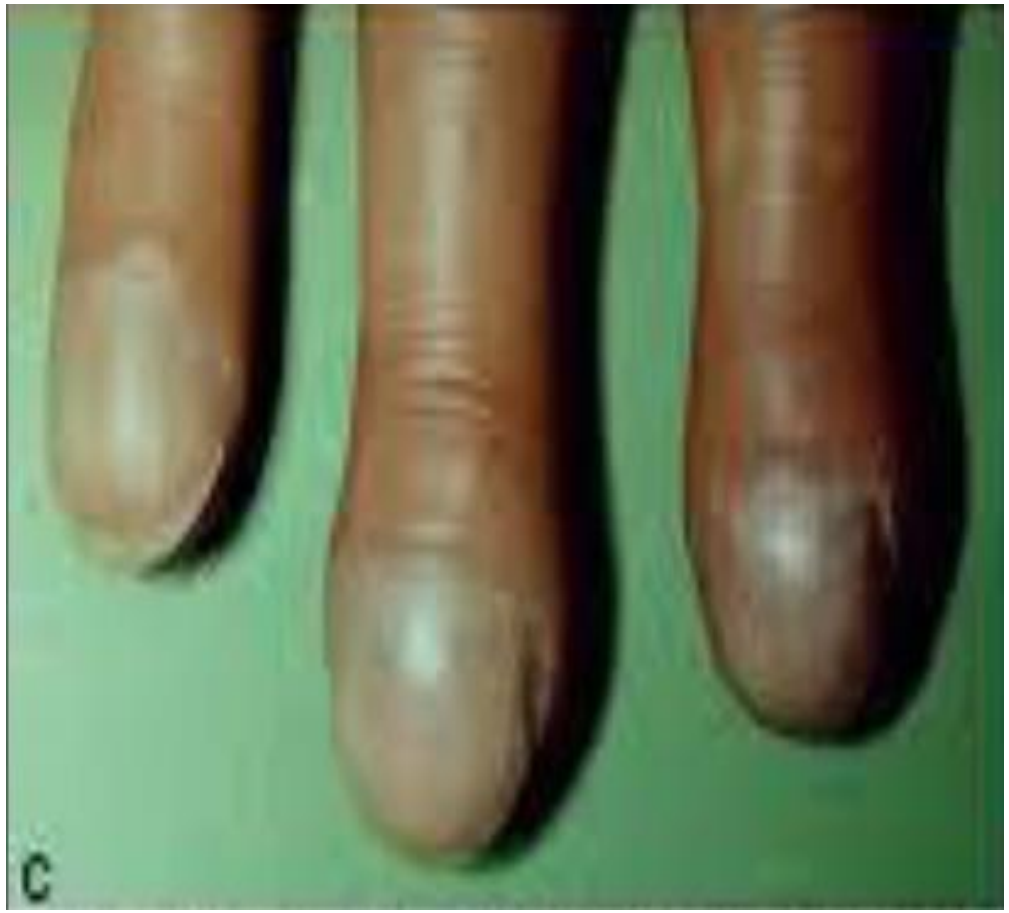
PRETIBIAL MYXEDEMA

- Specific for Graves Disease.



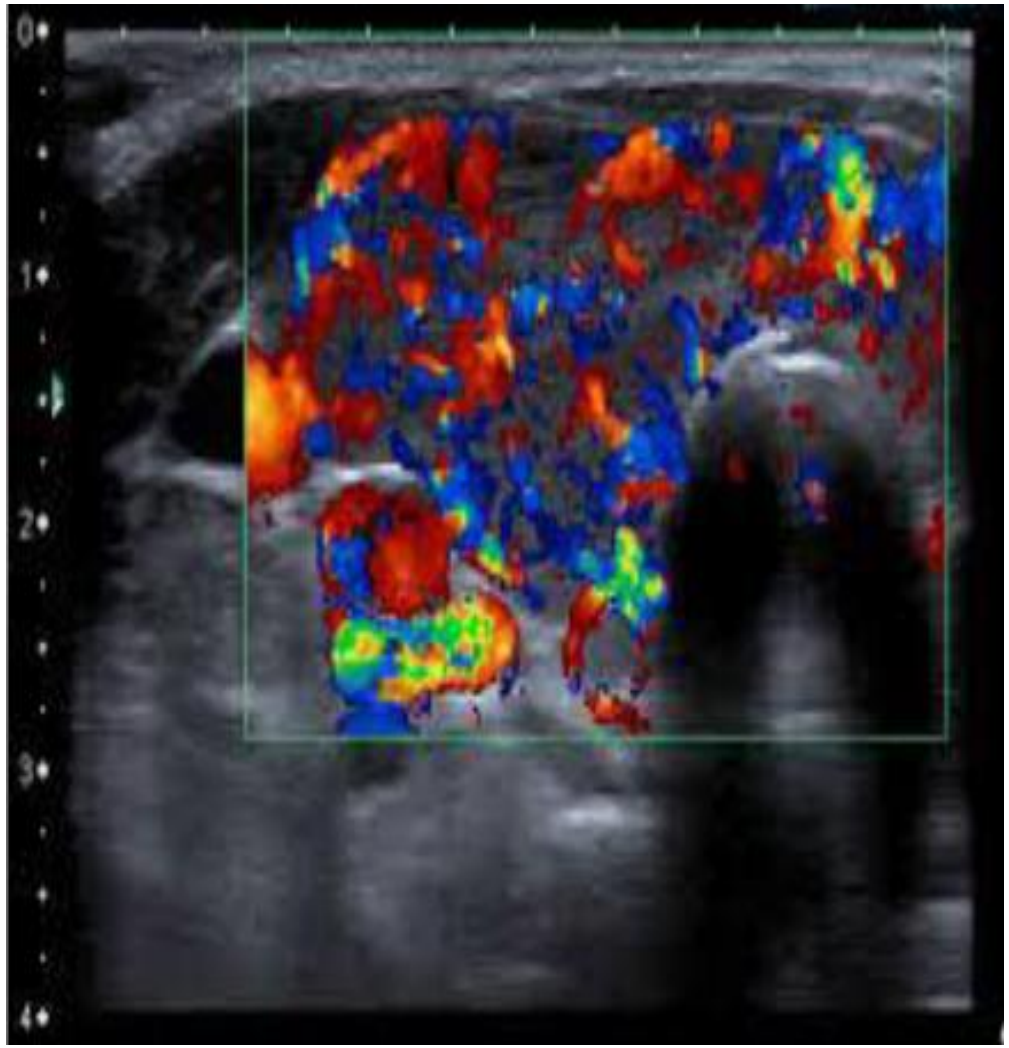
THYROID ACROPACHY

- Specific for Graves Disease.



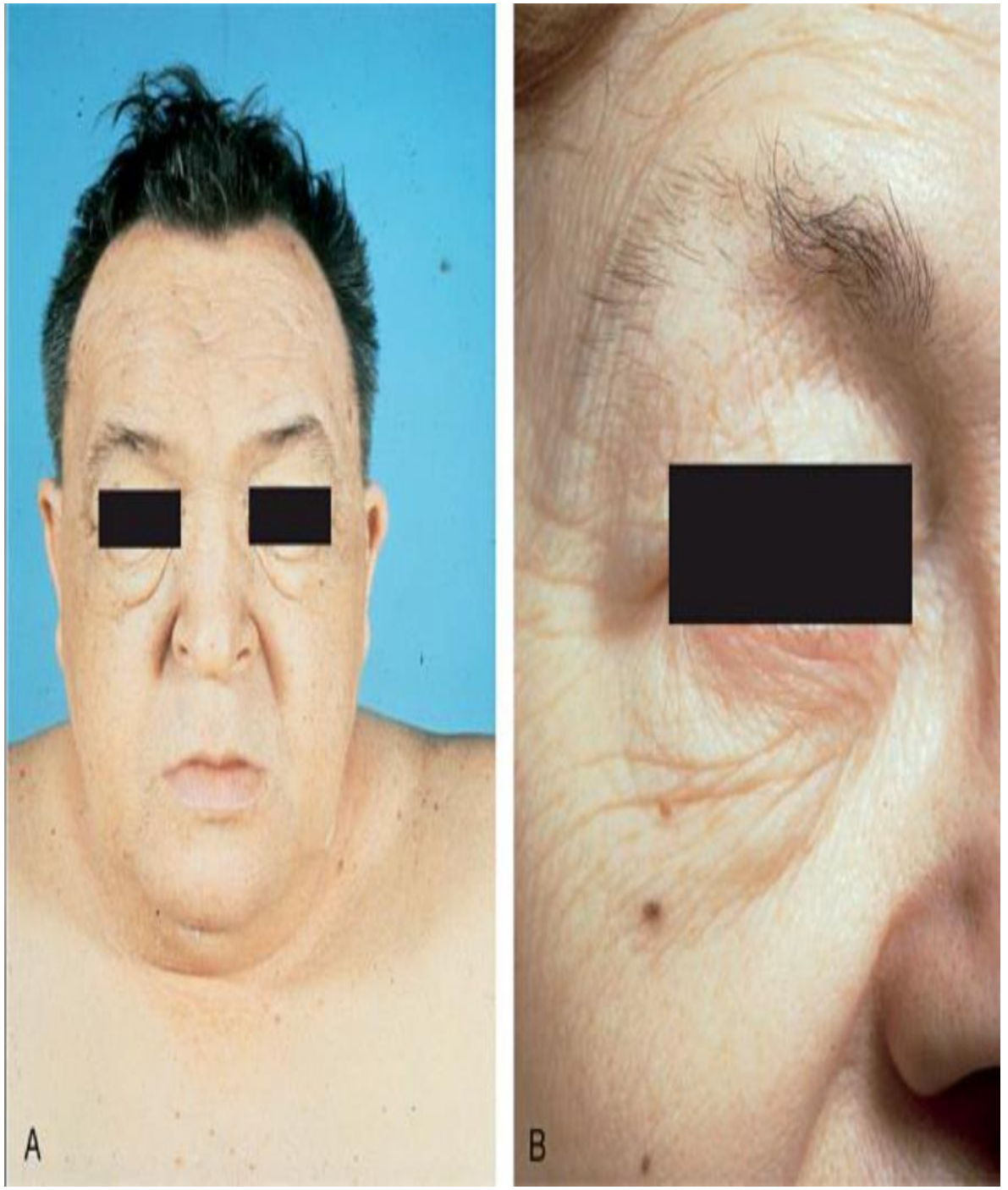
BRUITS

- Specific for Graves Disease.



HYPOTHYROIDISM

- Frontal Hair loss.
- Dry skin
- Obesity
- Periorbital Puffiness
- Outer third loss of eyebrows.
- Also associated with Proptosis.



Myxedema coma / myxedema crises

- An uncommon but a life-threatening form of untreated Hypothyroidism with physiological decompensation.

- Precipitated by a secondary insult, like Climate-induced hypothermia, infection or other systemic condition, or drug therapy (Sedation).

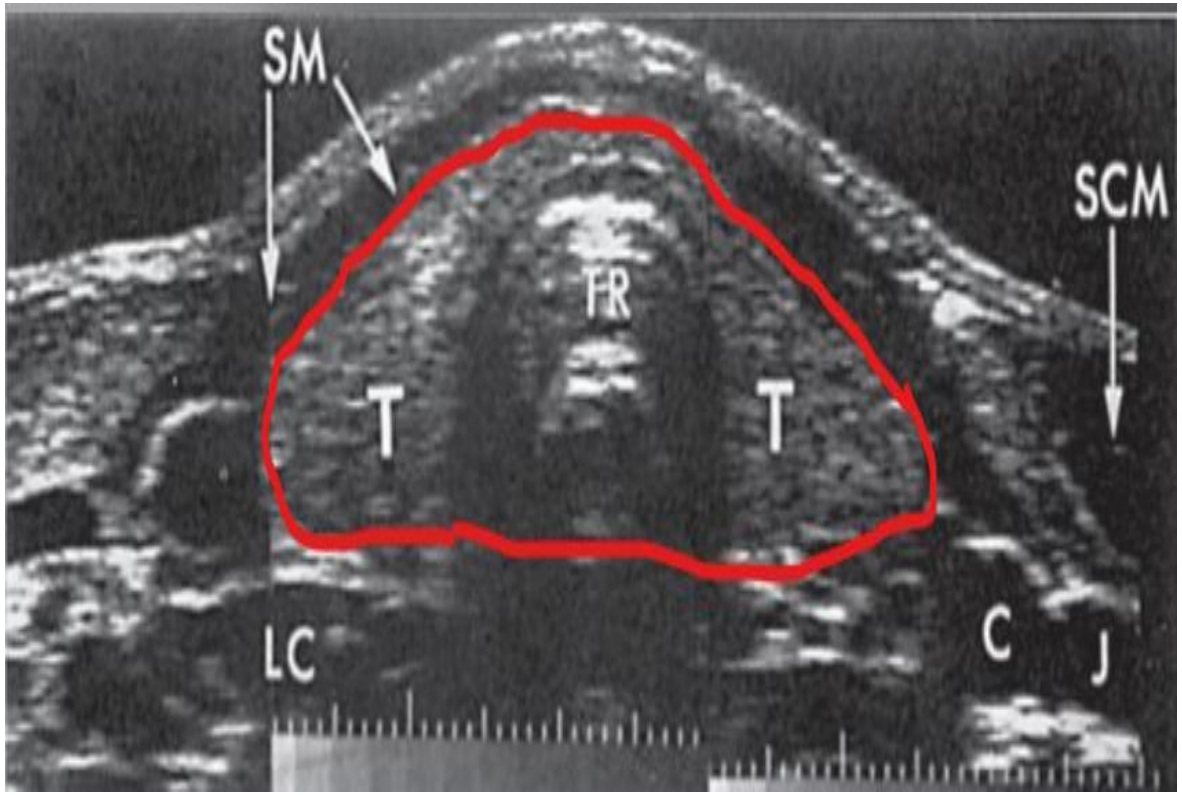
- Patients present with changes in their mental status including lethargy, stupor, delirium and coma, and Hypothermia.

- Treatment: Supportive measures (Intubation) + IV Levothyroxine (if not available use an NG tube) + Stress steroid replacement after cortisol level is obtained (in the light of the possibility of Adrenal Insufficiency).

- Always remember to give Corticosteroids to reduce Adrenal Insufficiency since it's one of the causes of Coma.

NORMAL THYROID GLAND

- Normally the Thyroid is Gray and Homogenous.

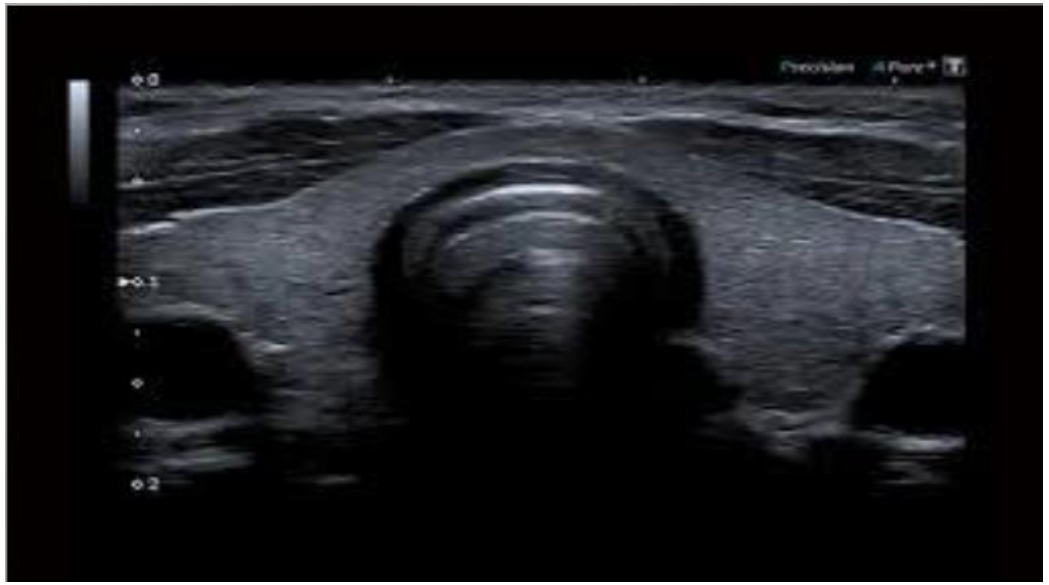


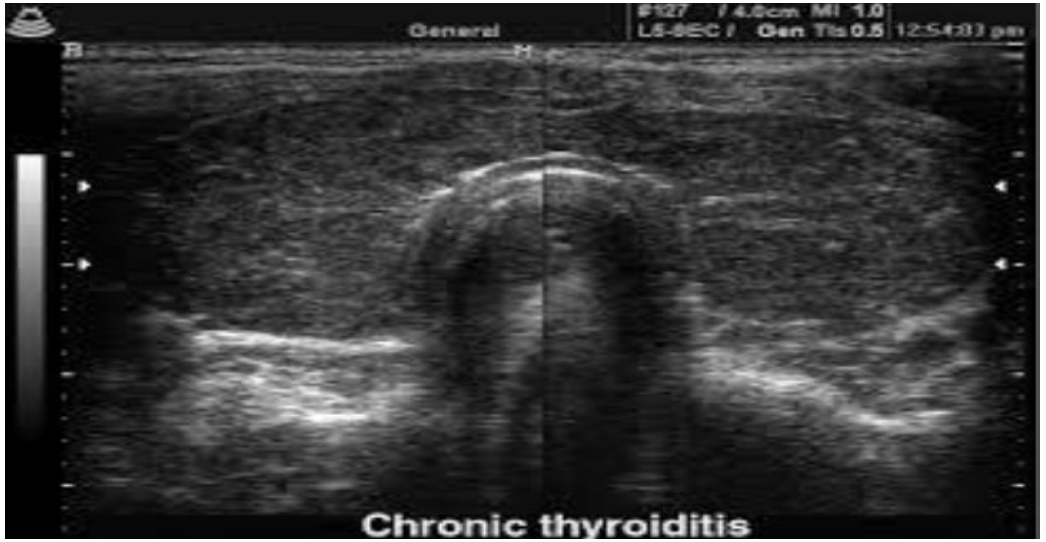
Nontoxic goiter: Diffuse and nodular

- Nontoxic means Thyroid enlargement with Normal Thyroid Function Test and doesn't result from inflammation or neoplasia.
- A thyroid nodule is a Discrete lesion within the Thyroid Gland that is due to an abnormal focal growth of thyroid cells.
- Thyroid nodule are benign if (Cystic, Solid or mixed) however if it is a big nodule do FNA to rule out malignancy.
- If the patient has Goiter with mild Dyspnea when lying flat, before doing surgery you need to refer him to the respiratory clinic to do flow volume loop to make sure if thyroid is causing tracheal stenosis or not, to check if the dyspnea is due to the thyroid or not.
- Notice that the patient in the picture has a very large goiter that may be associated with Dysphagia, Dyspnea and Dysphonia.

ULTRASOUND OF THE THYROID GLAND

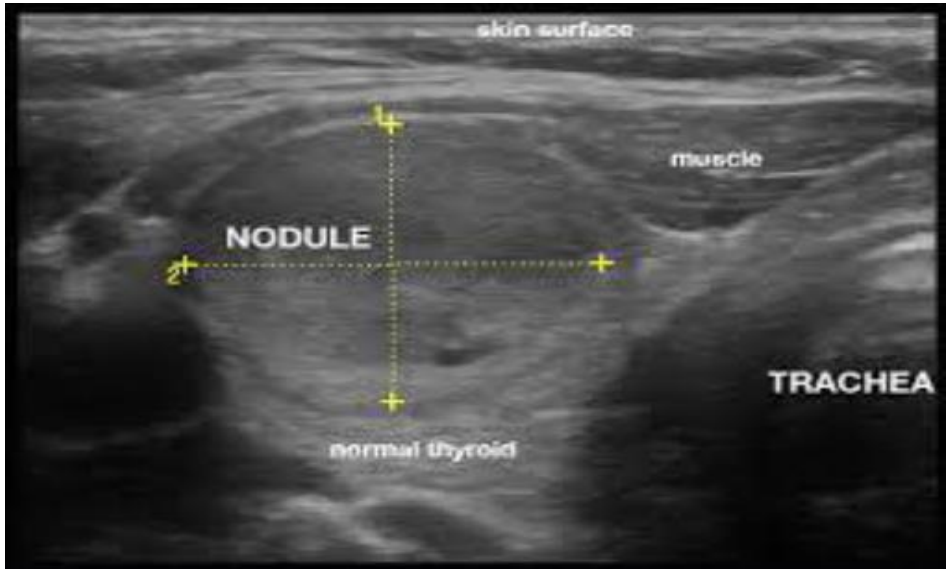
- The first picture shows Normal, Homogenous Thyroid Gland.
- The second picture shows Enlarged, Heterogenous, Darker (Hyperechoic) Thyroid Gland.
- The findings in the second picture are typical for Graves, Hashimoto thyroiditis and Thyrotoxicosis, So Ultrasound doesn't help to differentiate between them.

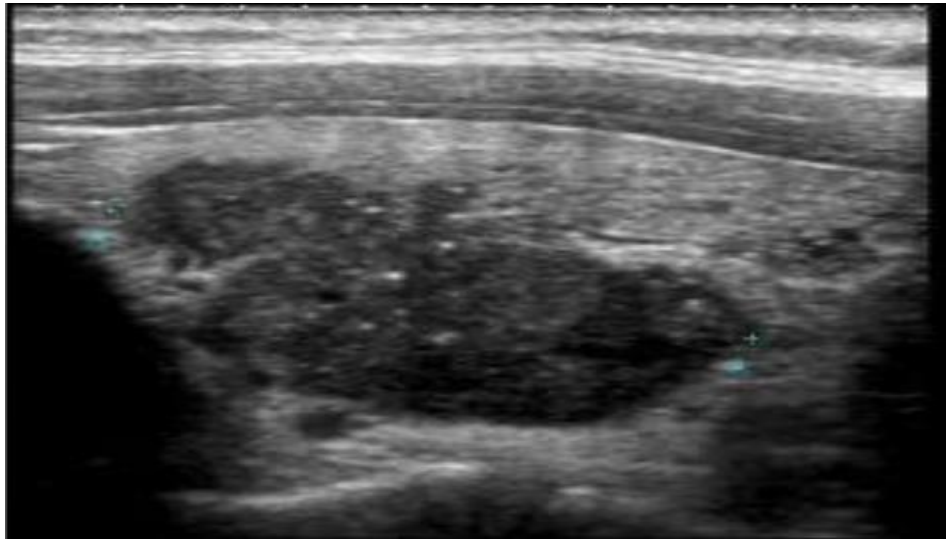




ULTRASOUND OF THE THYROID GLAND

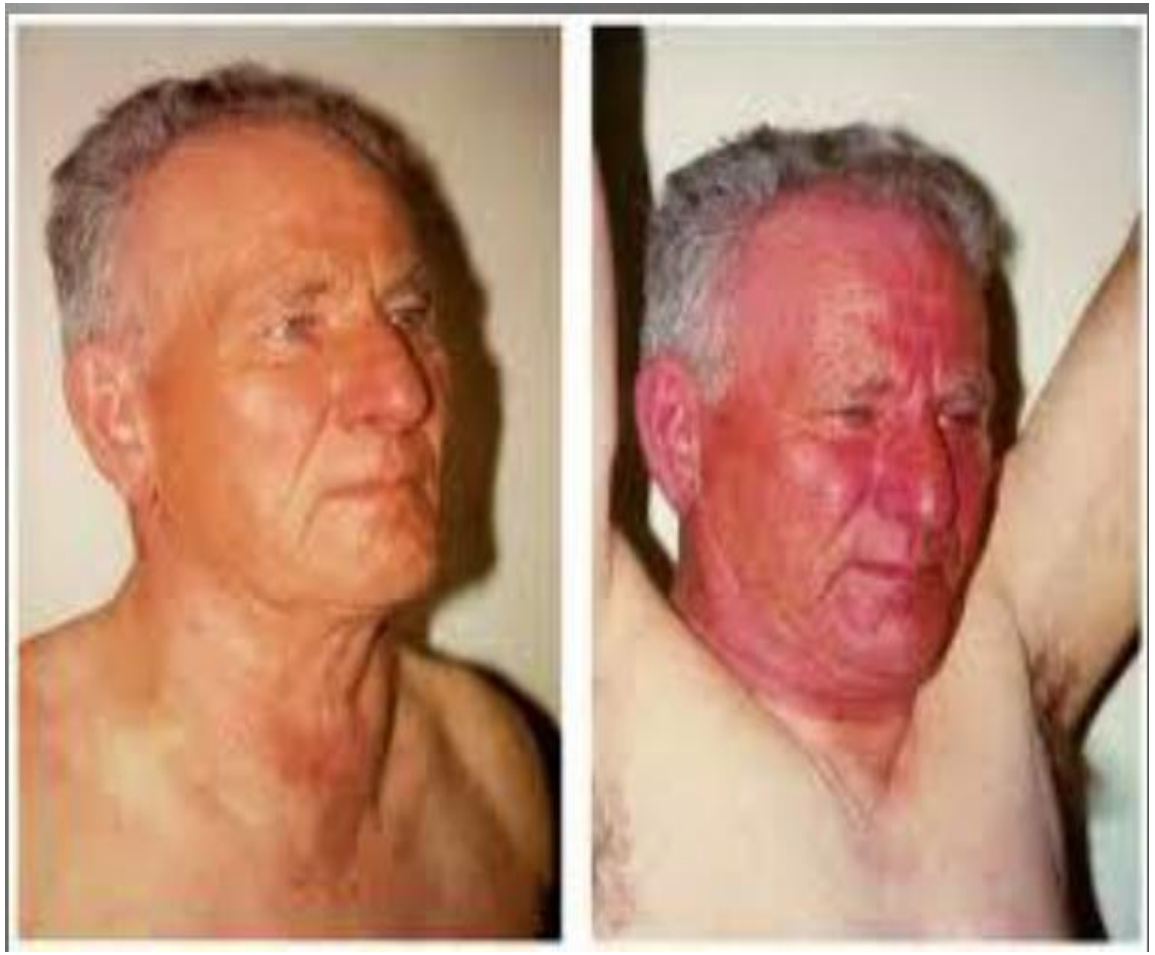
- The first picture shows a Thyroid nodule with smooth margin, benign looking and no calcifications.
- The second picture also shows a Thyroid nodule, but it has ill-defined margins, irregular surface, calcifications, and notice the size.
- The larger the nodule the higher the risk of malignancy.





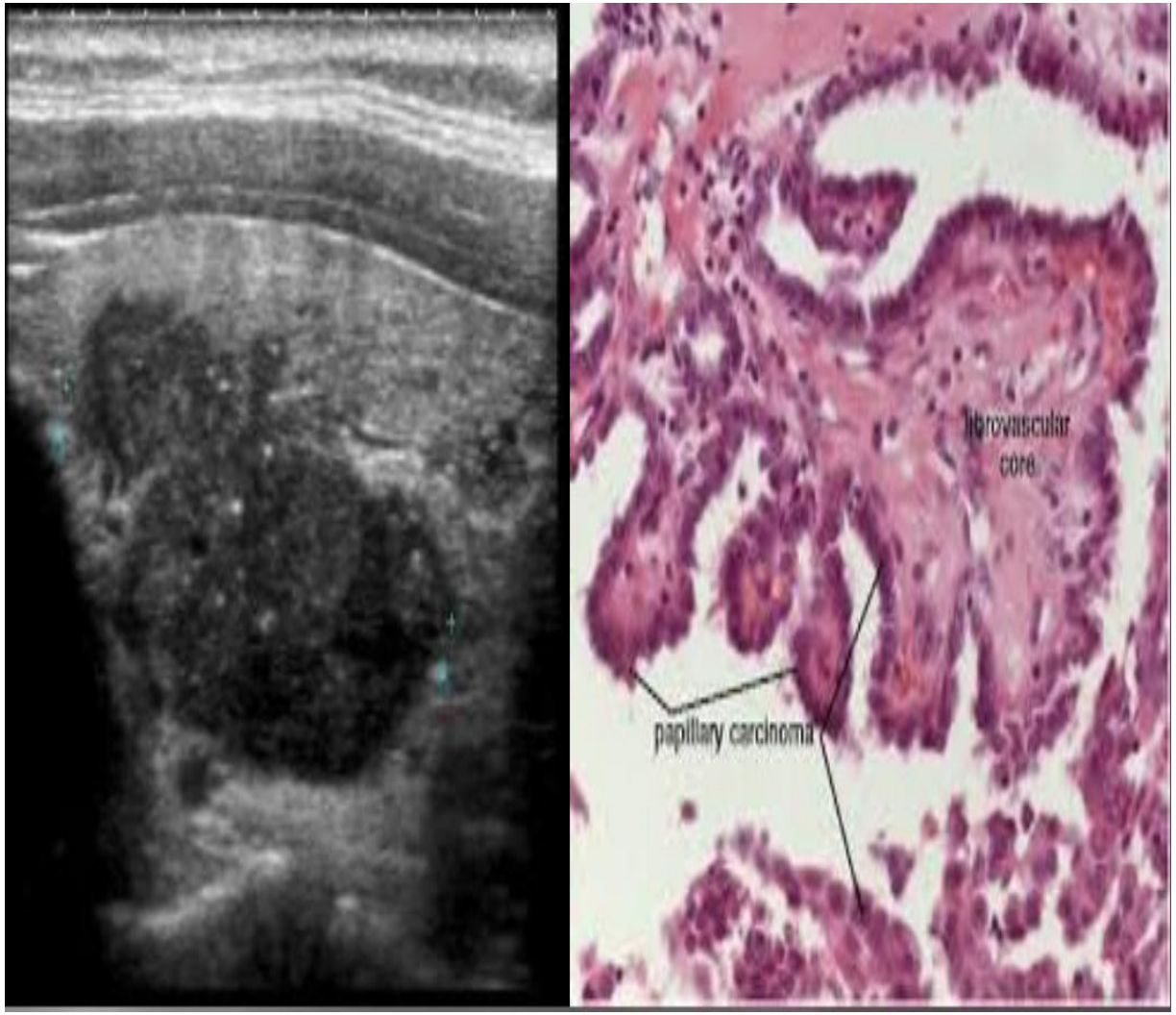
PEMBERTON'S SIGN

- Indicates SVC obstruction by Enlarged Thyroid Gland.
- It is one of the indications for Thyroid Surgery.



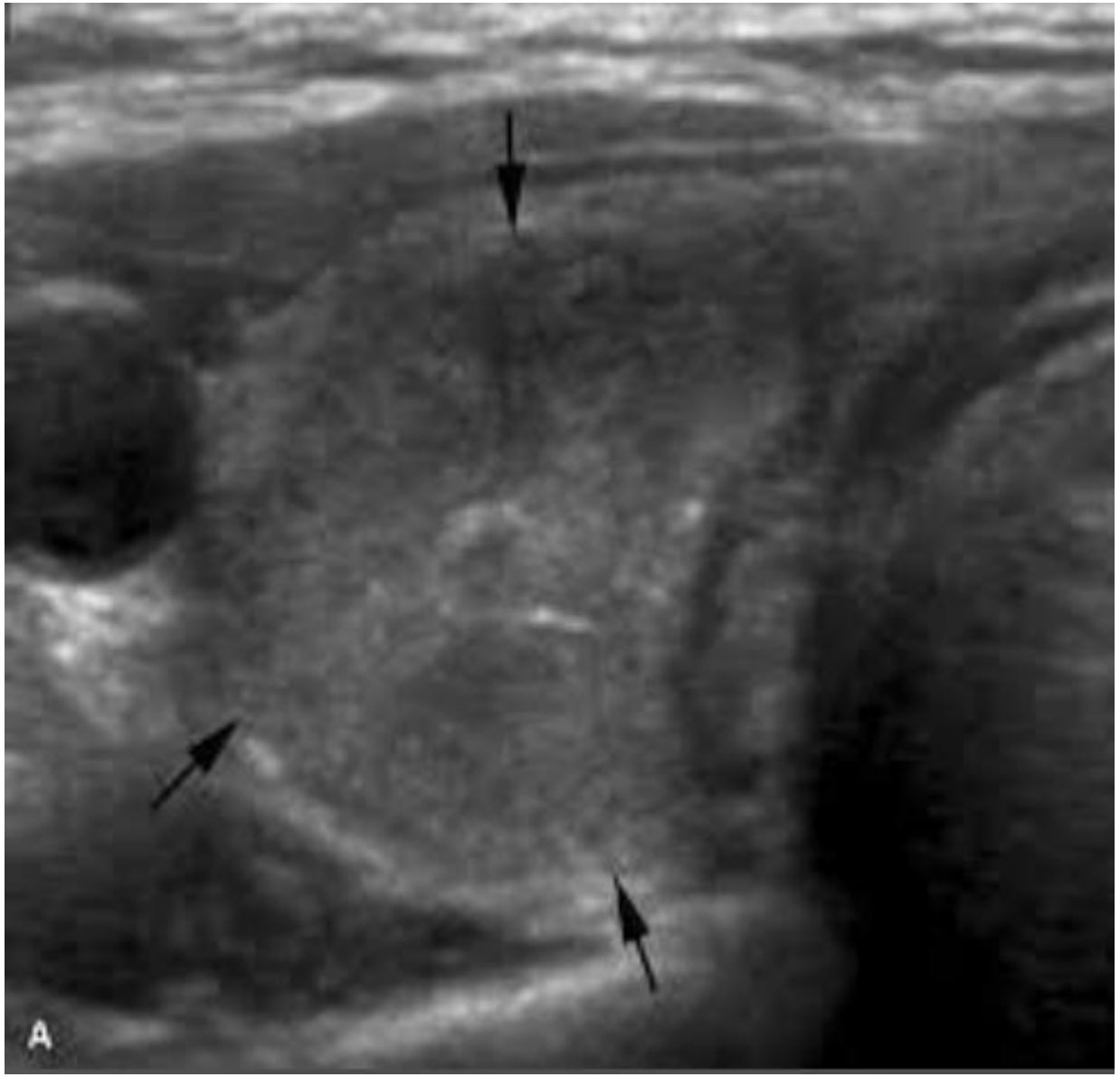
THYROID CANCER

- Thyroid cancer is generally first Suspected by a Lump or nodule in the Thyroid Gland.



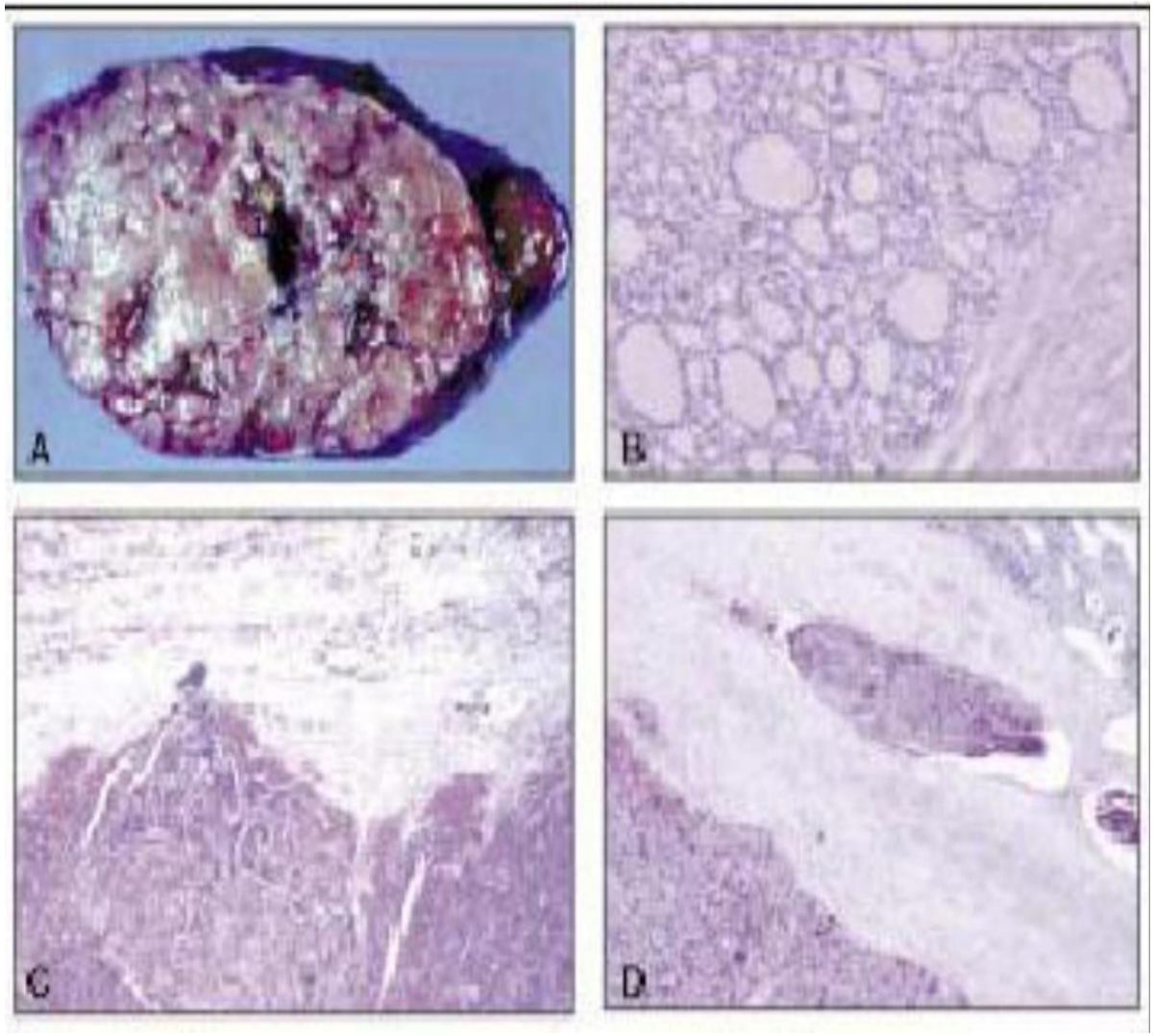
PAPILLARY THYROID CANCER

- Most common type of thyroid cancer.
- Usually not aggressive.
- May spread, but usually not beyond the neck.
- Papillary cells resemble finger-like projections.
- Tumor development can be related to radiation exposure, such as radiation treatment for Acne or adenoid problems in Children.
- Mass Description on Ultrasound: Thyroid nodule with ill-defined margins, irregular surface, and calcifications.



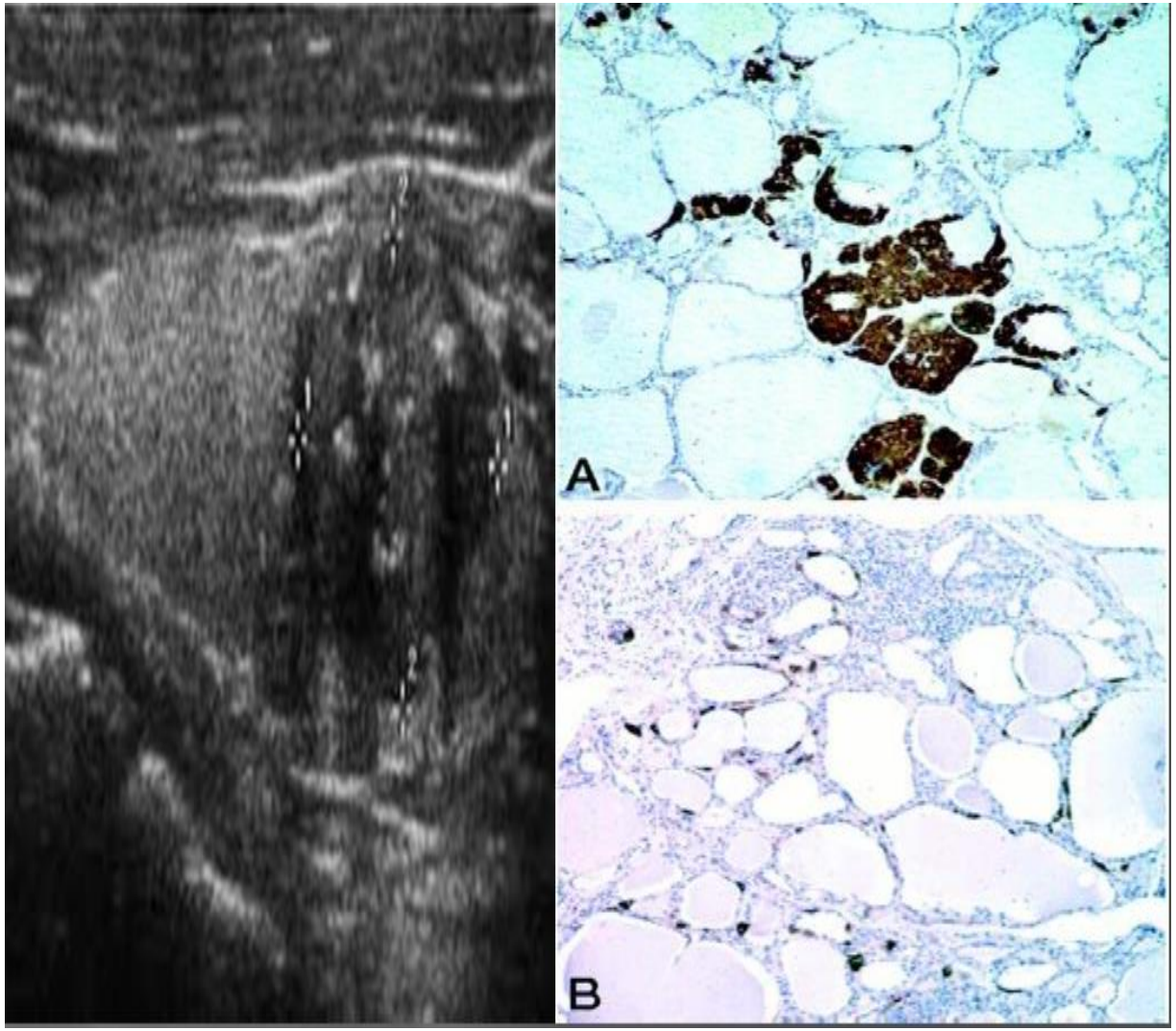
FOLLICULAR THYROID CANCER

- The second most common Thyroid cancer.
- Cancer cells may invade blood vessels and travel to other body parts such as bone or lung tissues.



FOLLICULAR THYROID CANCER

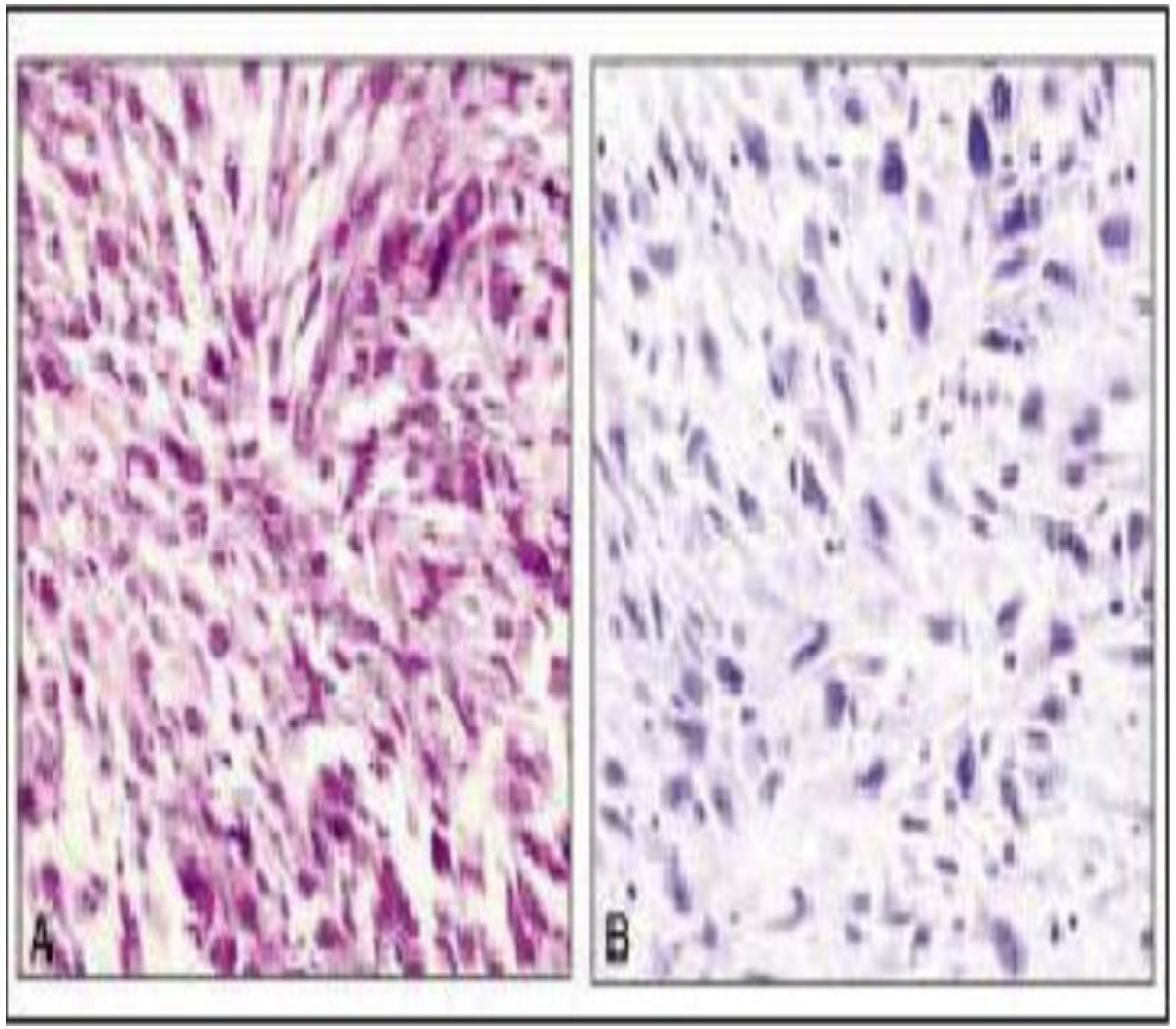
- Follicular cells are Sphere-shaped.
- A → Follicular adenoma with variegated gross appearance.
- B → Follicular adenoma (the periphery of the tumor is surrounded by a fibrous capsule).
- C → Follicular adenoma with indentation of the inner aspect of the tumor capsule.
- D → Follicular carcinoma with vascular invasion with tumor attachment to the endothelium.



MEDULLARY THYROID CANCER

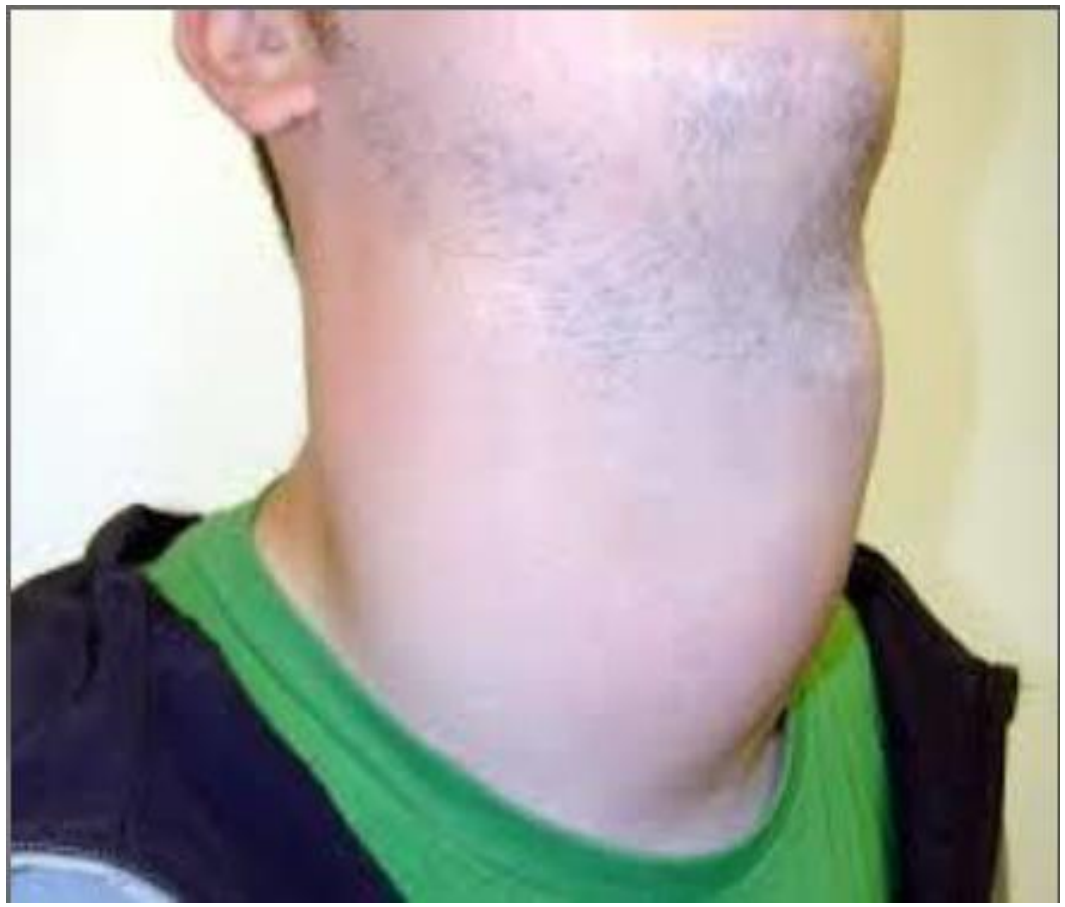
- Develop from C cells or parafollicular cells that produce Calcitonin.
- Elevated Calcitonin level can indicate Cancer.
- 4 forms of this cancer:

1- Sporadic 2- MEN2A 3- MEN2B 4- Familial(Genetic but not linked to other MEN-related endocrine tumors).



ANAPLASTIC THYROID CANCER

- Very rare.
- Poor prognosis.
- Least responsive to treatment.
- The figure shows undifferentiated (Anaplastic) carcinoma.
- A → Spindle cells in storiform growth pattern.
- B → Prominent Hyperchromatism and atypia of tumor cells.



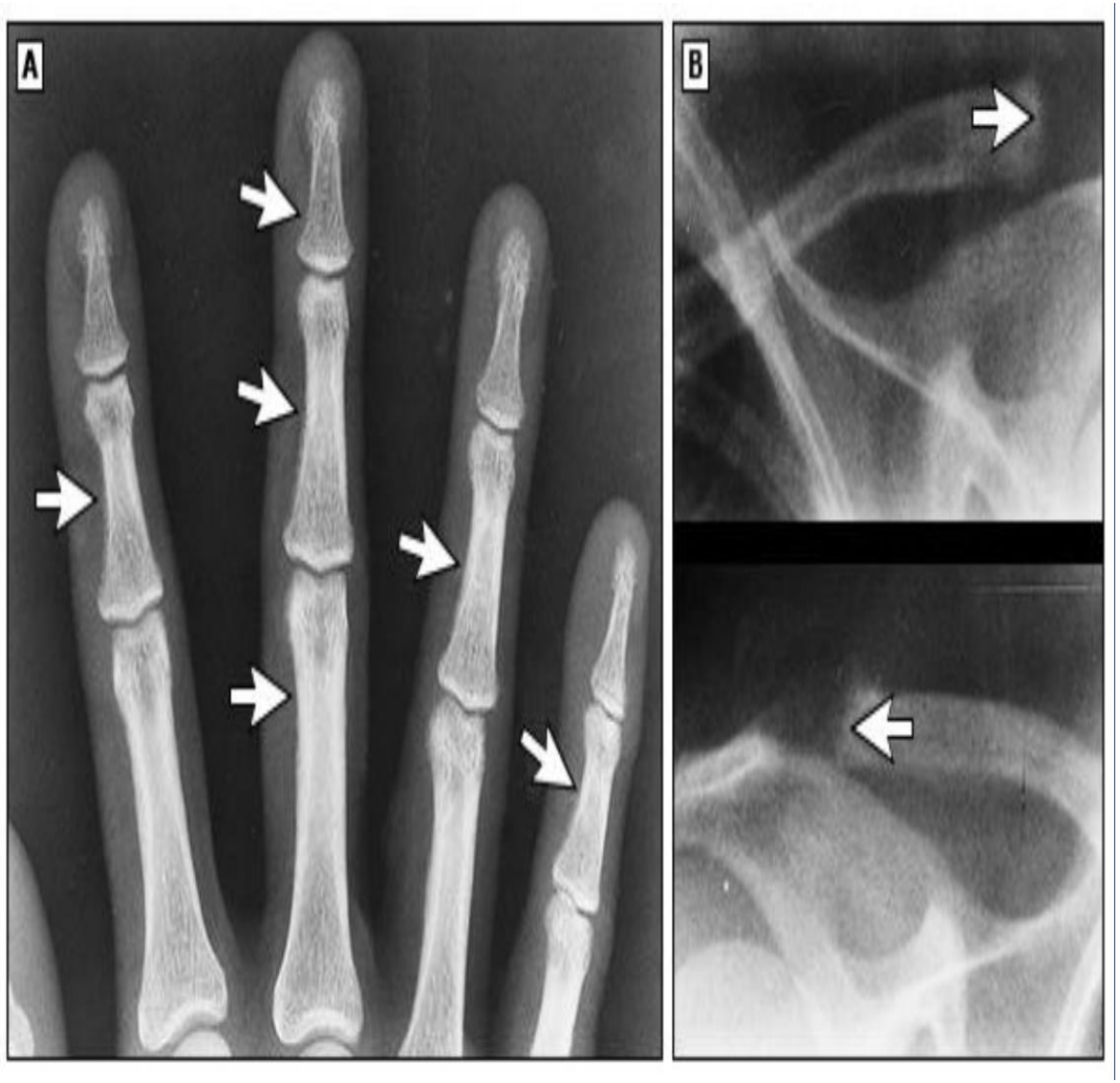
THYROID LYMPHOMA

- Secondary thyroid tumor.

CALCIUM METABOLISM - PRIMARY HYPERPARATHYROIDISM

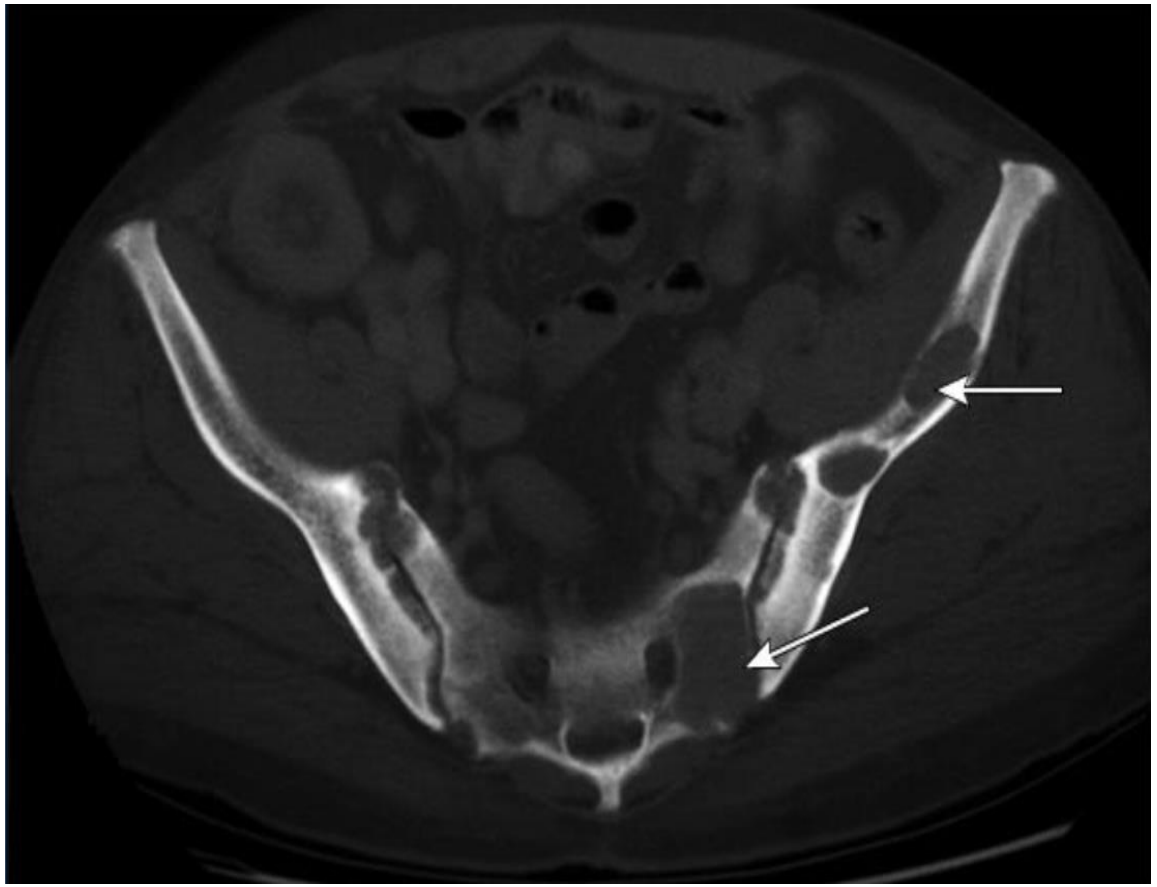
OSTEITIS FIBROSA CYSTICA

- One of the clinical manifestations of Primary Hyperparathyroidism.
- Bone pain.
- A → on X-ray we can see Subperiosteal bone resorption.
- B → Tapering of distal clavicles.



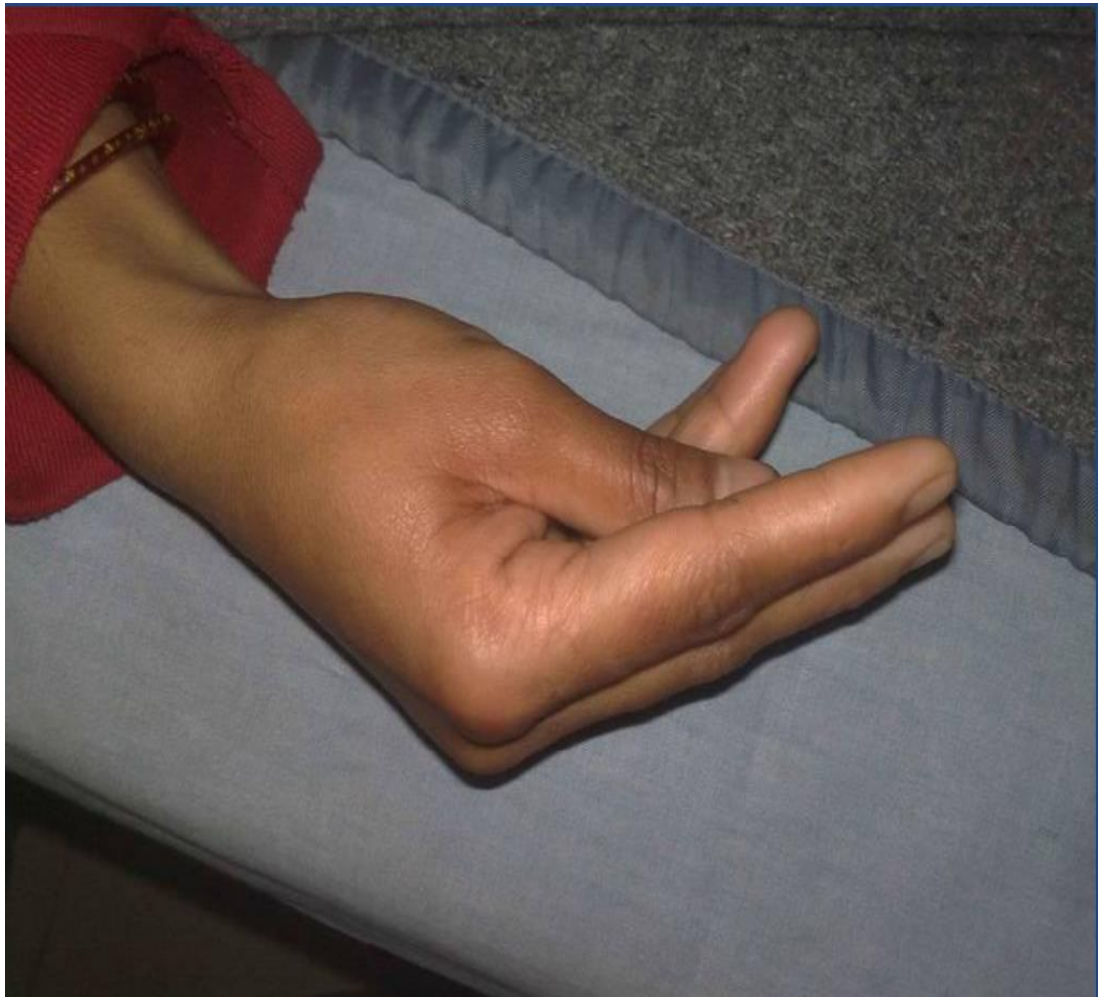
BROWN TUMORS OF THE PELVIS

- It may indicate Parathyroid Carcinoma.

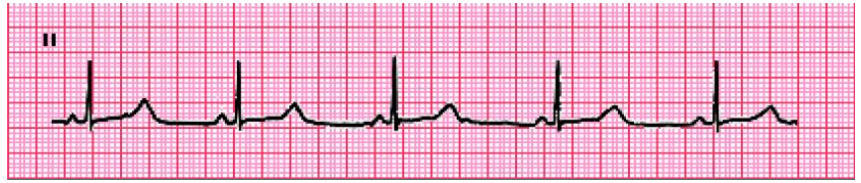


TETANY

- A condition that causes involuntary muscle contractions and changes in the brain cells.
- It is a sign of Hypocalcemia.



Prolonged QT interval due to hypocalcemia

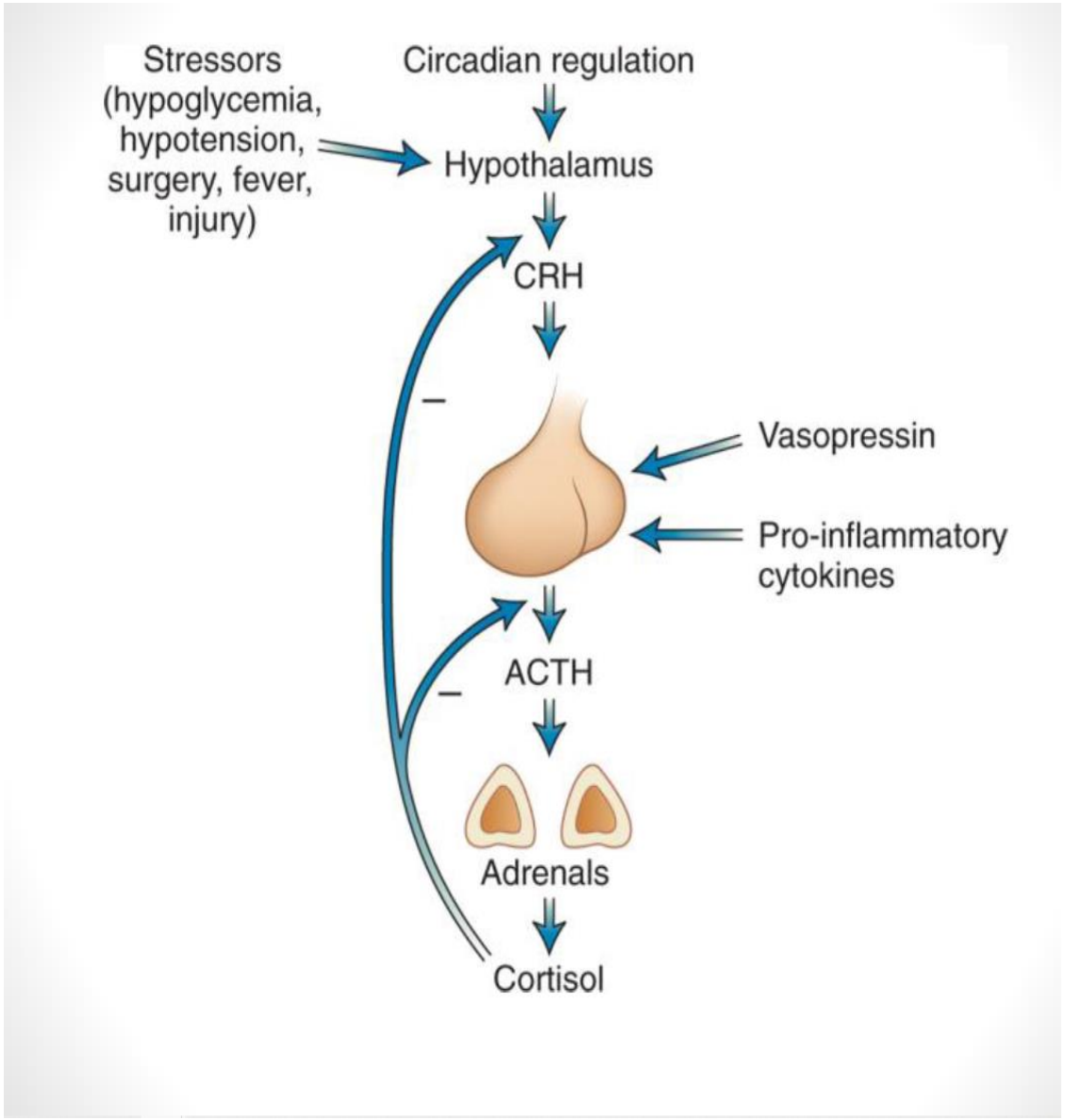


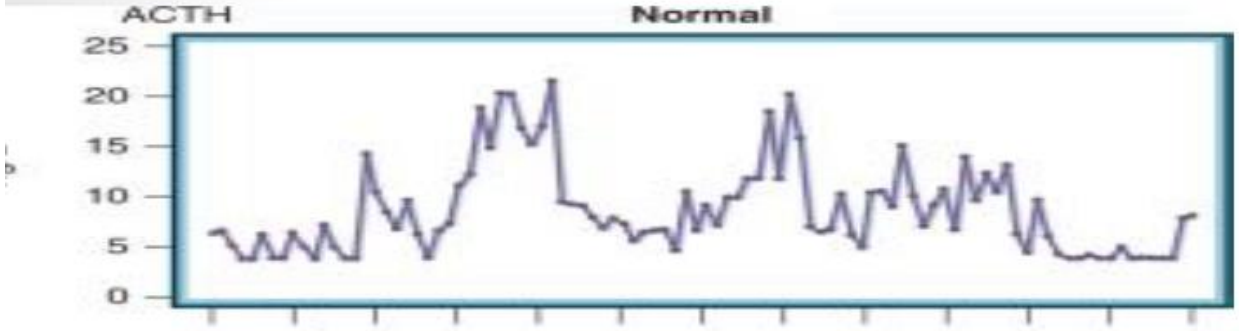
- The QT interval in this figure is prolonged (0.50 sec).
- A long QT interval with a stretched-out ST segment and normal T wave is most consistent with hypocalcemia.
- Hypercalcemia shortens the QT interval.
- Hyponatremia usually has no effects on ECG.
- Hypokalemia prolongs repolarization with flattened or broad T waves and prominent U waves.

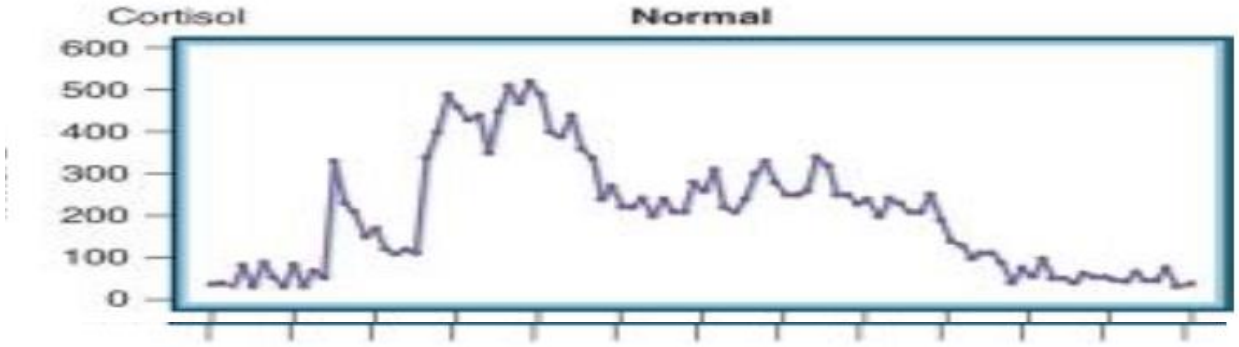
ADRENAL DISORDERS

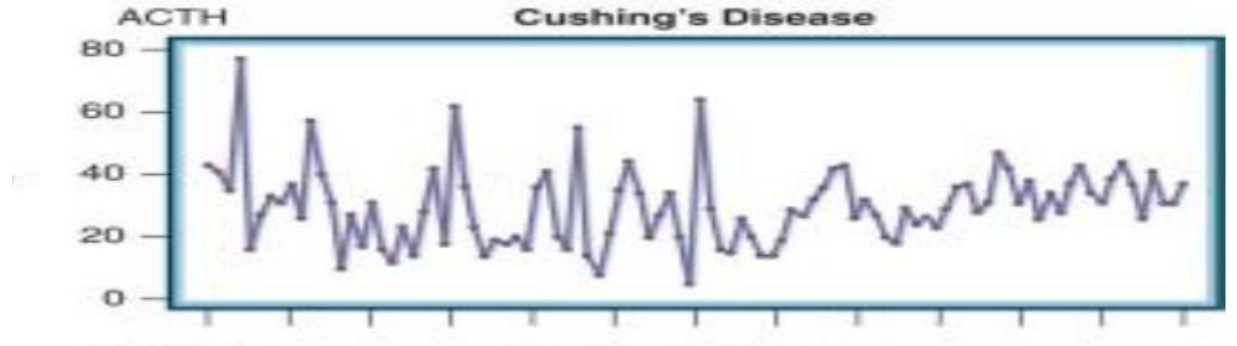
HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

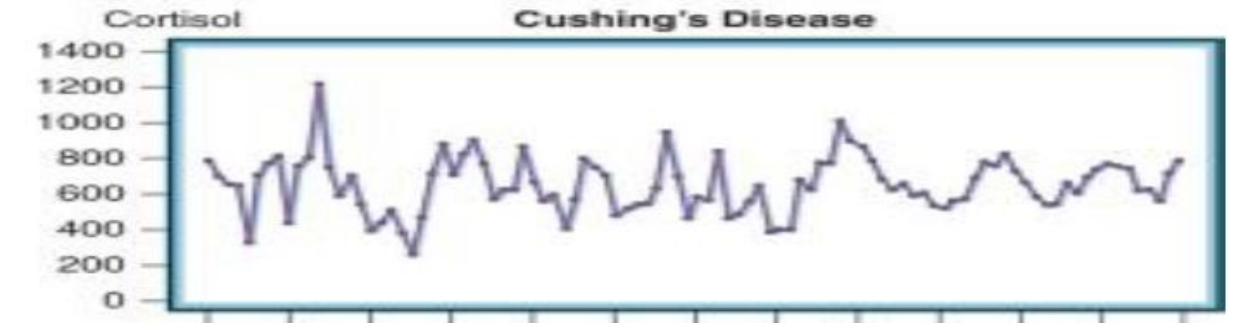
- The adrenal gland is by higher centers: the hypothalamus secretes CRH which acts on the anterior pituitary to release ACTH which affects the adrenals to release Cortisol.











CIRCADIAN AND PULSATILE SECRETION OF ACTH AND CORTISOL

- Note that there is Diurnal variation (that is higher in the morning and lower at midnight) and Pulsatile frequent variation in Cortisol and ACTH release.
- In a normal subject secretion of ACTH and Cortisol is highest in early morning and falls at midnight.
- In Cushing disease, ACTH pulse frequency and pulse amplitude are increased, and Circadian rhythm secretion is lost.

Cushing Syndrome

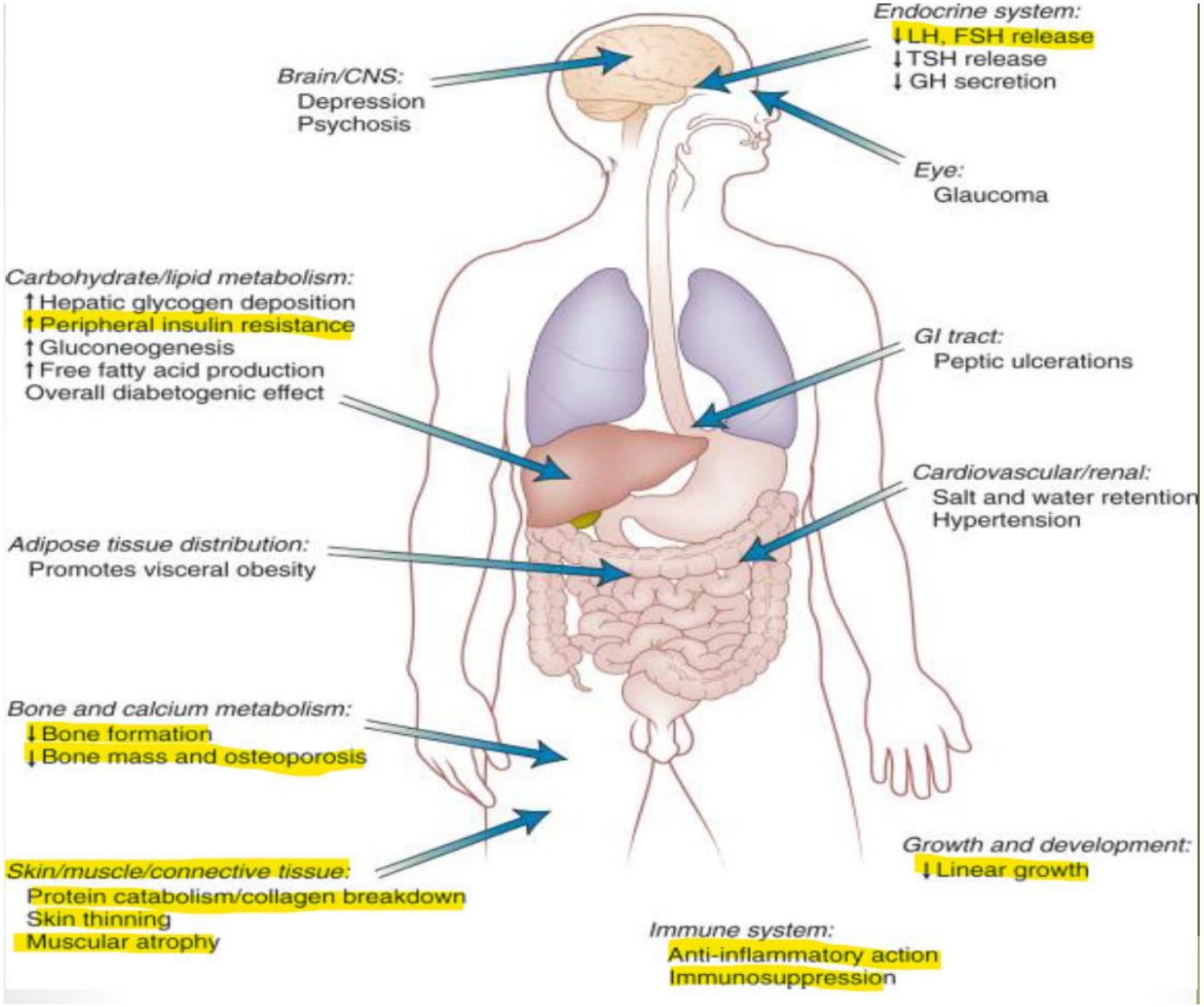
- Cushing syndrome is a state of Hypercortisolism, either Endogenous or Exogenous (in long term treatment with corticosteroids).
- It spares extremities.
- Striae are found most on the abdomen, thighs and breast, they're >1 cm in width, pink or purple in color due to the color of the underlying vessel by atrophy of the skin. (Striae due to pregnancy, obese or weight loss start pink or purple but eventually become white or pale.)
- Easy bruising due to thinning of the skin due to thinning of the skin.
- Effects of Cortisol:

1- Peptic ulceration 2- Secondary HTN due to salt and water retention (most severe in Ectopic ACTH secretion – very high cortisol levels-) 3- at young age there will be short stature due to decrease linear growth by premature closure of epiphyseal plate 4- Diabetogenic effect: Cortisol is a stress hormone (counter-regulatory hormone) that opposes the action of insulin thus causing insulin resistance and T2DM 5- Immunosuppression (immunocompromised individuals due to long term therapy of Cortisol) leading to a high risk of fungal infections specially Tinea Versicolor. 6- Psychological (Depression, Insomnia, Poor Cognition).

- Females with adrenal carcinoma may develop Hirsutism, Acne and Virilization (development of male physical characteristics) due to increase Androgen secretion because they're inefficient in converting Cholesterol into Cortisol.
- Adrenal Adenomas don't secrete Androgens.
- ACTH dependent Cushing may cause hirsutism and acne in females but no virilization due to mild increase in the levels of Androgens.
- In ACTH dependent Cushing there is high ACTH and MSH thus Hyperpigmentation.

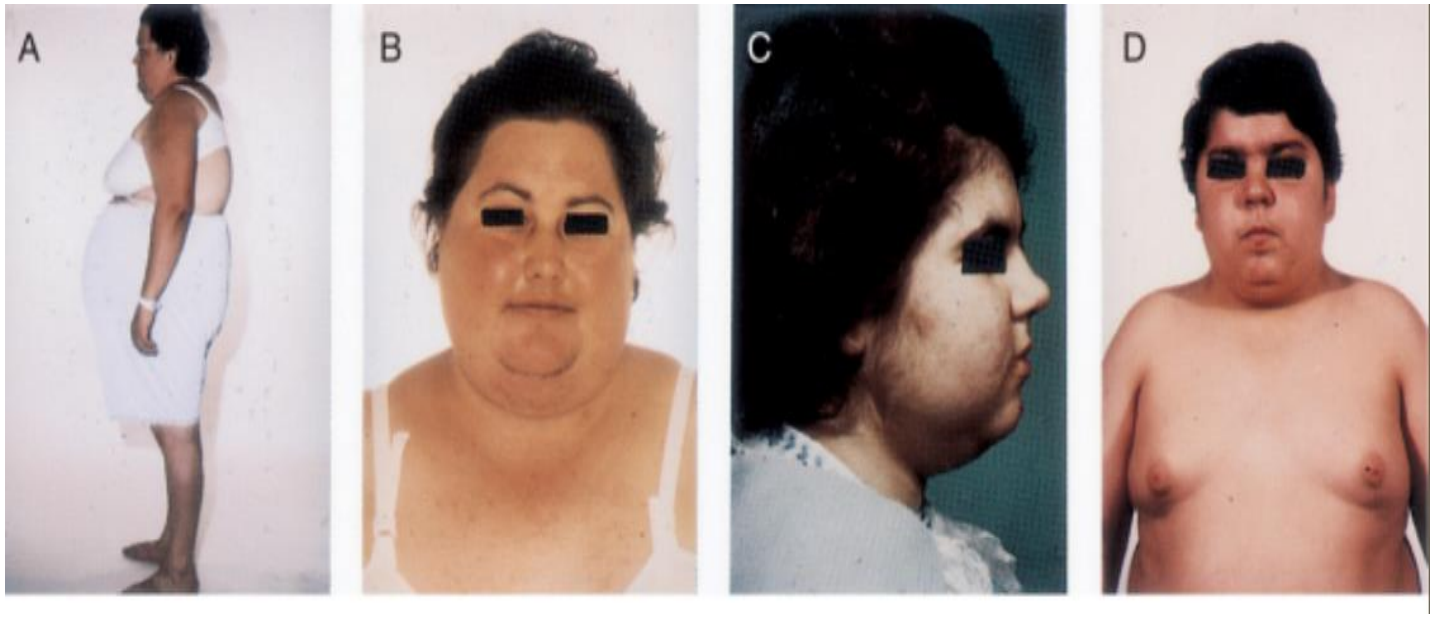
Clinical manifestations in Cushing syndrome

- Cortisol → Counter-regularity → Insulin resistance → Secondary DM (T2DM).
- Low GnRH → Low LH, FSH release → menstrual irregularity, infertility or hypogonadism.
- Skin, muscle and connective tissue manifestation are very unlikely to occur in other conditions. These manifestations are highly suggestive of Cushing (Skin atrophy, Striae, Myopathy).
- Immune system effects are due to long term cortisol intake.
- Decrease in linear growth due to premature closure of epiphysis.

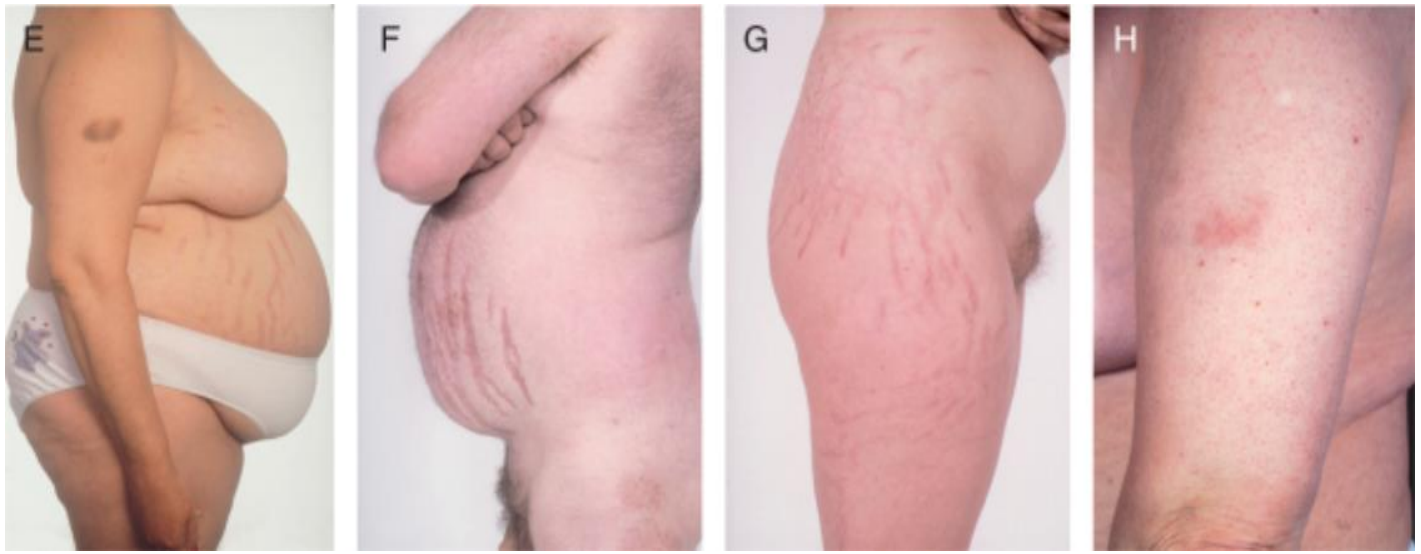


Clinical features of Cushing syndrome

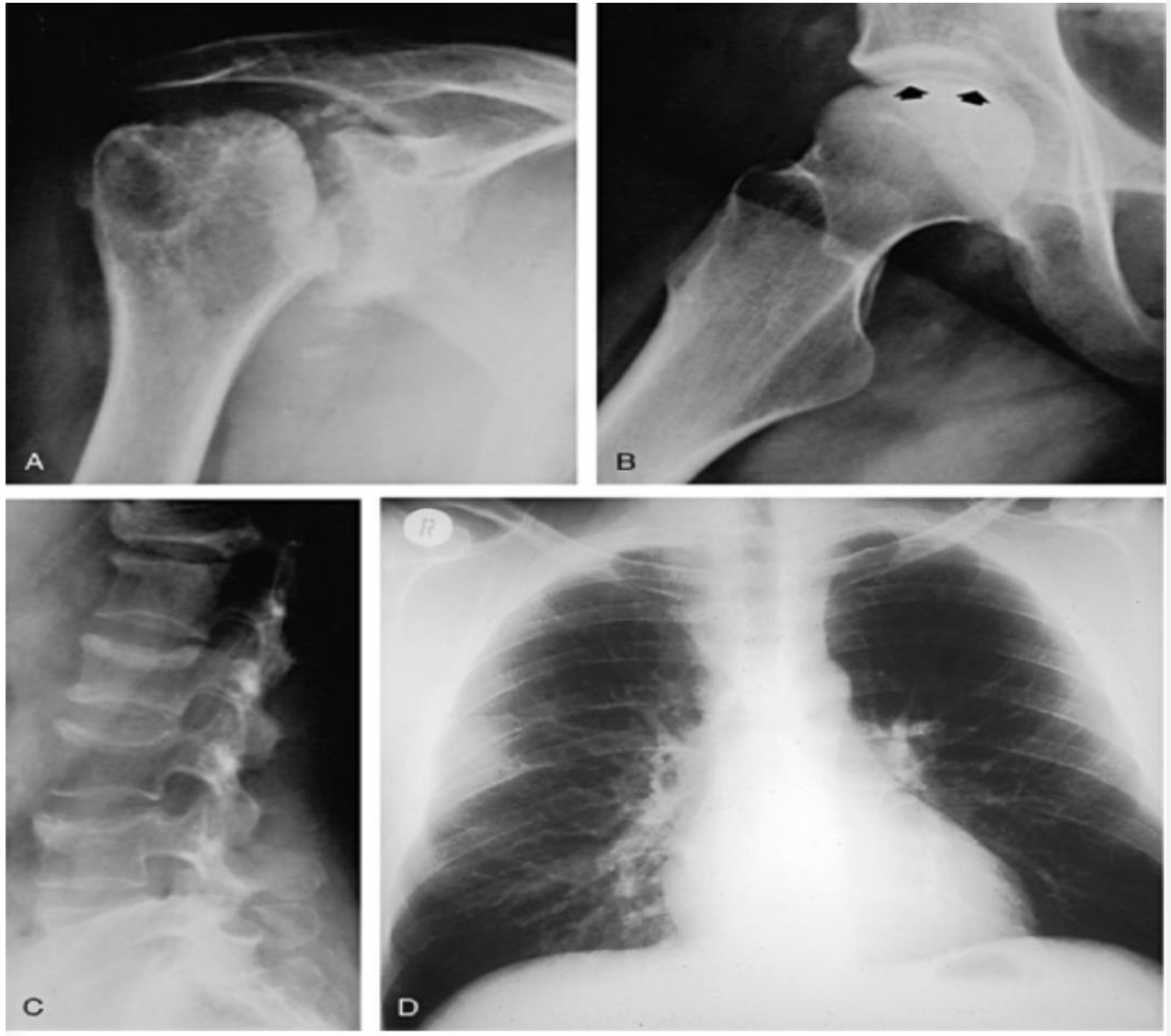
- A → Centripetal and some Generalized obesity + Dorsal Kyphosis.
- B → Moon Facies + Plethora (Excess of blood marked by turgescence and reddish complexion) + Hirsutism (excessive growth of dark or Coarse hair in male like pattern – on the face, chest, and back) + Enlarged supraclavicular fat pads.
- C → Facial rounding + Hirsutism + Acne.
- D → Central and Generalized obesity + Livid abdominal Striae (Indented, reddened streaks that usually appear on the skin from rapid weight gain or from weight changes).



Clinical features of Cushing syndrome



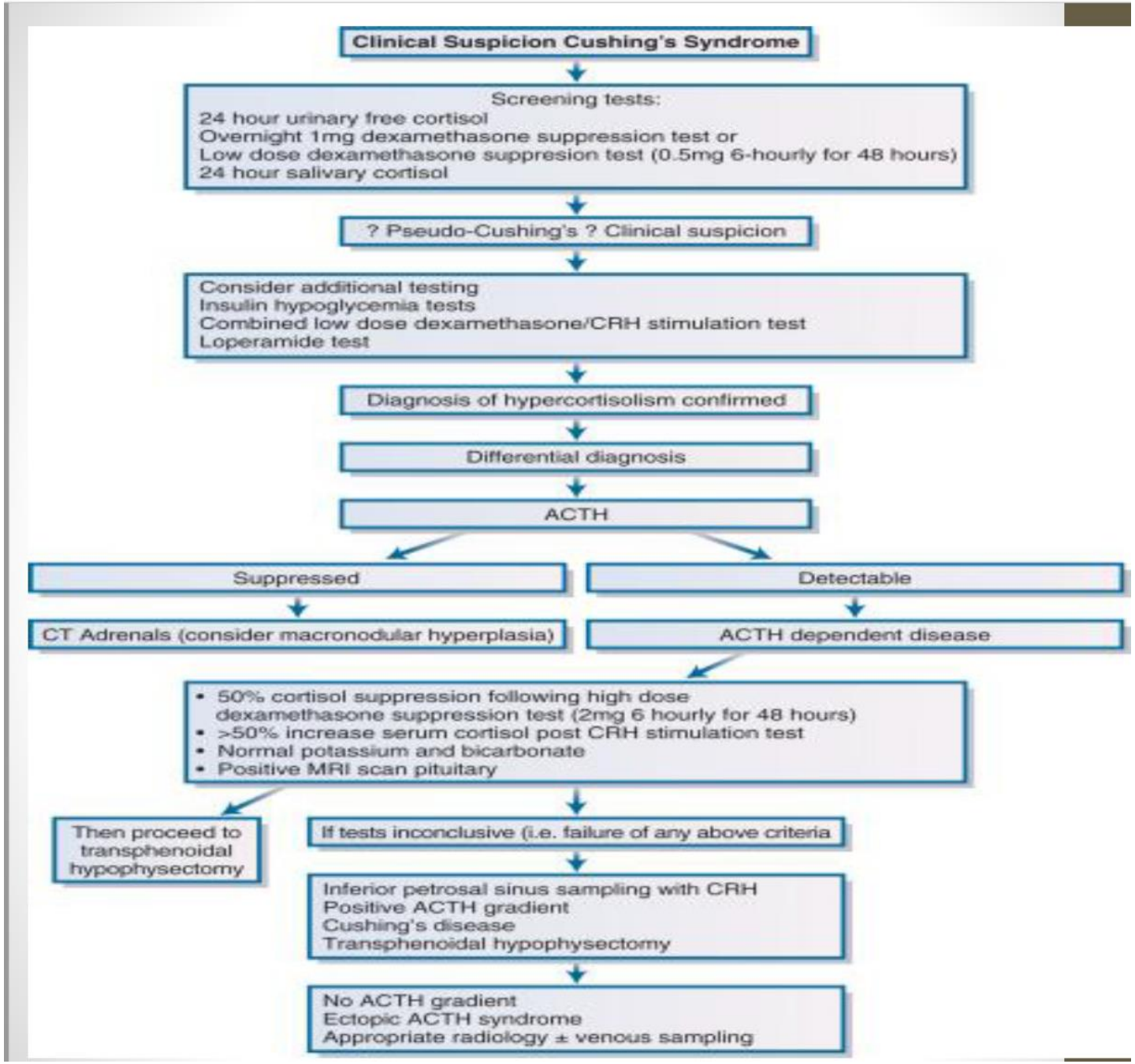
- E + F → Centripetal and Generalized Obesity + Striae.
- G → Striae (caused by the treatment of Congenital Adrenal Hyperplasia with excessive doses of Dexamethasone as a replacement therapy).
- H → Typical bruising + Thin skin of Cushing syndrome. (In this case the bruising occurred without obvious injury)



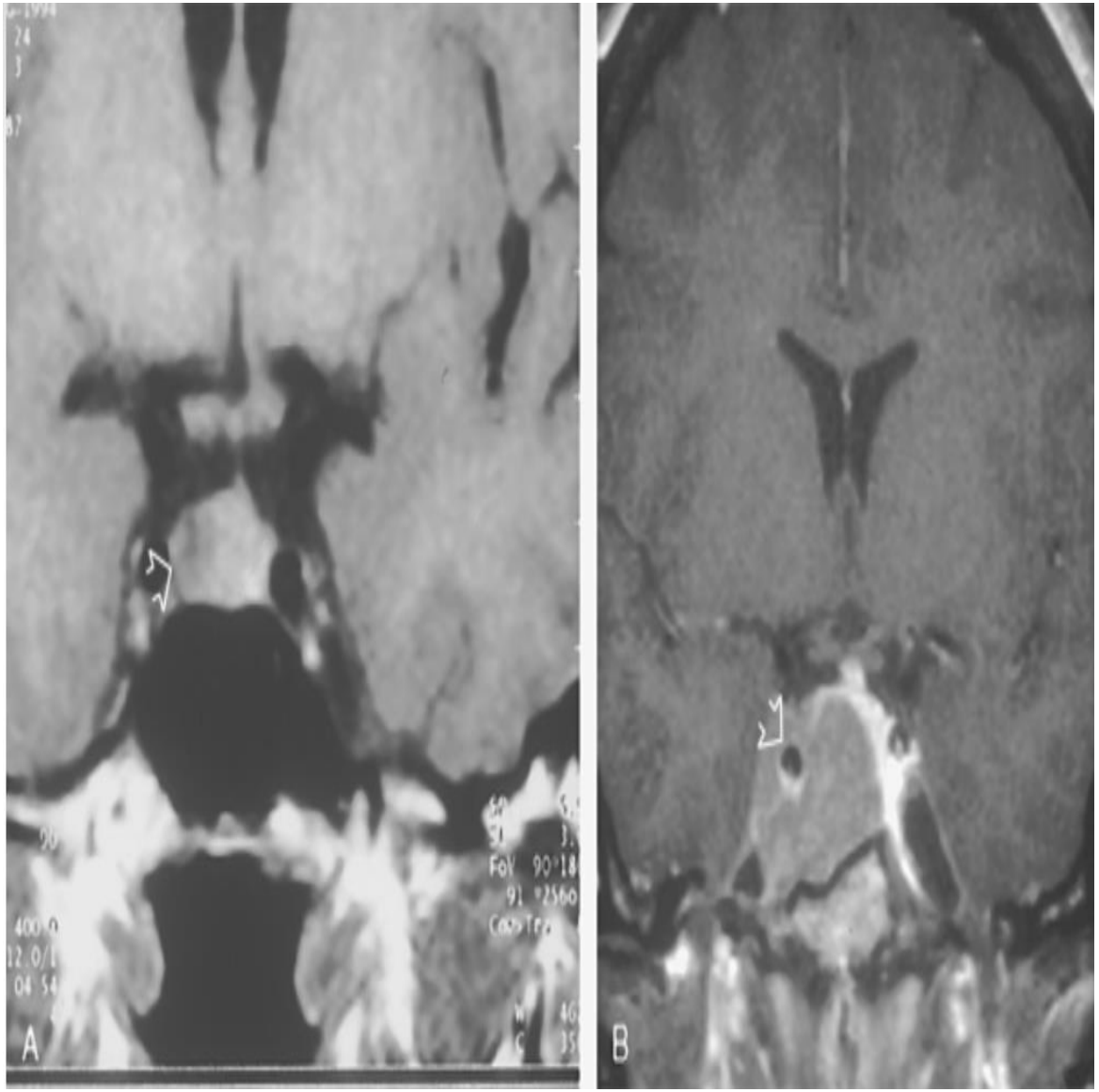
BONE ABNORMALITIES IN CUSHING DISEASE

- A → Aseptic necrosis of the Rt humeral head.
- B → Avascular / Aseptic necrosis of the Rt femoral head, the arrows indicate the crescent subchondral radiolucency best seen in lateral view + Osteoporosis.
- C → Diffuse Osteoporosis + Vertebral Collapse + Subchondral Sclerosis.
- D → Rib Fracture in a patient with Cushing disease.

INVESTIGATIONS IN CUSHING SYNDROME



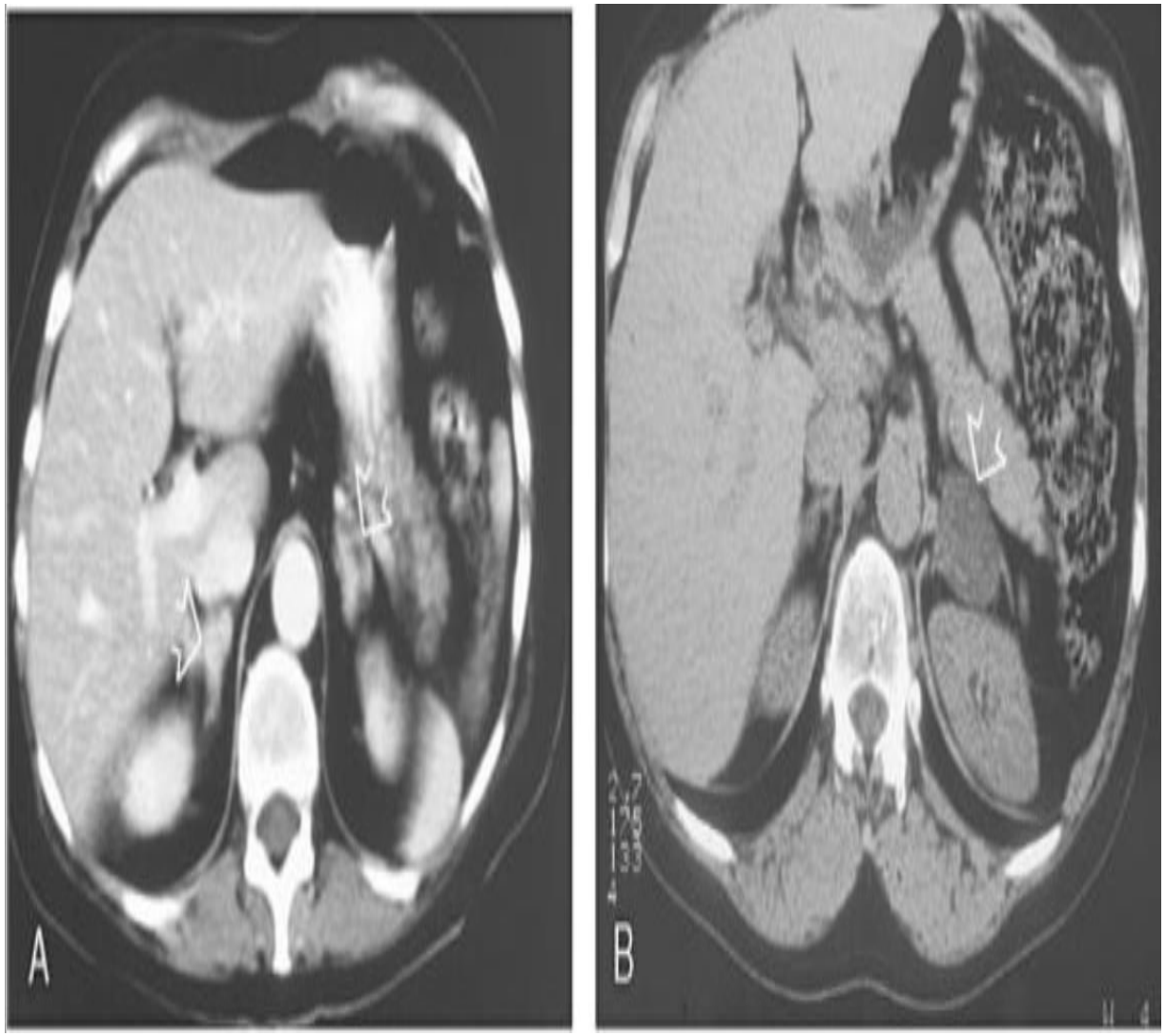
MRI SCAN OF THE PITUITARY GLAND



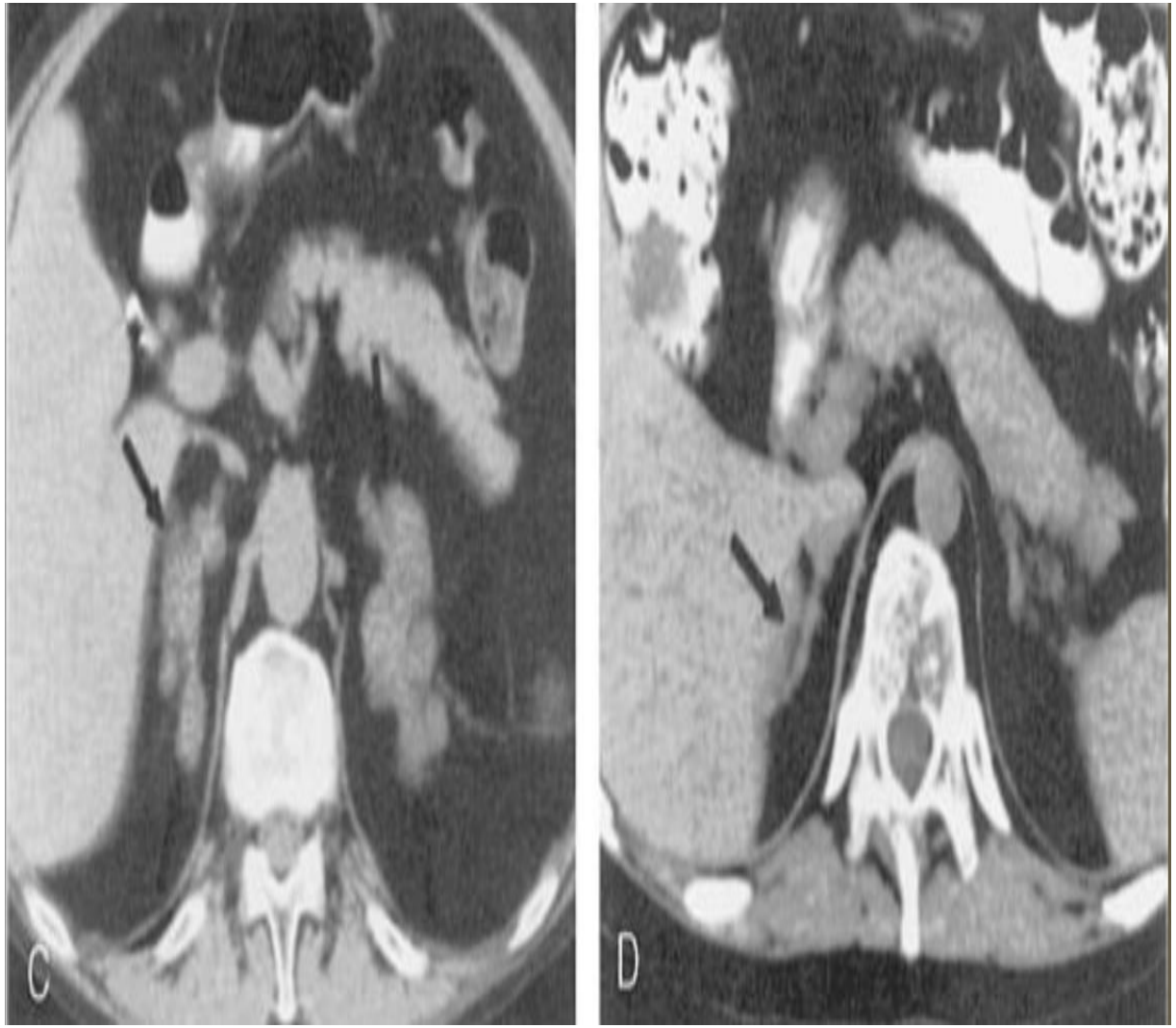
- A → MRI scan demonstrating the typical appearance of Pituitary Microadenoma (a Hypodense lesion is seen in the Rt side of the gland with deviation of the pituitary stalk away from the lesion).
- B → MRI scan of the pituitary gland demonstrating a large Macroadenoma in a patient with Cushing disease.
- These Tumors are invariably Invasive and Recur after surgery

ABDOMINAL CT SCANS

- A → Adrenal CT scan demonstrating bilateral adrenal hyperplasia in a patient with Cushing Disease.
- B → CT scan of a typical Solitary Lt Adrenal Adenoma causing Cushing Syndrome.



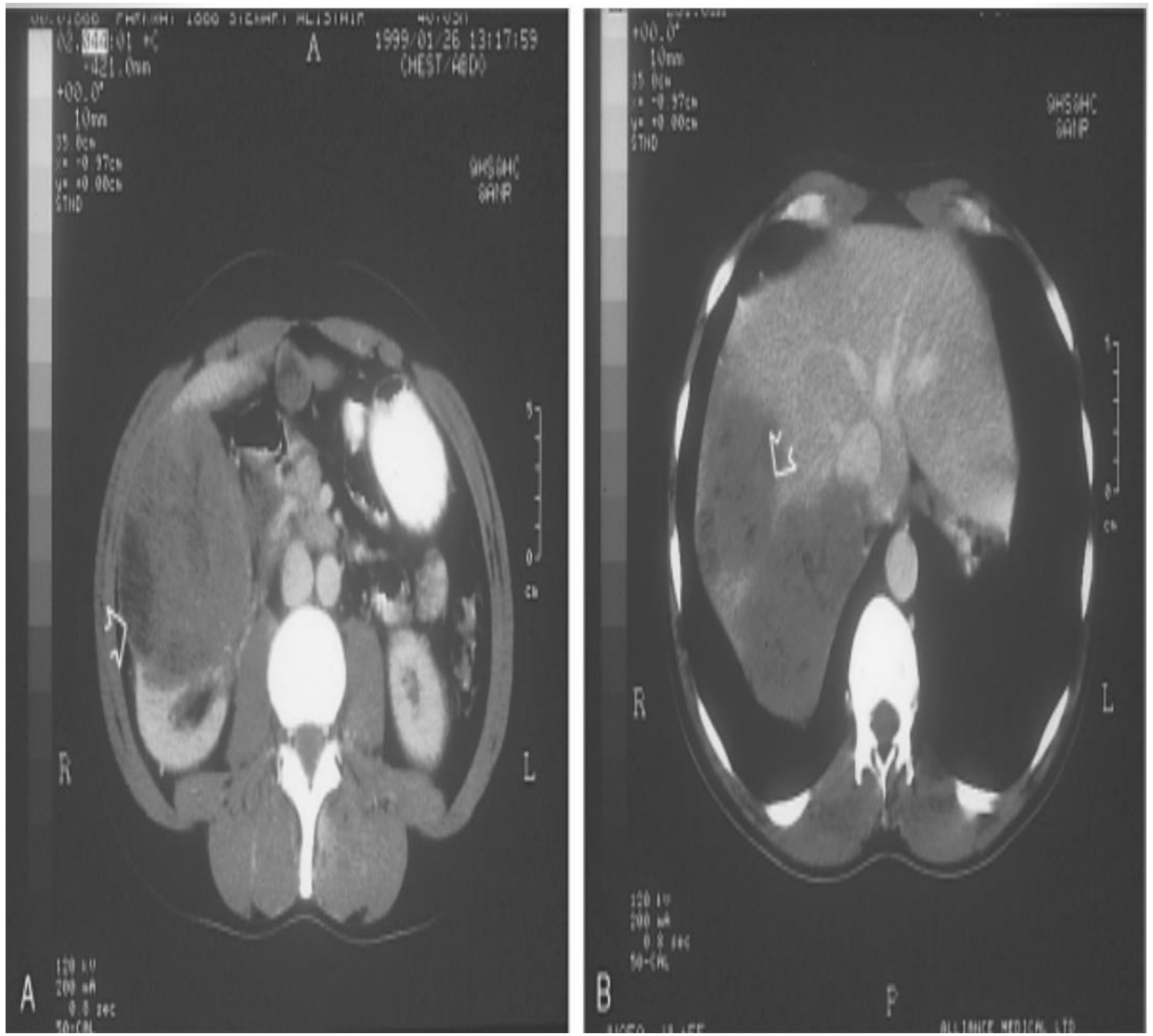
ABDOMINAL CT SCANS



- C → Cushing syndrome caused by Massive Macronodular Hyperplasia (Adrenal Glands are replaced by multiple nodules –arrows-).
- D → Cushing syndrome caused by surgically proven Primary Pigmented Nodular Adrenal Disease (notice the multiple small nodules with the relatively atrophic internodular adrenocortical tissue involving the medial limb of the Rt adrenal gland –arrow-).

ABDOMINAL CT SCAN

- CT scan of a patient with rapidly progressing Cushing Syndrome caused by Adrenal Carcinoma.
- A → the CT shows an irregular Rt Adrenal Mass.
- B → the CT shows Large Liver Metastasis.



TREATMENT OF CUSHING SYNDROME

- In the case of Adrenal Source:
- If you have a Non-functioning adrenal mass and <4 cm → only monitor the mass
- If you have a Functioning adrenal mass → remove it surgically regardless of the size.

- After Surgical removal of the adrenal gland we should give replacement therapy.

Treatment

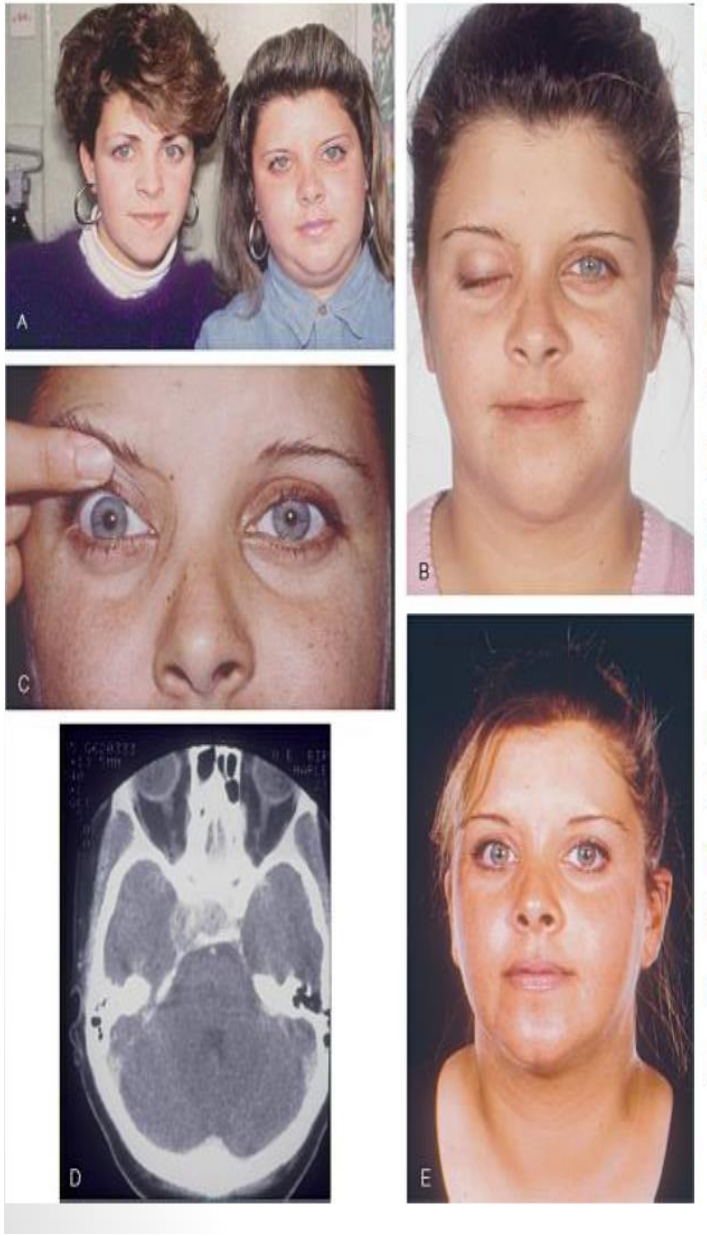
1. Adrenal source → Unilateral or bilateral adrenalectomy
2. Pituitary source → Pituitary surgery, rarely have to do bilateral adrenalectomy

3. Ectopic ACTH secretion → Treat the primary cancer+-medical therapy.

4. Medical treatment if patient refuses surgery, or surgery is contraindicated or failed to achieve a complete cure.

PLZ READ THIS CASE THOROUGHLY

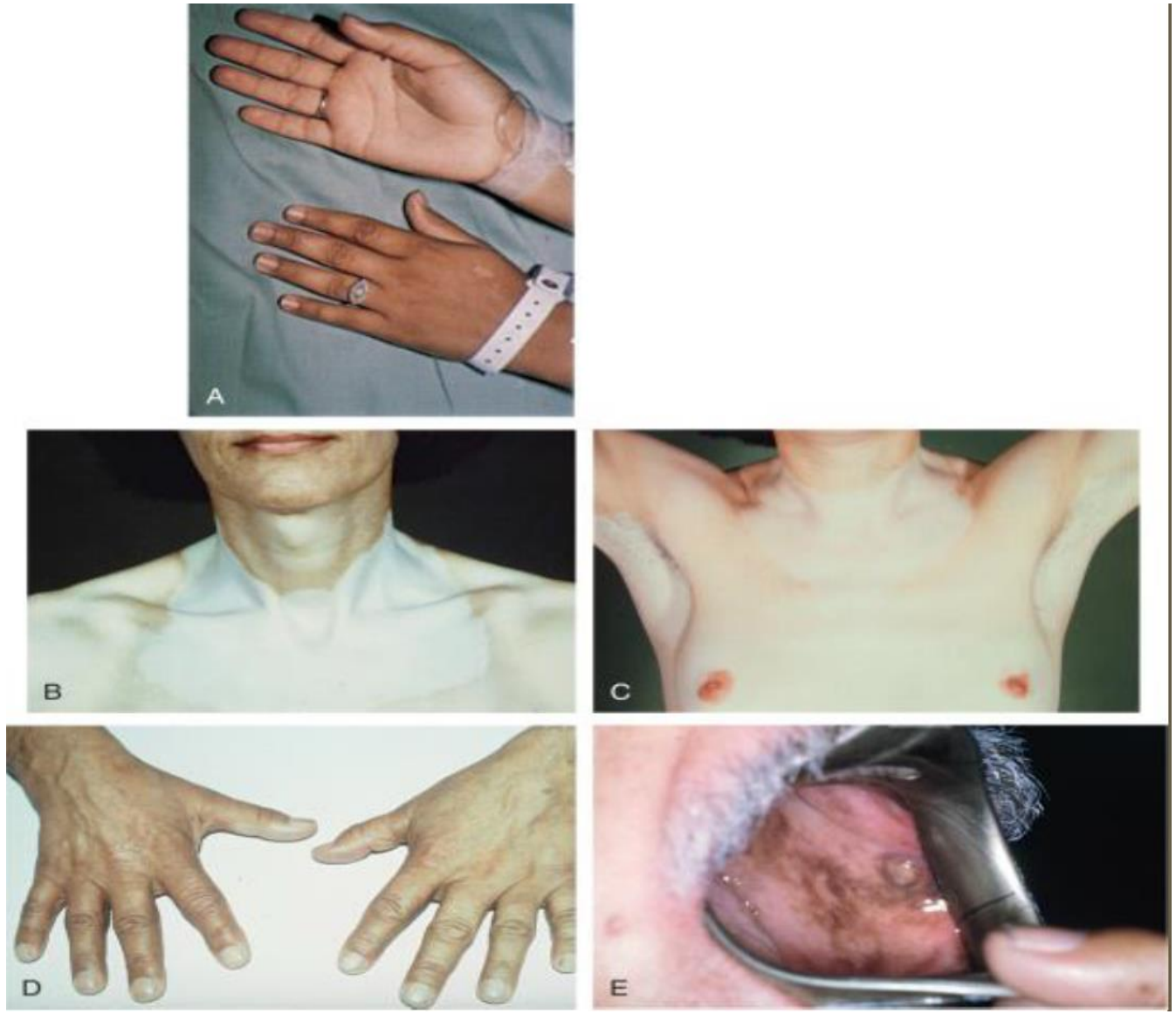
- Nelson Syndrome: Enlargement of Pituitary adenoma and compression of adjacent structures.



A young woman with Cushing's disease, photographed initially beside her identical twin sister (A). In this case, treatment with bilateral adrenalectomy was undertaken. Several years later, the patient presented with Nelson's syndrome and a right third cranial nerve palsy (B and C) related to cavernous sinus infiltration from a locally invasive corticotropinoma (D). Hypophysectomy and radiotherapy were performed with reversal of the third nerve palsy (E). Note the advancing skin pigmentation of Nelson's syndrome.

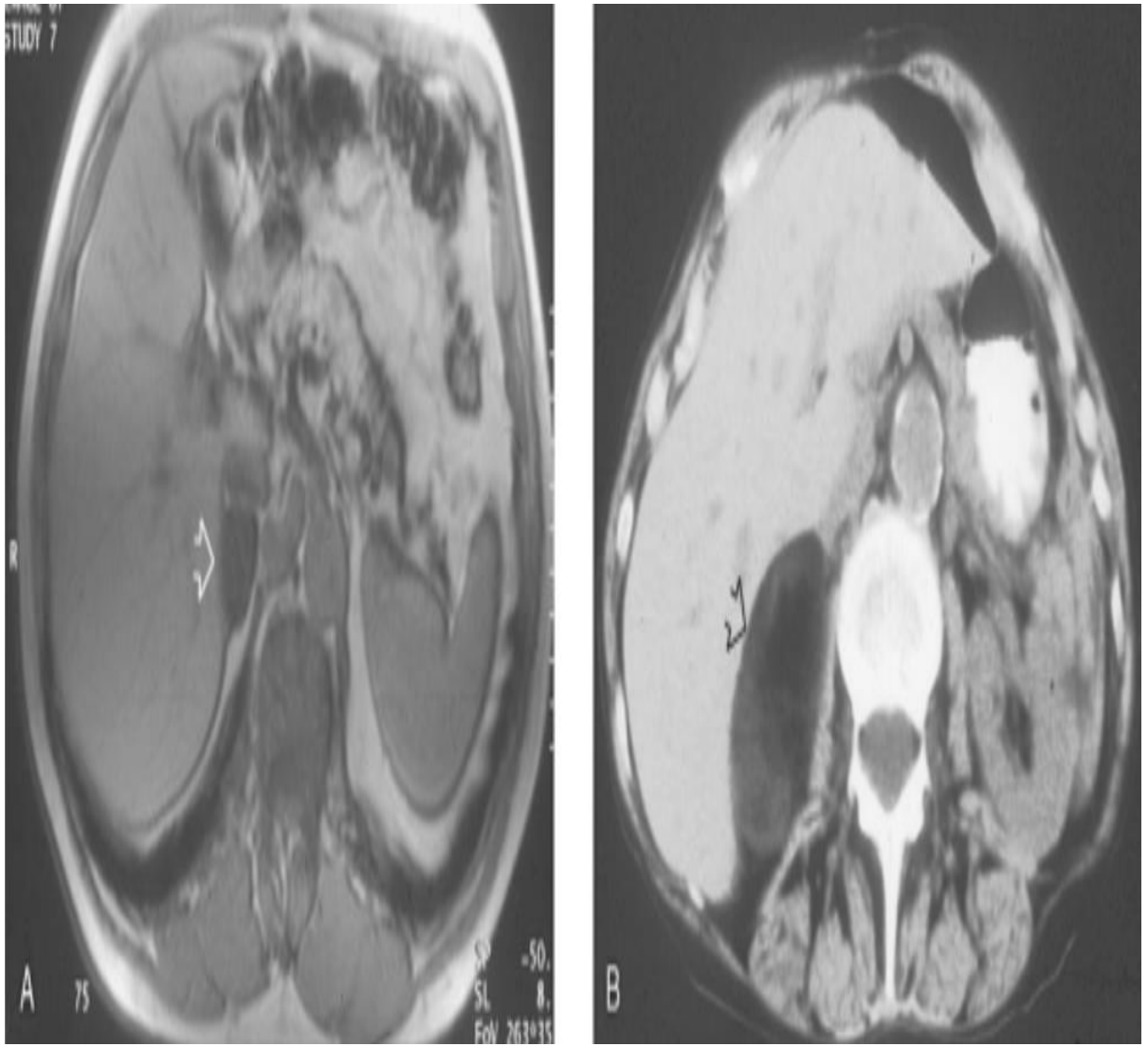
Hyperpigmentation in Addison's Disease

- A → Hands of a patient with Autoimmune Polyendocrine Syndrome and Addison's disease (Caused by High ACTH and Low Cortisol levels).
- B → Pigmentation in a patient with Addison's disease before treatment with Hydrocortisone and Fludrocortisone.
- C → Pigmentation in a patient with Addison's disease after treatment with Hydrocortisone and Fludrocortisone (note the additional presence of vitiligo).
- D → a patient with Tuberculous Addison's disease before and after treatment with corticosteroids.
- E → Buccal pigmentation in a patient with Tuberculous Addison's Disease.

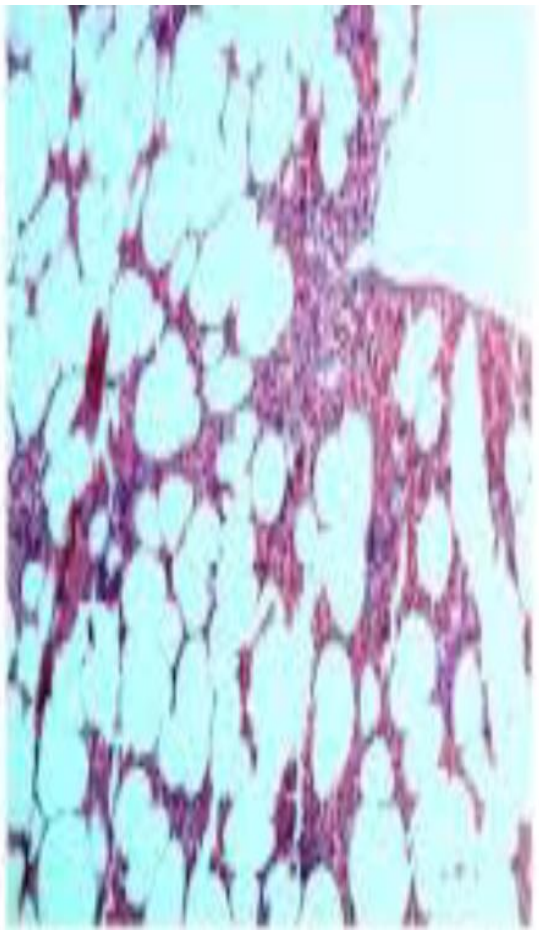


Adrenal Incidentalomas

- In this condition, the patient comes to the clinic to have imaging for non-adrenal diseases (like stones, hematuria, constipation…), so he'll have US / CT and an Adrenal mass will appear incidentally.
  - We refer the patient to endocrine consult to evaluate the incidentaloma, we do 3 screening tests to detect if the mass is functioning or not in Zona Glomerulosa, Fasciculata, Reticularis.
    - To know whether the mass is benign or malignant, we check Histopathology after resection.
      - A → Adrenal Incidentaloma
      - B → Incidentally discovered Rt Adrenal Myelolipoma.

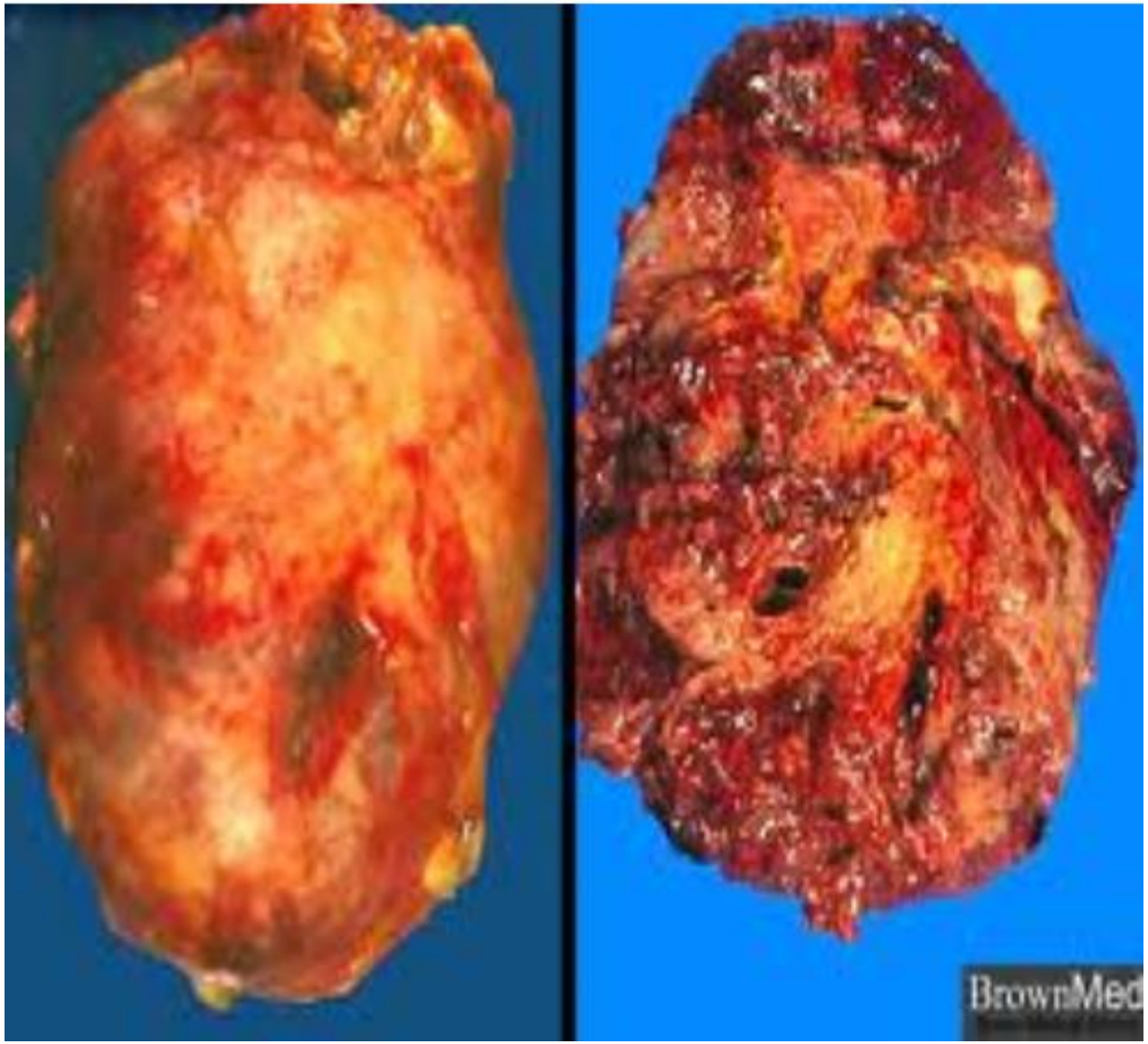


ADRENAL MYELOLIPOMA



Adrenocortical Carcinoma

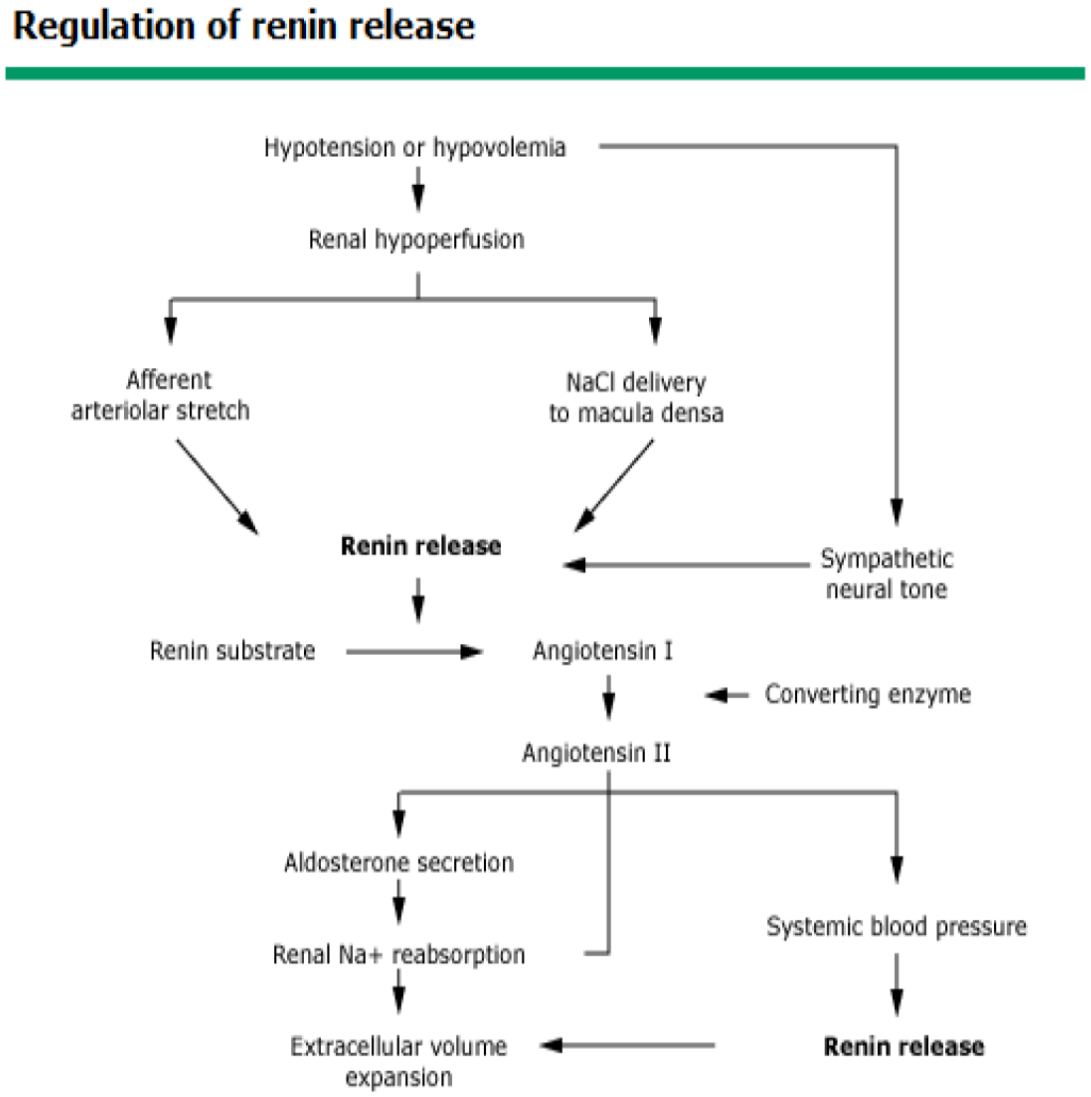
- Primary Adrenal Carcinoma
- Very rare
- More common in Females
- 80% of the tumors are functional (most commonly secreting Glucocorticoids alone 45%, Glucocorticoids and Androgens 45%, and Androgens alone 10%, Less than 1% of all cases secrete Aldosterone).
- Patients present with features of hormone excess state (Glucocorticoid and/or Androgen excess), but abdominal pain, weight loss, anorexia and fever occur in 25% of the cases.
- An abdominal mass may be palpable.
- Poor prognosis
- 75% of the cases have metastasis.
- Surgery is the only cure for local disease, Radiotherapy is ineffective.



NEPHROLOGY

STRUCTURE AND FUNCTION OF THE KIDNEY

REGULATION OF RENIN RELEASE

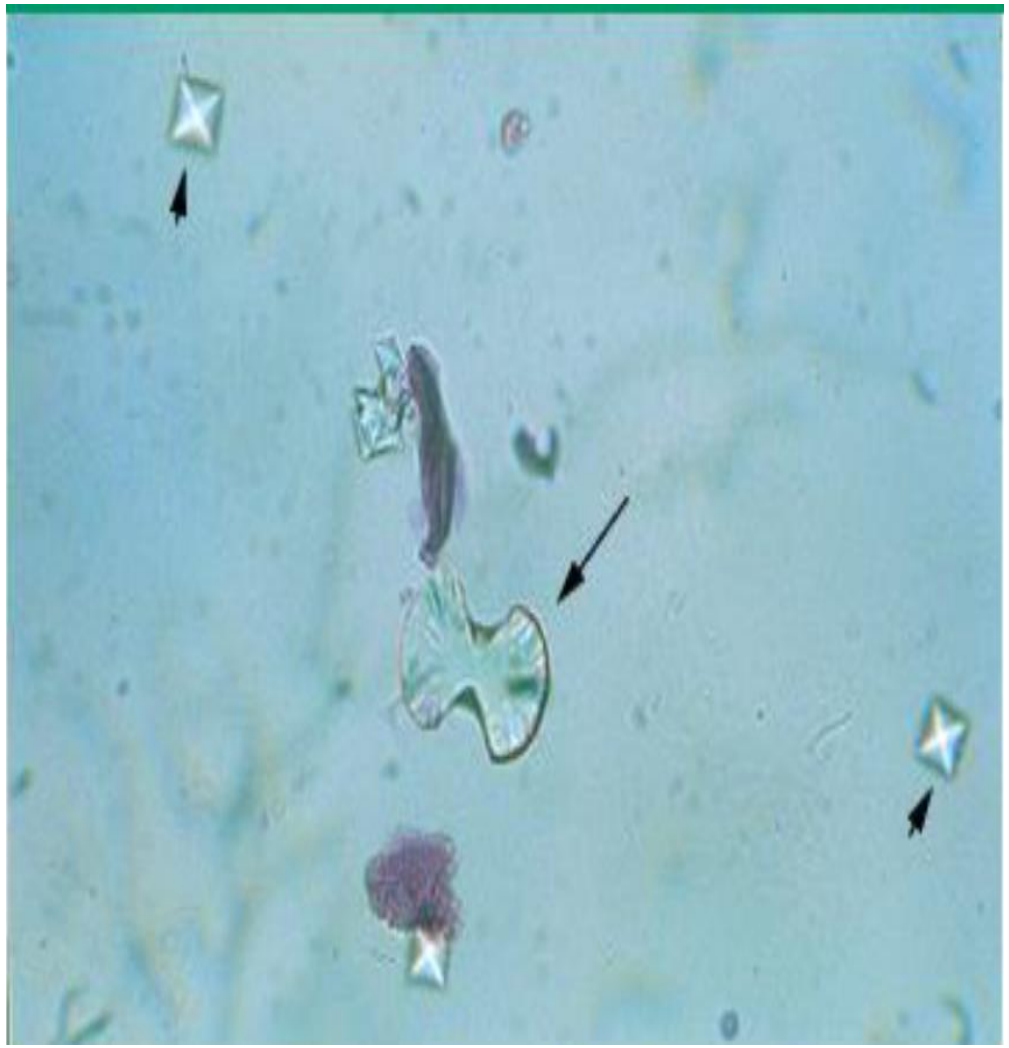


URIC ACID CRYSTALS IN THE URINE

- This figure shows urine sediment loaded with Uric Acid Crystals.
- The crystals are pleomorphic, most often appearing as rhombic plates or rosettes.
- They are yellow or reddish-brown and form only in an acidic urine (pH 5.5 or less).

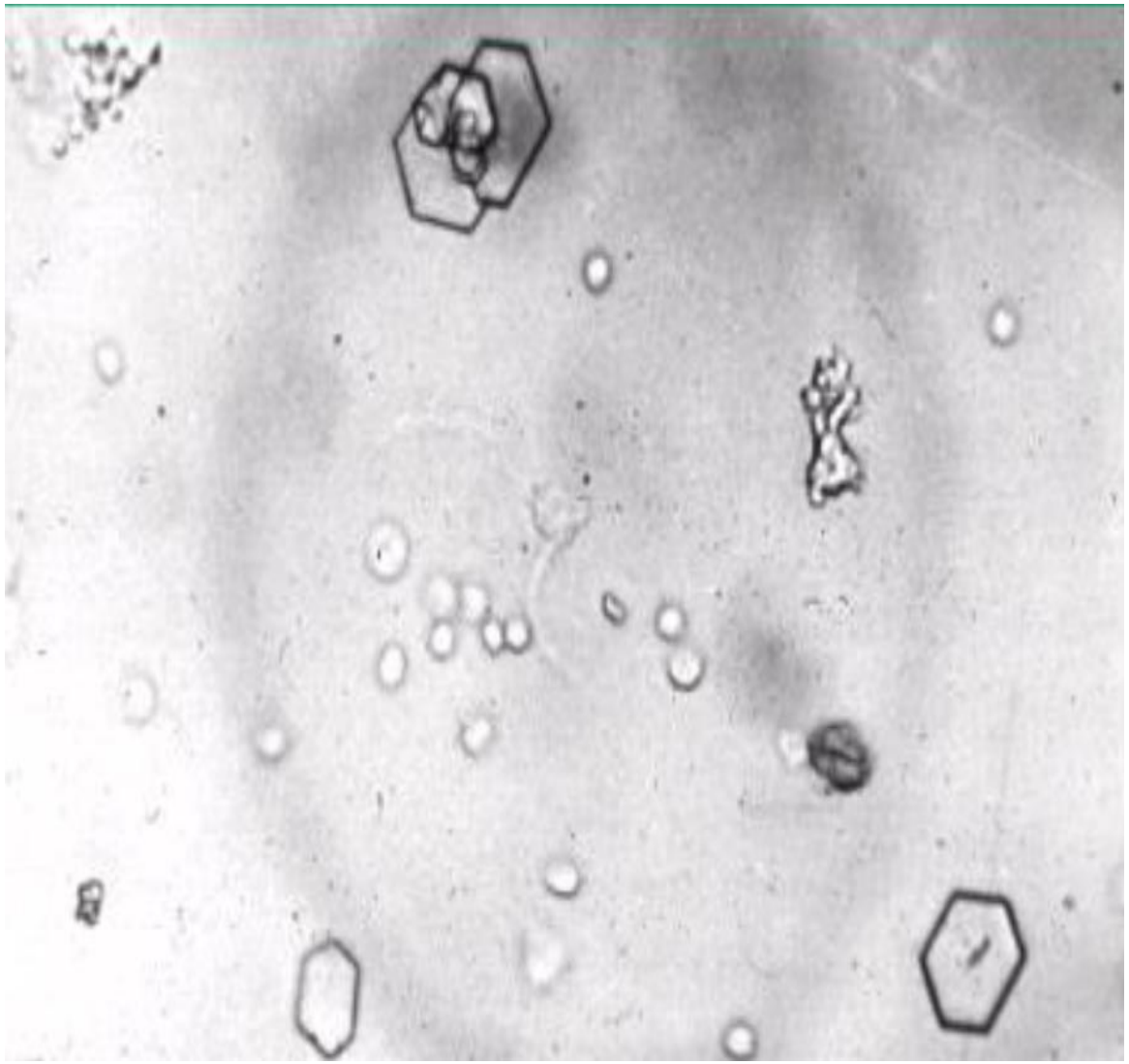
CALCIUM OXALATE CRYSTALS IN THE URINE

- This urine sediment shows both Dumbbell-shaped Calcium Oxalate Monohydrate (Long arrow), and Envelope-shaped Calcium Oxalate Dihydrate (Short arrow) crystals.
- The monohydrate crystals may also have a Needle-shaped appearance (not shown here).
- The formation of Calcium Oxalate Crystals is independent of the urine pH.

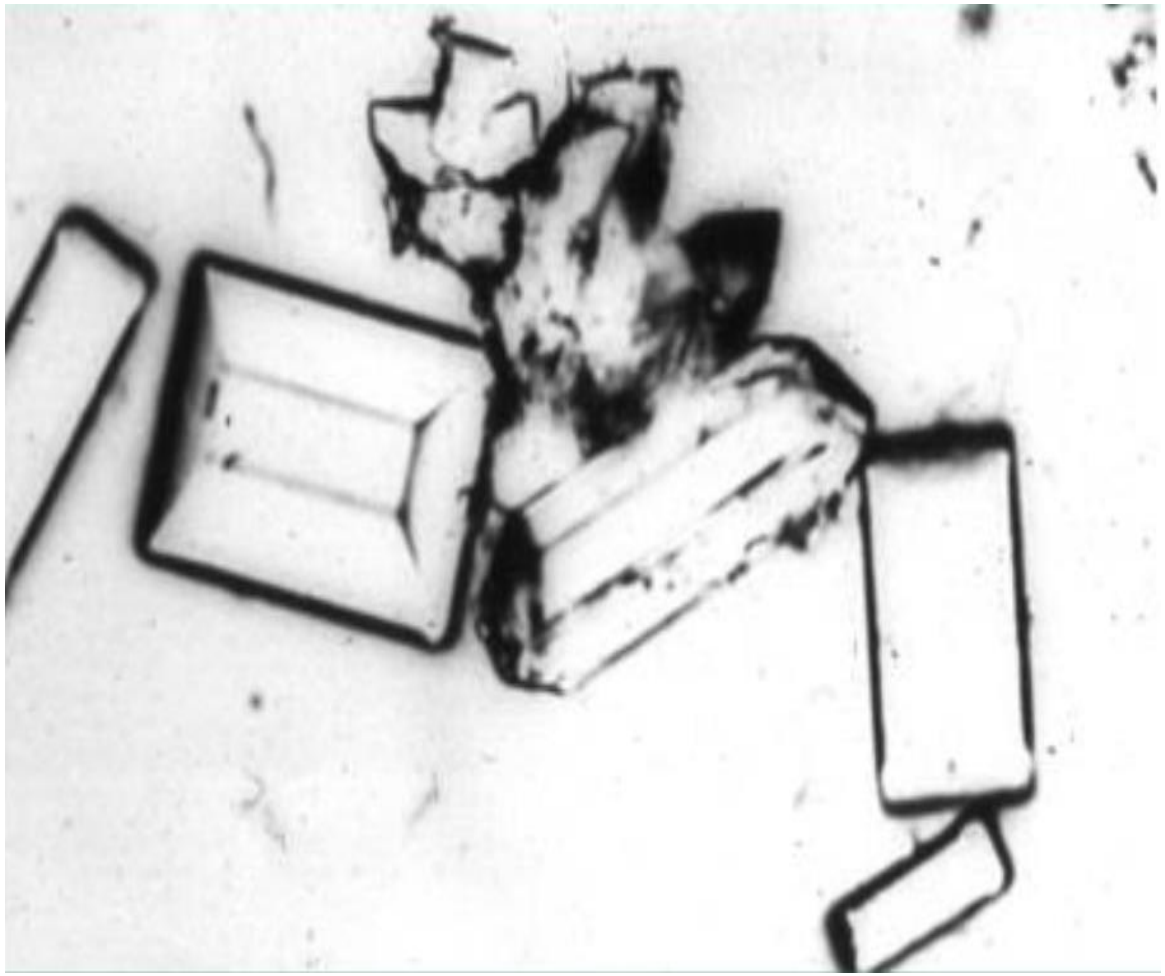


CYSTINE CRYSTALS IN THE URINE

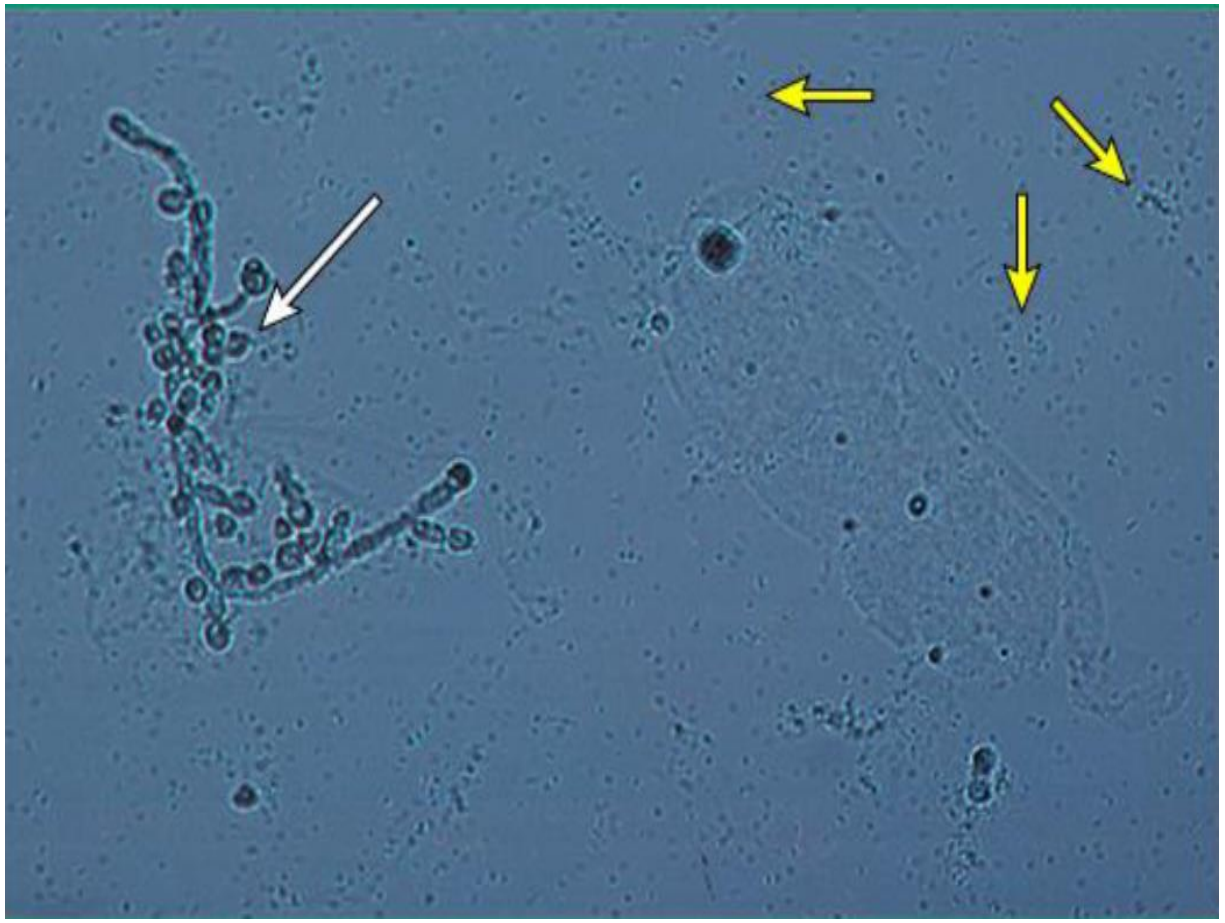
- it's rare but specific.
- This urine sediment shows a Hexagonal Cystine Crystals that are essentially pathognomonic of Cystinuria (inherited metabolic disorder characterized by excessive amounts of undissolved cystine in the urine).



STRUVITE (MAGNESIUM AMMONIUM PHOSPHATE) CRYSTALS IN THE URINE

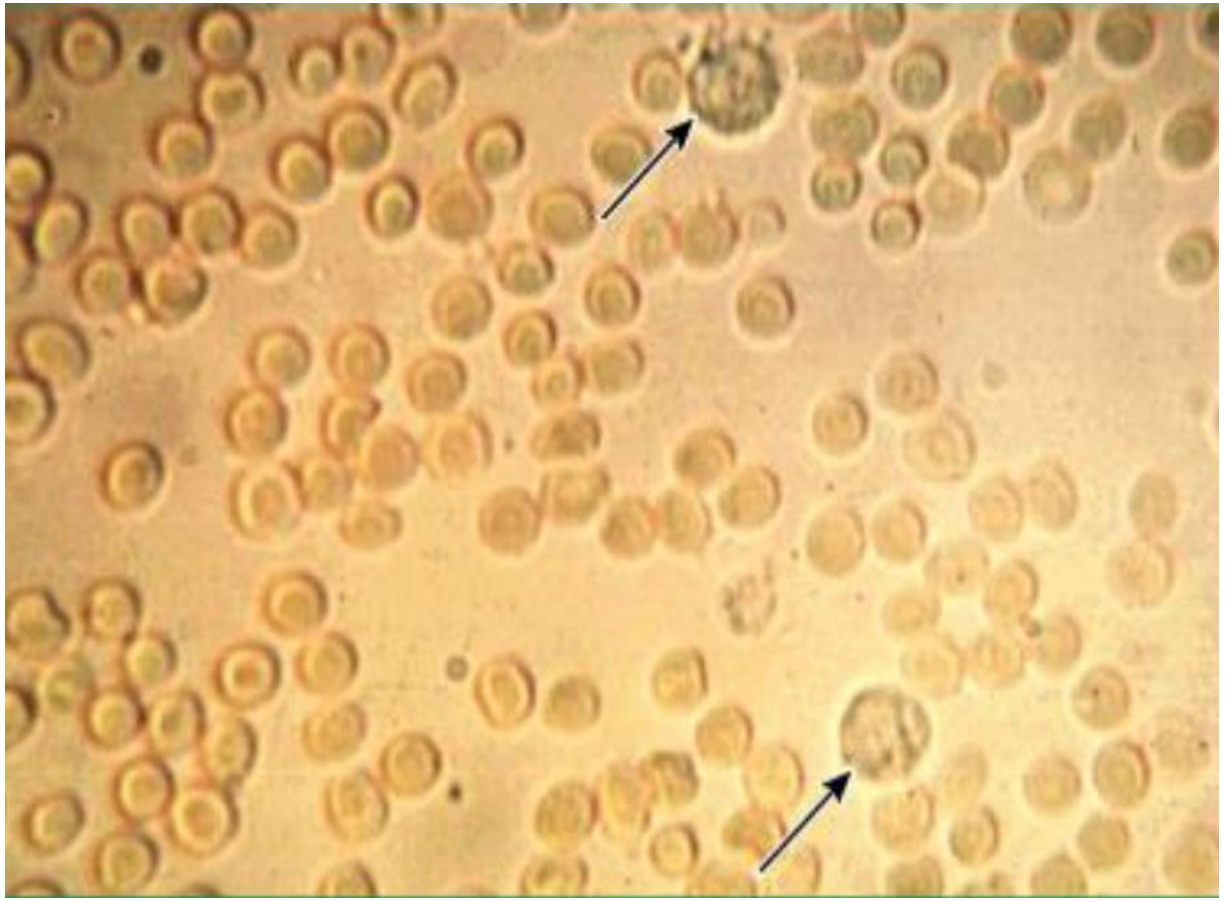


- This urine sediment shows multiple “Coffin lid” Magnesium Ammonium Phosphate Crystals (Struvite) that form only in Alkaline urine (pH usually above 7.0).
- Caused by Upper UTI with a Urease producing Bacteria.



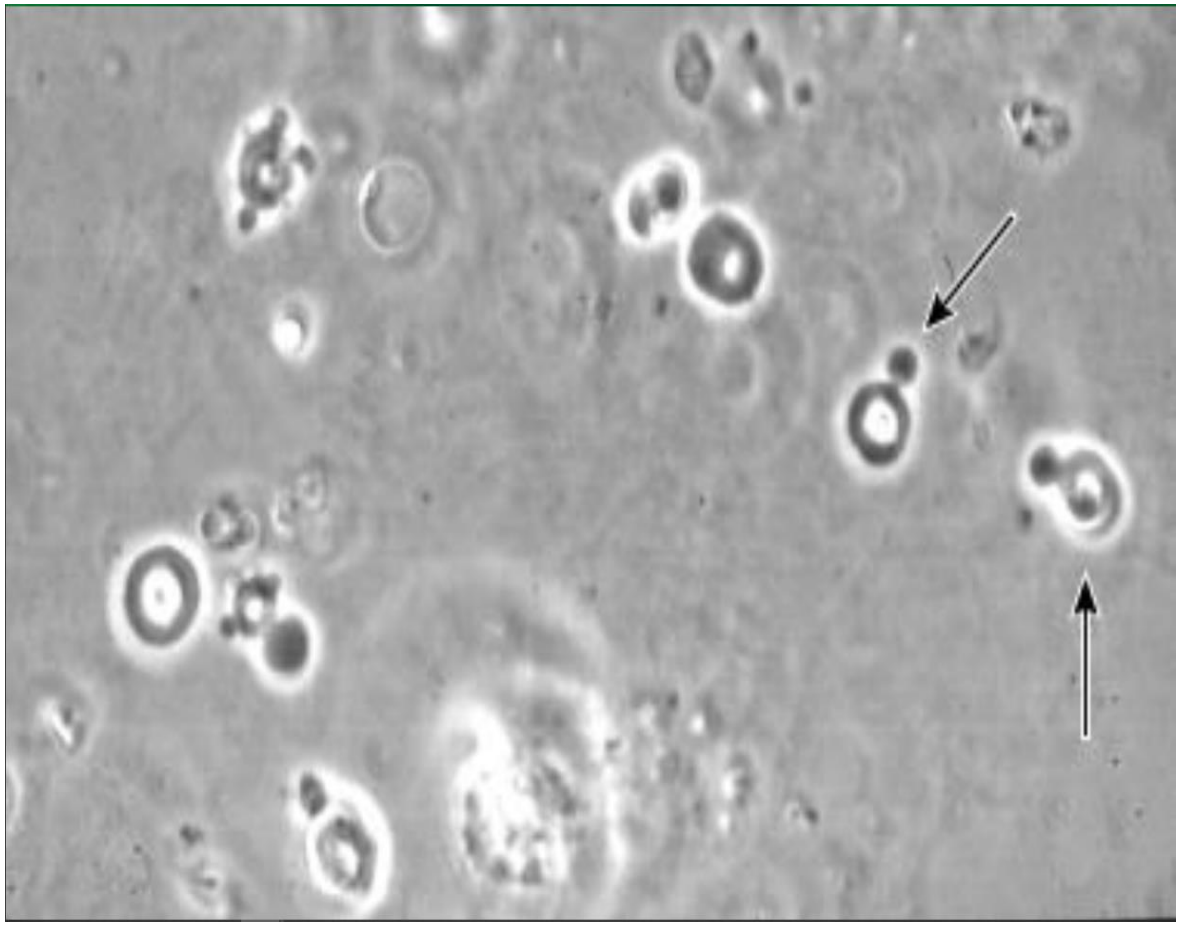
BACTERIA, BUDDING YEAST, AND HYPHAE IN THE URINE

- This urine sediment shows Budding Yeast and Hyphae (white arrow) + Bacteria (yellow arrows).
- There is also a Broad Hyaline Cast.



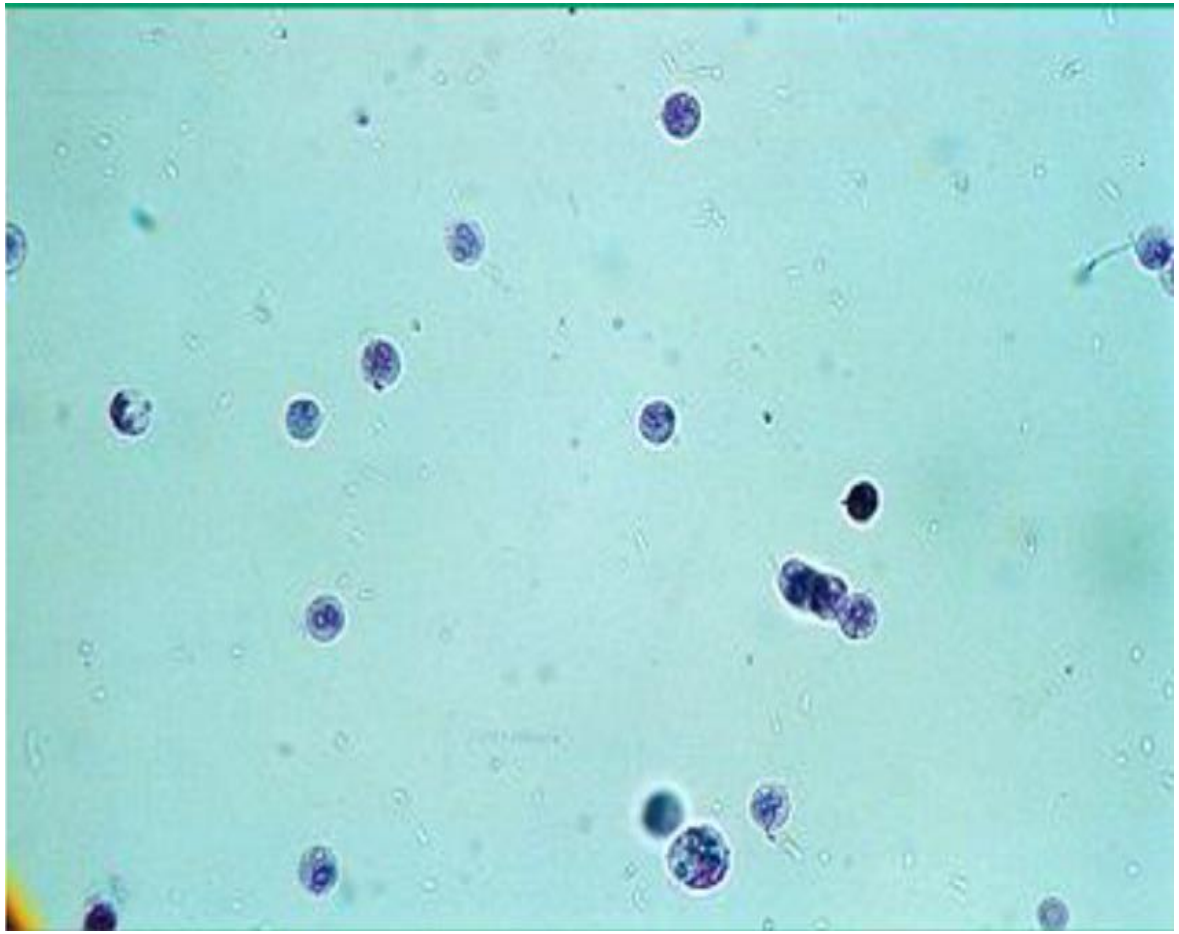
MONOMORPHIC RED CELLS IN THE URINE

- This is a Phase-Contrast Micrograph.
- This urine sediment viewed by phase-contrast micrograph shows many red cells and an occasional larger white cell with a granular cytoplasm (the arrows).
- The red cells have uniform size and shape, suggesting that they’re of Non-glomerular origin.
- When we see such manifestation, we should rule out urologic problems like stones or tumors by doing CT / US / Cystoscopy



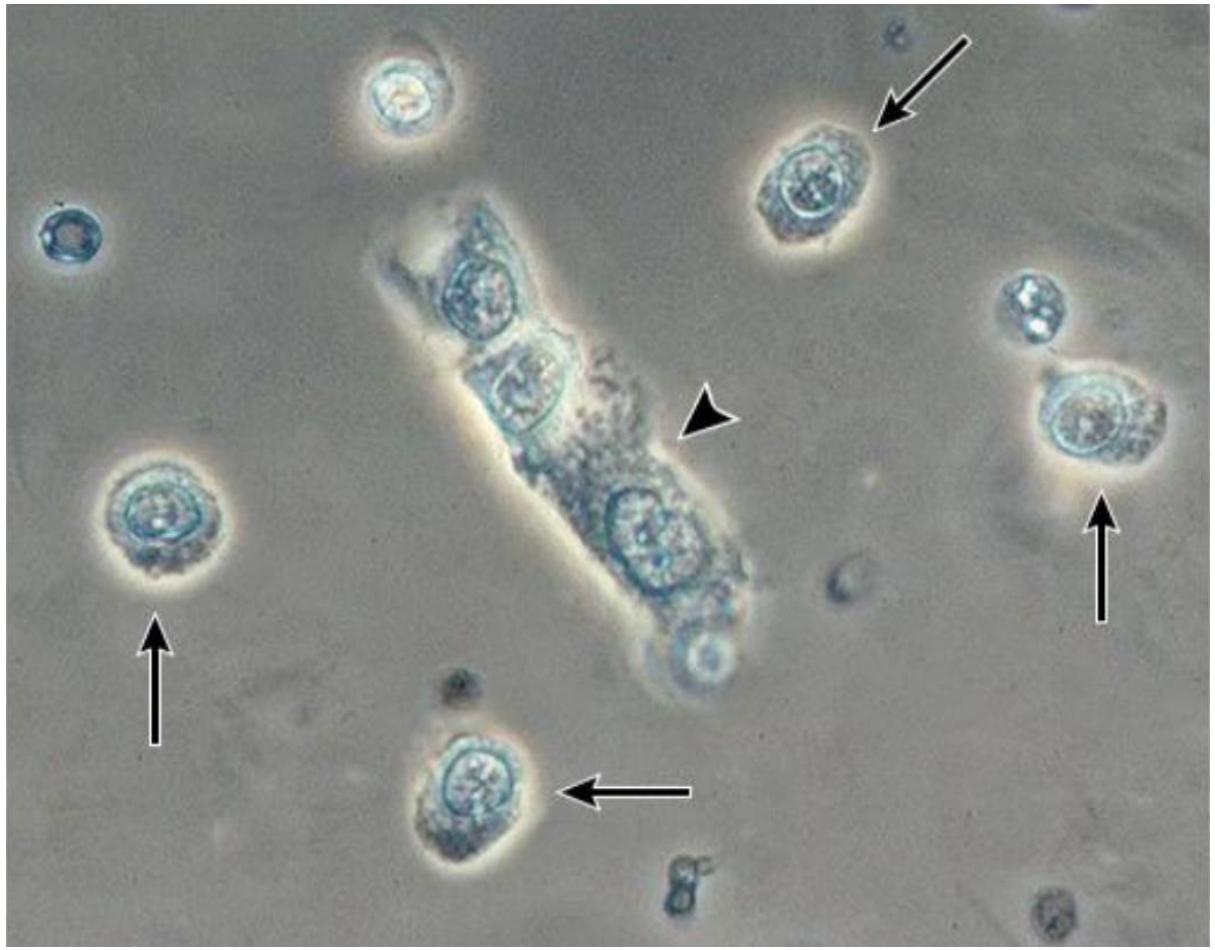
DYSMORPHIC RBCS IN THE URINE

- Those indicate Glomerulonephritis until proven otherwise (because of inflammation cells get squeezed in the tubule).



WBCS IN THE URINE

- This is a Photomicrograph.
- This urine sediment shows WBCs with nuclei and granular cytoplasm.
- Normally we should have 0 WBCs in the urine.
- If we have >5 WBCs, then it's abnormal and we should think of UTI.

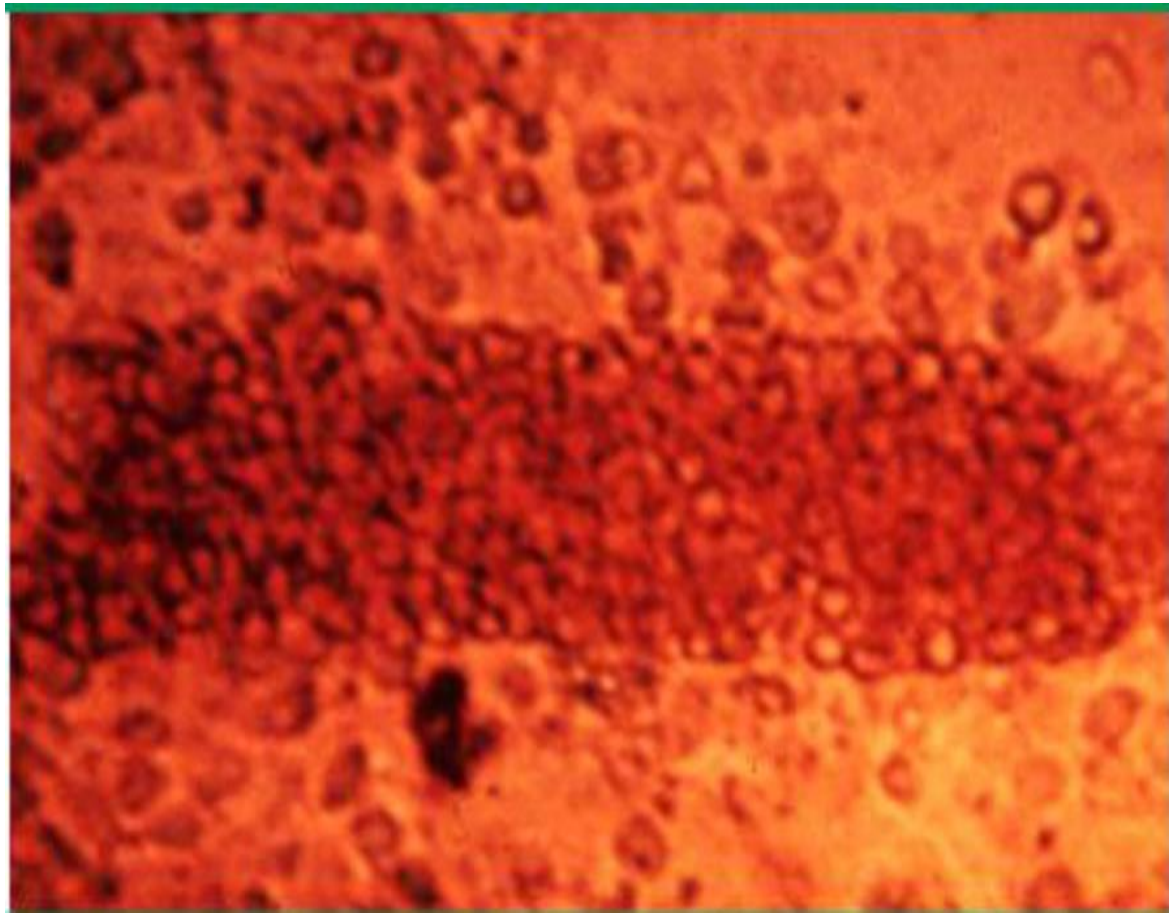


RENAL TUBULAR EPITHELIAL CELLS IN THE URINE

- This urine sediment shows Renal Tubular Epithelial cells (arrows), together with a fragment of Tubular Epithelial Cell Cast (arrowhead).
- The Tubular cells are characterized by one central nucleus and many cytoplasmic granules.

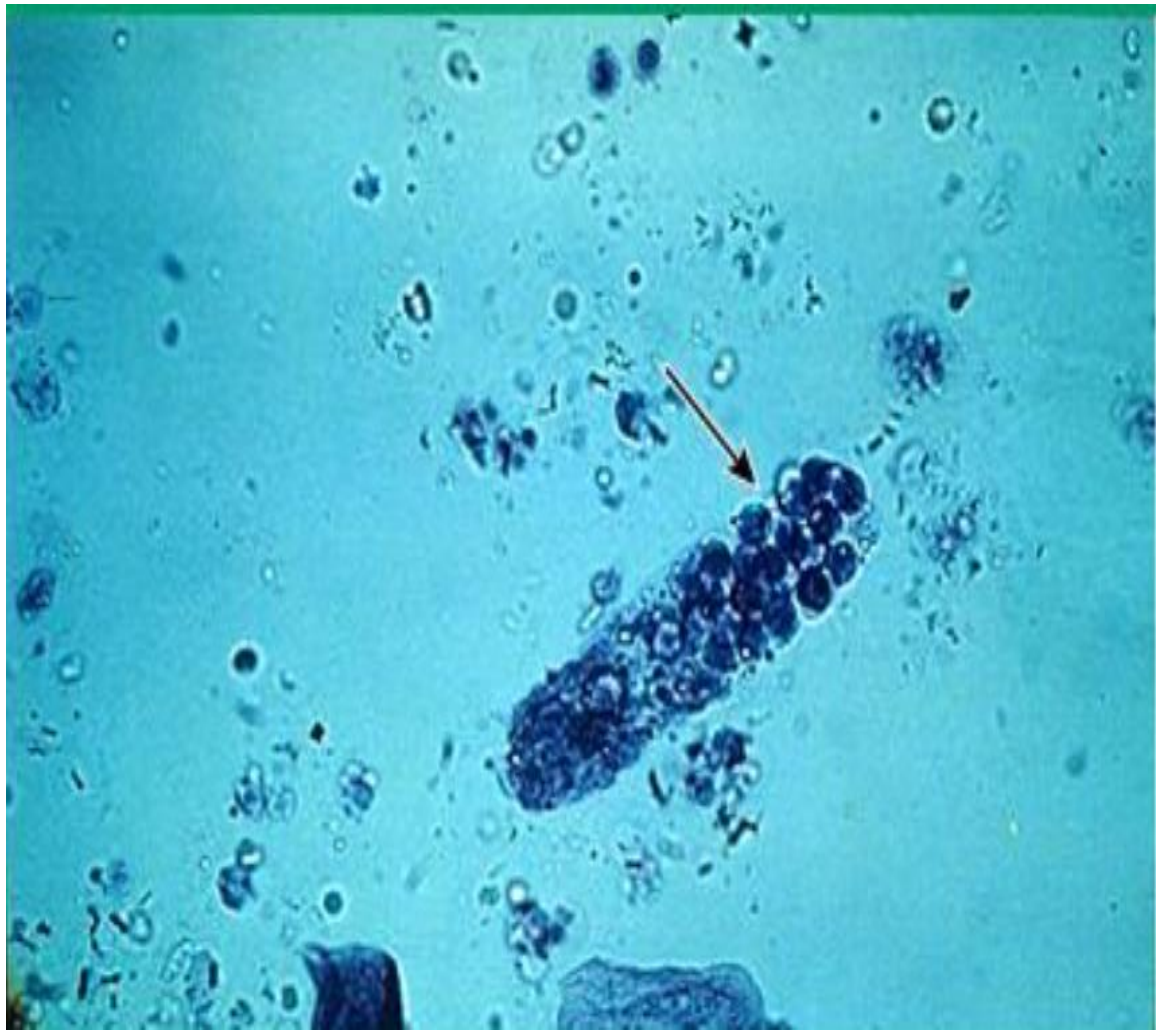
RBC CASTS IN THE URINE

- This is a Photomicrograph.
- This urine sediment shows Free Red Cells and a Red Cell Cast that is tightly packed with red cells.
- It's more common for red cell casts to have fewer red cells trapped within a hyaline or granular cast.
- Red Cell Casts are virtually diagnostic of Glomerulonephritis (Glomerular Hematuria), or Vasculitis.



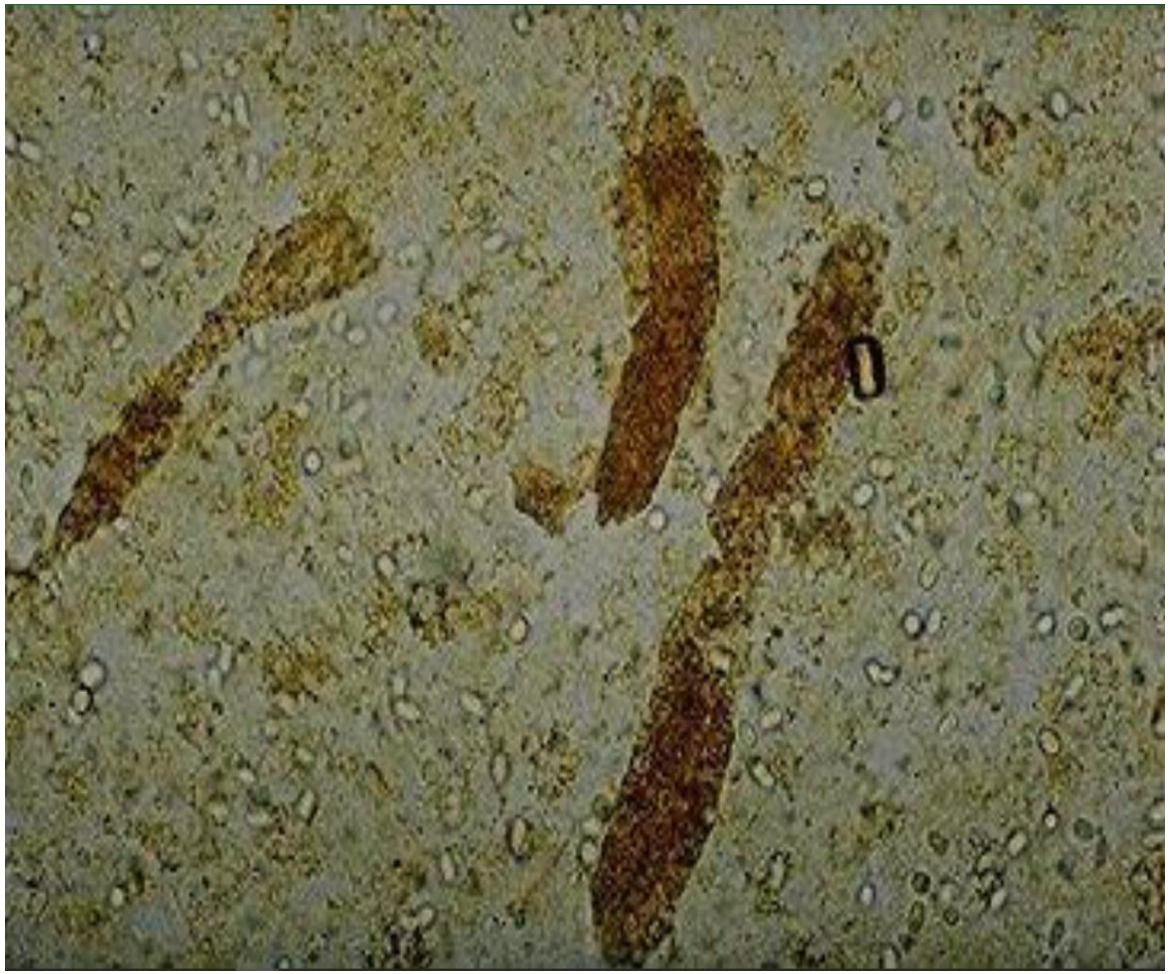
WBC CAST IN THE URINE

- This is a Photomicrograph of the urine.
- This urine sediment shows White Cell Cast in which blue-stained white cells (arrow) are contained within a granular cast.
- It is indicative of kidney inflammation (Pyelonephritis –Upper UTI , the problem is in the kidney- , or Interstitial Nephritis).

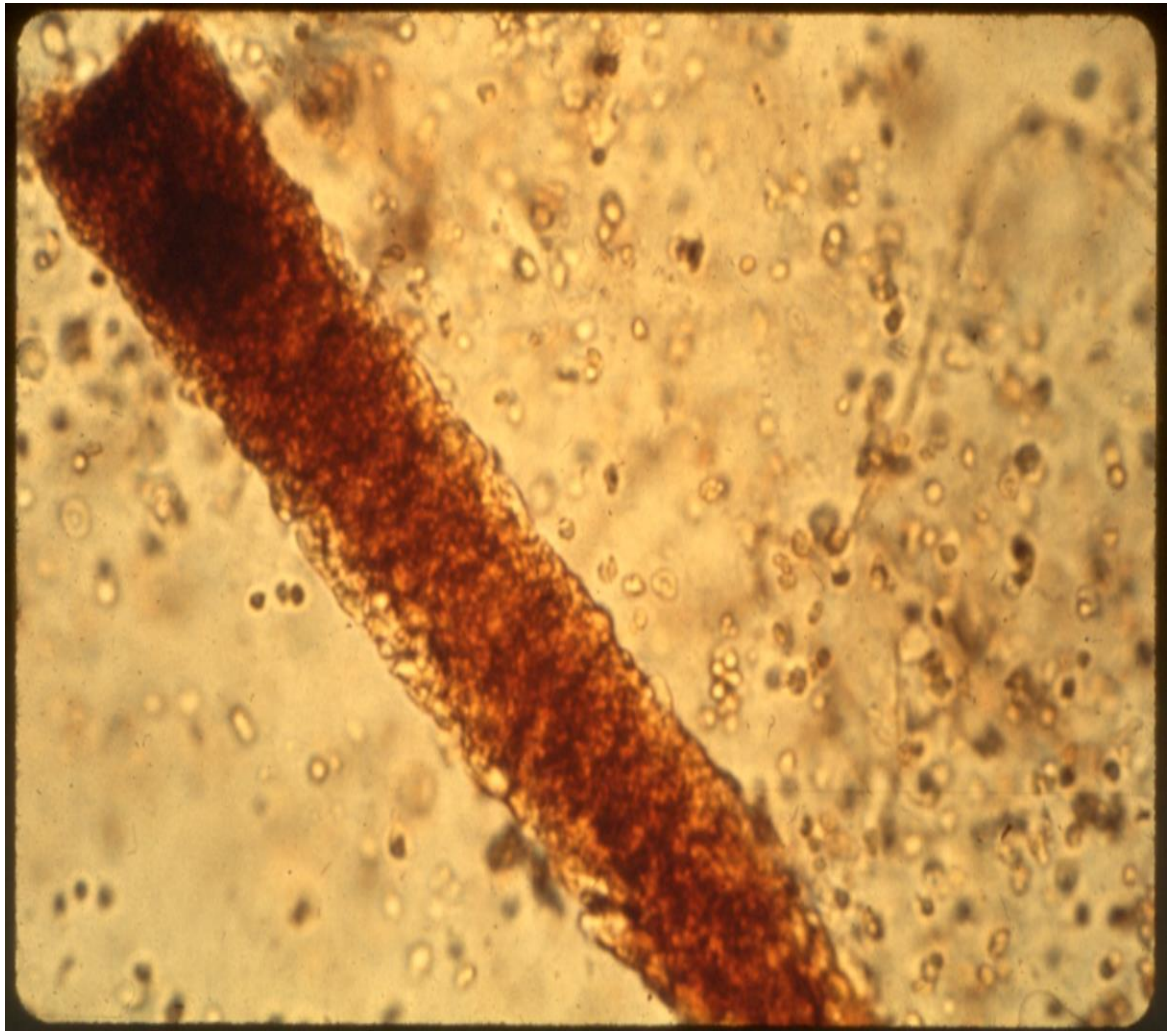


MUDDY BROWN CASTS IN THE URINE

- It's an Old Cast of Acute Tubular Necrosis.

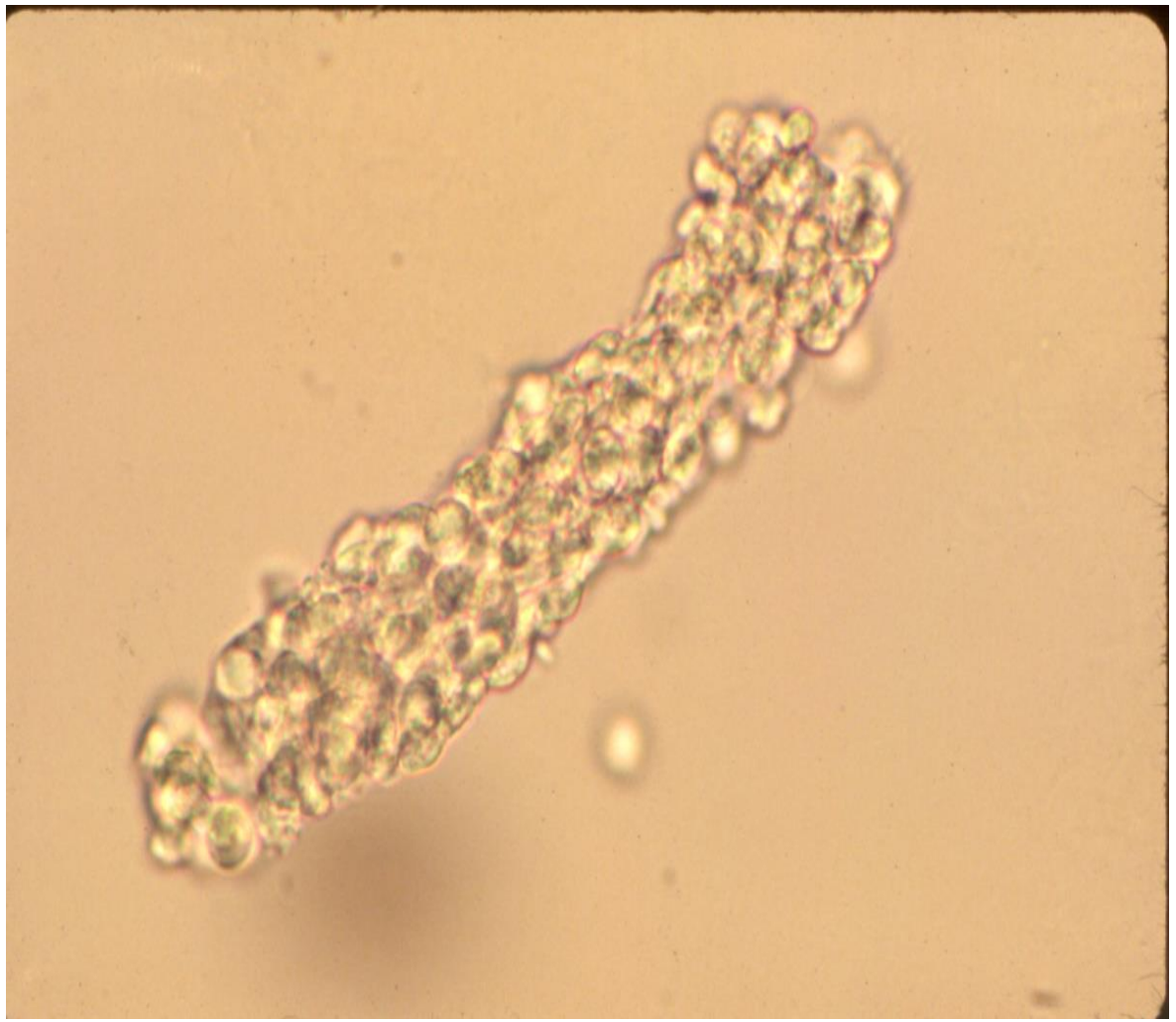


ACUTE KIDNEY INJURY



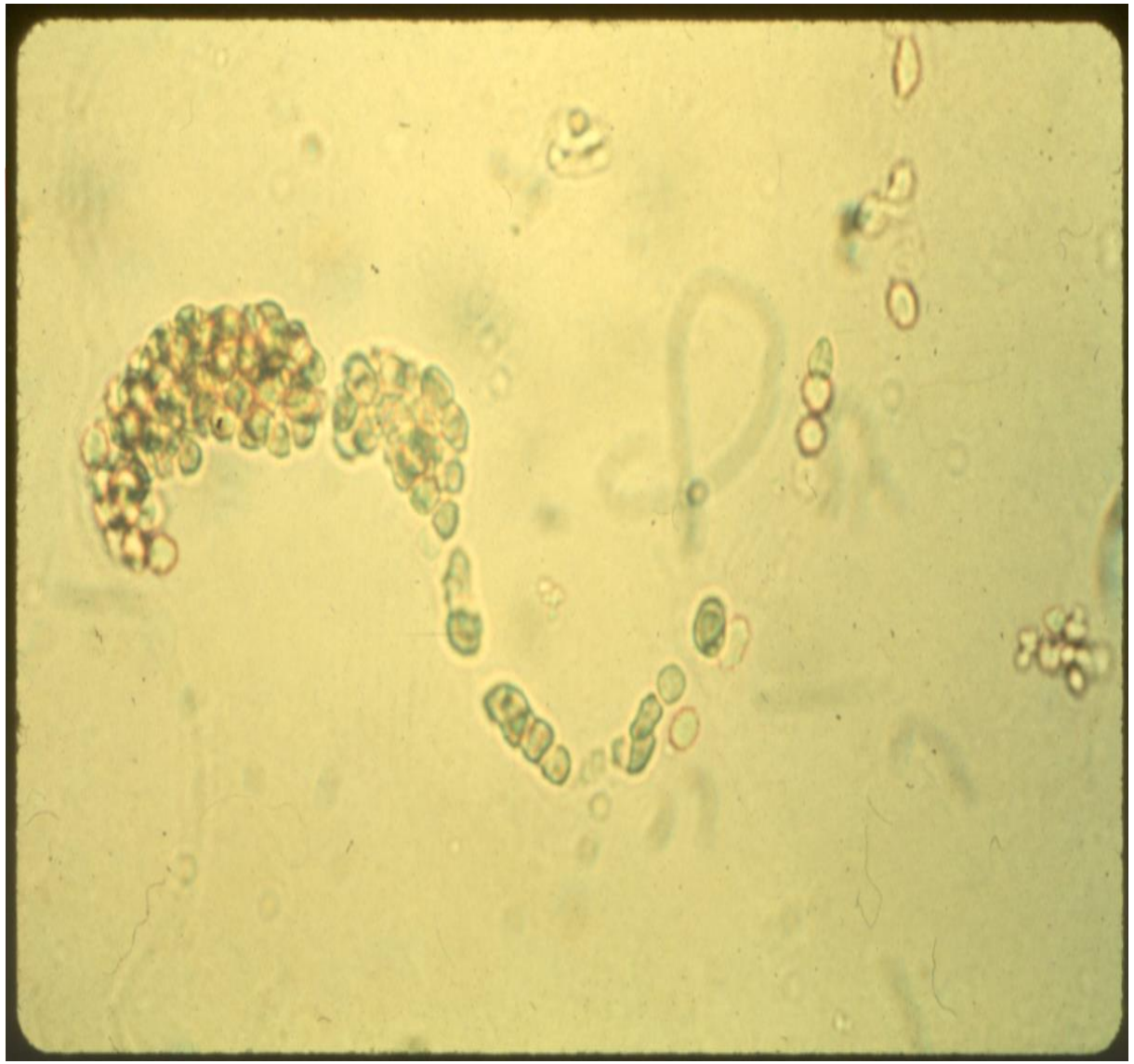
HEME GRANULAR CASTS IN THE URINE

- This Cast consists of Protein, Debris, Hemoglobin, Sloughed Cells, Intact Cells, RBCs.
- Hb + RBCs give this characteristic Brown color.
- It is diagnostic for Acute Tubular Necrosis.
- It doesn't respond to normalization of Volume and BP.
- Characterized by rapid rise in Creatinine, Oliguria and Anuria.



WBC CASTS IN THE URINE

- The circular multinucleated cells are Neutrophils.
- It indicates Allergic Interstitial Nephritis.
- Associated with prolonged exposure to Drugs (Penicillin, Allopurinol – used in hyperuricemia- , Cipro, NSAIDs, Sulphonamides).
- Characterized by a Triad of Rash, Fever, and Eosinophils in Blood and Urine.
- There is always Pyuria and WBC casts in the urine



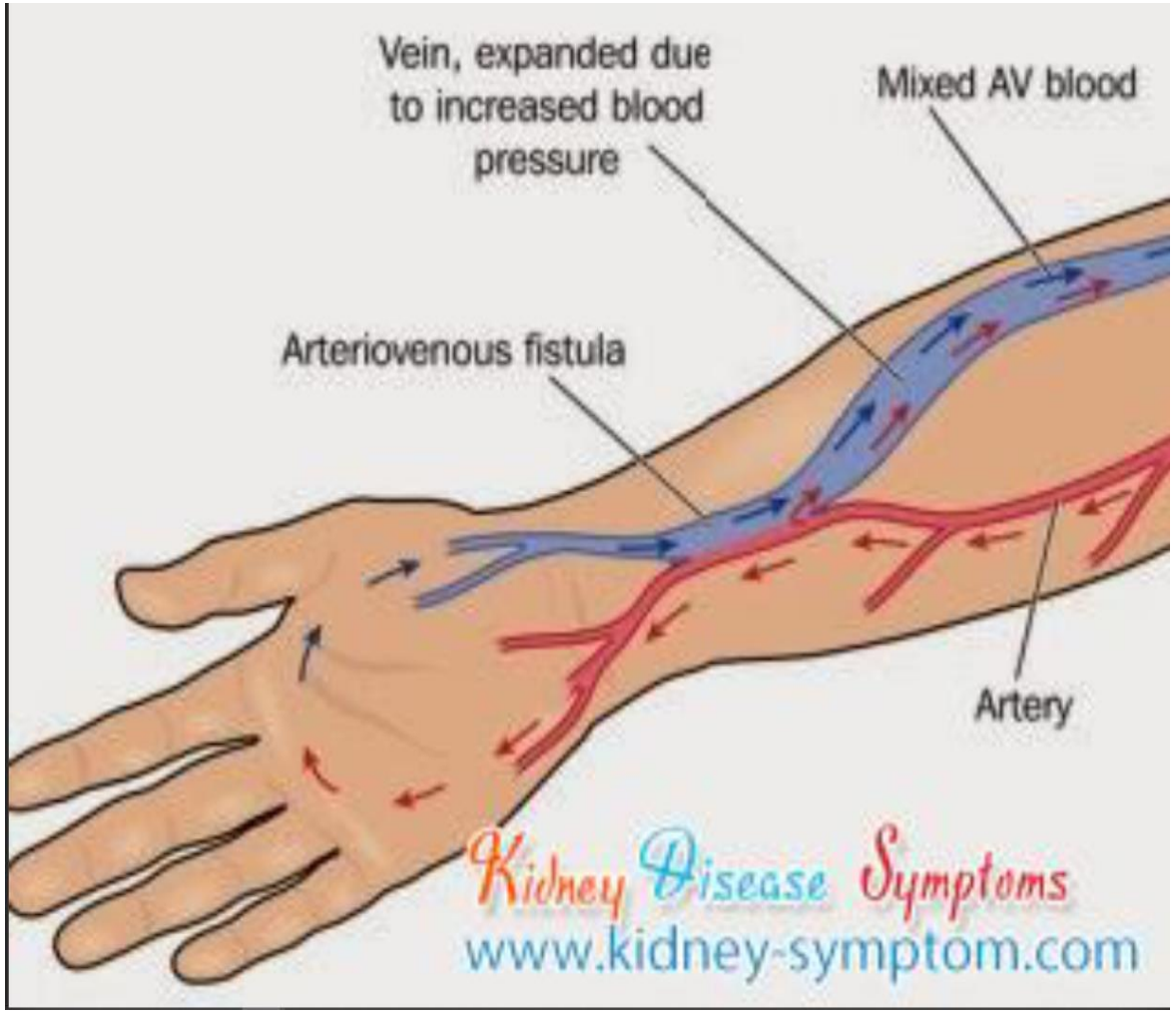
RBC CASTS IN THE URINE

- Notice that the cells here are Circular with NO nucleus.
- It indicates Rapidly Progressive Glomerulonephritis.
- Associated with Anti-GBM antibodies (Goodpasture's).
- Immune complex mediated, so seen with SLE, Post-infectious, IgA nephritis (rarely), and Hepatitis.
- Pauci Immune (ANCA positive), so seen also with Wegener's Granulomatosis, and Microscopic Polyangitis.
- The patient comes with Hematuria, Proteinuria, Low urine output, Creatinine at first 1 but within days increases to 3,6,7, and the patient deteriorates quickly, and he'll need dialysis over few days to weeks

RENAL REPLACEMENT THERAPY

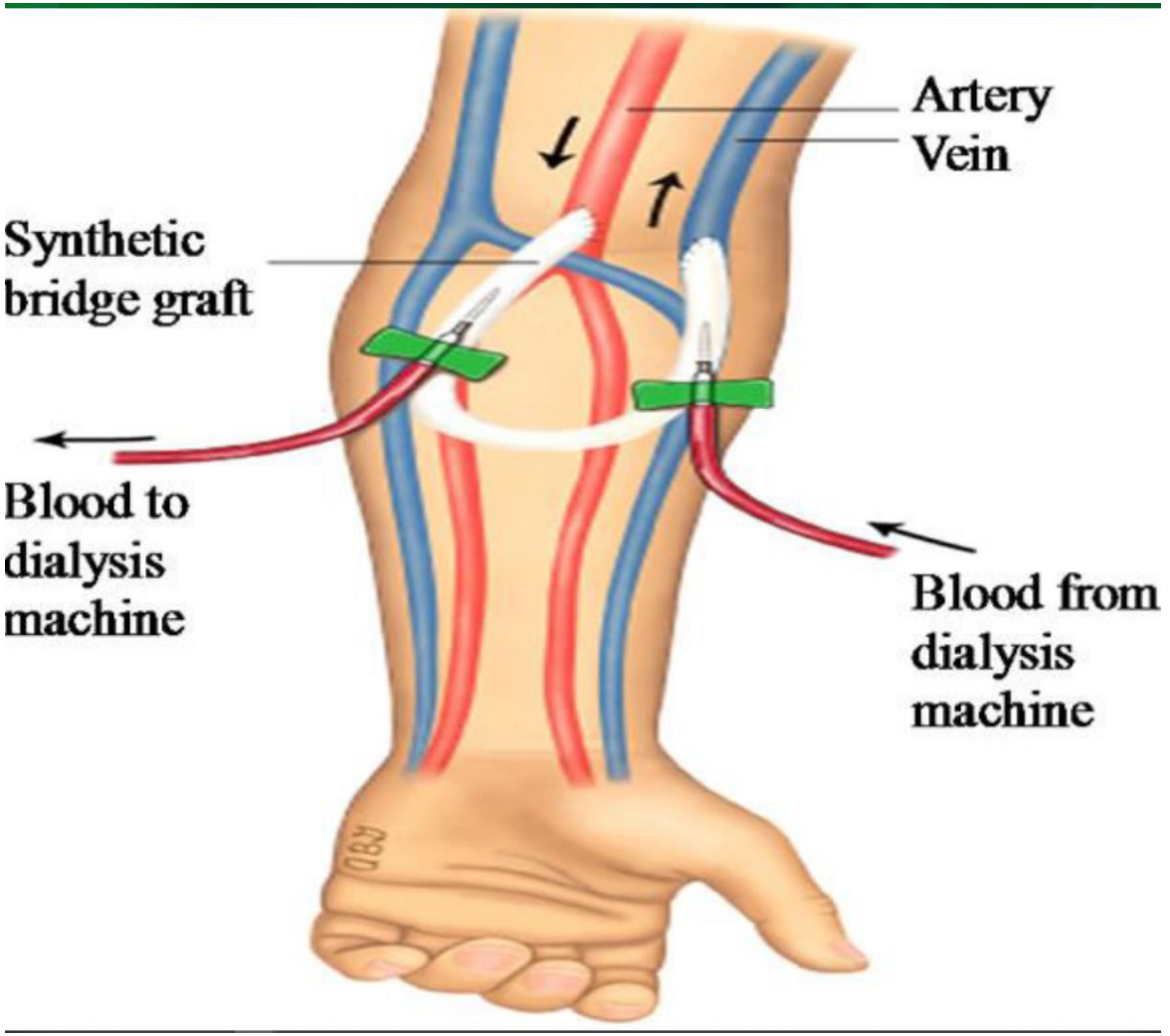
ARTERIOVENOUS FISTULA

- The best access for Dialysis.
- A Vascular Surgeon connects an artery and a vein most commonly in the forearm (Radio-Cephalic) so blood returns to the vein, which causes better blood supply to the vein causing vein arterialization / maturation producing strong vein and then we inject with 2 injections
- To be able to do it over years, we need strong veins and very good blood supply.



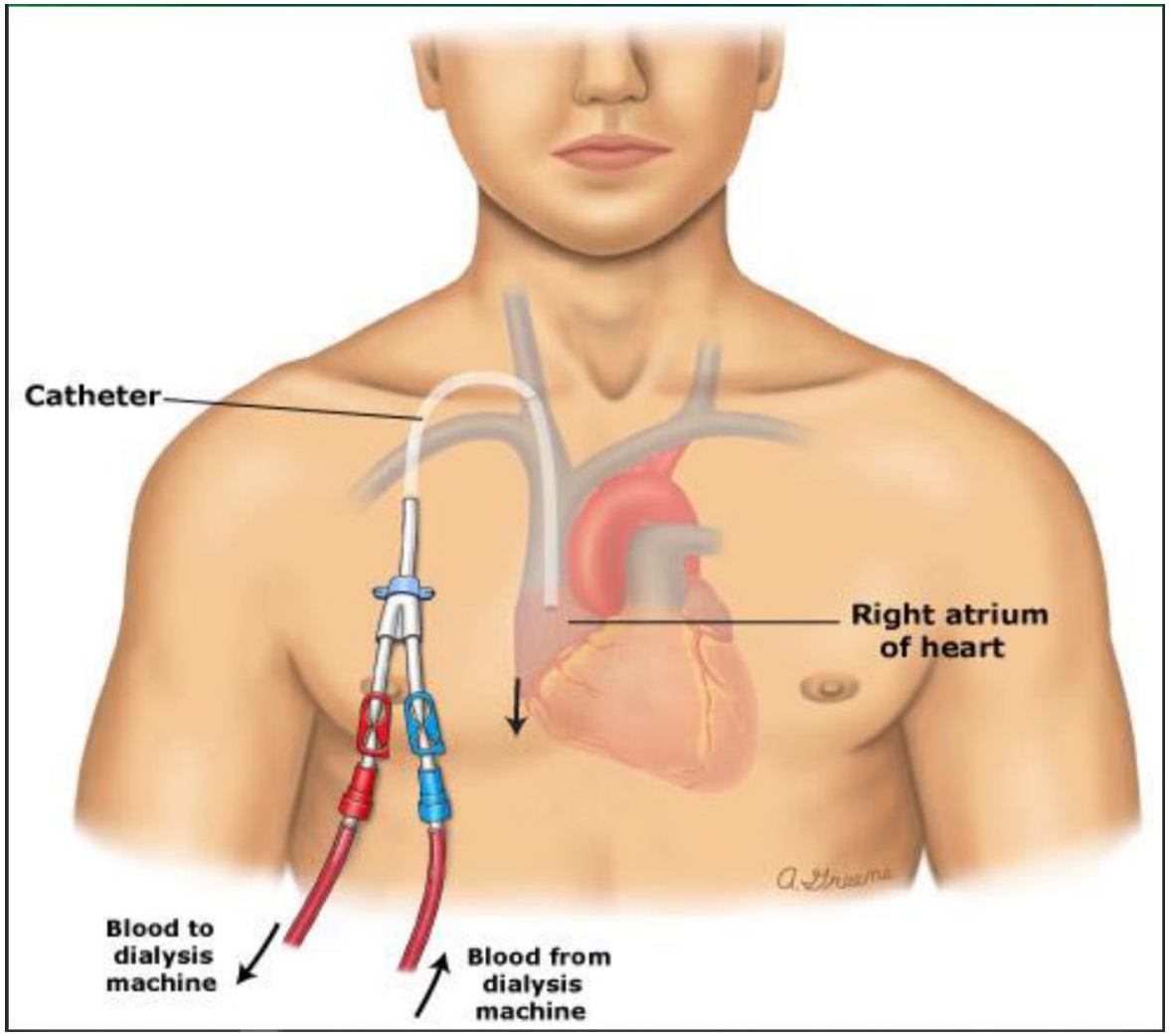
ARTERIOVENOUS GRAFT

- The second-best access.
- If veins are too small, we add an AVG which is a synthetic material connecting Arteries and Veins and we inject the graft itself.
- The Fistula needs 6 weeks to be mature.
- The Graft needs 2 weeks to be used (for healing at the site of anastomosis).



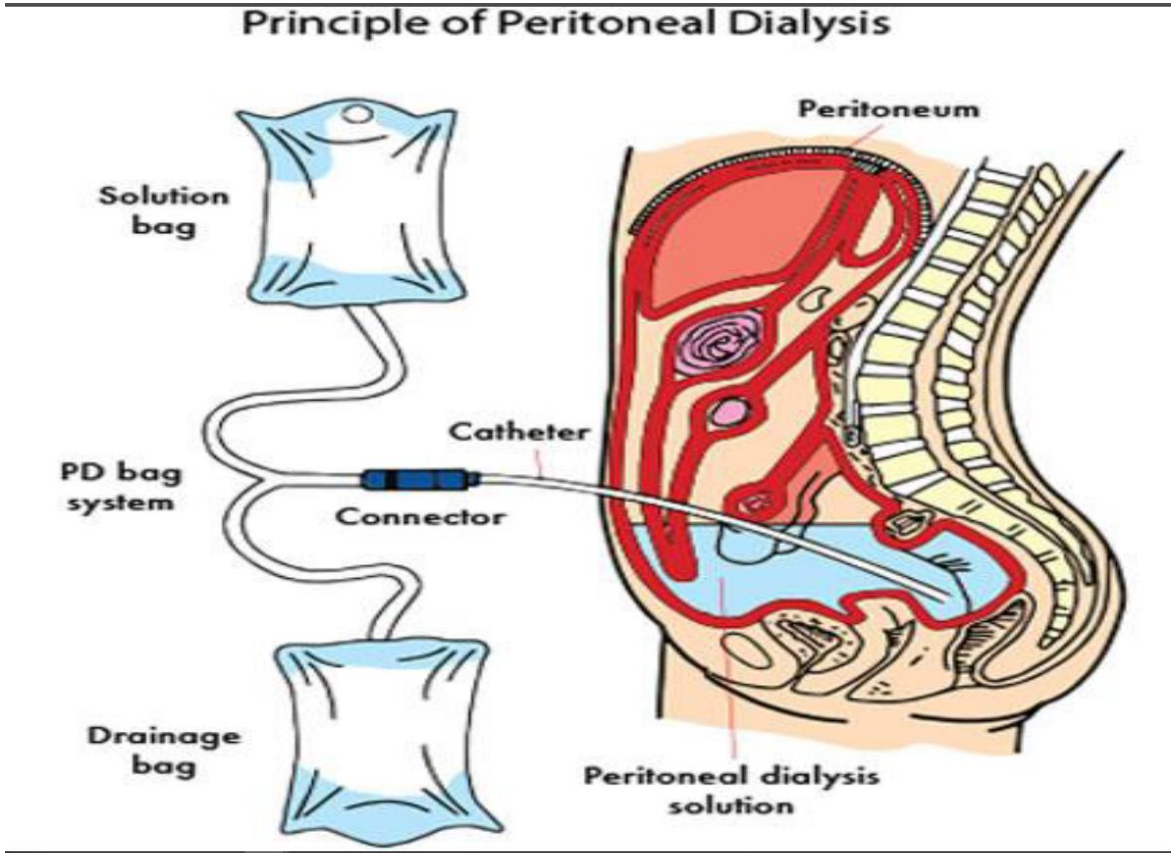
HEMODIALYSIS CATHETER

- It is a permanent catheter.
- We insert the catheter under the skin to reduce the risk of infection.
- We use it only if urgent dialysis is needed and no fistula or graft is present
- There is a risk of infection from this catheter which may reach the heart and may cause Tricuspid Valve Vegetation with Septic Emboli to the lung.
- Temporary from the neck and descend under the skin to the internal jugular vein with the tip of the catheter found between Rt atrium and SVC



PERITONEAL DIALYSIS

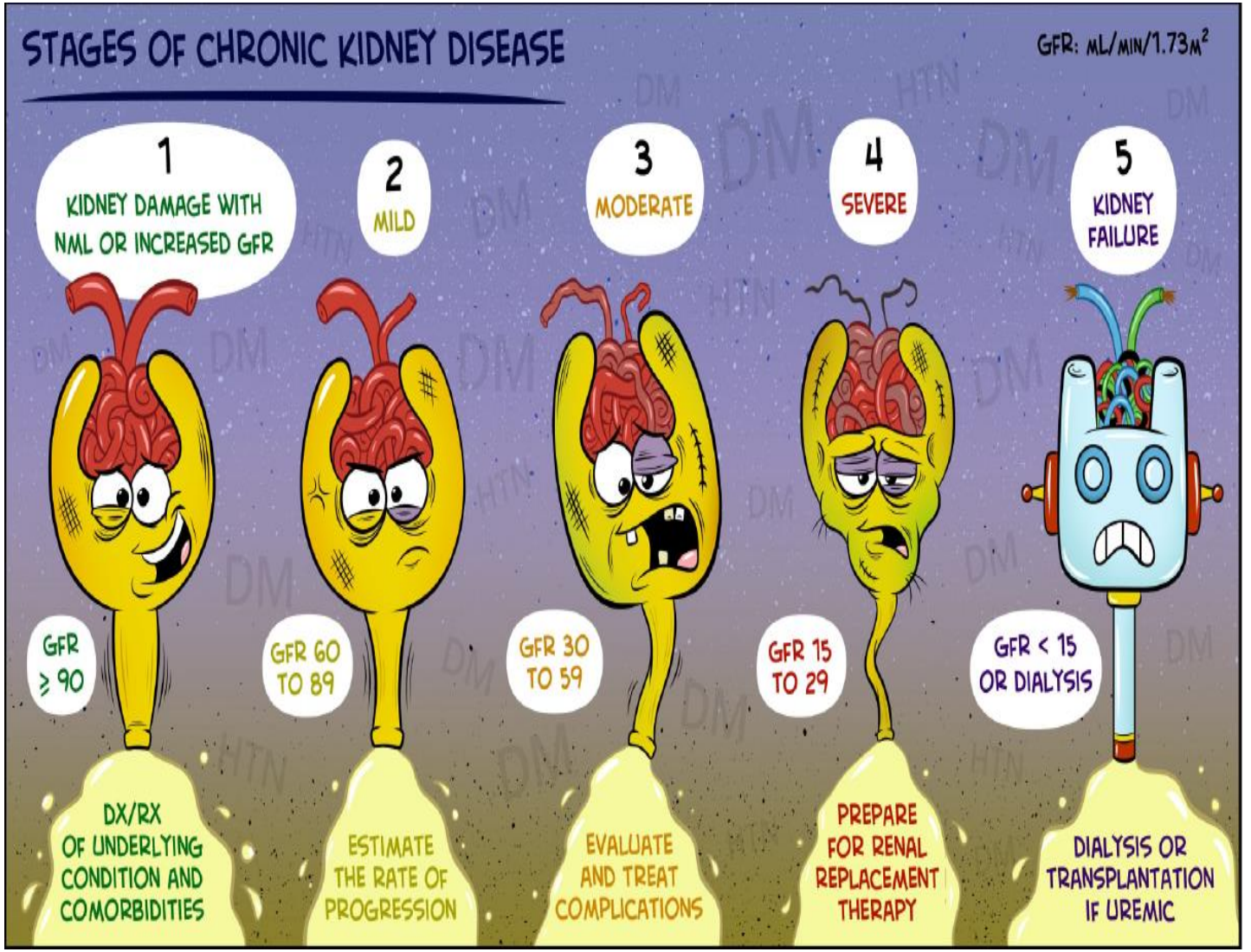
- In the abdominal cavity and the peritoneal membrane there are capillaries with blood, and we have large surface area, so we only need to give the dialysis, we put in the bag and the peritoneal dialysis catheter, we leave it there for 3-4 hours and then we drain it.
- Highly concentrated components of the blood leave the blood via dialysis in 3-4 hours.
- There is a problem of volume overload, to solve it we add hypertonic solution mainly (1-4.25%) Dextrose and through osmotic pressure it pulls water to the dialysis system.



- There is a high risk of Peritonitis with PD catheter infection, so we must be cautious while inserting the catheter.

CHRONIC KIDNEY DISEASE

STAGES OF CKD



Clinical Features of CKD / Head And Neck

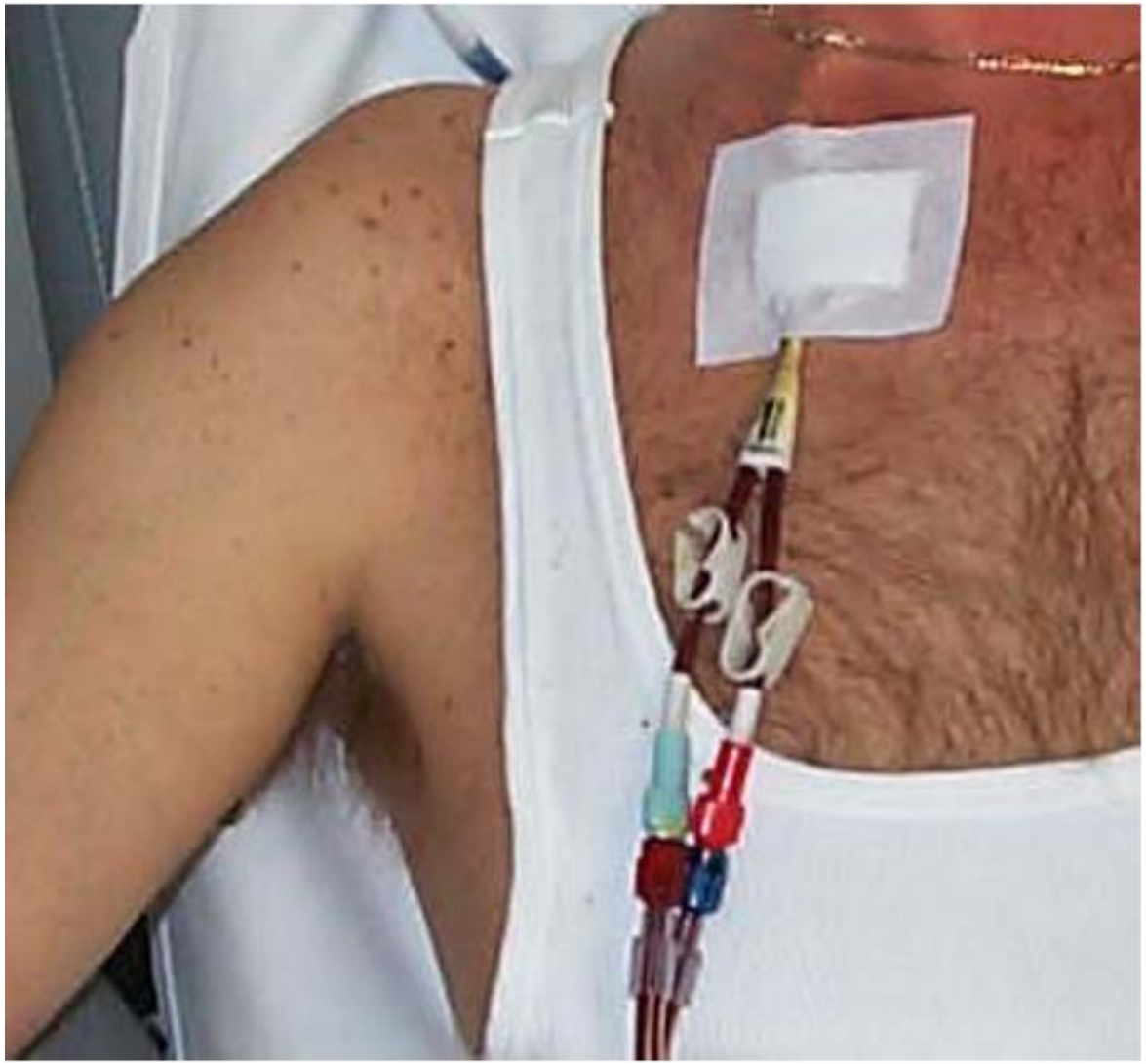
- Earthy color, Pallor, Dark pigmentation.
- There may be Swollen Face.
- Conjunctival Pallor → Due to Anemia.
- Periorbital puffiness, Arcus in the eyes (indicating Dyslipidemia, with increased risk for Cardiac Disease and Peripheral Vascular Disease).
- Fundal Examination or Fundoscopy: shows signs of HTN (retinopathy), DM, Vasculitis, Subacute Bacterial Endocarditis
- Odors of the mouth: because Ammonia is excreted through sweat and saliva due to accumulation of urea in the body since it's not excreted in the urine due to low GFR.
- Rash of Lupus, Vasculitis, Connective Tissue Disease.
- Neck: Access for Dialysis, Bruit in the carotid artery (due to peripheral vascular disease), we must check all pulses.

INTERNAL JUGULAR HEMODIALYSIS CATHETER

- Site of Lines on IJV to take blood from SVC (it is the shortest route).

SUPRACLAVICULAR VEIN HEMODIALYSIS CATHETER

- SCV Catheter → Tunneled Line → to the Jugular Vein



Clinical Features of CKD / Chest

Dialysis Catheter: IJ HD Catheter / SCV HD Catheter.

Signs of liver Disease: Hepatorenal Disease / CKD with chronic liver disease.

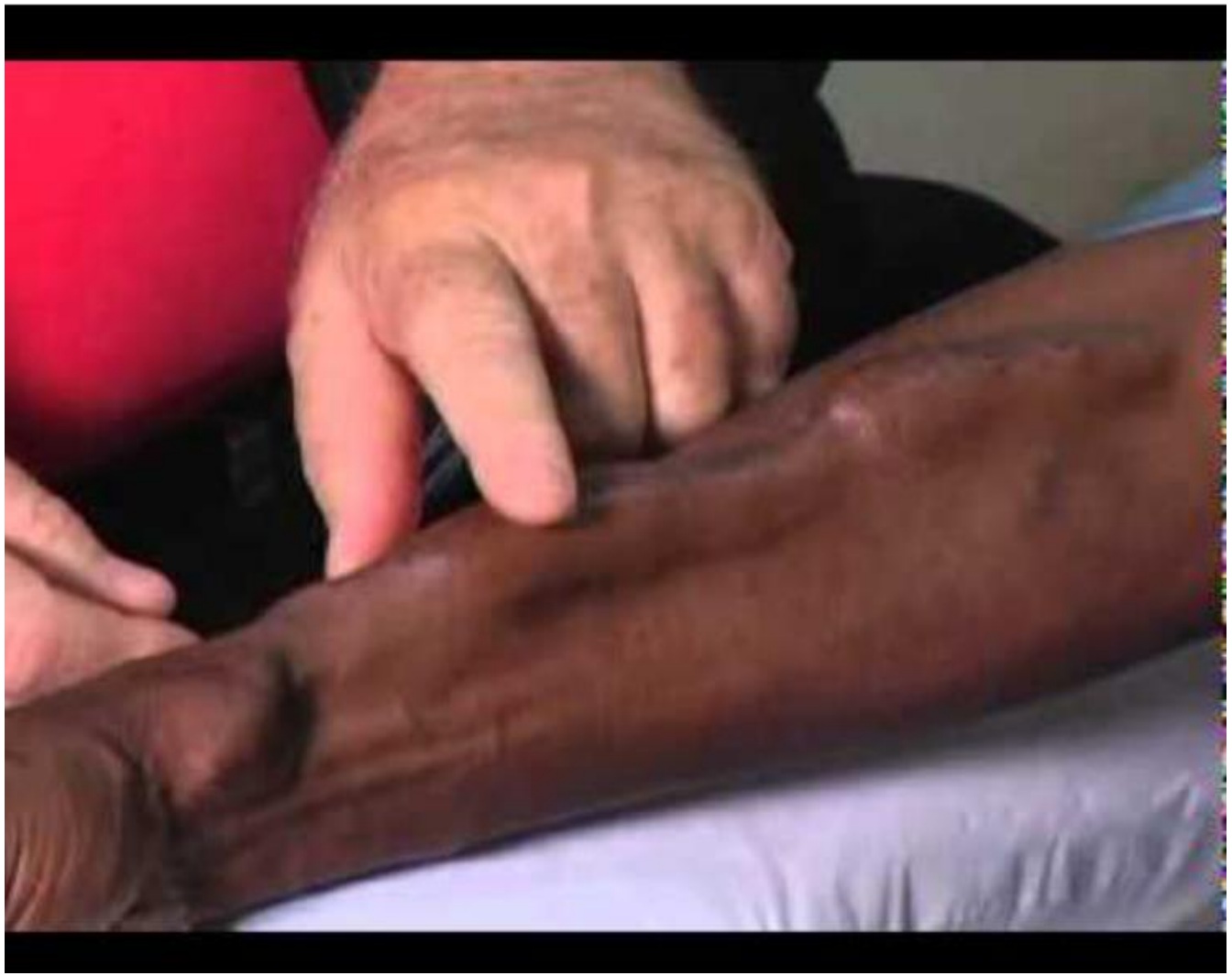
Tattoos.

Scratch mark: Pruritis (Itching) in CKD indicates advanced disease.

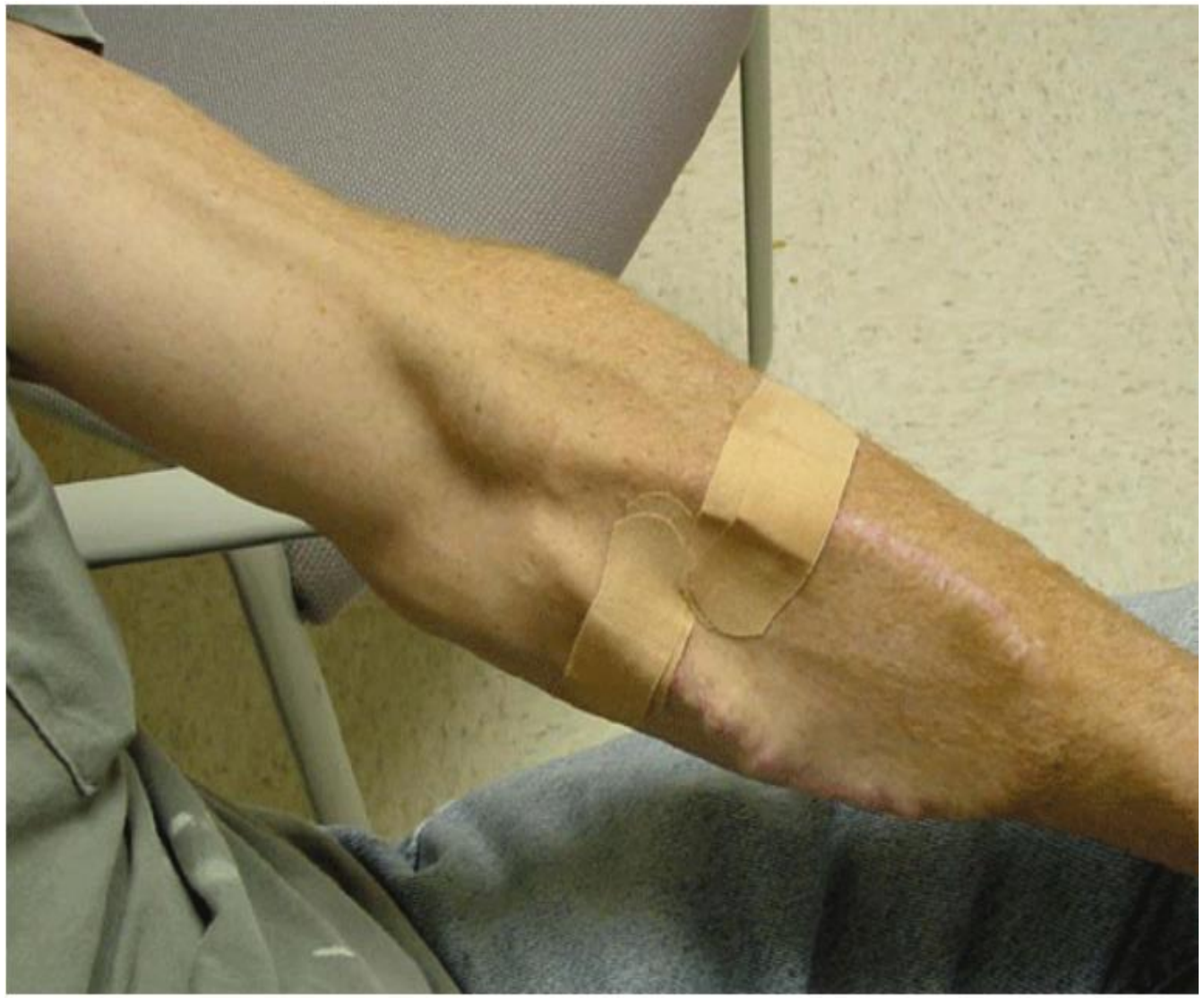
Brown Tumors affecting the Ribs: Focal Replacement of bone due to renal Osteodystrophy due to Primary Hyperparathyroidism.

Clinical Features of CKD / Cardiovascular System

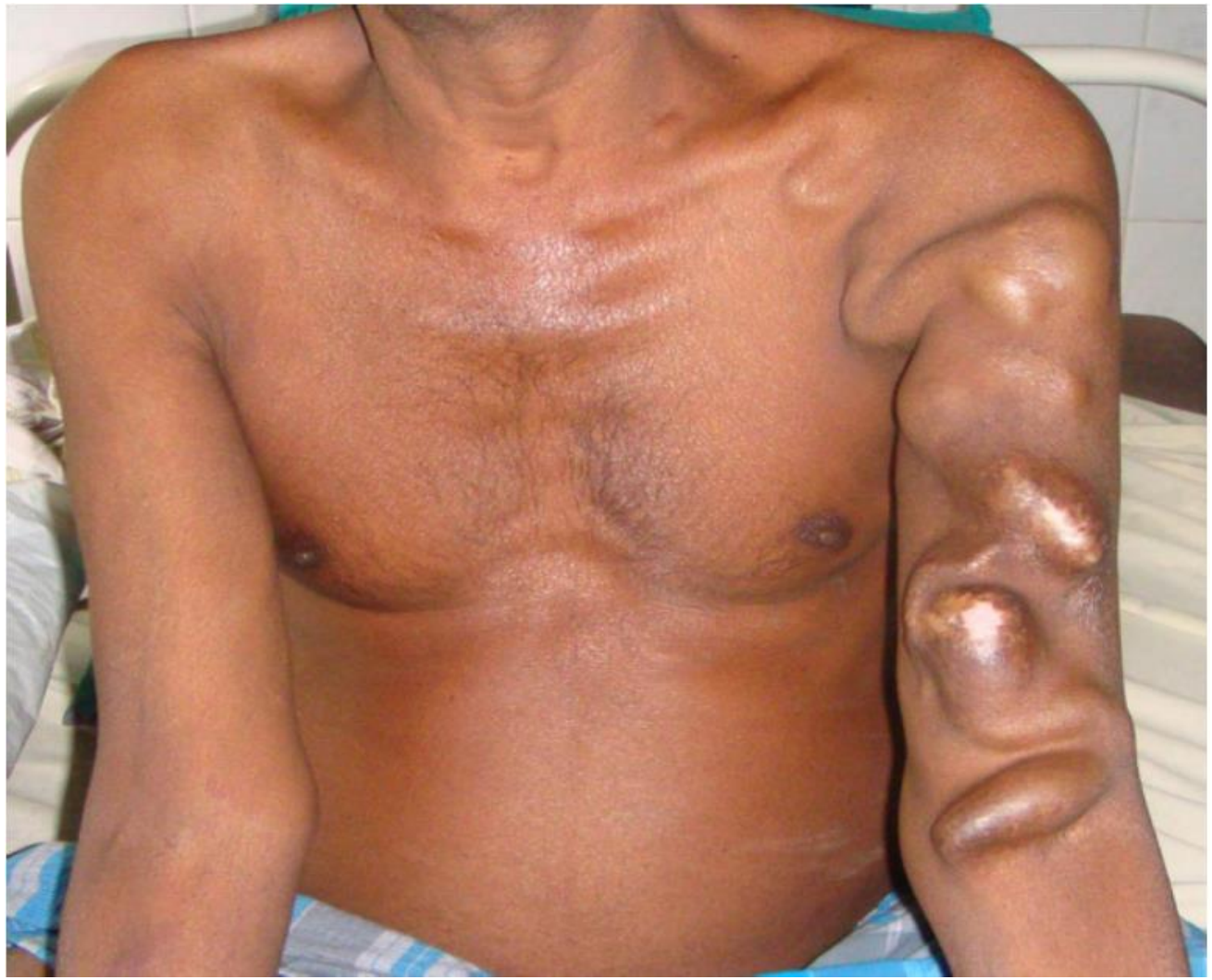
- Friction Rub: Due to Uremic Pericarditis, Treated by extensive daily dialysis.
- Abnormal Heart Sounds: S3 (CHF leading to Cardiorenal Syndrome), S4 (Stiff ventricles due to HTN), Muffled Heart Sounds (In pericardial Effusion, due to low GFR and Volume overload).
- AVF or Graft and their complications (mainly Aneurysms).



AV FISTULA



AV GRAFT

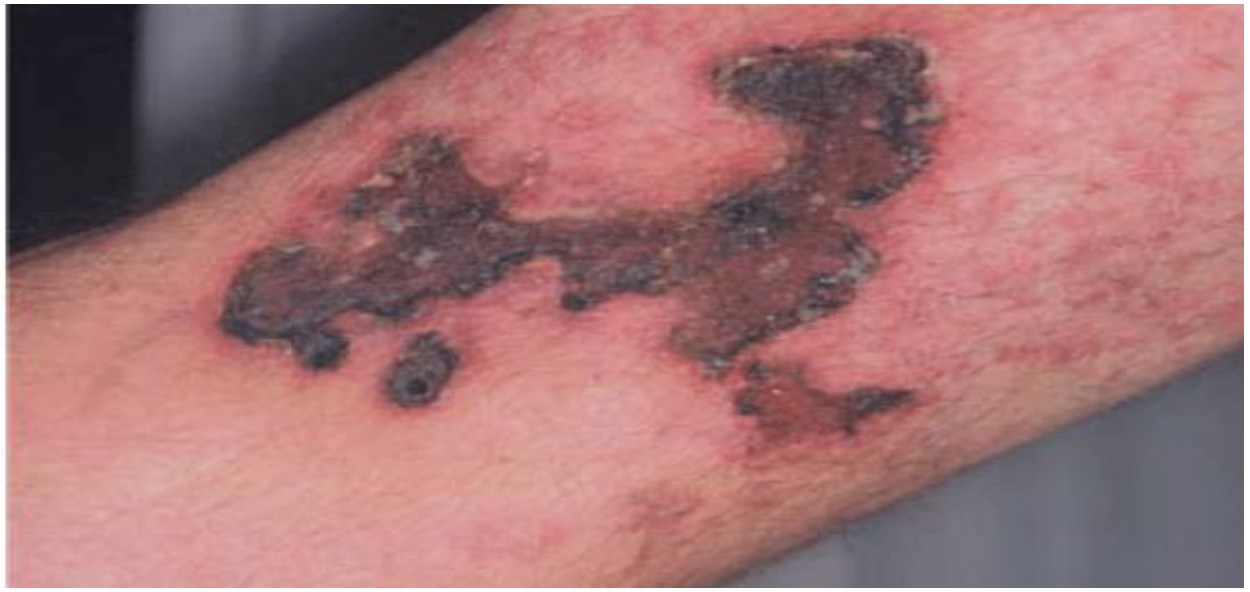


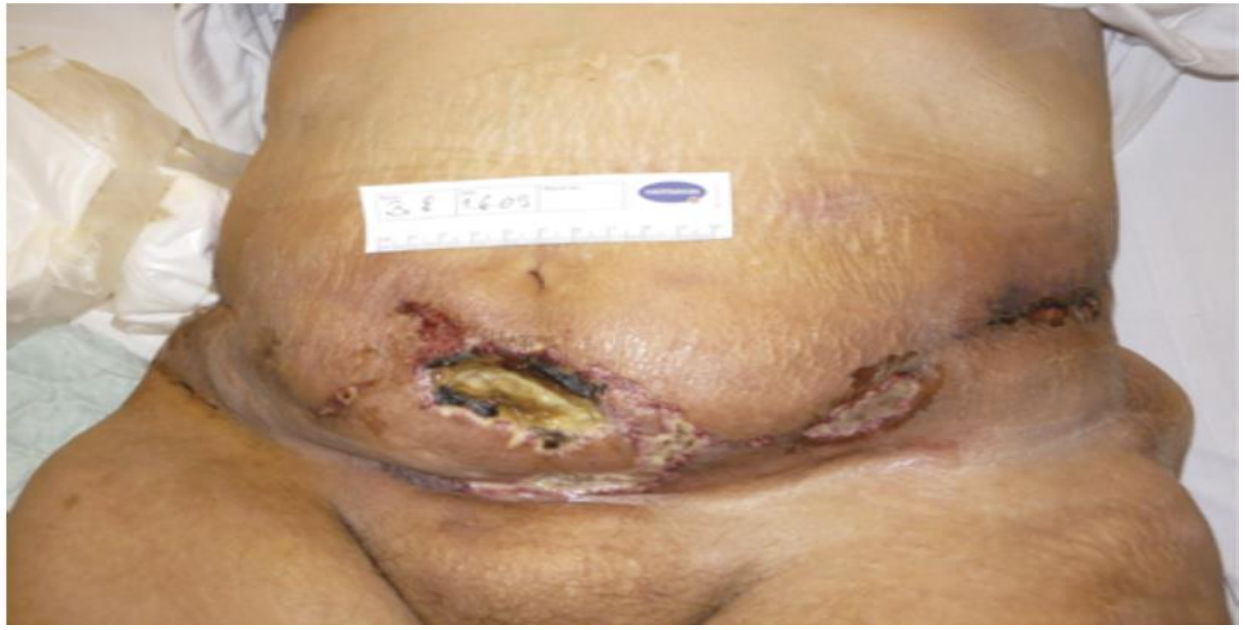
ANEURYSM

- As a complication of AVF or AV Graft.

Clinical Features of CKD / Abdomen

- Ascites: seen in Nephrotic Syndrome.
- Scratch mark: Pruritis indicating Advanced Stage of the Disease.
- PD Catheter.
- Scar of Renal Transplant.
- Polycystic kidneys.
- Renal Bruits.
- Calciphylaxis.



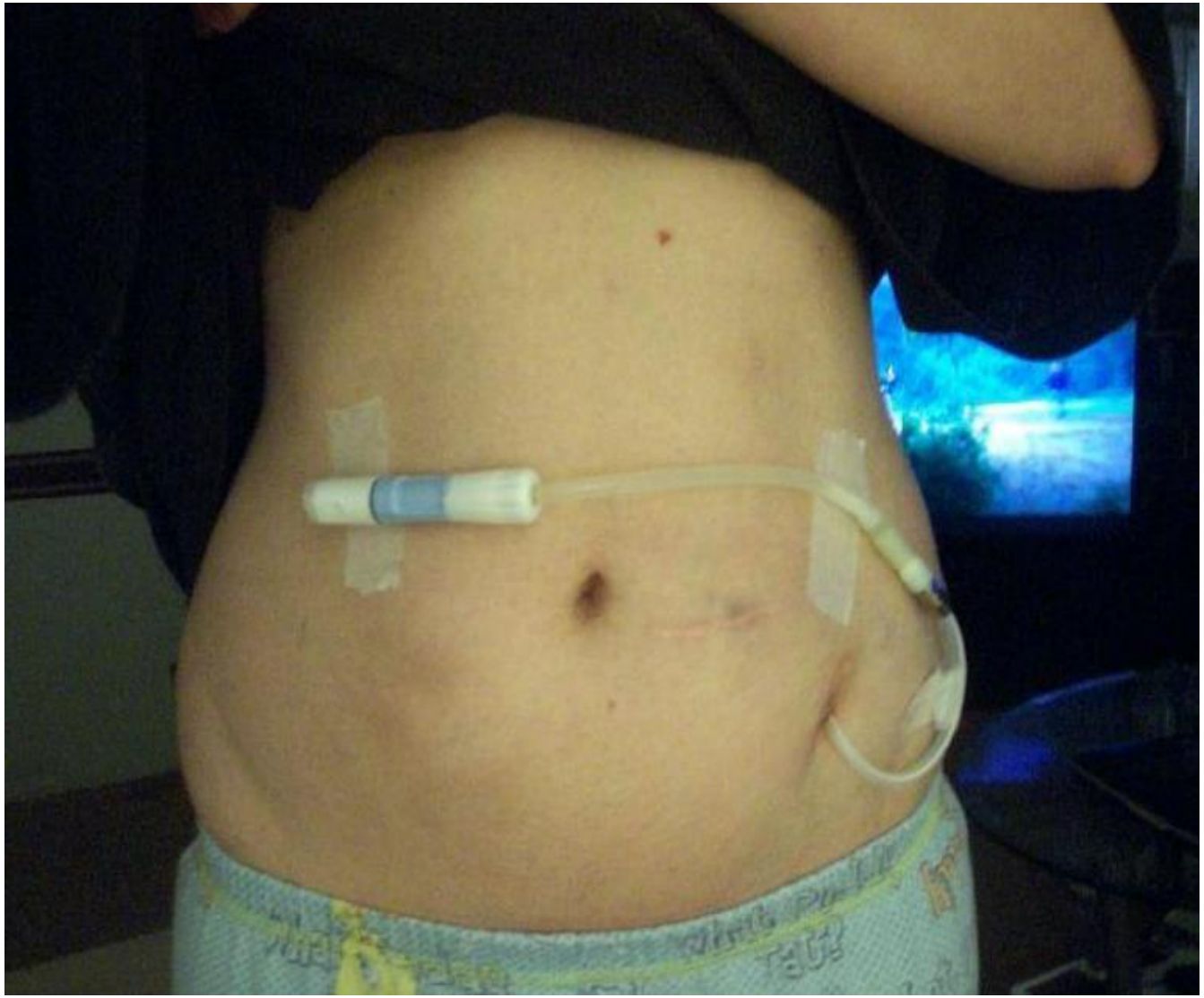


Calciphylaxis

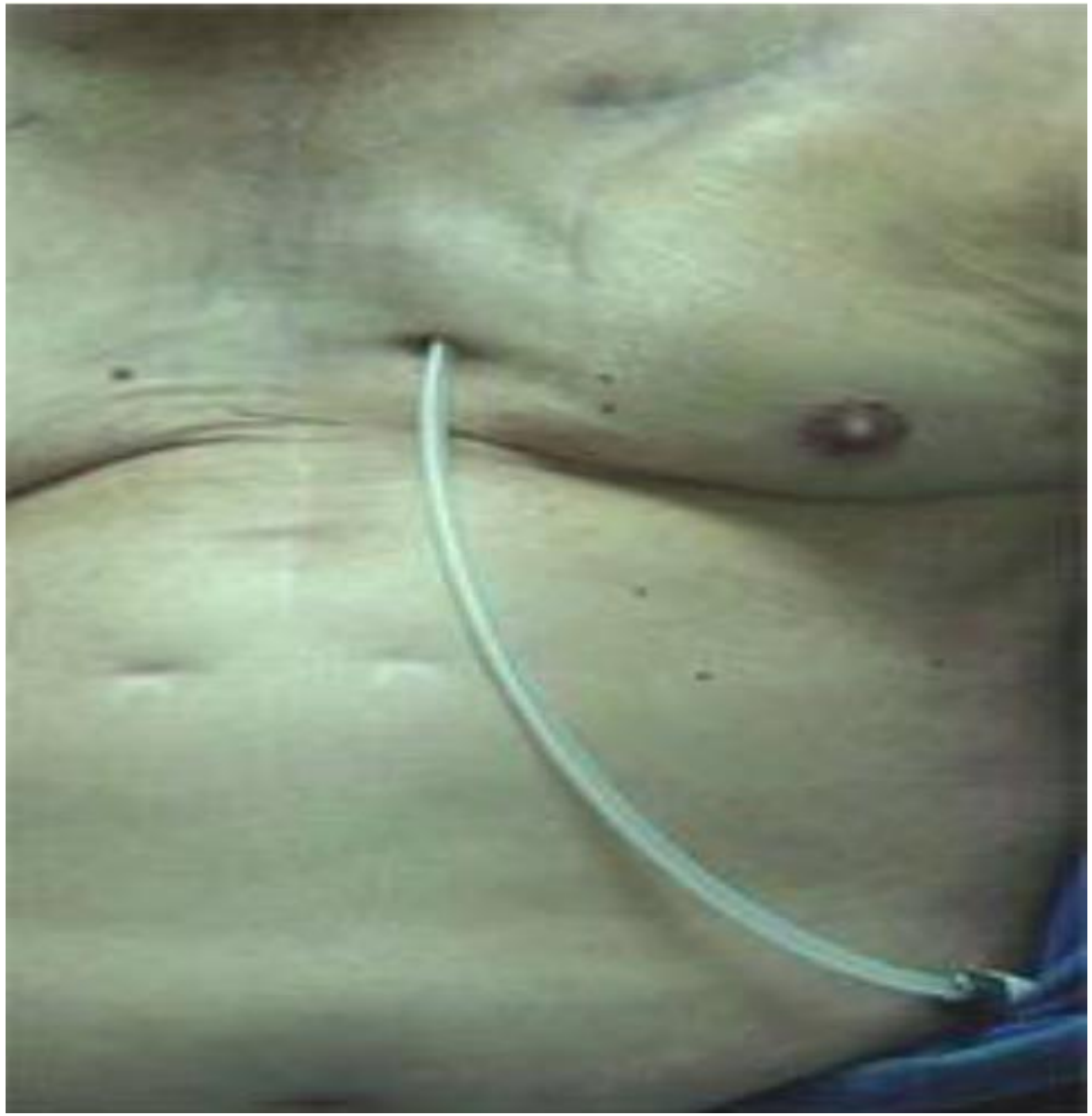
- It's a serious, uncommon disease in which Calcium accumulates in small blood vessels of the fat and skin tissue, which causes blood clots, painful skin ulcers, and may cause serious infections that can lead to death.
- Treatment:

1- Restoring Oxygen and blood flow to the skin (using Anticoagulants like Apixaban and Hyperbaric oxygen therapy).

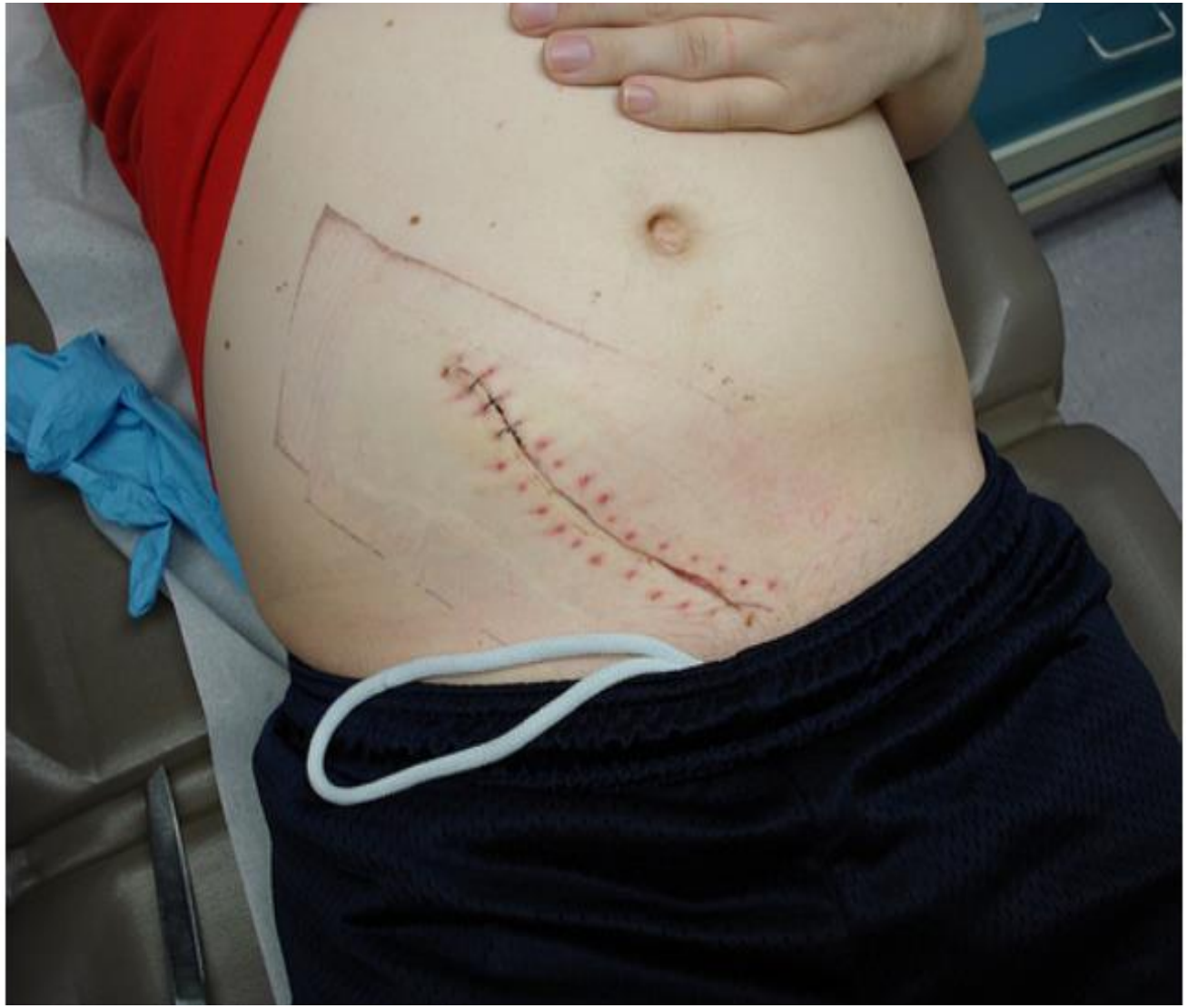
2- Decreasing Calcium deposits: via Dialysis, Medications (Sodium thiosulfate which decreases calcium build up in the arterioles) and Surgery (if the condition is due to Parathyroid gland overactivity, we perform a surgery to remove all or part of the gland).



PD CATHETER



PARASTERNAL PD CATHETER



RENAL TRANSPLANT SCAR

KIDNEY DONORS

Clinical Features of CKD / Limbs

- Edema.
- Amputation.
- Scratch Marks.
- AVF or Graft.
- Femoral Lines.
- Calciphylaxis.
- Abnormal Pulses.

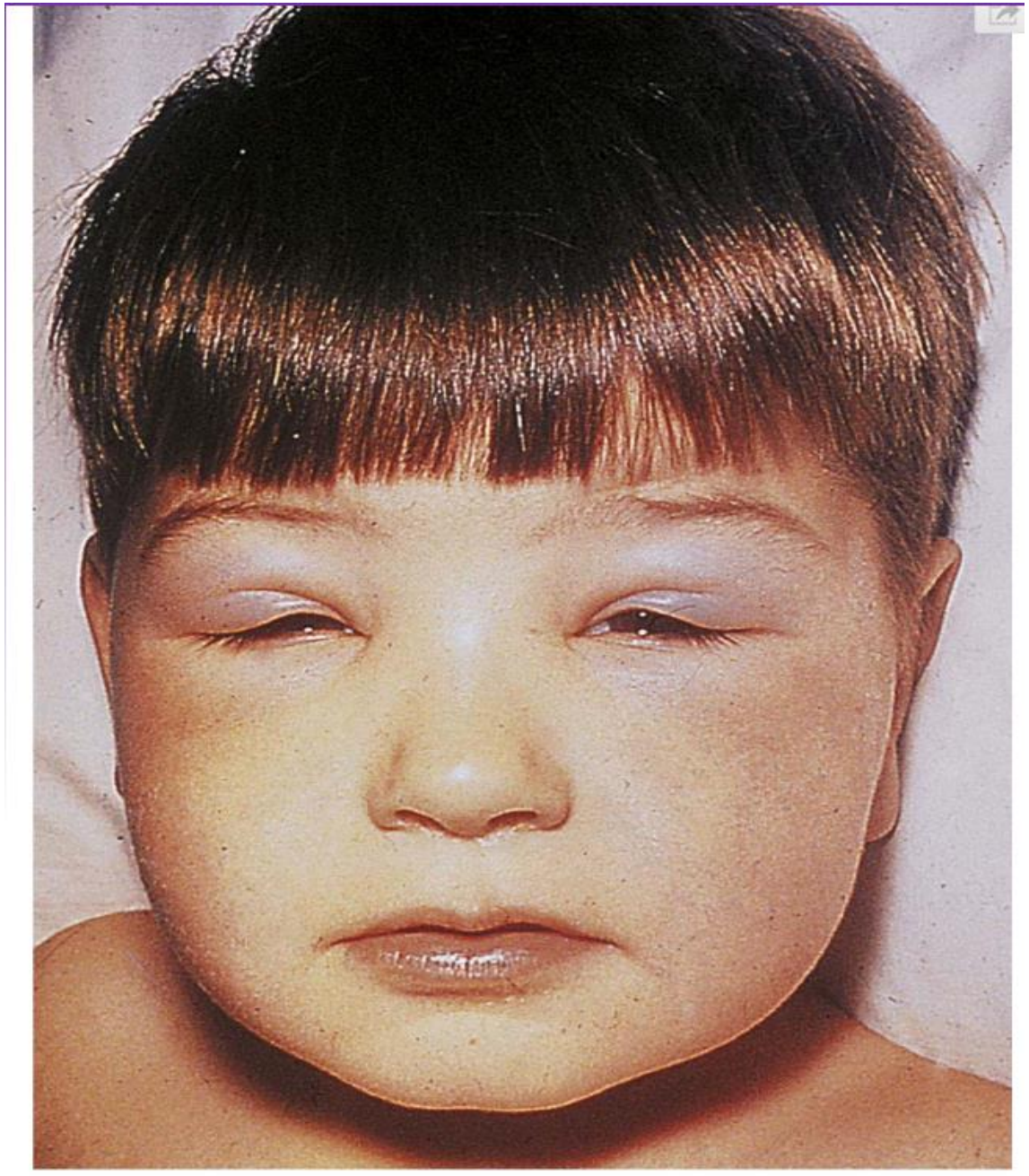
GLOMERULONEPHRITIS

Diagnosis of Glomerular Disease

- Vital Signs: Specially BP, looking for Hypertension.
- Dependent Pitting Edema (Lower limb or Sacral Edema).
- Periorbital Edema.
- Genital Edema, Ascites, Pleural Effusion.
- Xanthelasma in Nephrotic Syndrome.
- Muehrcke's Bands (White nails and White bands in nephrotic syndrome).
- Pulmonary Sign in Pulmonary Renal Syndrome.
- Palpable Purpura in Vasculitis, SLE, Cryoglobulinemia or Endocarditis.

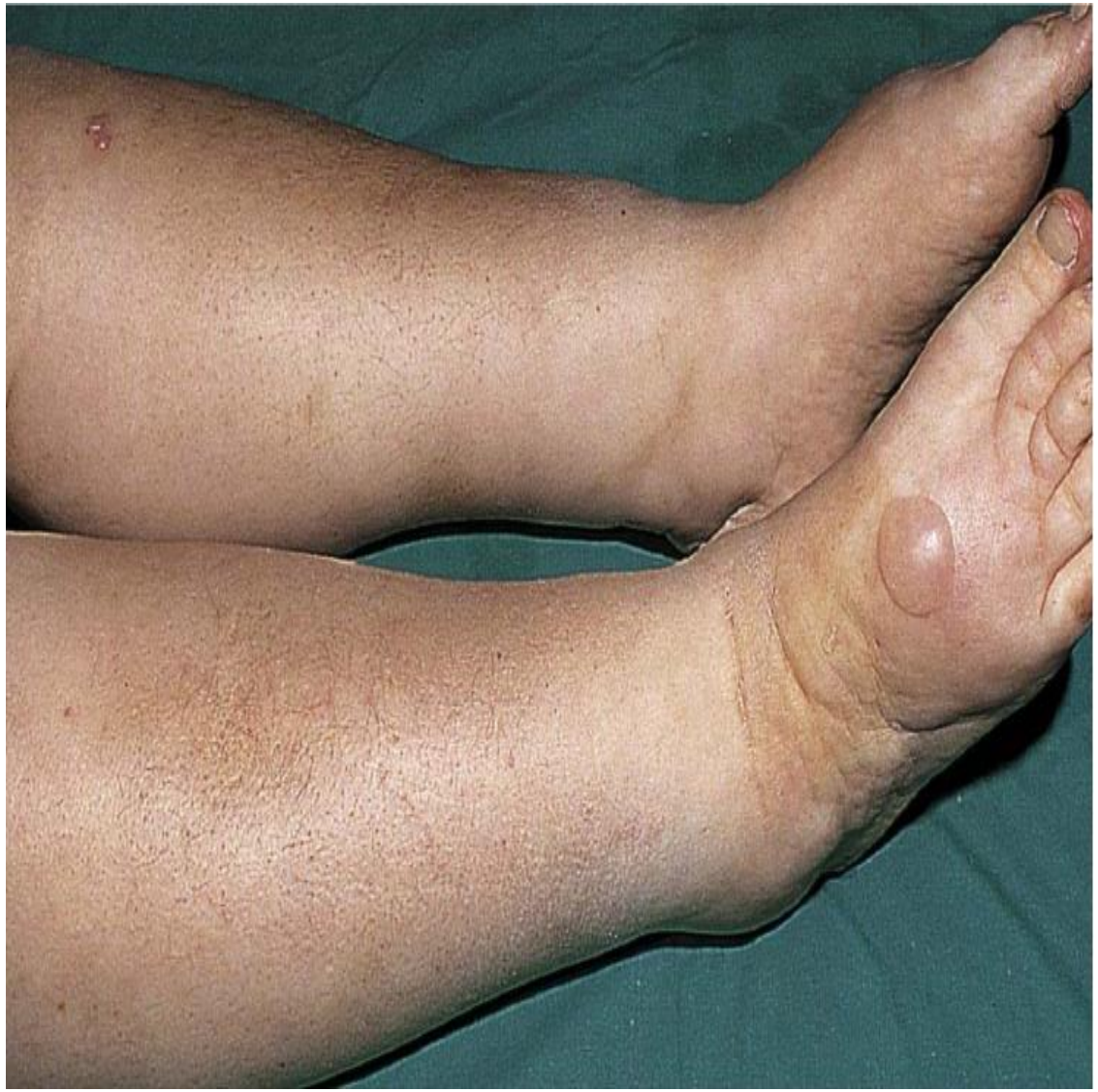
NEPHROTIC EDEMA

- Periorbital edema in the early morning in a nephrotic child.
- It resolves during the day under the influence of Gravity.



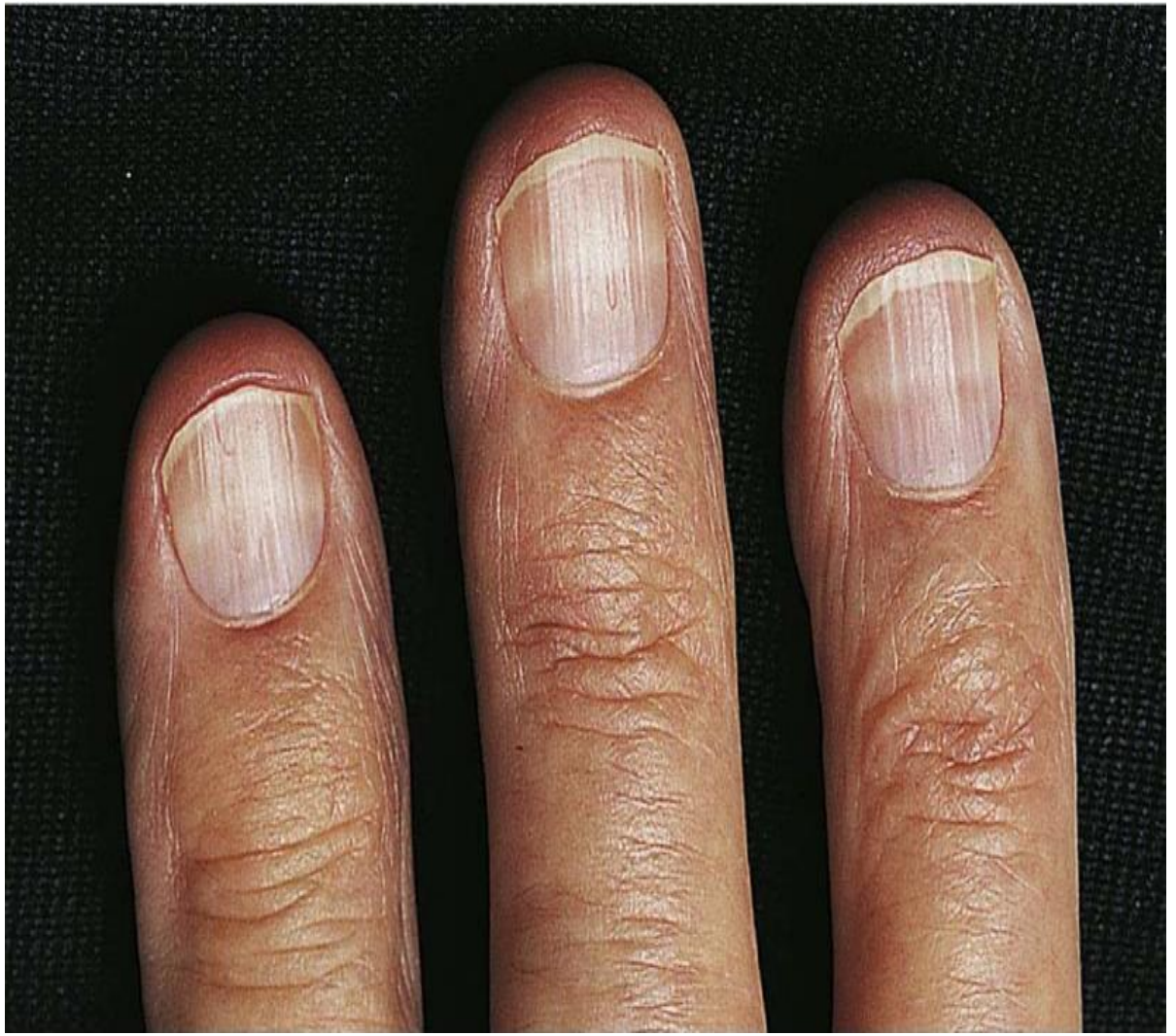
NEPHROTIC EDEMA

- Severe peripheral edema in nephrotic syndrome.
- Note the Blisters caused by intradermal fluid.

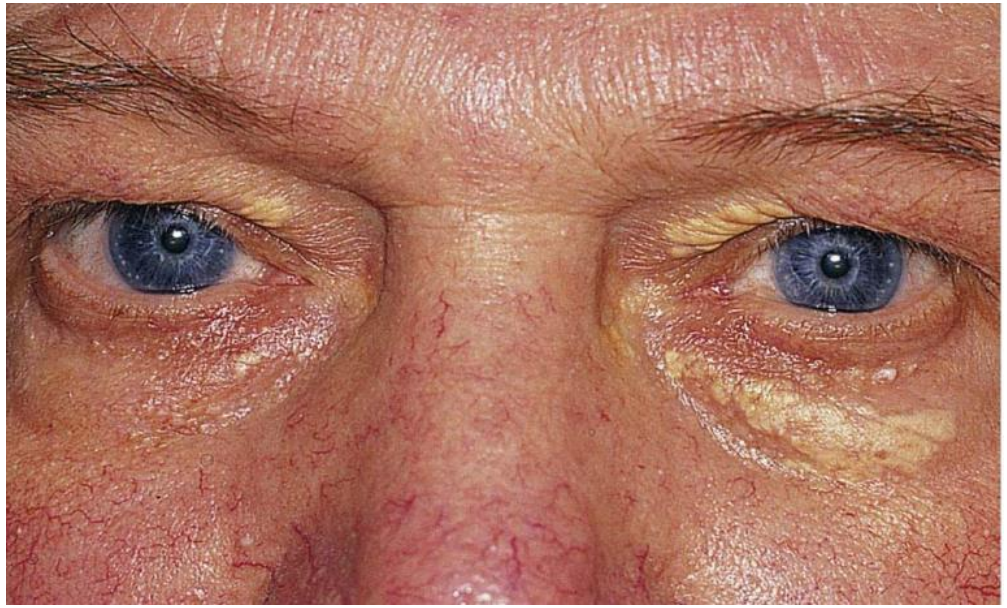


MUEHRCKE'S BANDS IN NEPHROTIC SYNDROME

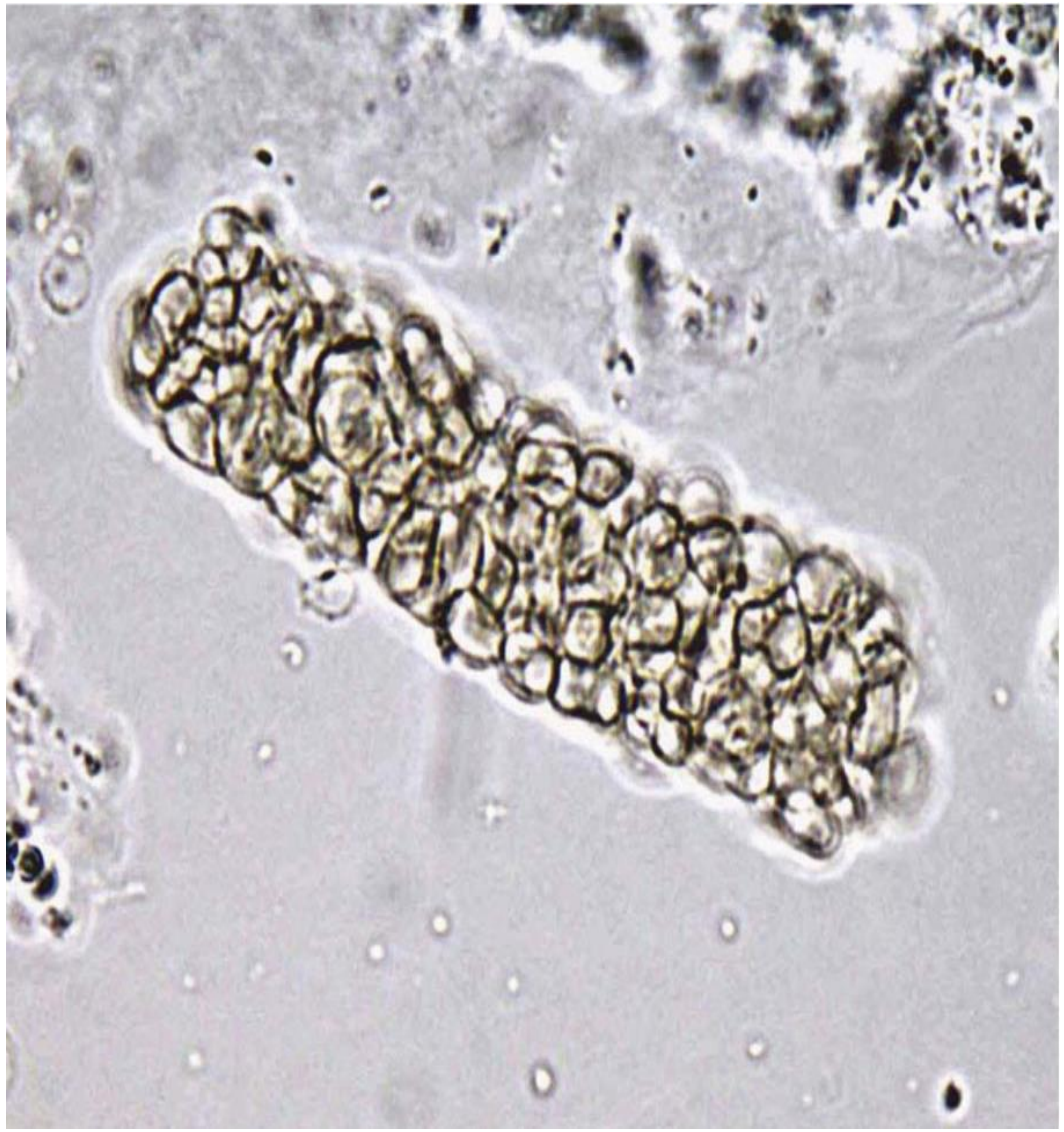
- The white band grew during transient period of Hypoalbuminemia caused by the nephrotic syndrome.



XANTHELASMAS IN NEPHROTIC SYNDROME



- These Prominent Xanthelasmas developed within a period of 2 months in a patient with a recent onset of severe nephrotic syndrome and serum cholesterol level of 550 mg/dl (14.2 mmol/l)



RBC CAST IN URINE

- Detected by Urine Microscopy.
- It indicates Nephritic Syndrome or Rapidly Progressive Glomerulonephritis.
- It is associated with Dysmorphic RBCs (indicate leak of RBCs through Capillary loop which indicate Nephritic Syndrome or RPGN).

Nephritic Syndrome

Hematuria with variable degree of proteinuria usually dysmorphic or often RBCs cast.

Associated with 1- Oedema 2- Hypertension 3- Elevated Serum Creatinine and Oliguria.

Diagnosed based on History, PE, and sometimes Renal Biopsy.

Acute Nephritic Syndrome: Serum Creatinine rises over many weeks or less.

Chronic Nephritic Syndrome: Renal insufficiency may progress over years.

Postinfectious / Diffuse proliferative Glomerulonephritis

It's a Glomerular disease associated with Nephritic Syndrome (Proliferation which collapse Capillary loop).

Typical Presentation: A patient with infection e.g., Sore throat 2 weeks ago, then improved then noticed that urine output is significantly low with dark urine.

Kidney Biopsy: Significant proliferation with neutrophils covering glomeruli leading to collapse of the capillary wall and low GFR (renal impairment), low Urine output, RBCs and RBCs casts in urine, HTN, Edema.

Onset 1-4 weeks after upper respiratory / cutaneous infection with Group A Streptococci / Infective endocarditis.

Elevated Antistreptococcal Antibody and Decreased C3.

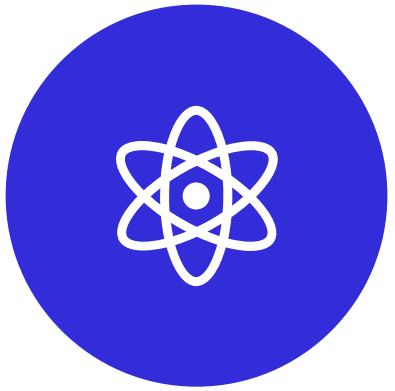
Secondary to Anti-strep antibodies binding to glomerular Components.

Resolves within 6 weeks.

Postinfectious / Diffuse Proliferative Glomerulonephritis

ON LIGHT MICROSCOPY: DIFFUSE GLOMERULAR PROLIFERATION AND CELLULAR INFILTRATION.

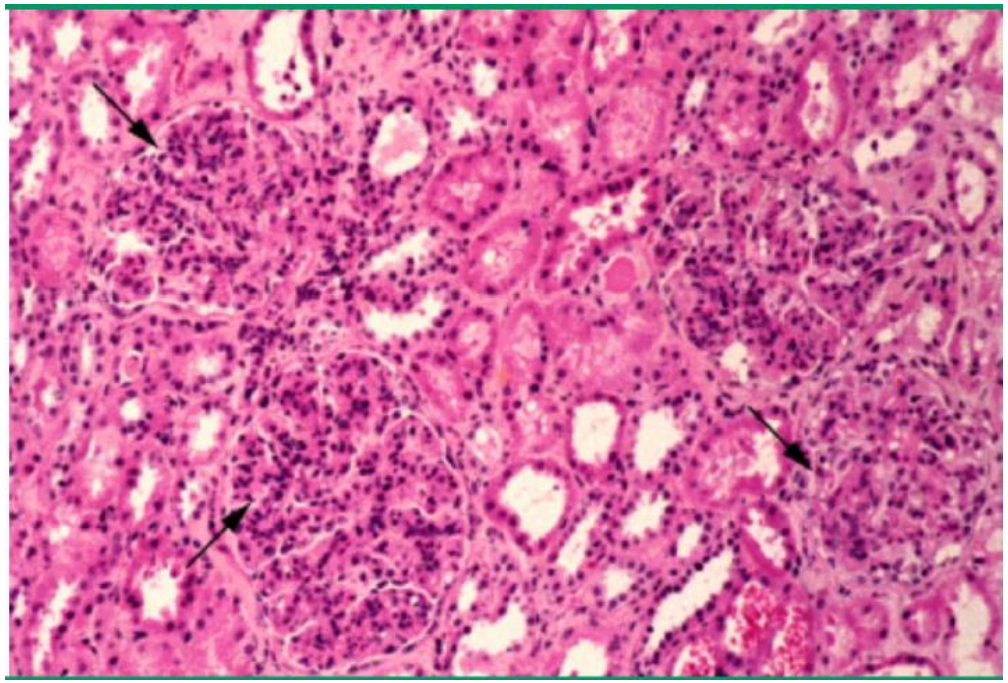
ON IMMUNOFLUORESCENCE: GRANULAR BASEMENT MEMBRANE IGG, IGM, C3.



ON ELECTRON MICROSCOPY: DOME SHAPED SUBEPITHELIAL DEPOSITS.

POSTINFECTIOUS GLOMERULONEPHRITIS

- Low-power light micrograph showing diffuse proliferative glomerulonephritis as may be seen in postinfectious glomerulonephritis.
- The Glomeruli are so Hypercellular (arrows) that open capillary lumens cannot be seen, and the glomeruli may be hard to distinguish from the surrounding interstitium.



Treatment of Postinfectious / Diffuse Proliferative Glomerulonephritis

Supportive Care.

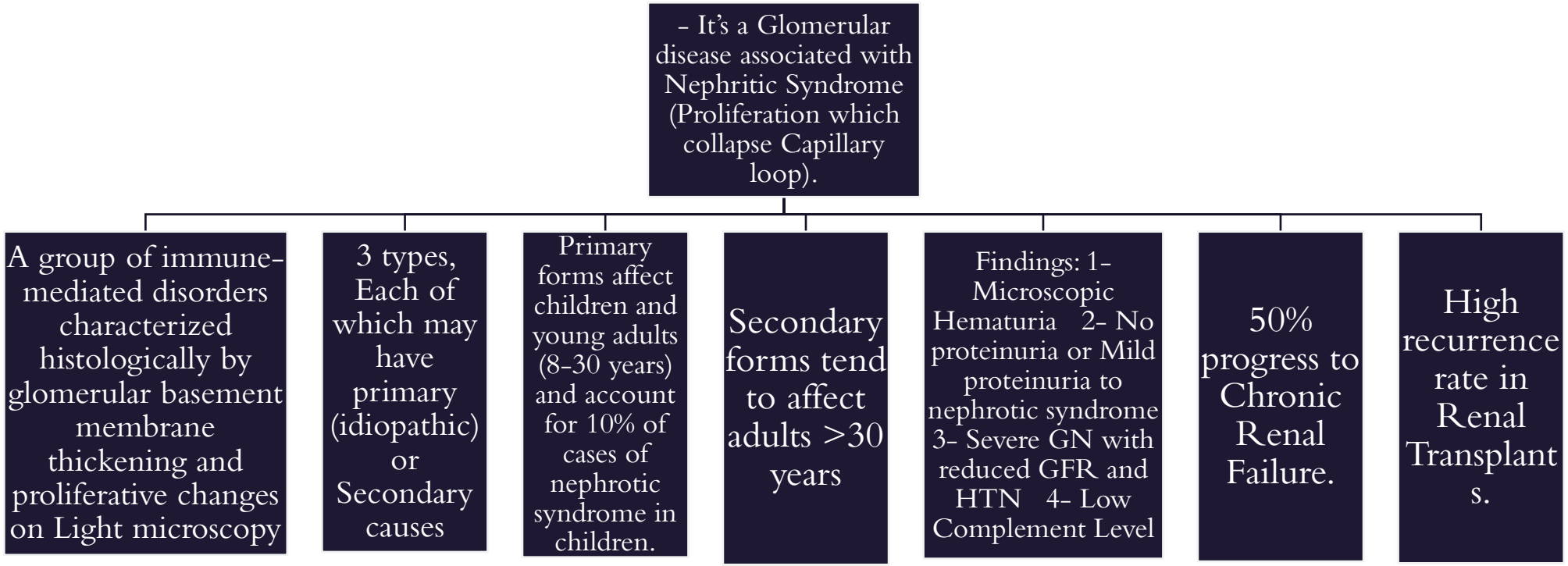
Restriction of dietary protein, sodium, and fluids.

In most severe cases, treatment of Edema, HTN.

Dialysis is occasionally necessary.

Antimicrobial therapy is preventive only when given within 36 hours of infection and before glomerulonephritis becomes established.

Membranoproliferative Glomerulonephritis



Membranoproliferative Glomerulonephritis

Nephrotic Syndrome seen in 60-80% of the cases.

Nephritic Syndrome (Acute Glomerulonephritis) seen in 15-20% of cases of type I and III disease and in higher percentage of type II disease.

At diagnosis, 30% of patients have HTN and 20% have Renal Insufficiency.

Prognosis is good if the condition causing Secondary Membranoproliferative Glomerulonephritis is successfully treated.

End Stage Renal Disease (ESRD) occurs in 50% of the patients at 10 years and in 90% at 20 years.

Type I MPGN recurs in 30% of Kidney transplantation patients.

Type II MPGN recurs in 90% but, despite this high recurrence rate leads to graft loss only infrequently.

Outcome is worse if proteinuria is in the Nephrotic Range.

Membranoproliferative Glomerulonephritis

ON LIGHT MICROSCOPY: MESANGIAL PROLIFERATION, THICKENED CAPILLARY LOOPS, GLOMERULAR HYPERCELLULARITY DUE TO MESANGIAL PROLIFERATION, MESANGIAL INTERPOSITION (DOUBLE GLOMERULAR BASEMENT MEMBRANE AND SILVER STAIN –TYPE I-

ON IMMUNOFLUORESCENCE:

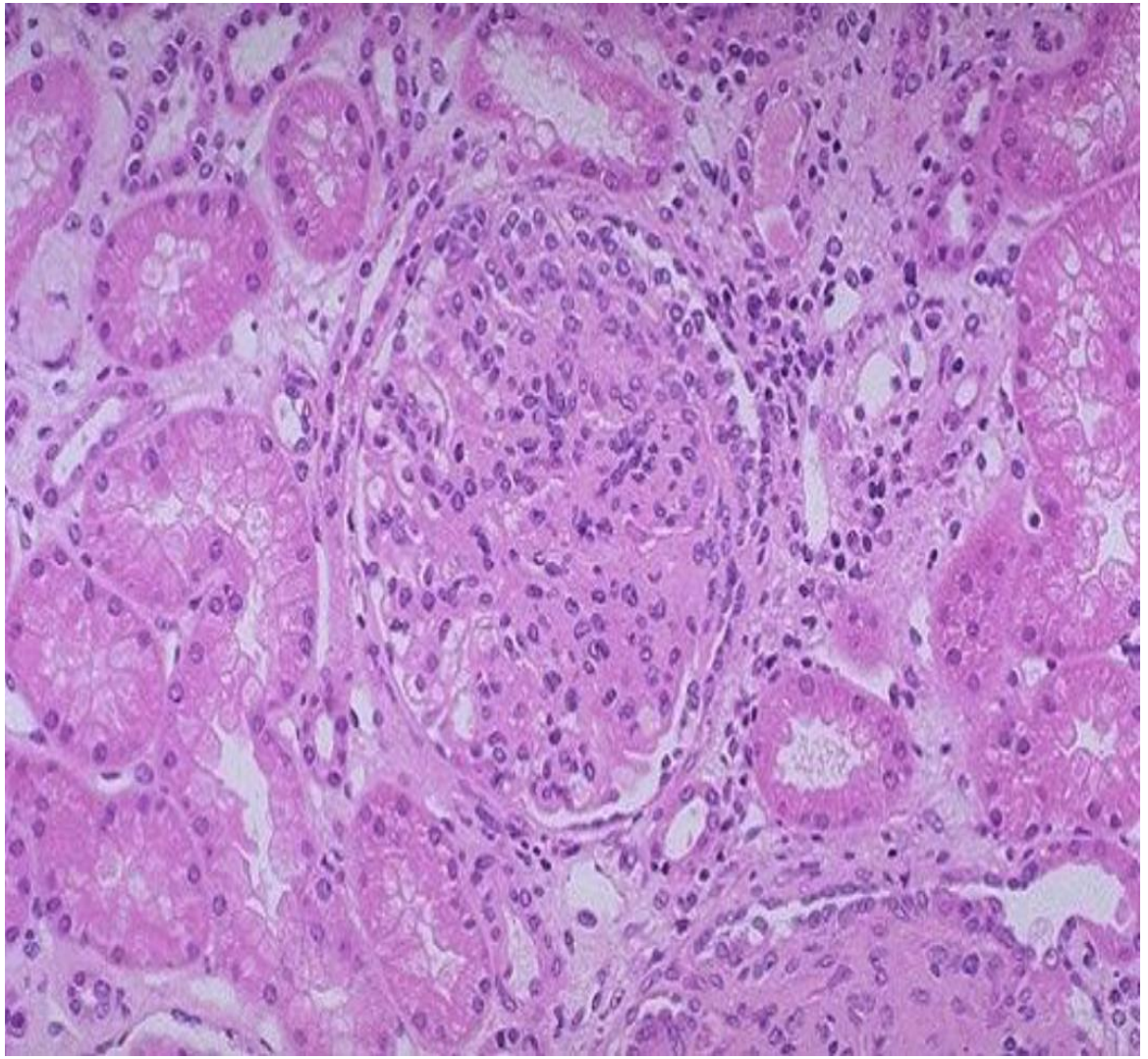
- TYPE I: GRANULAR BASEMENT MEMBRANE AND MESANGIAL IGG, IGM, C3
- TYPE II: GRANULAR BASEMENT MEMBRANE C3

ON ELECTRON MICROSCOPY:

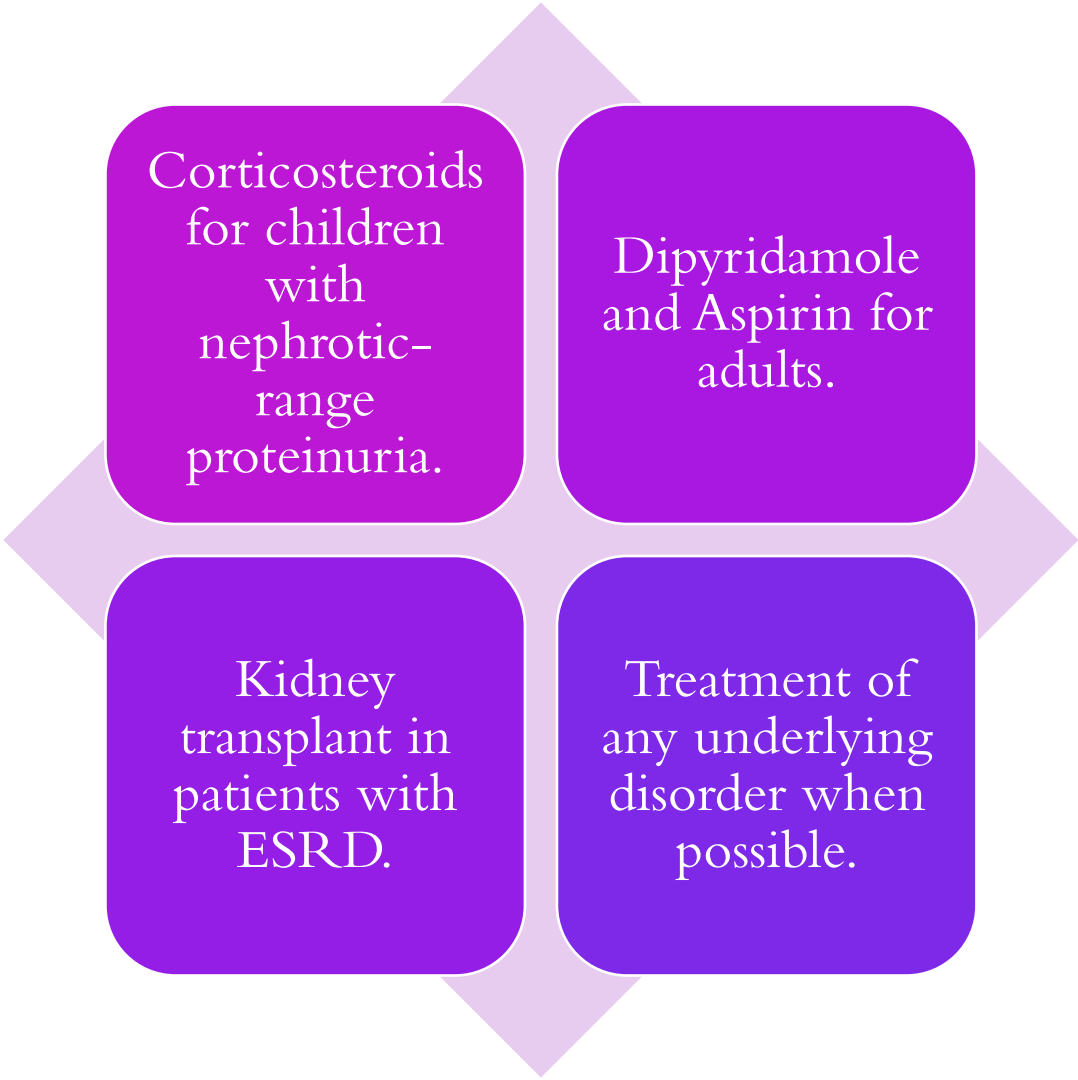
- TYPE I: SUBENDOTHELIAL DEPOSITS AND MESANGIAL INTERPOSITION
- TYPE II: DENSE DEPOSITS IN GLOMERULAR BASEMENT MEMBRANE

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

- If Proliferation is Dominant → Nephritic Syndrome.
- If Membrane Disease is Dominant → Nephrotic Syndrome.



Treatment of Membranoproliferative Glomerulonephritis



A nephritic syndrome, a form of chronic glomerulonephritis characterized by the deposition of IgA immune complexes in glomeruli.

Most common Primary Glomerulonephritis.

Affects Men 2-6 times more frequently than Females.

More common among Caucasians and Asians than Black.

Pathogenesis: Increased IgA1 production along with Defective IgA1 glycosylation causing increased binding to mesangial cells, Decreased IgA1 clearance, A Defective mucosal immune system, Overproduction of Cytokines stimulating mesangial cell proliferation, Familial Clustering has also been observed suggesting Genetic Factors at least in some cases.

Slow progression.

Renal insufficiency and HTN develop within 10-15 years to 20% of patients.

Progression to ESRD in 25% of the patients after 20 years

Diagnosed in Childhood with good prognosis.

Recurs in 20-60% of Transplants.

IgA Nephropathy / Mesangioproliferative Glomerulonephritis

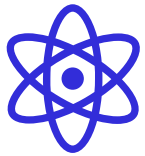
IgA nephropathy / Clinical Manifestations

- Persistent or recurrent Macroscopic Hematuria.
- Asymptomatic Microscopic Hematuria with Mild Proteinuria.
- Gross Hematuria usually begins 1-2 days after a febrile mucosal (upper respiratory, sinus, enteral) illness.
- Mimicking acute Postinfectious Glomerulonephritis, except that the onset of Hematuria is earlier.
- Rapidly Progressive Glomerulonephritis with Crescentic IgA nephropathy in <10% of the cases.

IgA Nephropathy / Mesangioproliferative Glomerulonephritis

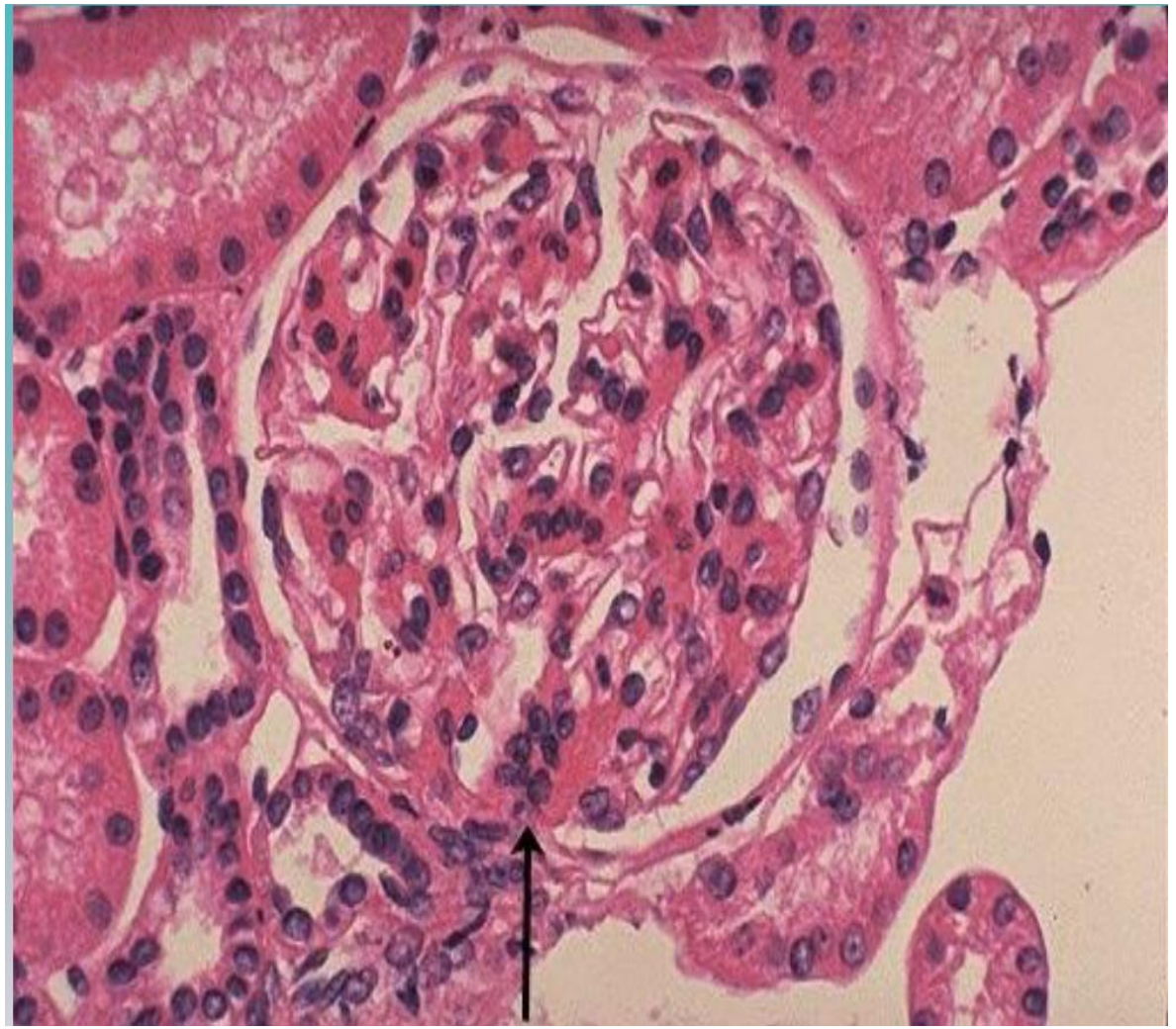
On Light Microscopy:
Increased mesangial matrix and Mesangial Proliferation due to collapse of capillary loop, Focal Sclerosis (FSGS)

On Immunofluorescence:
Mesangial IgA.



On Electron Microscopy:
Mesangial Deposits.

IGA NEPHROPATHY / MESANGIOPROLIFERATIVE GN



Treatment of IgA Nephropathy

ACE inhibitors or Angiotensin II receptor Blockers for: HTN, Serum Creatinine >1.2 mg/dL or Macroalbuminuria (urinary protein >300 mg/day), and with target urinary protein of <500 mg/day.

Corticosteroids for progressive disease, including increasing Proteinuria, especially into nephrotic range, or increasing serum creatinine level.

Normotensive patients with intact renal function (Serum Creatinine <1.2 mg/dL and only mild Proteinuria <0.5 g/day), usually are not treated beyond Angiotensin inhibition and Omega-3 fatty acids (fish oil).

Honcech-Schonlein Purpura (HSP)

Small Vessel Vasculitis affecting the Skin, Joint, Gut, and Kidneys.

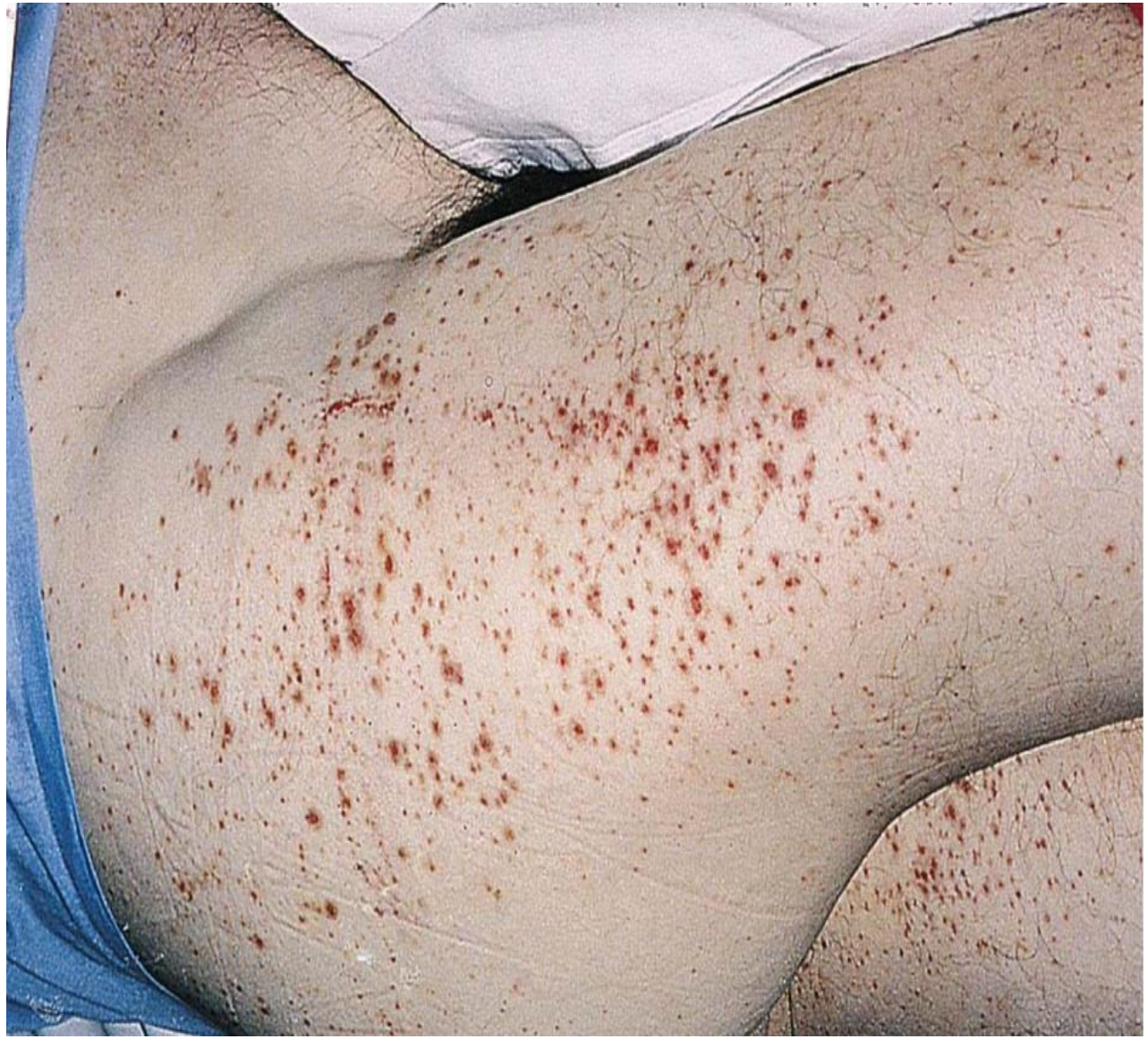
The Nephritis associated with HSP is characterized by mesangial IgA deposition.

Clinical Features: 1- Purpuric Skin Rash (on the lower abdomen, upper thigh, and buttocks) 2- Arthritis 3- Gastrointestinal Symptoms (abdominal pain)

Self limiting illness.

Confirm diagnosis by Skin or Kidney Biopsy

HONCECH-SCHONLEIN PURPURA / PURPURIC SKIN RASH



Crescentic / Rapidly Progressive Glomerulonephritis

- Nephritic Syndrome.
- Pathogenesis: Damage to Glomerular vessels + Egress of inflammatory cells and fibrin into Bowman's space + Proliferation of epithelial cells.
- Pathologic Diagnosis accompanied by extensive glomerular crescent formation (that is >50% of sampled glomeruli contain crescents which can be seen in a biopsy specimen): Accumulation of cells in Bowman's Space, Inflammatory cells + Fibrin + Epithelial cell proliferation, Compression of the glomerulus (thus collapsing capillary loop leading to severe deterioration of Renal function).
- If left untreated it progresses rapidly to ESRD over weeks to months.
- Relatively uncommon, affecting 10-15% of patients with Glomerulonephritis.
- Occurs predominantly in patients 20-50 years.

Rapidly Progressive Glomerulonephritis / Clinical Features

- Manifestations are usually insidious, with weakness, fatigue, fever, nausea, vomiting, anorexia, arthralgia, skin rash and abdominal pain.

- About 50% of patients have edema and a history of an acute influenza-like illness within 4 weeks of onset of renal failure, usually followed by severe oliguria.

- Nephrotic syndrome is present in 10 to 30%.

- Hypertension is uncommon and rarely severe.

- Patients with anti-GBM antibody disease Granulomatous with Polyangiitis and Microscopic polyangiitis may have pulmonary hemorrhage, which can manifest with hemoptysis or be detectable only by finding diffuse alveolar infiltrates on chest x-ray (pulmonary-renal syndrome or diffuse alveolar hemorrhage syndrome).

- Progression to End stage renal disease in most of untreated patient within weeks to months

Crescentic / Rapidly Progressive Glomerulonephritis Pathogenesis

Type I (Anti Glomerular Basement Membrane Antibodies): 1- Immunofluorescent Staining of Renal biopsy tissue demonstrates linear IgG deposits. 2- Combination of Glomerulonephritis and Alveolar Hemorrhage → Goodpasture's Disease.

Type II (Immune Complexes)- Associated with a major Systemic Disease -: Idiopathic or Secondary to autoimmune disease or other Glomerulonephritis (SLE, HSP, IgA nephropathy, Postinfectious GN).

Type III (Pauci-immune): Idiopathic or Secondary to Systemic Vasculitis (1- Granulomatosis with Polyangiitis Antiprotease-3 ANCA or Myeloperoxidase ANCA, and Systemic Vasculitis. 2- Microscopic Polyangiitis.)

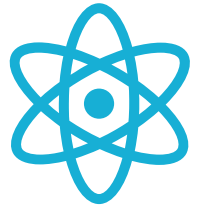
Crescentic / Rapidly Progressive Glomerulonephritis

On Light Microscopy:

Cellular Crescents of Epithelium and Inflammatory cells + Fibrotic Crescents.

On Immunofluorescence:

1- Type I: Linear IgG 2- Type II: Granular IgG 3- Type III: No deposits.

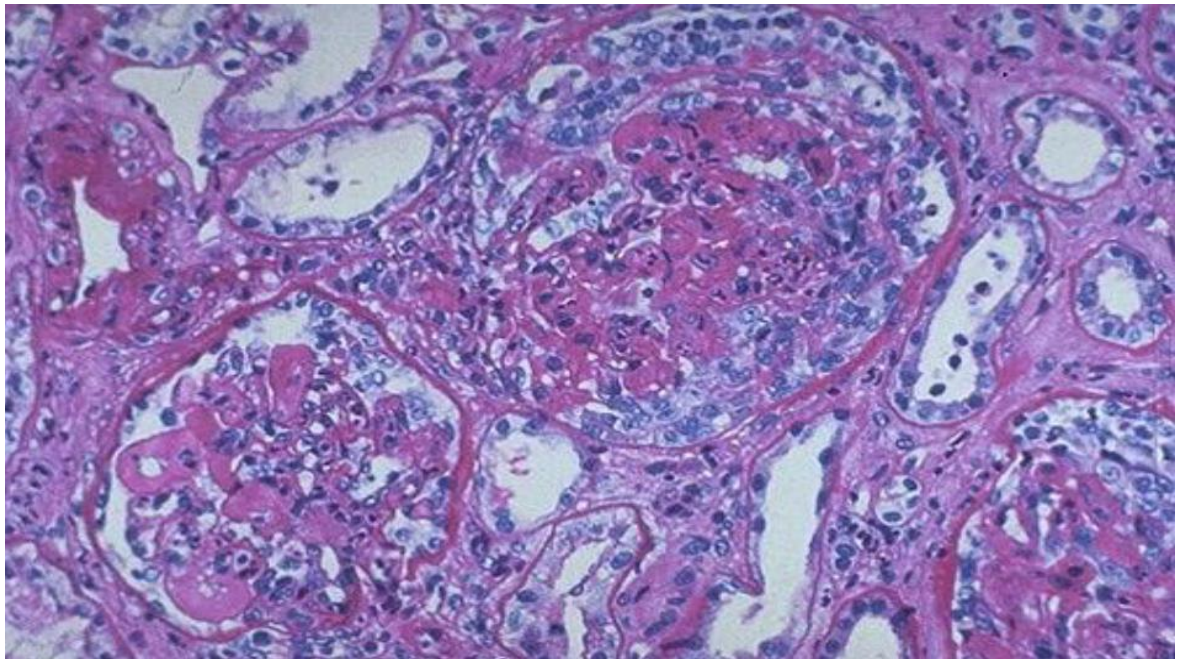


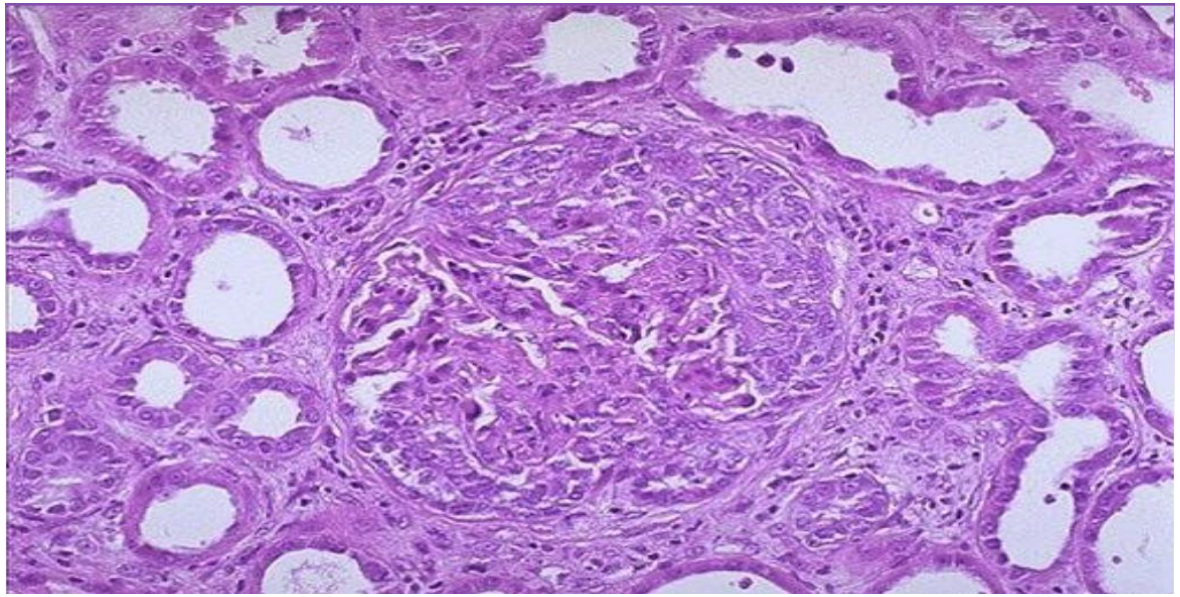
On Electron Microscopy:

Type II: Subendo, Mesangial and Subepi deposits.

CRESCENTIC / RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

- In the second picture, notice the proliferation around the Glomeruli which leads to loss of Kidney Capillary Loop and Renal Impairment.





Treatment of Crescentic / Rapidly Progressive Glomerulonephritis

- Corticosteroids.
- Cyclophosphamide.
- Rituximab.
- Plasma Exchange

Nephrotic Syndrome

Pathophysiology: Proteinuria occurs because of changes to capillary endothelial cells, the glomerular basement membrane, or podocytes which normally filter serum protein selectively by size and charge.

Complications of Nephrotic Syndrome: It results in urinary loss of macromolecular proteins, primarily Albumin, but also Opsonins, Immunoglobulins, Erythropoietin, Transferrin, Hormone-Binding Proteins (including Thyroid-binding Globulin and Vitamin D-binding protein), and Antithrombin III.

Deficiency of these proteins and other proteins contribute to several complications as: 1- Oedema (including Ascites and Pleural Effusions) 2- Anemia 3- Changes in thyroid function test results (among patients previously hypothyroid, increased dose requirement for thyroid replacement hormone) 4- Dyslipidemia 5- Chronic Kidney Disease.

Hypercoagulability and thromboembolism (especially Renal Vein Thrombosis and Pulmonary Embolism, which occur in up to 5% of children and 40% of adults).

Protein undernutrition in children (sometimes with Brittle hair and nails, Alopecia, and Stunted Growth).

Proximal Tubular Dysfunction (Acquired Fanconi Syndrome), secondary to toxic effects of large amounts of proteins that they reabsorb.

Nephrotic Syndrome

Hypercoagulability is attributed to the following factors: 1- Higher concentration of Factor I, II, V, VII, VIII, X and Fibrinogen. 2- Lower levels of Anticoagulants as Antithrombin III (due to the leak into the urine). 3- Decrease Fibrinolysis. 4- Higher Blood Viscosity (due to blood volume depletion). 5- Increase Platelet aggregation.

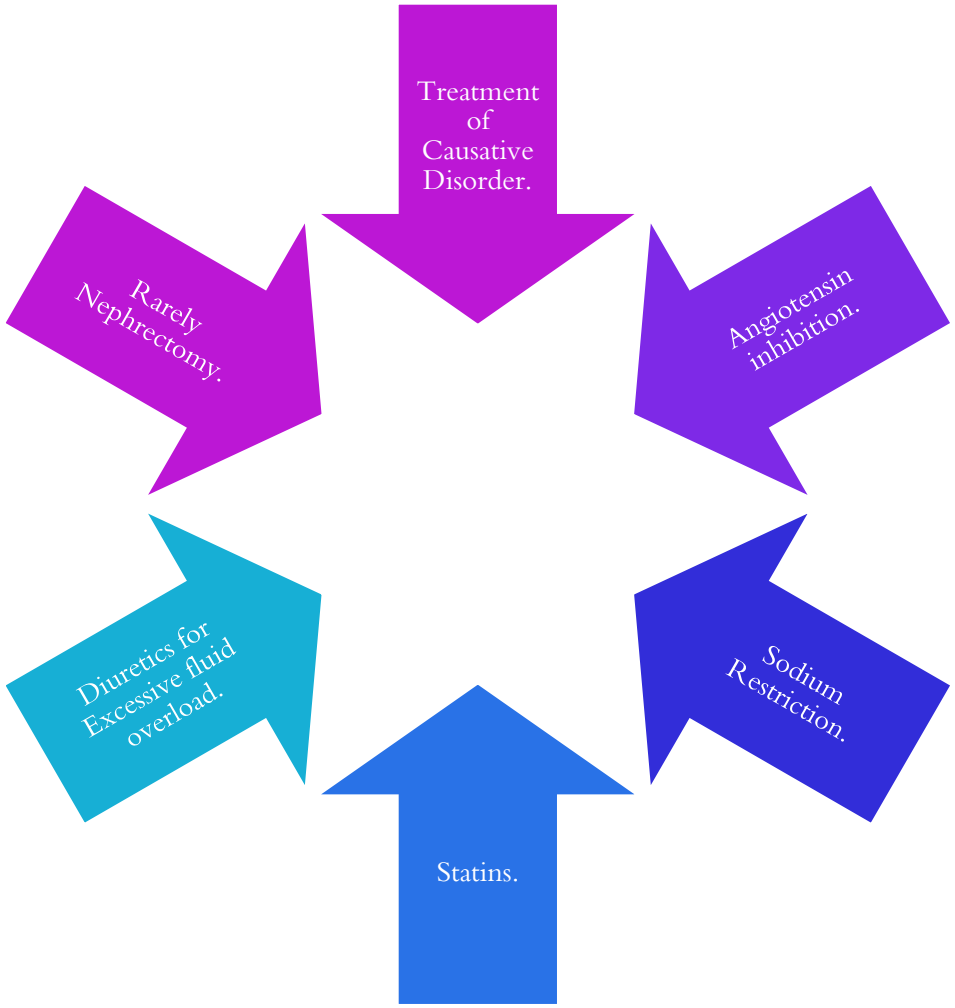
Prognosis varies by cause.

The prognosis is generally favorable in corticosteroid-responsive disorders.

In all cases, prognosis may be worse in the presence of 1- Infection. 2- Hypertension. 3- Significant Azotemia. 4- Hematuria. 5- Thrombosis in cerebral, pulmonary, peripheral, or renal veins.

The recurrence rate is high in Kidney Transplantation with Focal Segmental Glomerulosclerosis.

Treatment of Nephrotic Syndrome



Minimal Change Disease

The most common cause of Nephrotic Syndrome in children 4-8 years (80-90%).

It also happens in adults (10-20% of adult nephrotic syndrome).

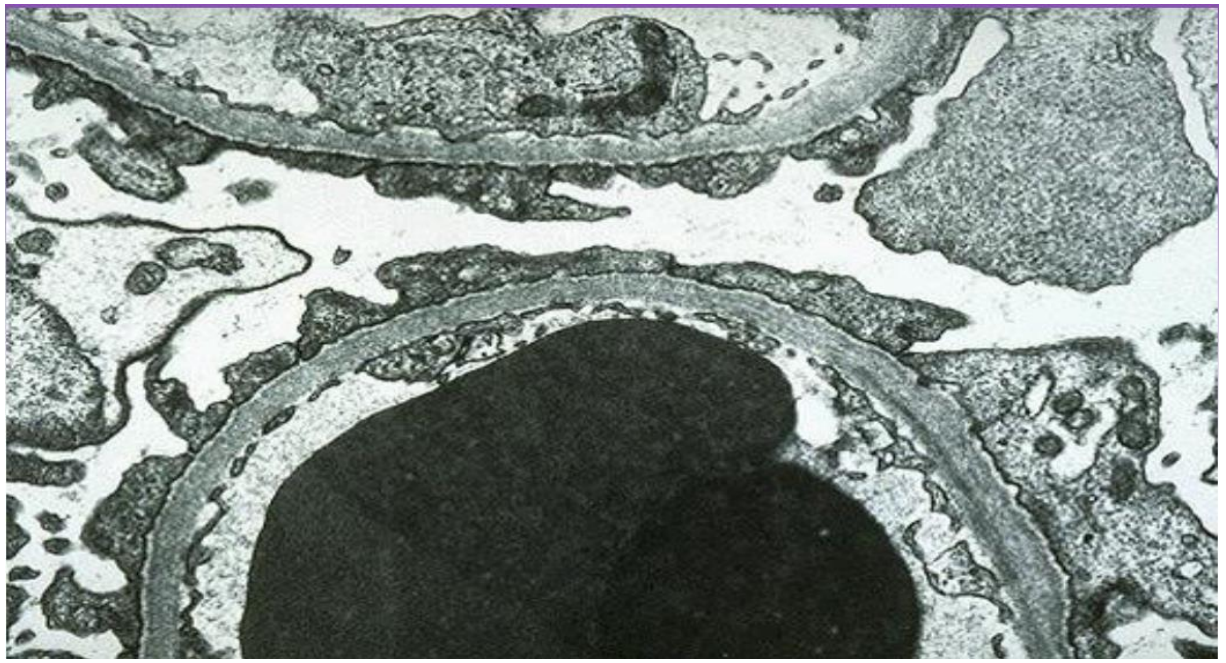
Most cases are Idiopathic.

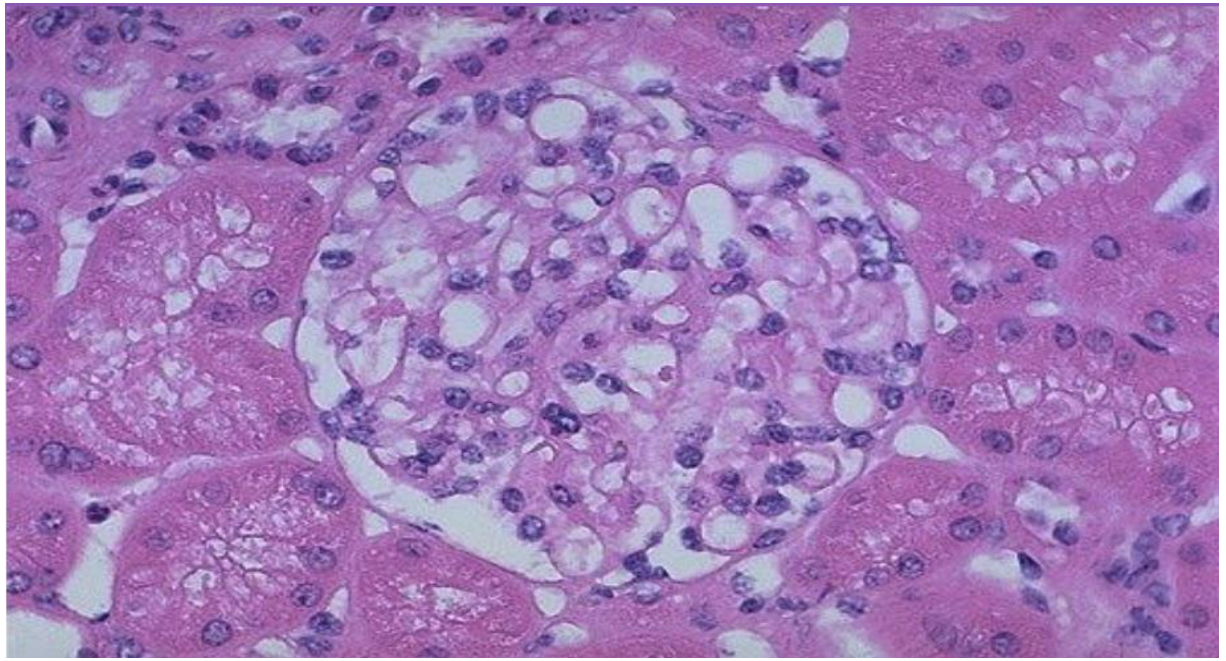
It can be secondary to Drug use (especially NSAIDs) and Hematologic Cancers (especially Hodgkin Lymphoma).

Pathogenesis: Circulating Factors causing damage to Podocytes (Glomerular Epithelial Cells).

Kidney Biopsy characterized by 1- Lack of Glomerular changes on light microscopy. 2- Lack of immune deposits. 3- Good response to Steroids. 4- Electron microscopy- Fusion of podocyte foot processes.

MINIMAL CHANGE DISEASE





Treatment of Minimal Change Disease

- Measures to Clear Proteinuria, Reverse Hypovolemia, and Reduce Edema.
- Corticosteroids are the treatment of choice leading to complete remission of proteinuria in most cases.
- Recurrence is common.
- Options for Steroid-sparing therapy and Steroid-resistant cases include Cyclophosphamide, Chlorambucil, Mycophenolate, Rituximab, and Tacrolimus.

Membranous Glomerulonephritis

The most common cause of Nephrotic Syndrome in Adults.

Idiopathic (85%).

Secondary (15%) to 1- Drugs (Gold, Penicillamine, NSAIDs). 2- Infections (Hepatitis B or C, Syphilis, HIV). 3- Autoimmune disorders (SLE). 4- Thyroiditis. 5- Cancer. 6- Parasitic diseases (Malaria, Schistosomiasis, Leishmaniasis).

40% progress to Chronic Renal Failure (CRF).

Pathogenesis: Subepithelial immune deposits + Thickening of the basement membrane between deposits (eventually envelops and covers the deposits).

It's a rare condition in children, and when it occurs it's usually due to hepatitis B virus infection or SLE.

DVT is more frequent in Membranous Glomerulonephritis.

Renal Vein Thrombosis is more frequent in Membranous Glomerulonephritis and is usually asymptomatic, but may manifest with Flank Pain, Hematuria, and HTN.

Membranous Glomerulonephritis

Diagnosis: 1- Anti-Phospholipase A2 receptor (Anti-PLA2R) antibody (found in 70-80% of patients with idiopathic membranous nephropathy). 2- Evaluation for Secondary causes. 3- Diagnosis is suggested by development of nephrotic syndrome, particularly in patients who have potential causes of membranous nephropathy (age group or evidence of secondary causes). 4- Proteinuria in the nephrotic range in 80% (laboratory testing is done as indicated for nephrotic syndrome). 5- GFR, if measured, is normal or decreased. 6- Confirm diagnosis by renal biopsy.

About 25% of patients undergo spontaneous remission, 25% develop persistent, non-nephrotic range proteinuria, 25% develop persistent nephrotic syndrome, and 25% progress to End Stage Renal Disease.

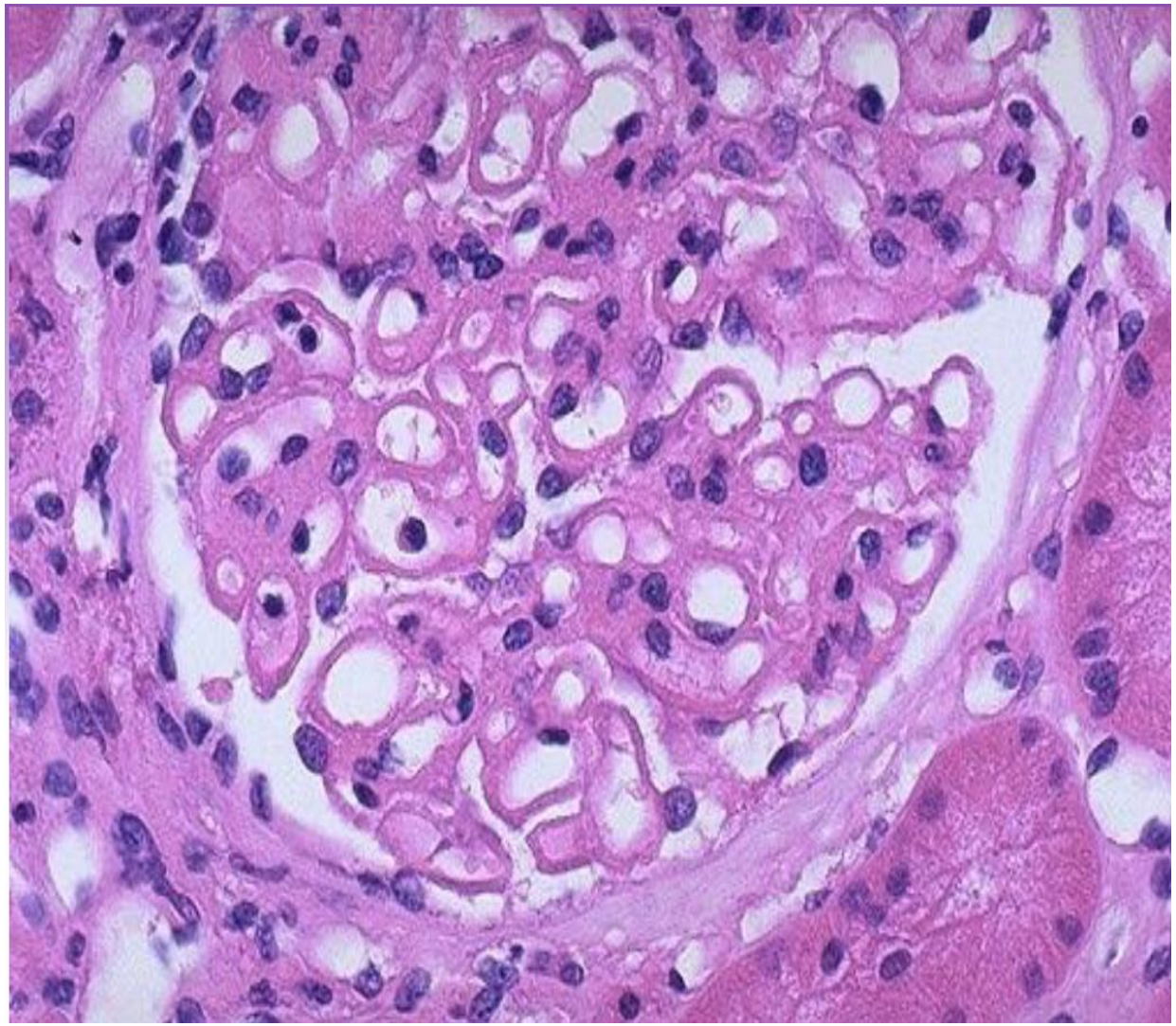
ON LIGHT MICROSCOPY:
THICKENED CAPILLARY BASEMENT MEMBRANE + BASEMENT MEMBRANE SPIKES ON SILVER STAIN.

ON IMMUNOFLUORESCENCE:
DIFFUSE GRANULAR IGG AND C3 + GRANULAR BASEMENT MEMBRANE STAINING.

ON ELECTRON MICROSCOPY:
SUBEPITHELIAL DEPOSITS.

Membranous Glomerulonephritis

MEMBRANOUS GLOMERULONEPHRITIS



Treatment of Membranous Glomerulonephritis

- Treatment of Secondary causes of Nephrotic Syndrome.
- Immunosuppressive therapy for patients with at high risk of progression
- Asymptomatic patients with non-nephrotic range proteinuria don't require treatment; just monitor renal function (twice yearly when apparently stable).
- Nephrotic-range proteinuria and asymptomatic or who have edema that can be controlled with diuretics and treat for nephrotic syndrome.
- HTN with membranous glomerulonephritis should be given an ACE inhibitor or Angiotensin II receptor blocker (ARB) to reduce Proteinuria.
- Kidney transplantation for patients with End Stage Renal Disease.

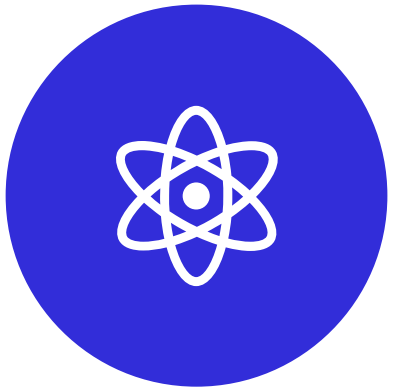
Focal Segmental Glomerulosclerosis

- The most common cause of Idiopathic (Primary) Nephrotic Syndrome among adults.
- Histologic Lesion rather than the disease.
- Idiopathic or Primary FSGS (mostly in children): typically presented with nephrotic syndrome.
- Secondary FSGS to 1- Drugs (Heroin, Lithium, Interferon Alpha, Pamidronate, Cyclosporine, NSAIDs) [causing Analgesic Nephropathy]. 2- Atheroembolic Disease affecting the Kidneys. 3- Obesity. 4- HIV infection, and disorders causing nephron loss (Reflux nephropathy, Subtotal Nephrectomy). 5- Renal Dysgenesis (Oligomeganephronia: Renal Hypoplasia with a decreased number of nephrons). 6- Familial cases exist (Genetic Disease).
- Clinical Presentation: 1- Heavy Proteinuria, HTN, Renal Dysfunction, Oedema, or a combination. 2- Sometimes the only sign is asymptomatic proteinuria that is not in the nephrotic range. 3- Microscopic Hematuria is occasionally present.
- Diagnosis: 1- Renal Biopsy, when possible, with immunostaining and electron microscopy. 2- FSGS is suspected in patients with Nephrotic Syndrome, Proteinuria, Renal Dysfunction, with no obvious cause, particularly patients who have disorders or use drugs associated with FSGS. 3- Urinalysis is done and Blood Urea Nitrogen (BUN), Serum Creatinine, and 24-hour urinary protein excretion or spot urinary protein: Creatinine ratio are measured.
- - Renal biopsy: Sclerosis of Portions of some, not all glomeruli + Often progresses to Chronic Renal Failure + Recurs in 25-50% of Renal Transplants.

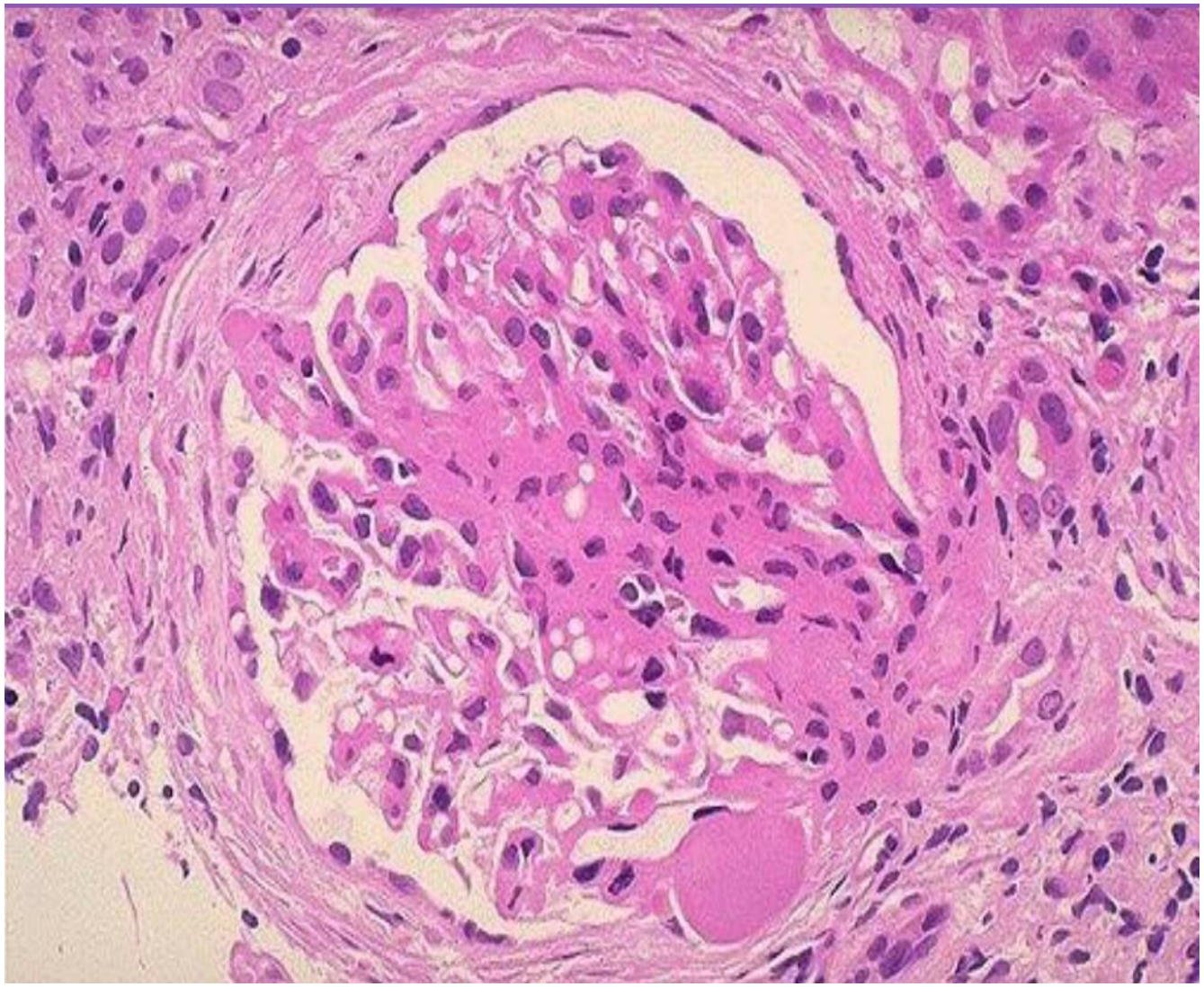
Focal Segmental Glomerulosclerosis

ON LIGHT MICROSCOPY:
FOCAL SEGMENTAL SCLEROSIS, SOME NORMAL GLOMERULI.

ON IMMUNOFLUORESCENCE:
IGM AND C3 DEPOSITION IN SCLEROTIC AREAS.



ON ELECTRON MICROSCOPY:
FUSION OF PODOCYTE FOOT PROCESSES.



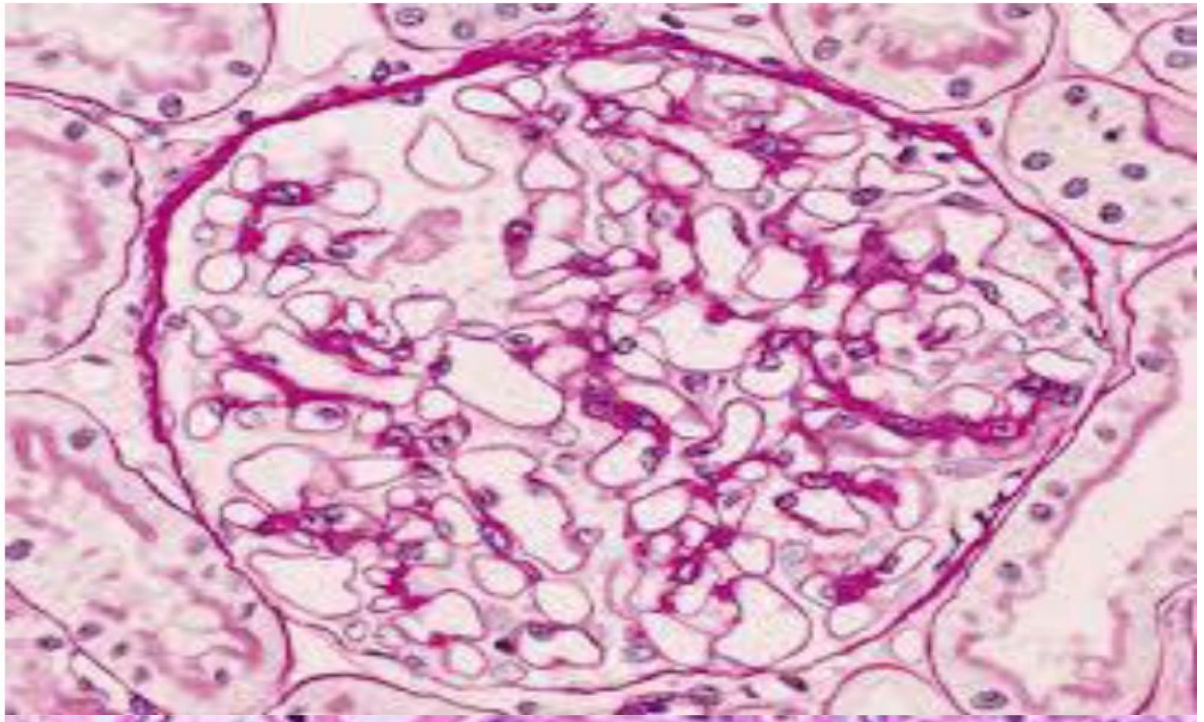
FOCAL SEGMENTAL GLOMERULOSCLEROSIS

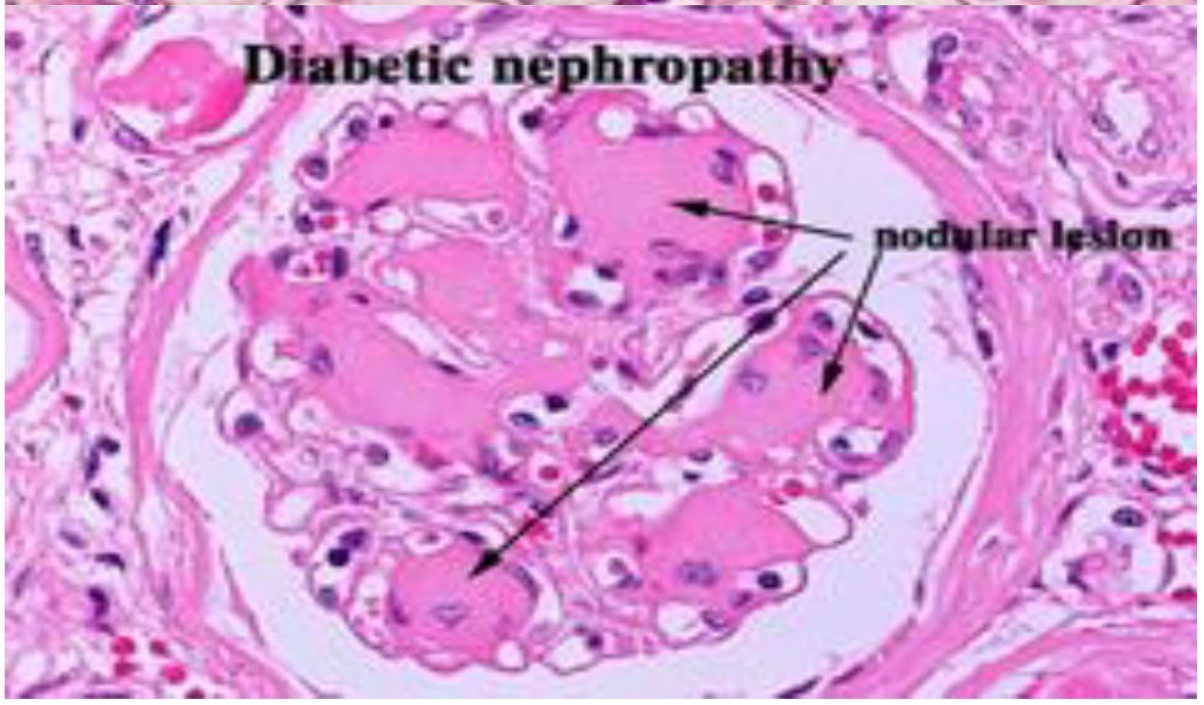
Treatment of Focal Segmental Glomerulosclerosis

- Angiotensin inhibition.
- Corticosteroids and sometimes Cytotoxic Drugs for Idiopathic Focal Segmental Glomerulosclerosis.
- Treatment often isn't effective.
- Kidney Transplantation for patients with End Stage Renal Disease.

DIABETIC NEPHROPATHY AND LUPUS NEPHRITIS

DIABETIC NEPHROPATHY





- The first picture shows normal Glomerulus, while the second picture shows a Glomerulus of a patient with Diabetic Nephropathy
- It's one of the causes of nodular Glomerulosclerosis.
- Note the large nodules of matrix within mesangial areas with lesser increase in mesangial cellularity.
- The Glomerular basement membrane is thick without apparent deposits.
- Periodic Acid-Schiff stain.

PATHOLOGY OF DIABETIC NEPHROPATHY

Pathology

- The expansion of the mesangium due to the accumulation of extracellular matrix correlates with the clinical manifestations of diabetic nephropathy
- The diffuse and generalized process of mesangial expansion has been termed diffuse diabetic glomerulosclerosis .
- Nodular glomerulosclerosis (Kimmelstiel- Wilson nodular lesions) represents areas of marked mesangial expansion appearing as large round fibrillar mesangial zones, often with extreme compression of the adjacent glomerular capillaries
- Afferent and efferent glomerular arteriolar hyalinosis can also be detected within 3 to 5 years after onset of diabetes.

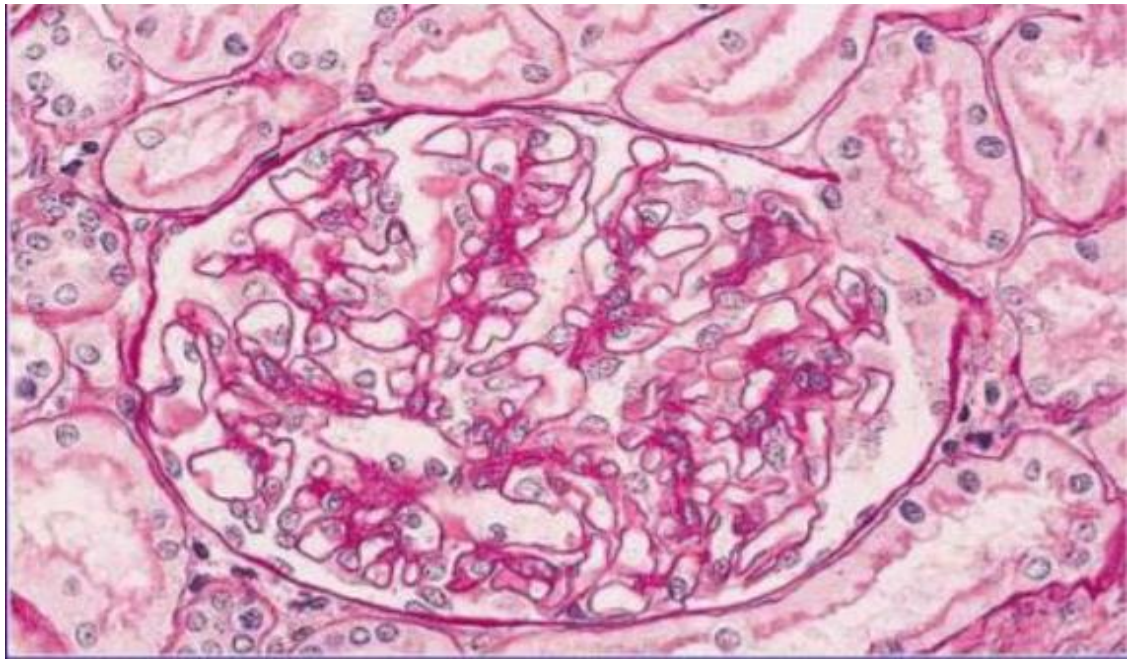
DIAGNOSIS OF DIABETIC NEPHROPATHY

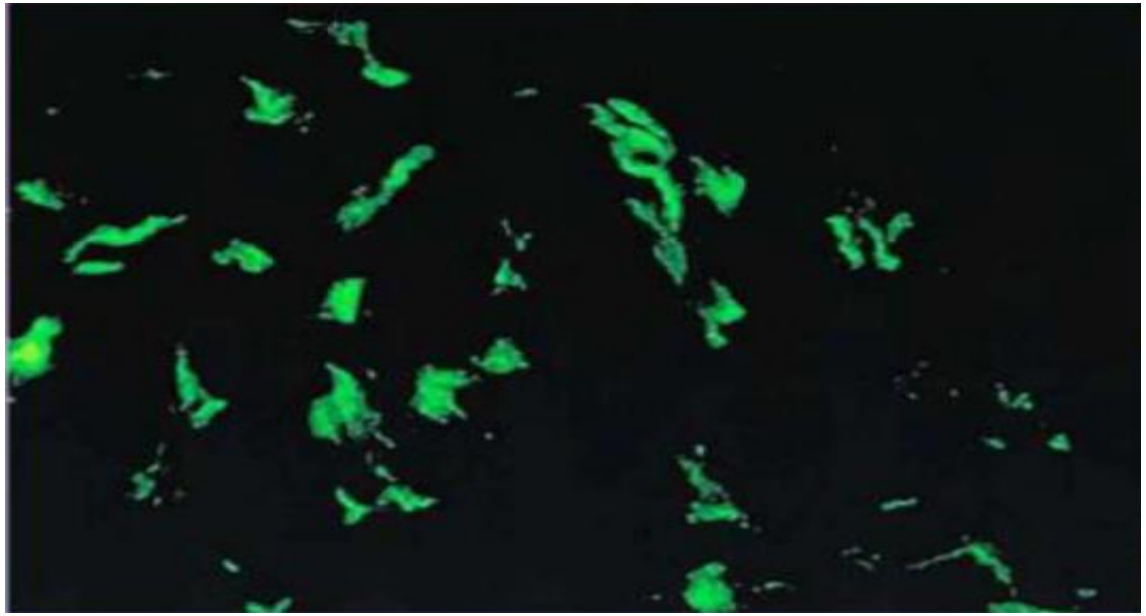
Diagnosis

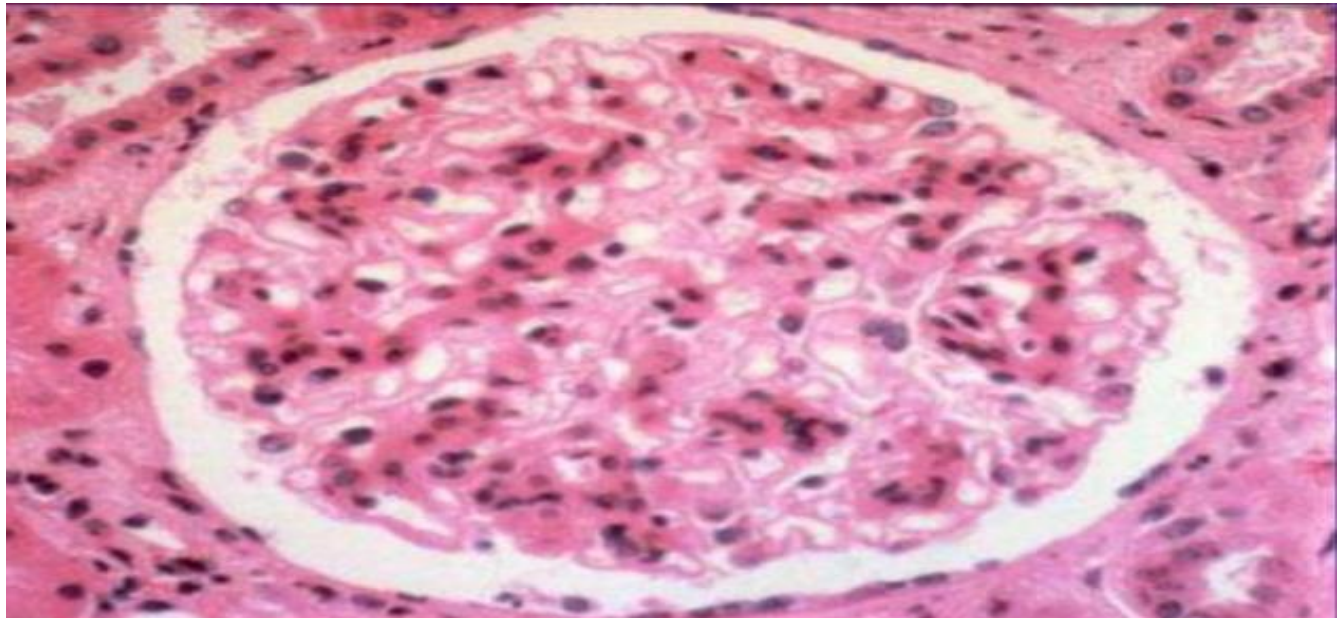
- Renal biopsy is the gold standard
- A renal biopsy may be deferred with the assumed diagnosis of diabetic nephropathy in the context of :
    - Macro albuminuria (>300 mg/24 hours) that has developed progressively,
    - Microalbuminuria (30-300 mg/24 h) with retinopathy
    - Microalbuminuria in patients with diabetes for more than 10 years .

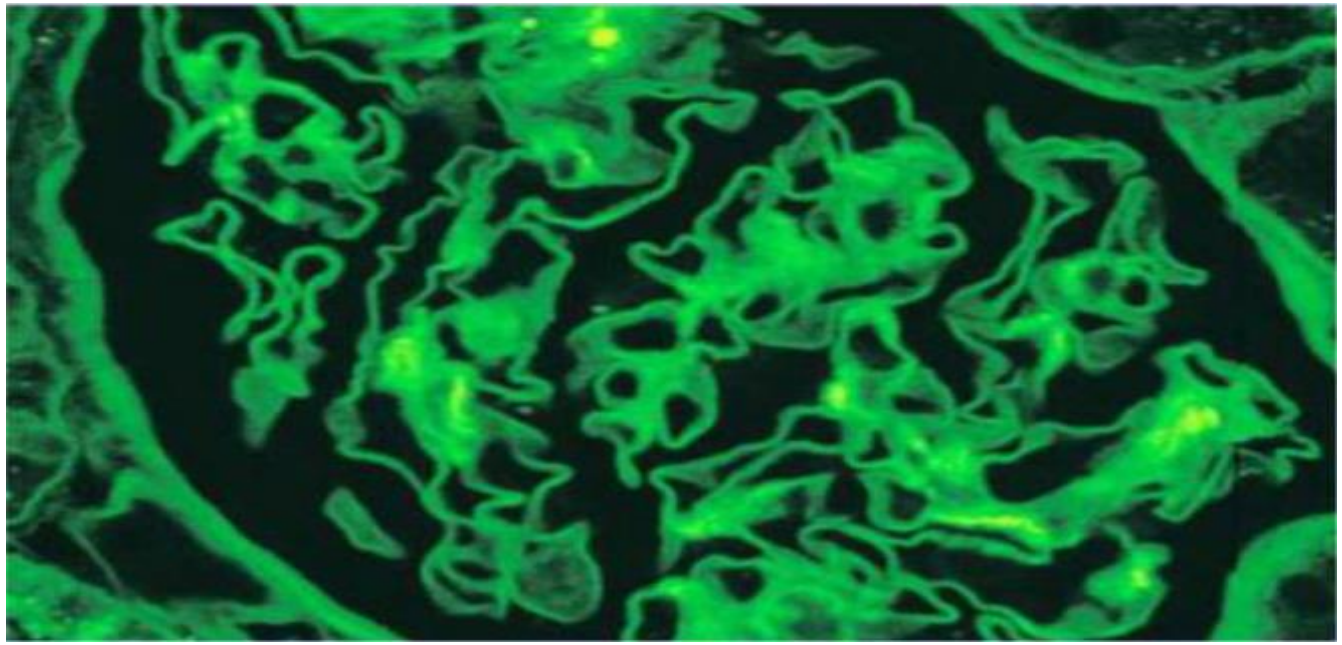
CLASS I LUPUS NEPHRITIS

- Normal (LM, IF, EM are all normal).
- Rare Incidence.
- Minimal Mesangial Lupus Nephritis.
- No Structural Changes on Light microscopy.
- Delicate mesangial positivity for IgG on Immunofluorescence.



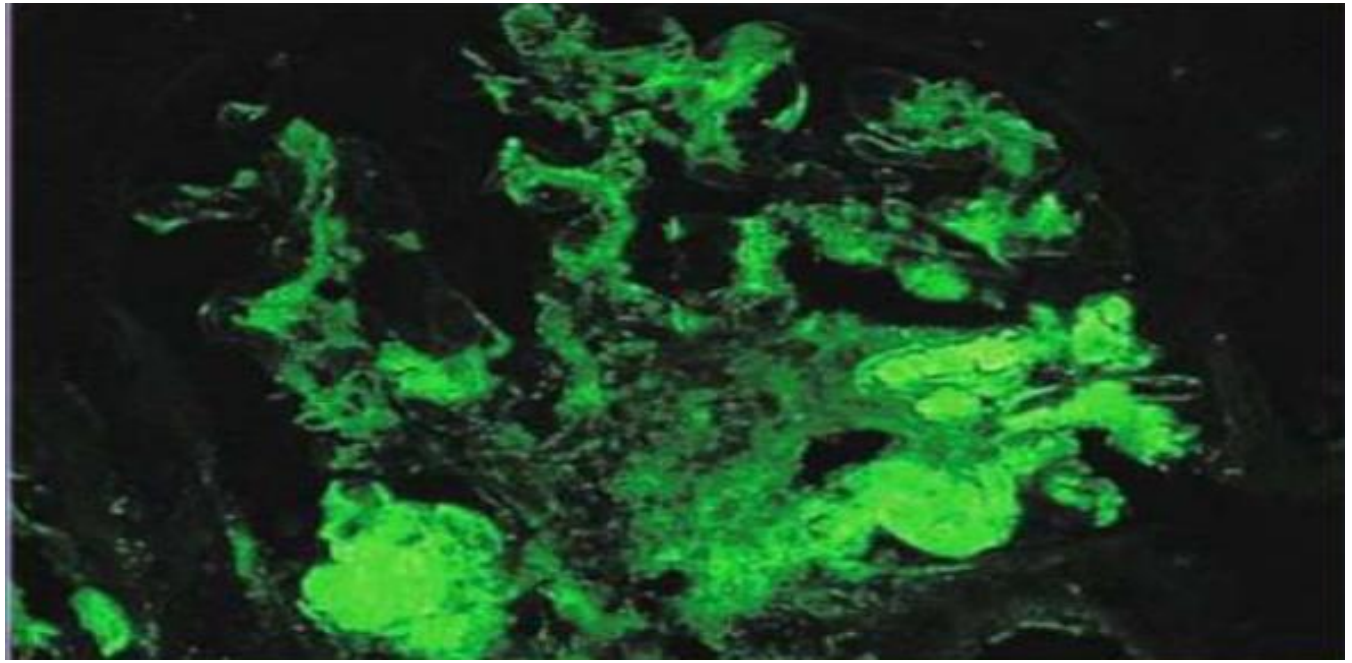


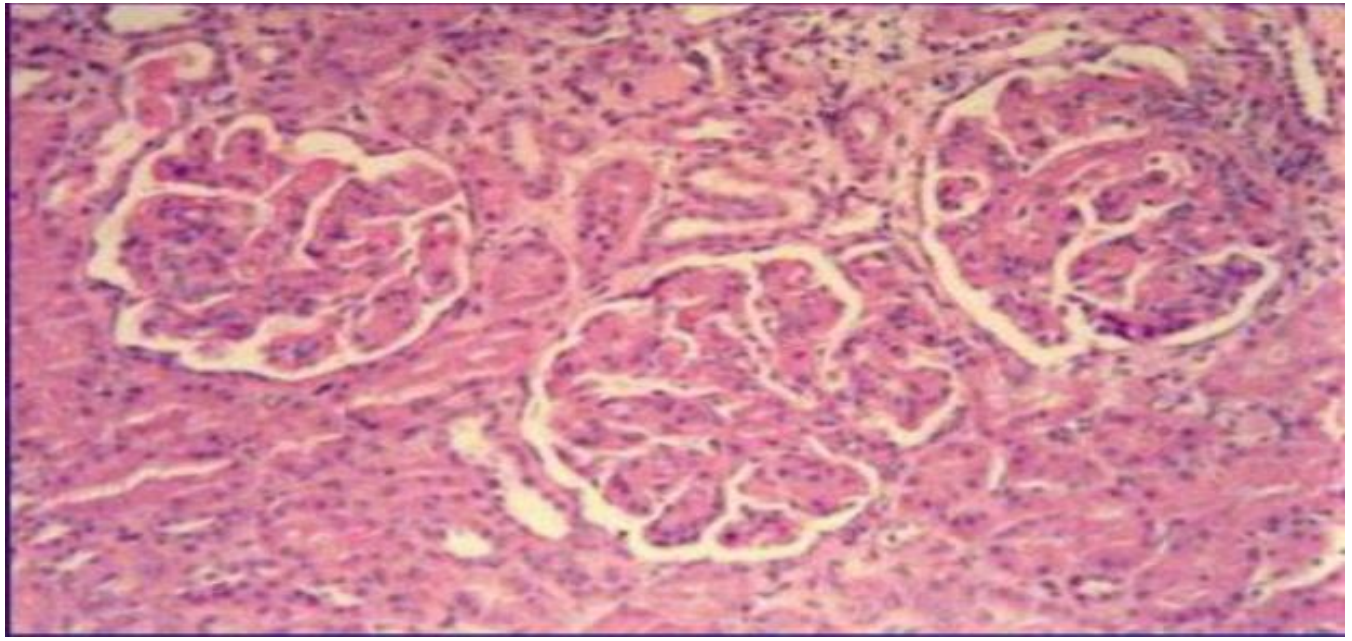




Class II Lupus Nephritis

- Mesangial Proliferative Lupus Nephritis.
  - 10-20% of cases.
  - Excellent Prognosis.
- Benign with low grade Proteinuria → doesn't require treatment.
  - On Light Microscopy: Mesangial Cell Proliferation + Mesangial Matrix Expansion + Mild Hypercellularity.
- On Immunofluorescence: Granular mesangial positivity of all three immunoglobulins and both complements (C1q and C3) "Full house" Pattern, with or without Subendothelial Deposits.
  - On Electron Microscopy: Similar to Immunofluorescence.





Class III Lupus Nephritis

- Focal Proliferative Lupus Nephritis (<50% of Glomeruli).
- 10-20% of the cases.
- Variable prognosis.
- May represent one end of spectrum with Class IV.
- Prognosis: with <25% of glomeruli involved, <5% progress at 5 years to ESRD. With 40-50% involved, 15-25% progress to renal death at 5 years.
- On Light microscopy: Less than 50% of all glomeruli, Segmental or Global swelling and proliferation of endothelial and mesangial cells associated with leukocyte accumulation, Diffuse mesangial hypercellularity, Capillary necrosis, Hyaline Thrombi, Extracapillary proliferation and Crescents.
- On Immunofluorescence: Full house pattern as in class II, Immune deposits also identified in tubular basement membranes interstitial capillary walls, Interstitial Collagen, Arterial intima, and media, Fibrinogen positivity (Granular mesangial and Capillary Ig, C3).
- On Electron microscopy: Mesangial and Subendothelial deposits.
- Subclassed depending on the degree of necrosis and Sclerosis:

1- Class III(A): Active Lesions

2- Class III(A/C): Active and Chronic Lesions

3- Class III(C): Chronic Lesions

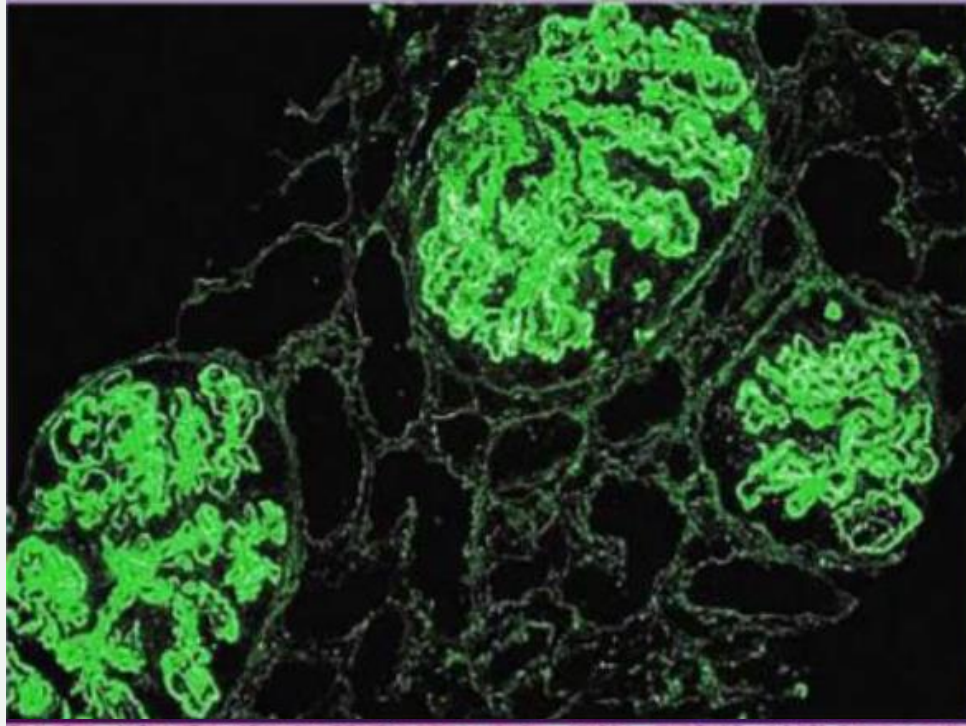
Class IV Lupus Nephritis

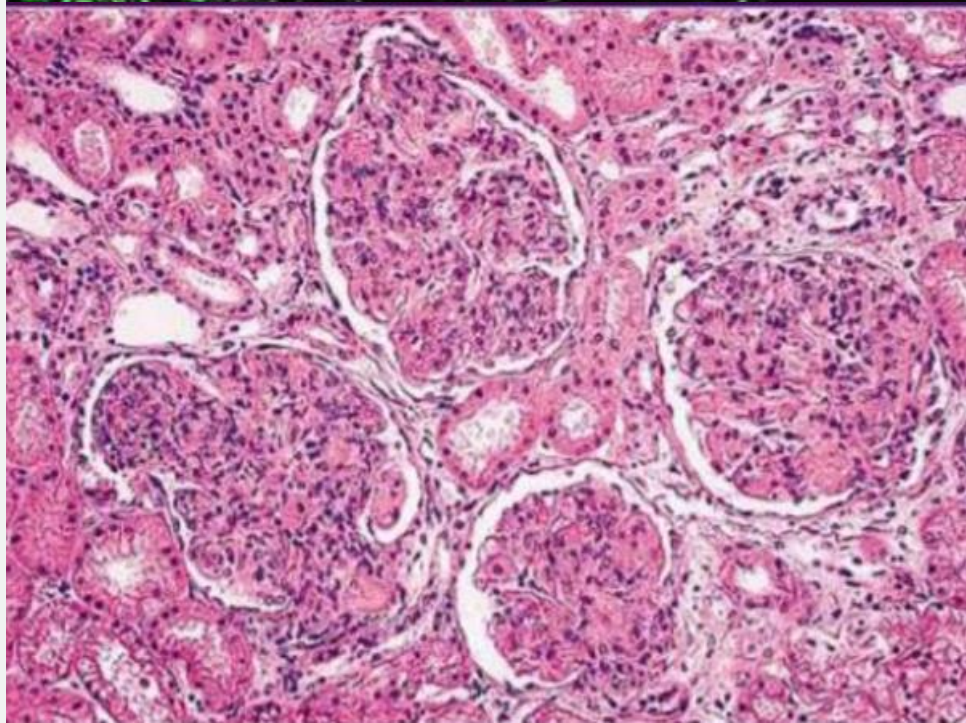
- Diffuse Proliferative Lupus Nephritis (>50% of glomeruli).
- Diffuse Segmental (Class IV-S) or Global (Class IV-G) Lupus Nephritis.
- Most common form (around 40-50%).
- Associated with worse prognosis: 5-year renal death rate 10-40%.
- Poor prognosis in African-American: Cr >2.4 mg/dL, Crescents, Tubulointerstitial Disease, Vascular Disease.
- General Indication for considering Cytotoxic therapy (treat Aggressively).
- Lesions Similar to Class III but involves >50% of Glomeruli.
- Light microscopy: Diffuse Hypercellularity, Mesangial and endocapillary Proliferation, Crescents, Leukocytic Infiltration.
- Immunofluorescent: Mesangial and Capillary Ig, C3, and Extraglomerular deposits "Full House"
- Electron Microscopy: Mesangial, Subendothelial, Subepithelial Deposits.
- Subclassed based on Degree of Necrosis and Sclerosis:

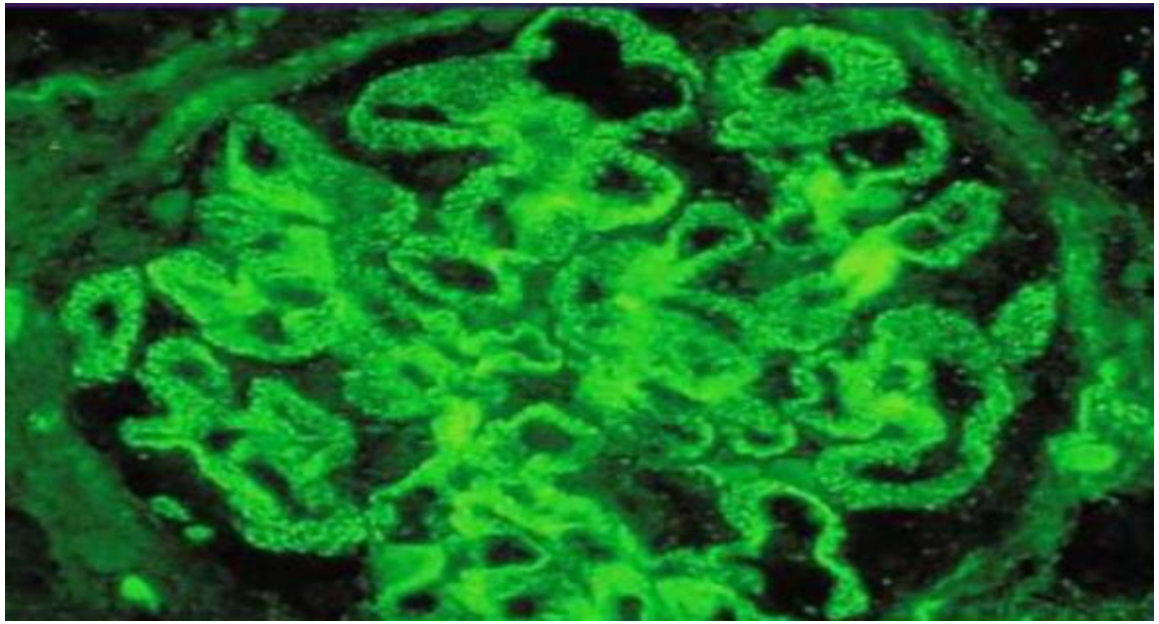
1- Class IV(A): Active Lesions

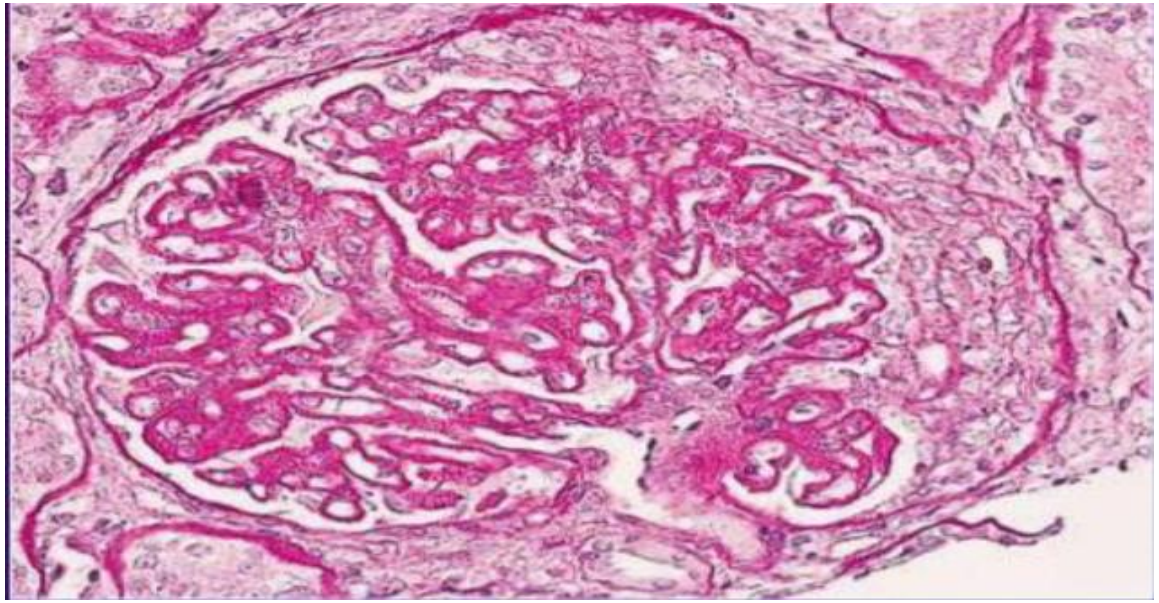
2- Class IV(A/C): Active and Chronic Lesions

3- Class IV(C): Chronic Lesions.





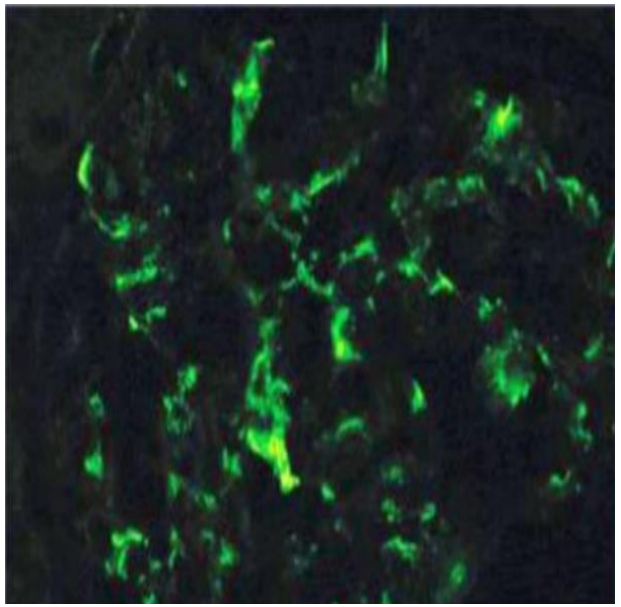


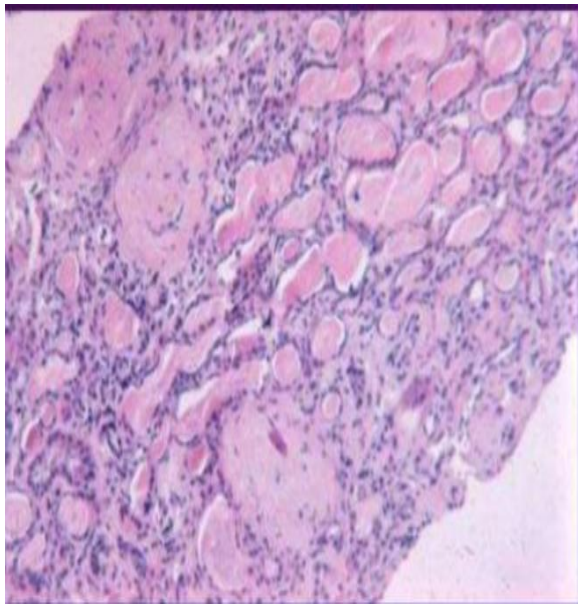


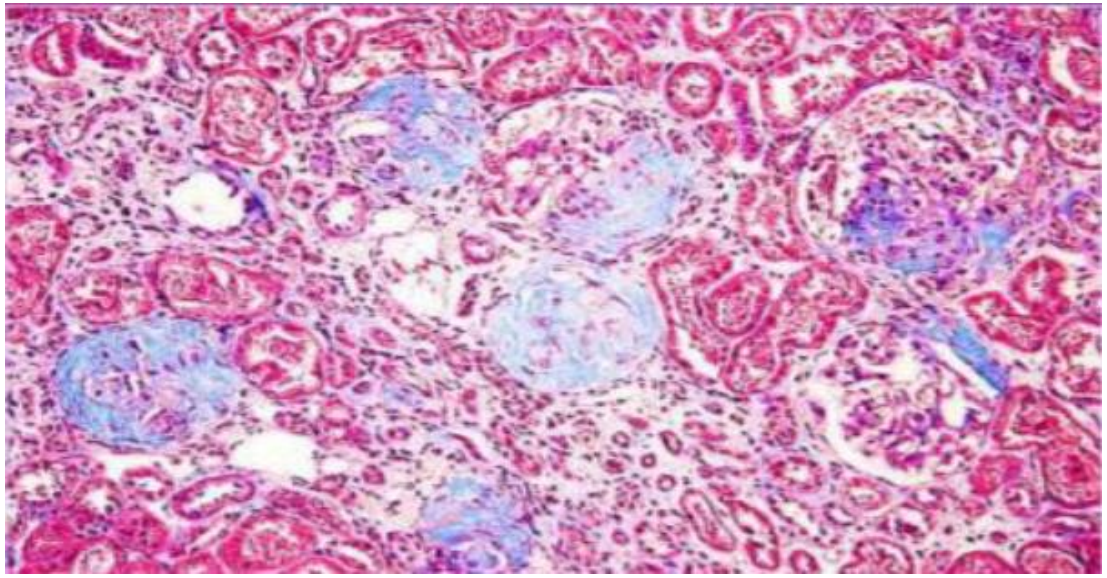
Class V Lupus Nephritis

- Membranous Lupus Nephritis.
- Presents with Proteinuria.
- Variable prognosis but better than Class IV, Patients may have partial or complete remission with stable Creatinine for 5 years or more.
- Overall 5-year renal death rate 10-30%.
- Therapy generally recommended for Florid Nephrosis or deterioration in renal function.
- Light Microscopy: Diffuse thickening of the capillary walls due to deposition of immune complexes, increased production of basement membrane-like material, Mesangial prominence.
- Immunofluorescence: there are delicate subepithelial immune deposits staining for IgG with or without mesangial deposits (Peripheral Granular IgG, C3).
- Electron Microscopy: Epi/intramembranous deposits, Mesangial Deposits.

CLASS VI LUPUS NEPHRITIS







- Advanced Sclerosing Lupus Nephritis (>90% globally Sclerosed Glomeruli without residual activity).
- Characterized by completely or segmentally sclerotic glomeruli as primary abnormality.
- May be considered as either end stage or arrested disease and not necessarily as separate class.
- On Microscopy: Sclerosis of more than 90% of the Glomeruli, End Stage Renal Disease, Severe Tubular Atrophy, Interstitial Fibrosis, Inflammation

TREATMENT OF LUPUS NEPHRITIS

TREATMENT

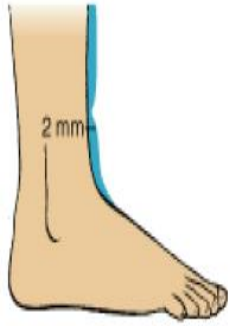
- The principal goal of therapy in lupus nephritis is to normalize renal function or, at least, to prevent the progressive loss of renal function.
- Therapy differs depending on the pathologic lesion. It is important to treat extrarenal manifestations and other variables that may affect the kidneys.
- Adjunctive Treatments
- Primary disease management by immunosuppressive agents Induction Therapy
- Maintenance Therapy
- Lifestyle Changes

SODIUM AND WATER DISORDERS

SYSTEM FOR GRADING EDEMA

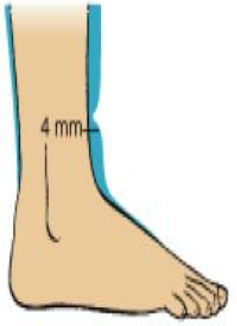
1+ Pitting Edema

- Slight indentation (2 mm)
- Normal contours
- Associated with interstitial fluid volume 30% above normal



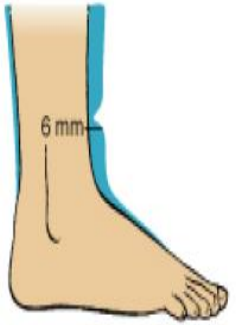
2+ Pitting Edema

- Deeper pit after pressing (4 mm)
- Lasts longer than 1+
- Fairly normal contour



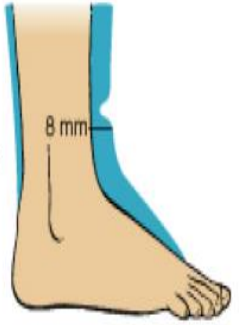
3+ Pitting Edema

- Deep pit (6 mm)
- Remains several seconds after pressing
- Skin swelling obvious by general inspection



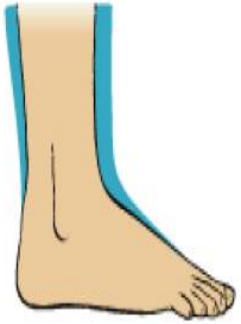
4+ Pitting Edema

- Deep pit (8 mm)
- Remains for a prolonged time after pressing, possibly minutes
- Frank swelling



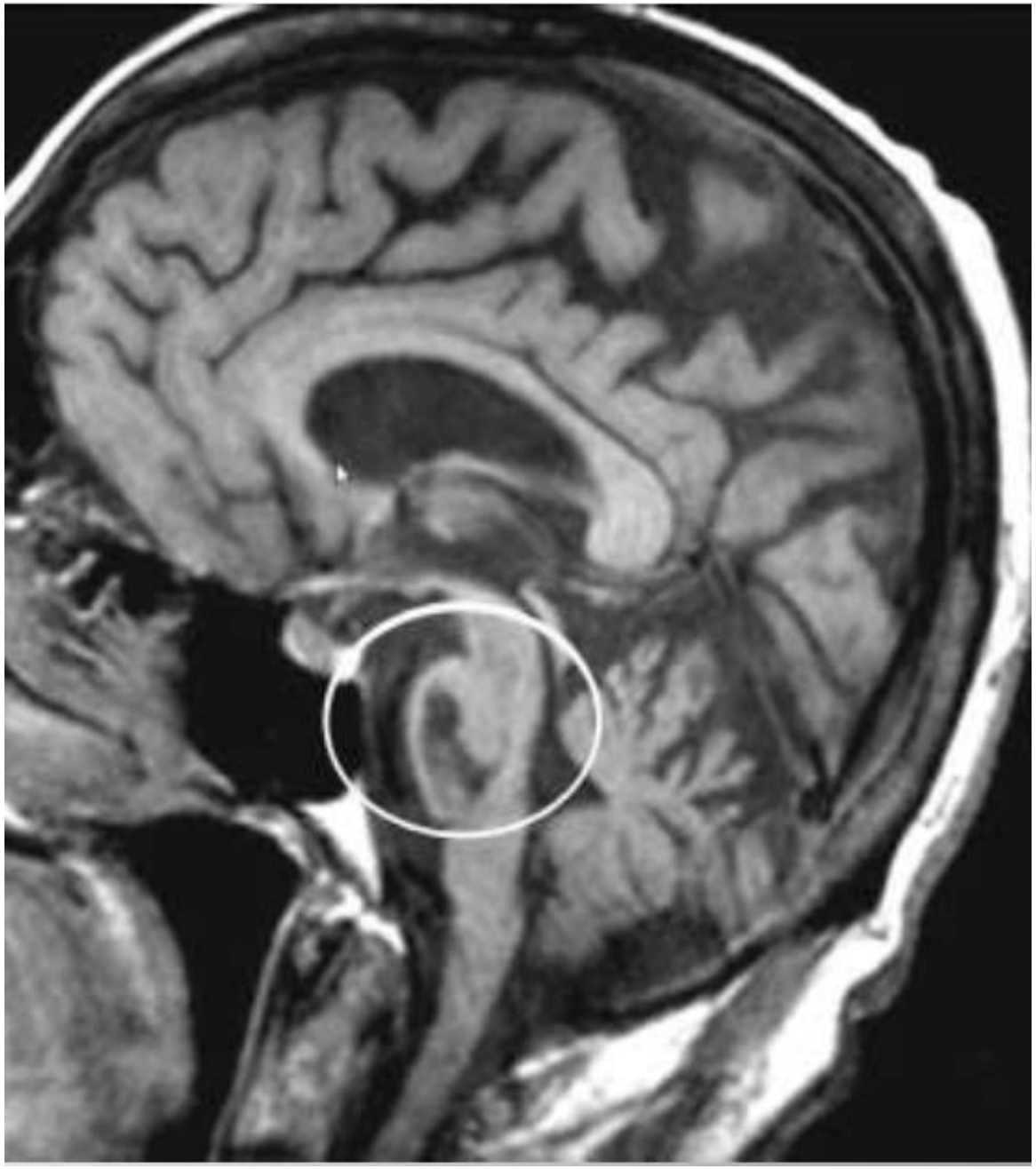
Brawny Edema

- Fluid can no longer be displaced secondary to excessive interstitial fluid accumulation
- No pitting
- Tissue palpates as firm or hard
- Skin surface shiny, warm, moist



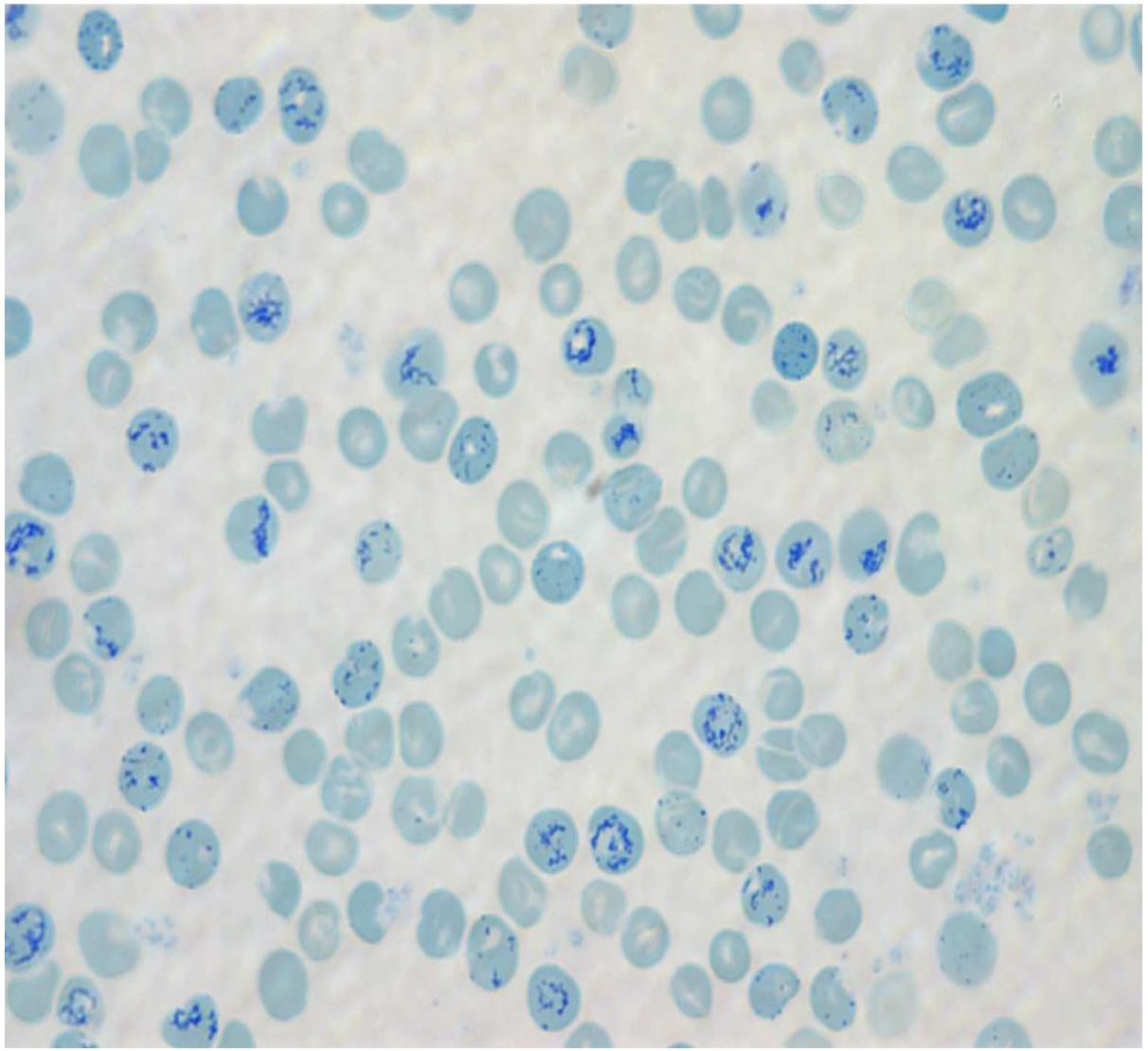
OSMOTIC DEMYELINATION SYNDROME

- A brain cell dysfunction caused by the destruction of myelin sheath covering nerve cells in the middle of the brainstem
- It occurs as a consequence of inappropriate management of Hyponatremia.



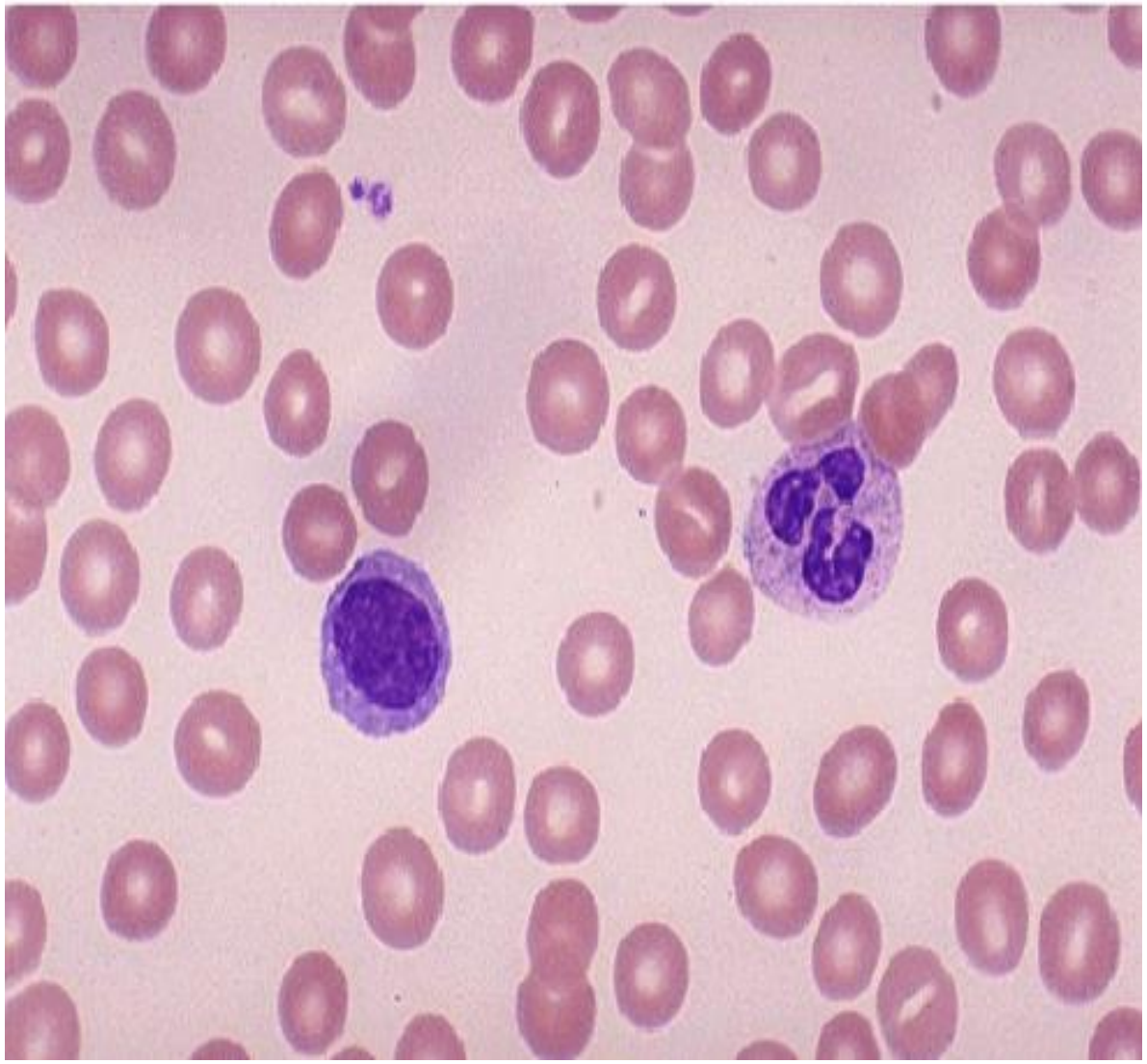
HEMATOLOGY AND ONCOLOGY

ANEMIA

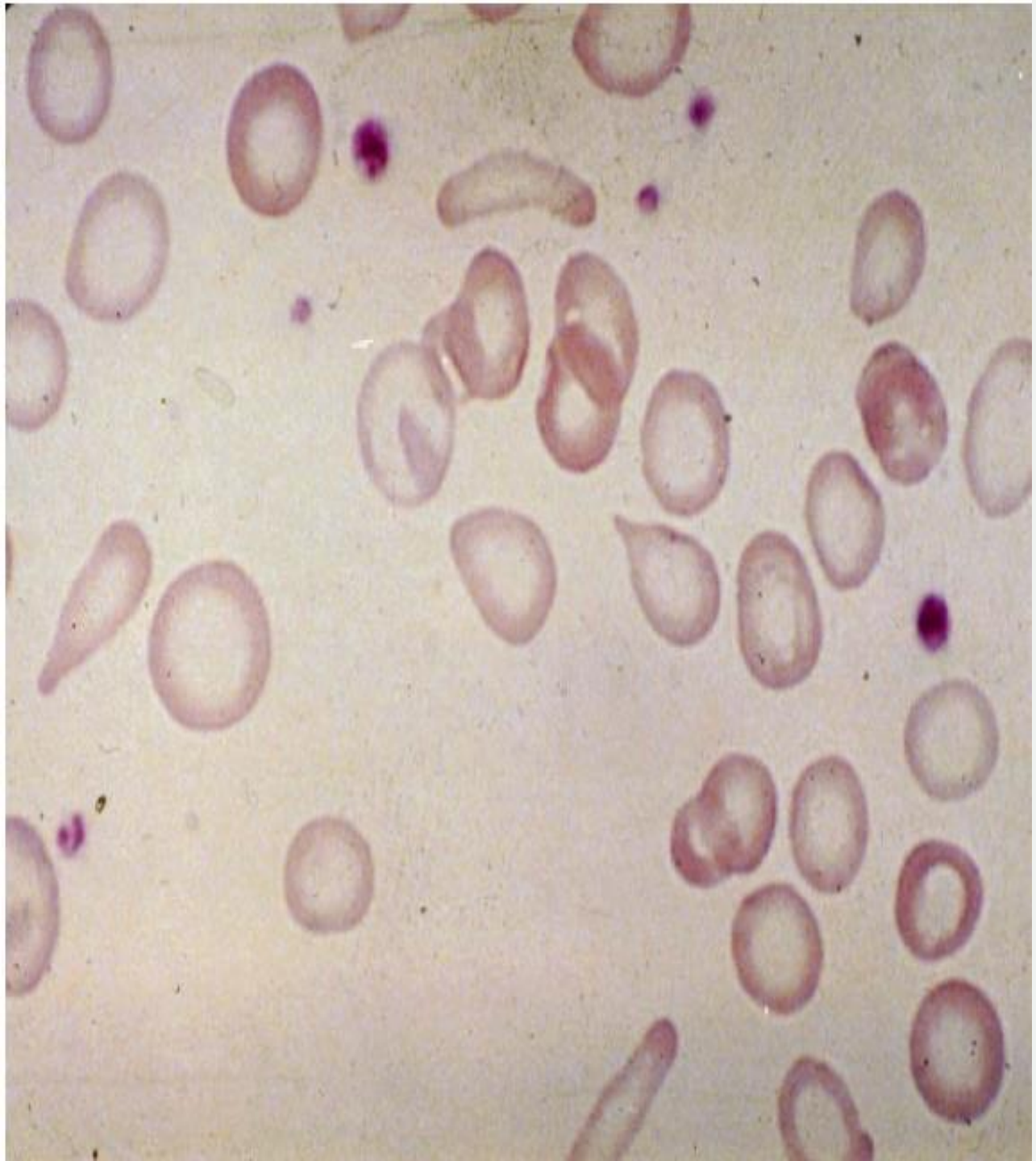


BLOOD FILM

- Blood film of Reticulocytes with Supravital stain which stains RNA in Red cells.
- Reticulocytes appear bluish and larger than mature RBCs



NORMAL BLOOD SMEAR



Iron deficiency Anemia

- This blood smear shows Severe Hypochromia (Central pallor of RBCs, about 1/3 of the total volume of RBCs), Anisocytosis (Altered RBCs Shape), and Poikilocytosis (Different RBCs Sizes).
- It indicates Iron Deficiency Anemia.
- Daily iron absorption: 1-3 mg
- Diet has 10-15 mg of iron.
- Daily loss: 1 mg from the skin
- The major categories of IDA:

1- Nutritional: Poor or absent red meat consumption.

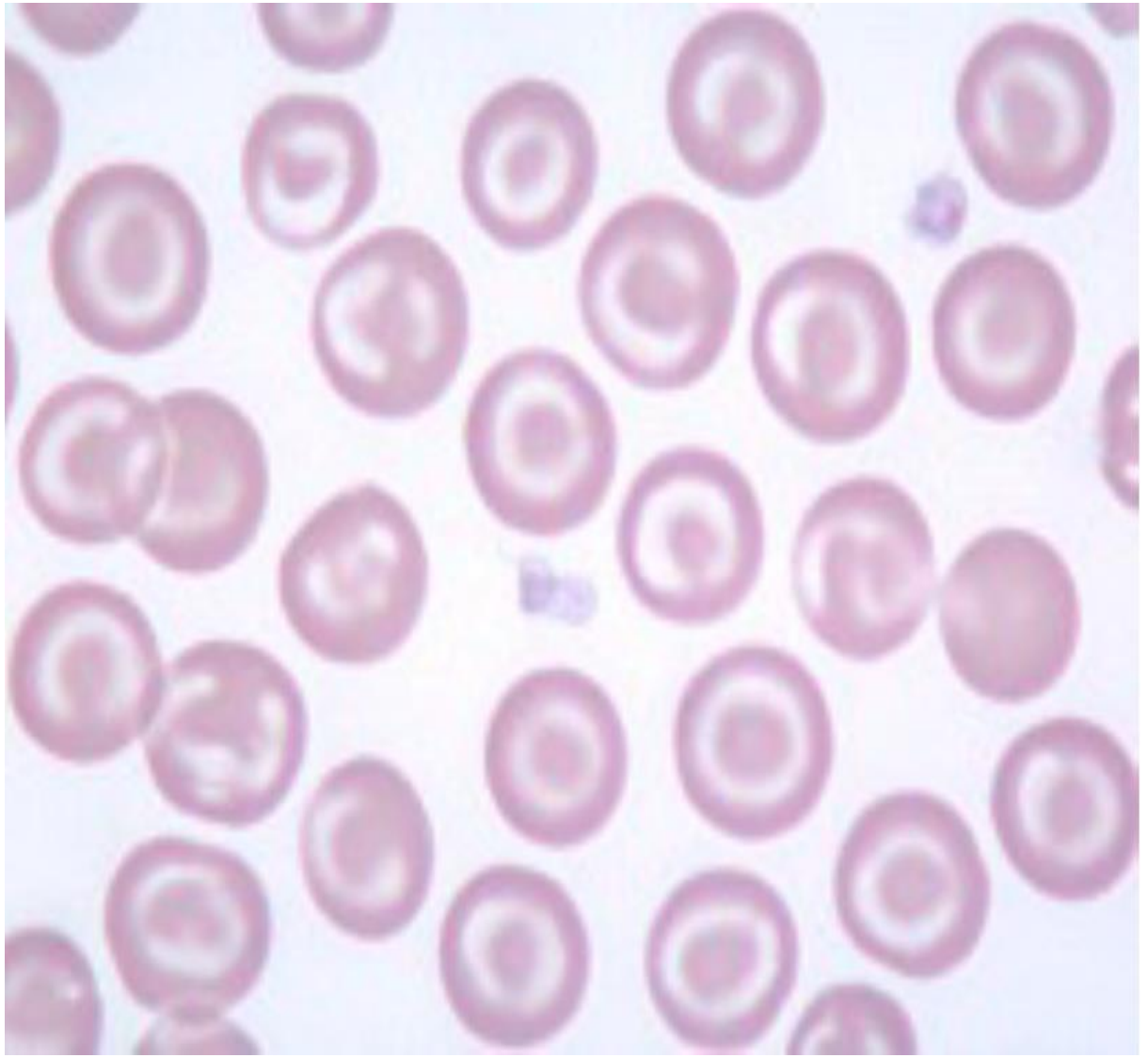
2- Blood loss (most common in developed countries.

3- Malabsorption: Gluten Enteropathy, Gastritis, H.Pylori, patient with chronic antacid use.

4- Repeated pregnancies: increased Fe demand.

THALASSEMIA TRAIT

- Hypochromia with target cells but without Anisocytosis.
- Indicates Thalassemia Trait.

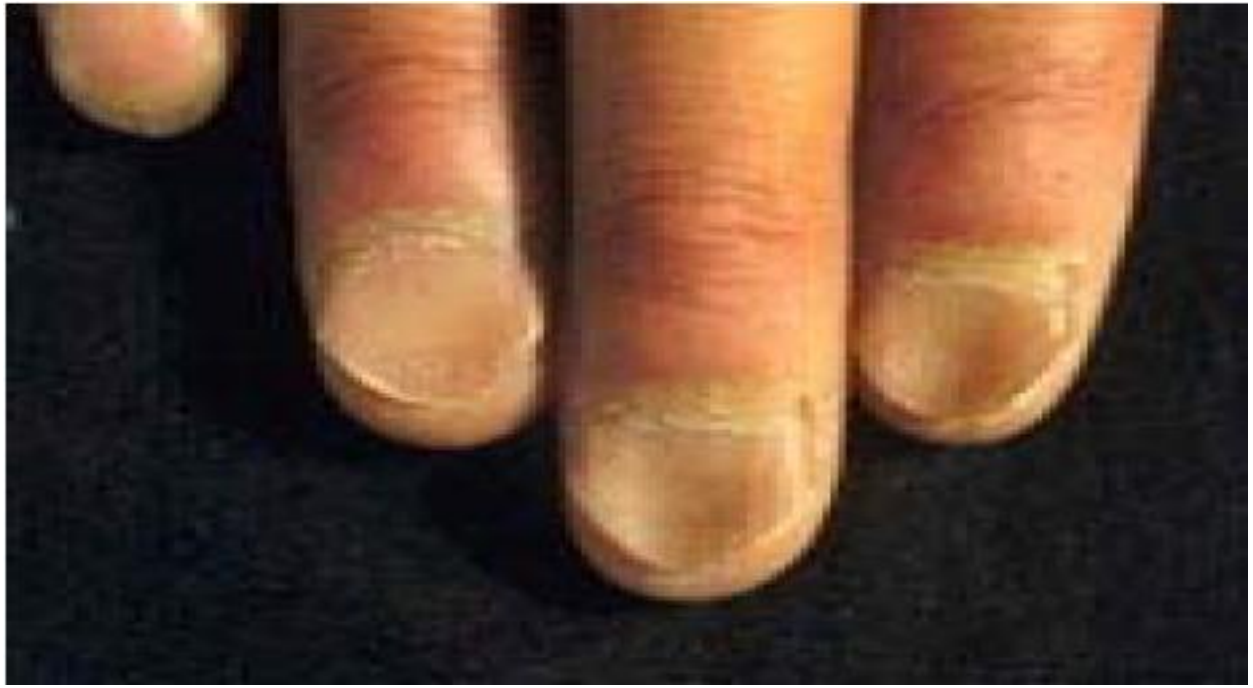


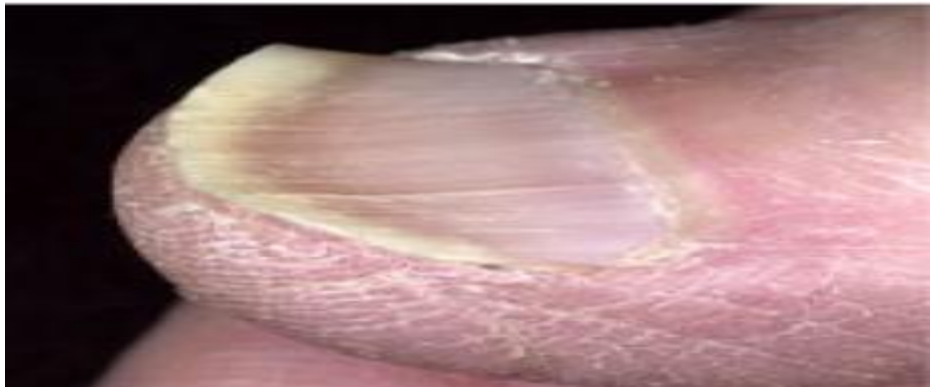
Laboratory Findings in Iron Deficiency Anemia

1- Low Hemoglobin.
2- Low MCV (Microcytic).
3- High RDW.
4- Low MCH.
5- Normal WBC count.
6- Normal Platelets count.
7- Low Serum Ferritin
8- High TIBC
9- Low Transferrin Saturation.
⋆ Low Ferritin + Hb → Diagnostic of Iron Deficiency Anemia.
Blood Film:
1- Microcytic.
2- Hypochromic.
3- Anisocytosis.
4- Poikilocytosis.
5- Low Corrected Reticulocyte count (indicates underproduction anemia).

KOILONYCHIA

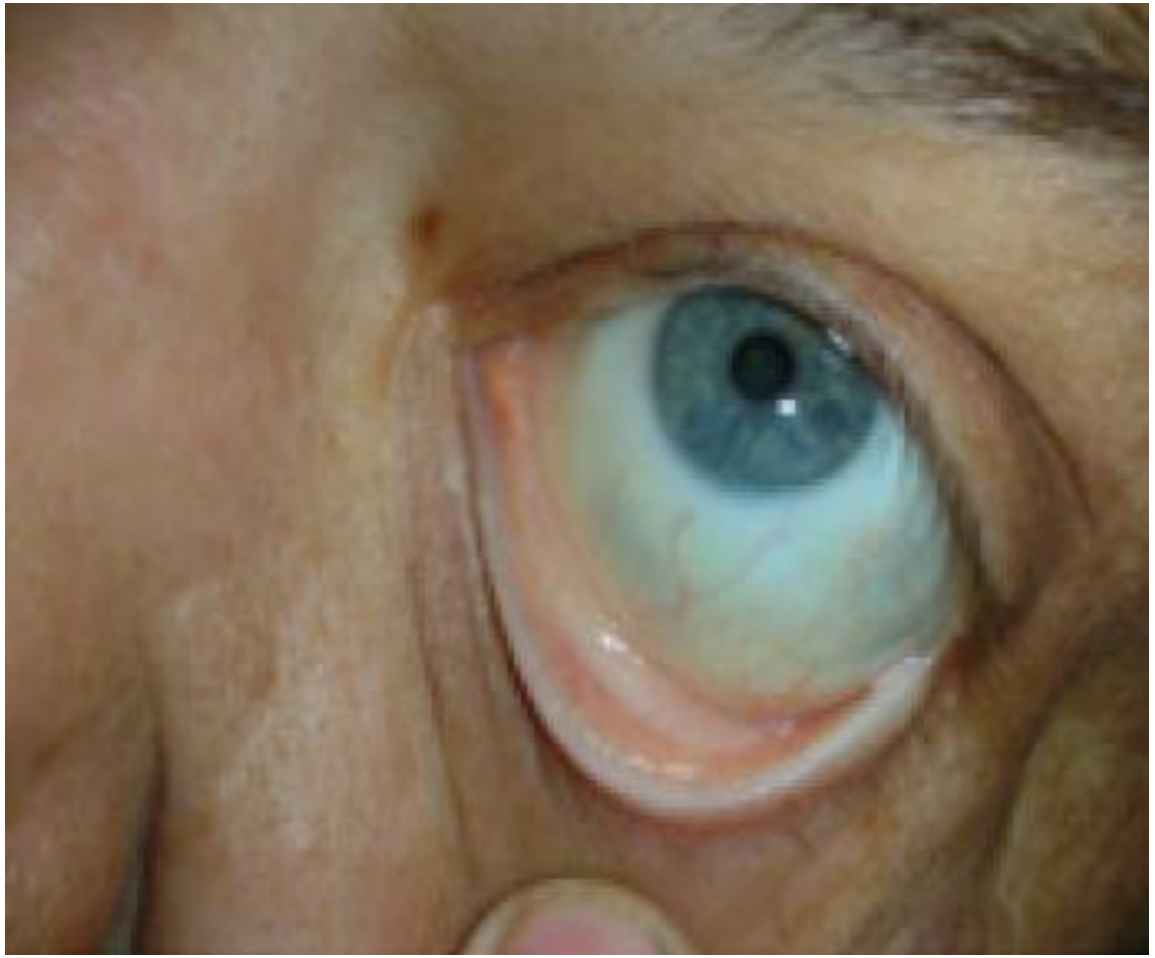
- A clinical feature of IDA.
- Also seen in Lichen Planus and due to repeated exposure to detergents.





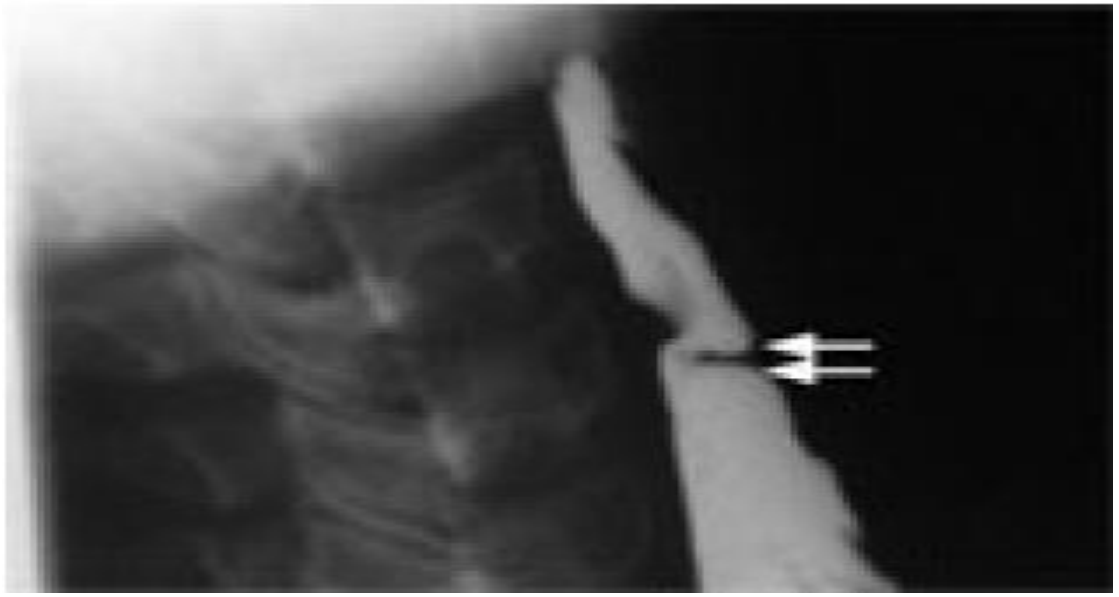
CONJUNCTIVAL PALLOR

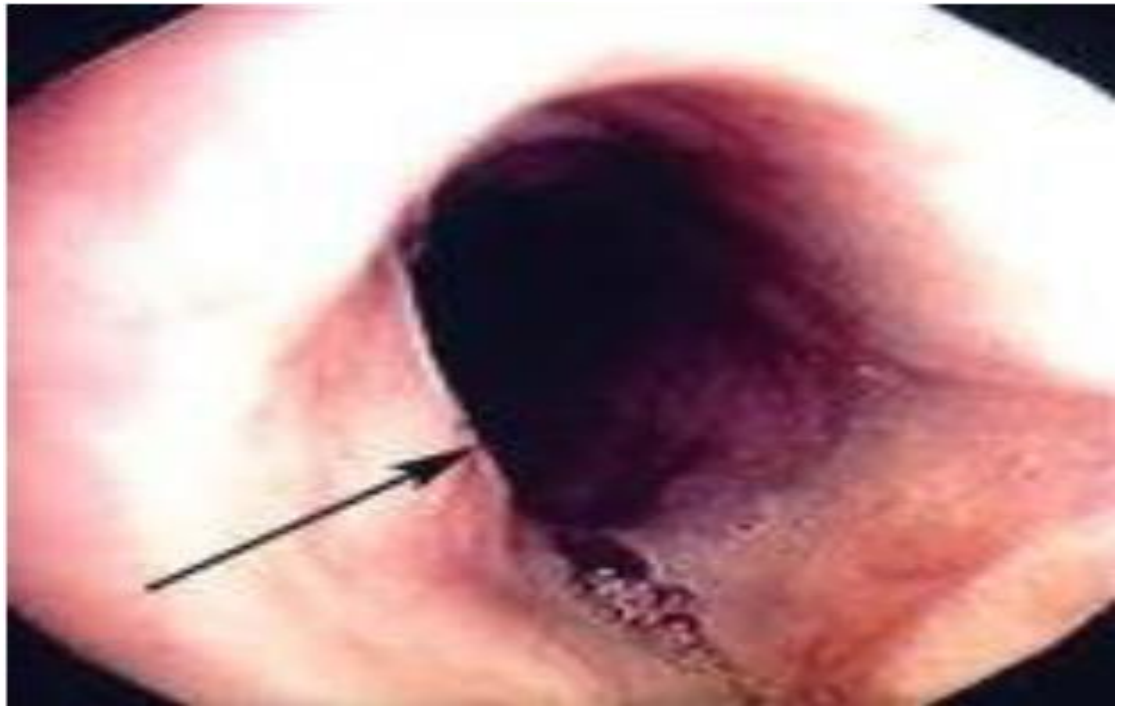
- A clinical feature of IDA.



ESOPHAGEAL STRICTURE

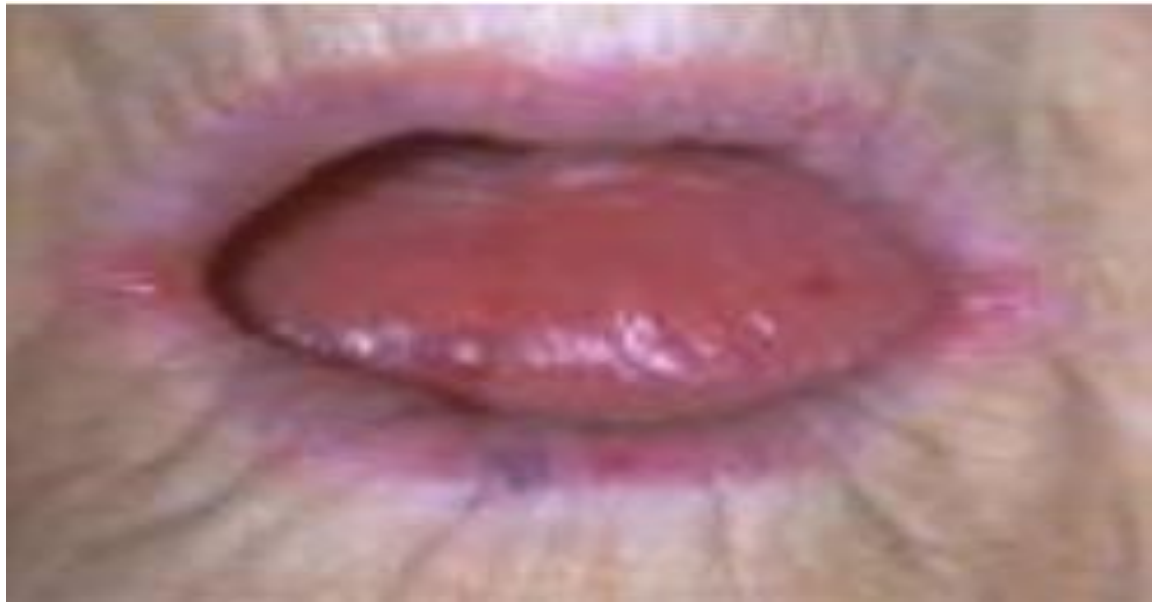
- A clinical Feature of IDA.
- Also seen in GERD and Esophagitis.

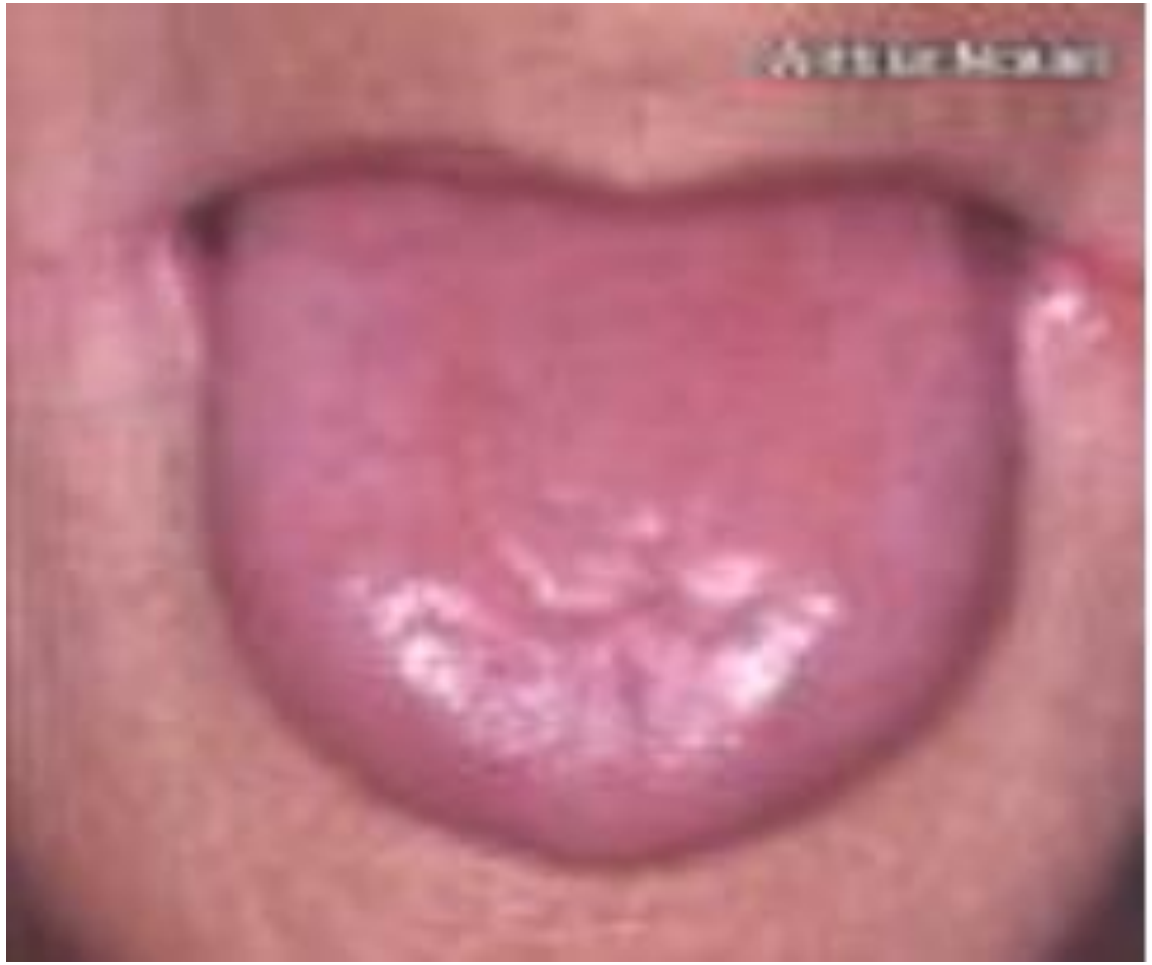




ANGULAR STOMATITIS

- A clinical feature of IDA.
- Also seen in association with Trauma, and Allergic contact dermatitis.



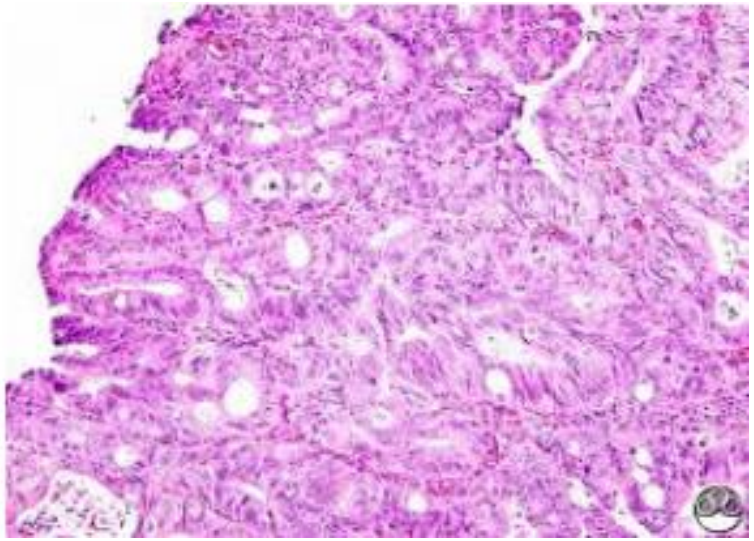


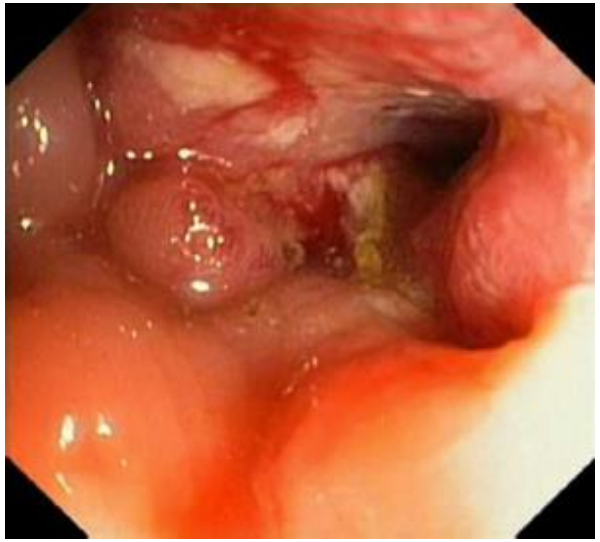
BEEFY RED TONGUE

- A clinical Feature of IDA.
- Also seen in Folate, and Vitamin B12 deficiency.

COLON ADENOCARCINOMA

- A common cause of IDA in Elderly





DIFFERENTIAL DIAGNOSIS OF MICROCYTIC ANEMIA

- Thalassaemia syndromes
- Certain haemoglobinopathies (Hb C)
- True (classical) iron deficiency secondary to blood loss, iron-poor diet, increased iron needs, *Helicobacter pylori* infection or gastric pathology
- Anaemia of chronic inflammatory diseases
- Certain forms of sideroblastic anaemia
- Genetic forms of iron deficiency anaemia

TREATMENT OF IRON DEFICIENCY ANEMIA

1- Oral Iron: Fe gluconate, sulphate

2- educate

3- IV Fe?? Fe sucrose/carboxymaltose or new Fe dextran

Follow up: check CBC every month : expected Hb rise ± 1g/ 10 days. Check Ferritin at 3 months. Follow other investigations and consulations

Pernicious Anemia / Vit B12 Deficiency

- It's an autoimmune disorder associated with Vit B12 deficiency since it's not absorbed from terminal ileum due to the absence of intrinsic factor.

Laboratory Findings:

1- Low Hemoglobin.

2- High MCV.

3- Very Low Corrected Reticulocyte count (underproduction anemia).

4- Low WBCs count (Leukopenia).

5- Low Platelets count (thrombocytopenia).

6- High Lactate dehydrogenase (LDH) (+ indirect bilirubin due to destruction of red cells, then bilirubin travels to the liver for conjugation until it's overwhelmed, followed by excess of indirect bilirubin, also LDH is one of the enzymes found in RBCs, so the level rise with destruction of RBCs).

7- Low Serum B12

8- Achlorhydria: the absence of hydrochloric acid in gastric secretions.

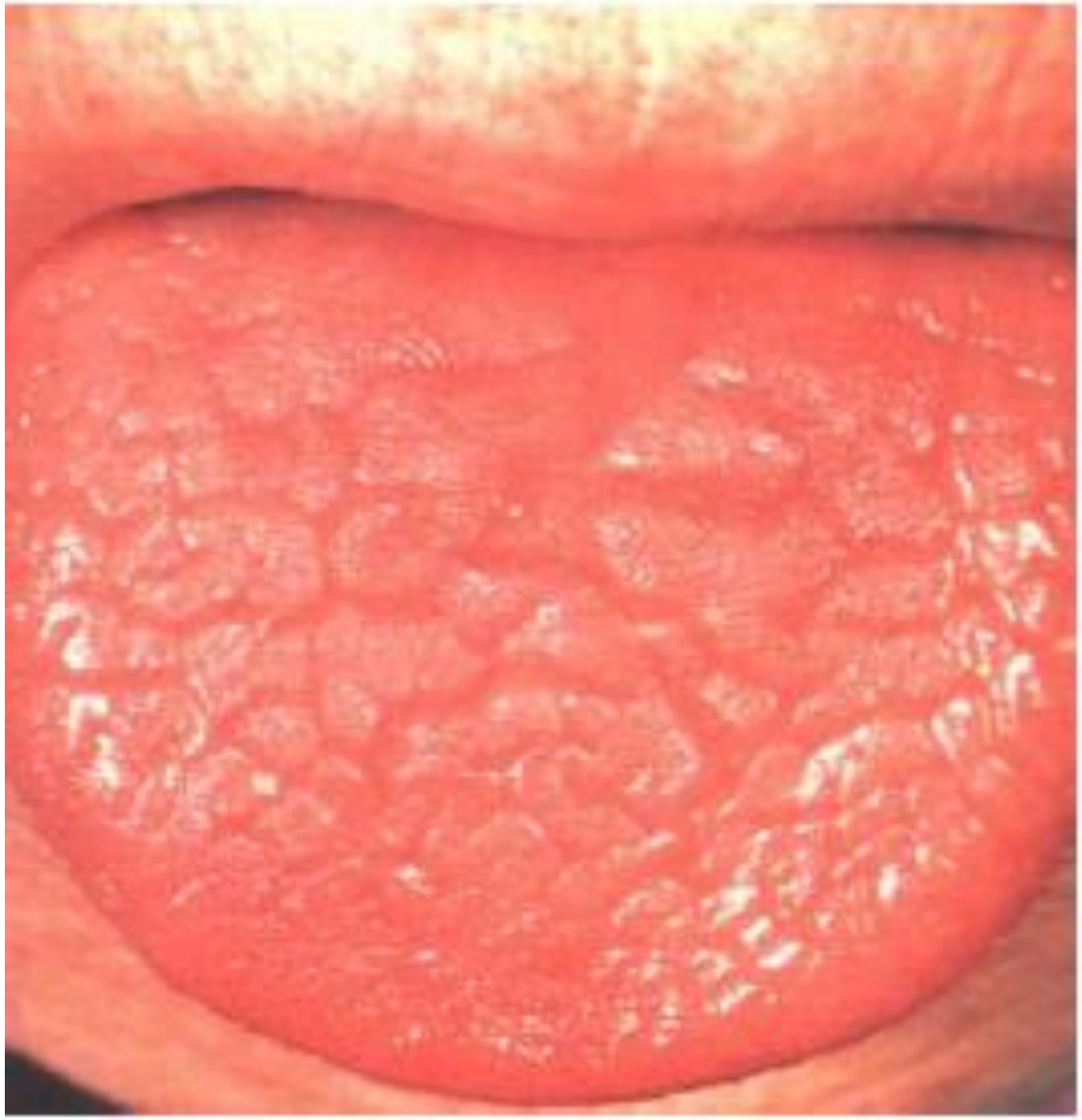
9- Gastric Biopsy reveals Atrophic Gastritis.

Severe Anemia secondary to Vit B12 deficiency → present with tissue hypoxia symptoms + Neurological symptoms specifically.

Additional test to prove B12 deficiency: 1- Intrinsic Factor Ab + Parietal cells Ab → those are positive. 2- Achlorhydria. 3- Endoscopy for upper GI (stomach) with biopsy → Reveals Atrophic Gastritis.

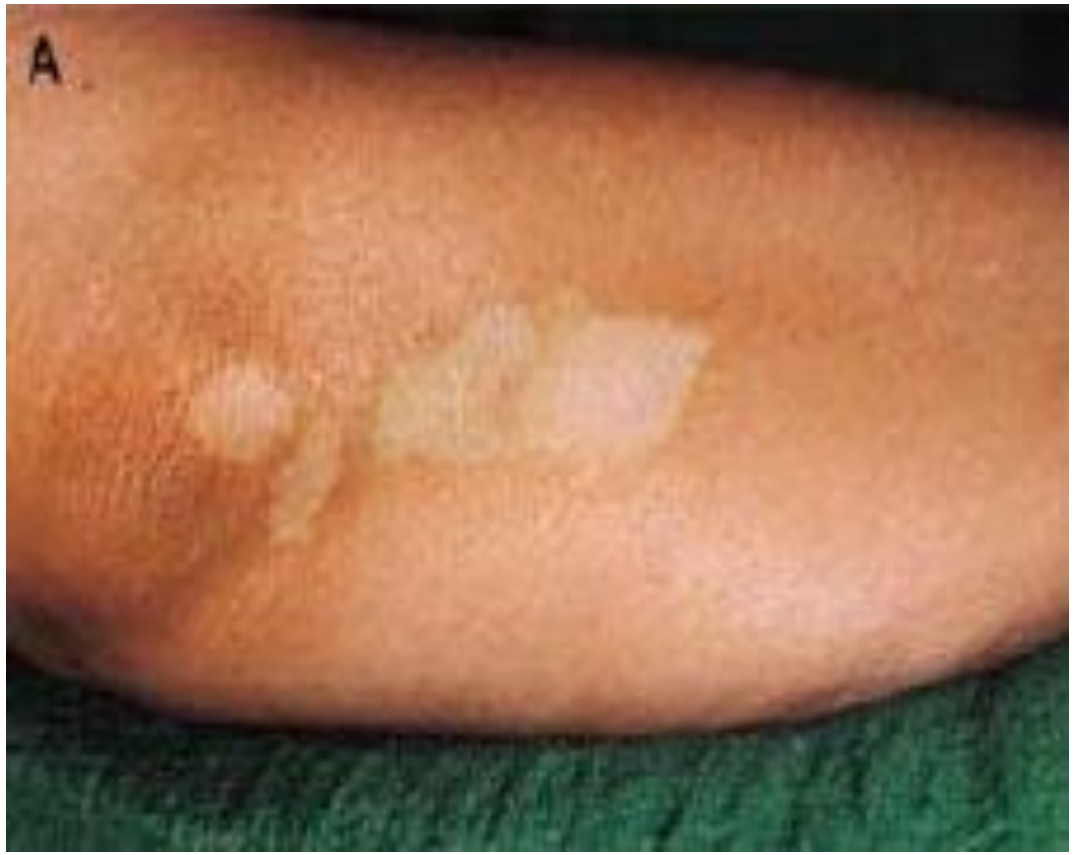
RED BEEFY TONGUE

- A clinical feature of Pernicious Anemia (Due to Vit B12 deficiency).
- Also seen in IDA.



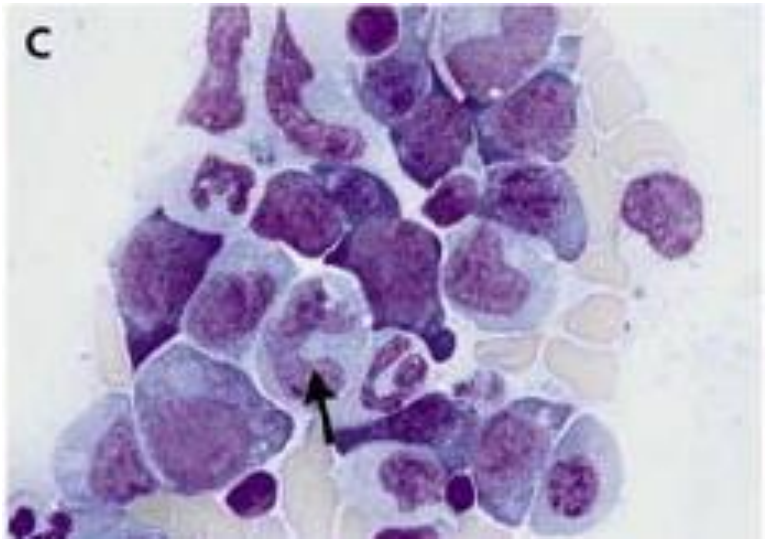
Vitiligo

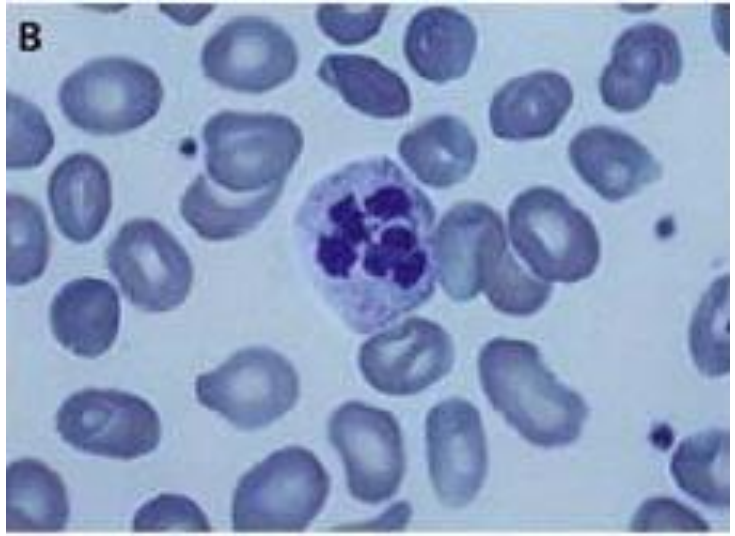
- A clinical feature of Pernicious Anemia.
  - May also be related to Autoimmune conditions (e.g., Thyroiditis, T1DM).



PERNICIOUS ANEMIA / BLOOD SMEAR

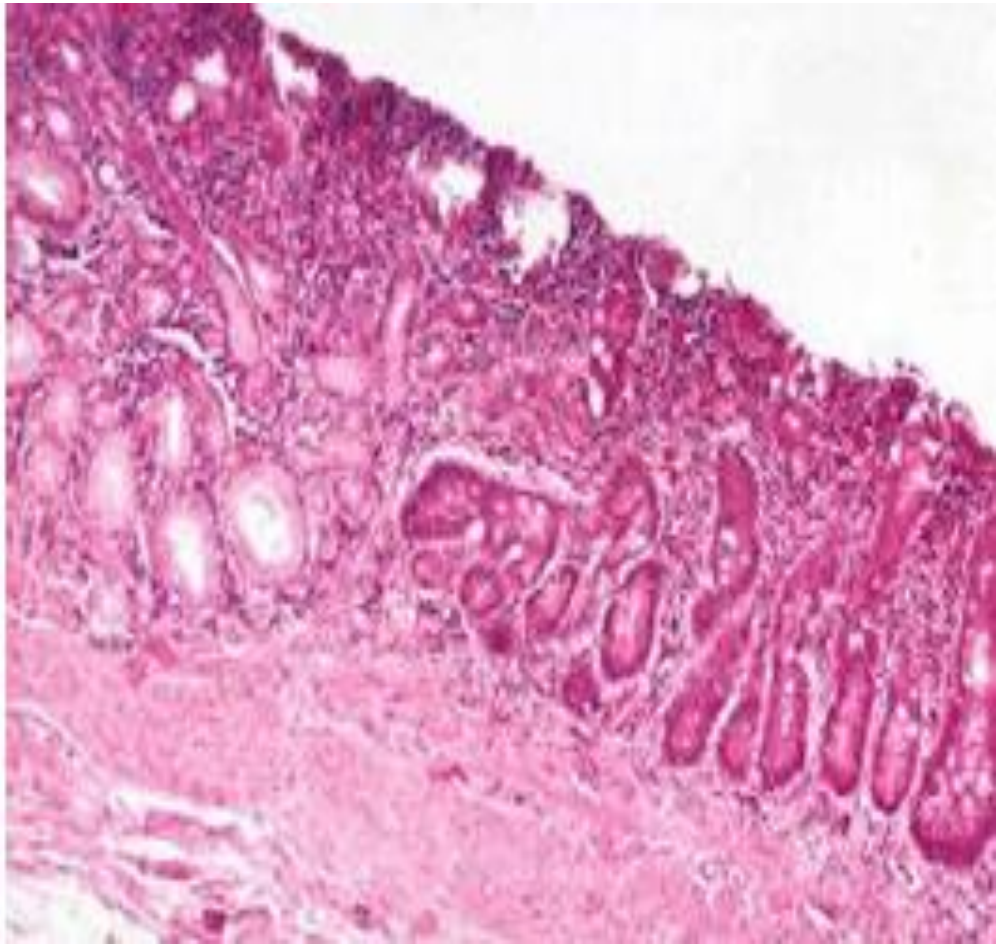
- The first picture is a blood smear from the Bone Marrow, it shows Megaloblasts (Large, abnormally formed RBCs)
- The second blood smear shows Macro-ovalocytes and Hypersegmented neutrophils (>5 lobes).





OXYNTIC GASTRIC MUCOSA ATROPHY

- A clinical feature of Pernicious Anemia.



PATHOGENESIS OF PERNICIOUS ANEMIA

- The most important Antibody is Intrinsic Factor Antibody (positive in 70% of the cases of PA).

Pathogensis of Pernicious Anemia (PA)

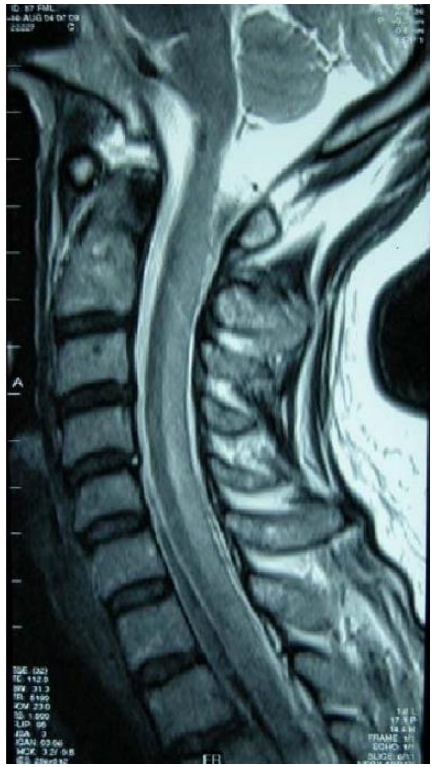
1-PA is the end-stage of Atrophic Body Gastritis (ABG) causing oxyntic gastric mucosa damage: achlorhydria.

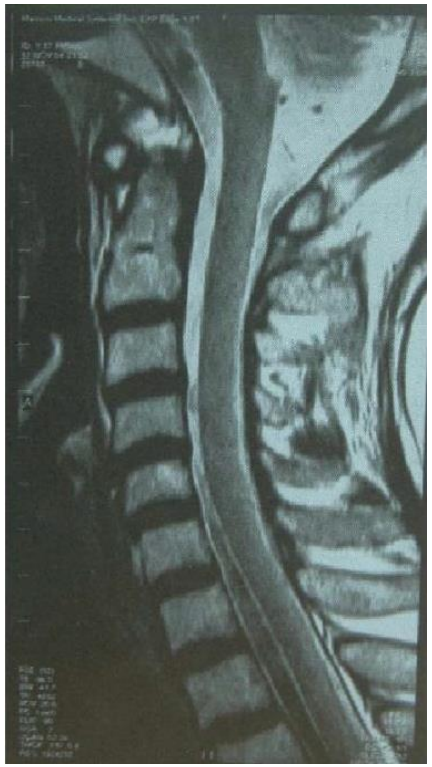
2-It is considered an autoimmune disease (AID).

3-AID theory is based on the presence of parietal cell and/or intrinsic factor autoantibodies
Frequent association with other autoimmune disorders: autoimmune thyroid disease (ATD), type 1 diabetes, and vitiligo

Neurologic Manifestations in Pernicious Anemia

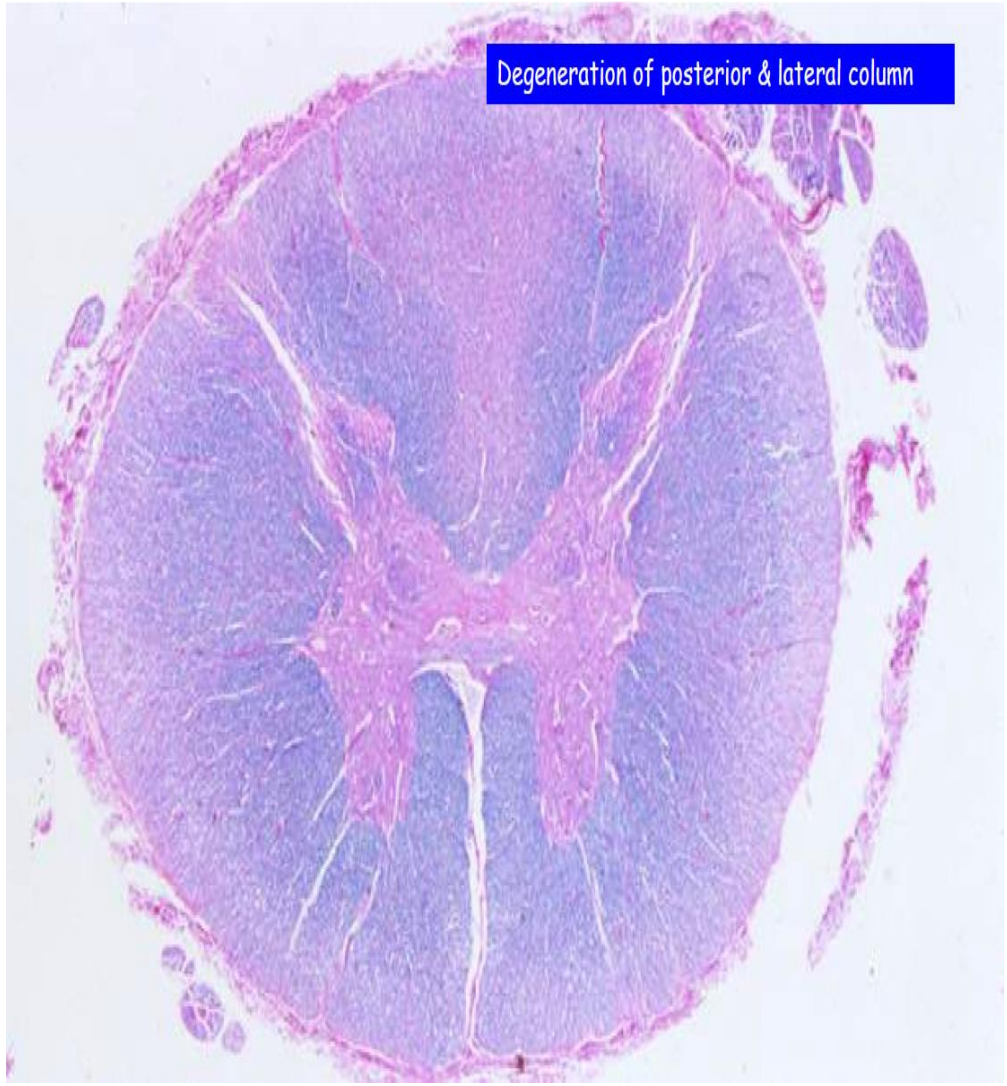
- Notice in the First Image there is Hyperintensity in Cervical Region, which is corrected in the second image.
- Neurologic manifestations are seen in Pernicious Anemia since Vit B12 is important in the myelination process of the neurons (plays a role in the methylation of neural lipid and protein which is important in Myelination).
- Loss of the Posterior and Lateral columns myelin which lead to loss of vibration and proprioception sensation in the lower limbs, may also start with Fullness, Numbness, Coma, Seizure, and if untreated leads to death.
- Once you suspect Vit B12 deficiency, you must initiate therapy without waiting for Lab results, and give it Parenterally not orally to reverse the damage.





SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD

- Degeneration of Posterior and Lateral columns, which is a characteristic of B12 deficiency.
- May also be seen with Vit E and Copper deficiencies (but Rarely).



Myelodysplastic Syndrome

Vit B12 and Folate are important for Nucleic Acid Synthesis, if they're deficient, there'll be impaired synthesis of RNA and DNA which arrest cell growth in the S-phase leading to early death of the cell (apoptosis).

So eventually there will be Hypercellular Bone Marrow (High number of cells in BM) because they're unable to mature due to abnormal synthesis of DNA and RNA leading to lagging of maturation of nuclei compared to cytoplasm (Nuclear-Cytoplasmic Asynchrony) → A hallmark of Megaloblastic Changes in BM (Not seen in cases of Macrocytosis).

Normally in food, B12 is bound to animal protein which need to be cleared from in the stomach by acidity and pepsin.

Malabsorption occur due to defected Pepsin or Acidity (mainly in elderly).

Stomach surgeries may also develop B12 deficiency.

Most important Active Significant absorption is in the terminal ileum → B12 deficiency may develop due to IBD, Surgery, Ulcer, Infection (Tapeworm), Deficiency of Intrinsic Factor, Metformin use which decrease the absorption in the terminal ileum by decreasing the levels of available Ca+2.

TREATMENT OF PERNICIOUS ANEMIA / B12 DEFICIENCY

- Monitoring thyroid function and DM, due to the risk to develop other autoimmune conditions if not found.
- Hemolytic markers: High LDH and Indirect Bilirubin and Haptoglobin and Reticulocyte count.
- Intramedullary Hemolysis: occur due to severe Vit B12 deficiency → Early destruction of Red cells in Bone marrow (apoptosis) since nucleic acid synthesis is affected.

No Blood Transfusion

Vit B12 IM injections daily 7-10 days. Then monthly lifelong.

Careful monitoring of response

Careful monitoring for thyroid function & DM

Response to Treatment

Reticulocytosis in 3-4days, peak 5-10 days
Rise in Hgb concentration within 10 days and normalization in 8-10 weeks as well as correction of MCV.
Fall of serum LDH levels within 2 days
Hypersegmented PMN disappear in 10-14 days
Watch closely for severe hypokalemia during early response.
Megaloblastic changes disappear within 2 days

Pernicious Anemia / Folate Deficincy

- Lab Findings:

1- Low Hemoglobin.

2- High MCV.

3- Normal WBC count.

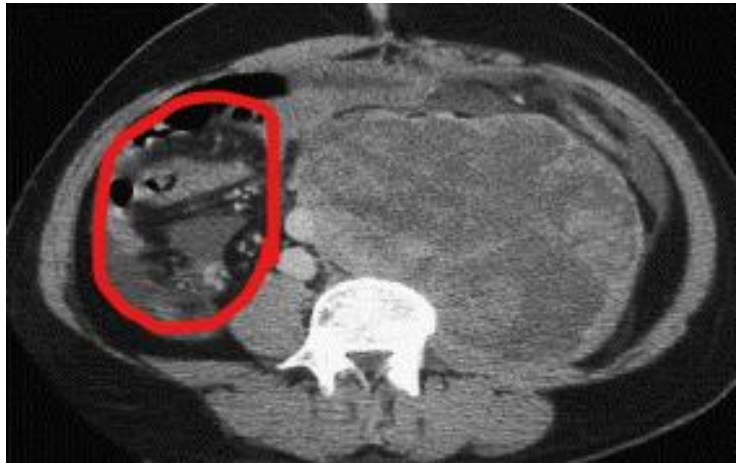
4- Slightly Low Platelets count.

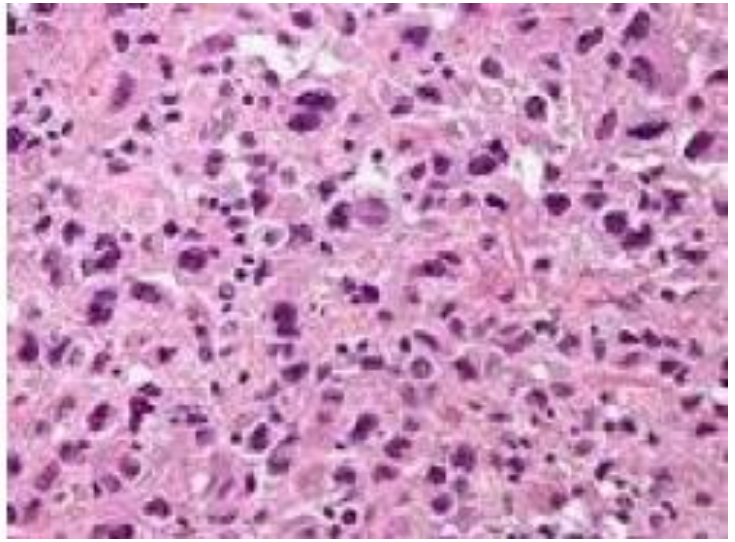
5- Low Serum Folate.

- Blood Smear:

Bone Marrow blood smear shows Megaloblasts (Large, abnormally formed RBCs) + Macro-ovalocytes and Hypersegmented neutrophils (>5 lobes).

ABDOMINAL CT OF A PATIENT WITH PERNICIOUS ANEMIA





- The patient presented with abdominal swelling, and the CT scan revealed a Retroperitoneal mass on the Rt side.
- On Biopsy, there was undifferentiated Soft tissue Sarcoma (indicating increased demand for Vit B12 due to increased production of cells).

Causes of Folic acid deficiency

1. Inadequate intake

- diet lacking fresh, uncook food; chronic alcoholism, total parenteral nutrition,

2. Malabsorption

- small bowel disease (sprue, celiac disease,)
- alcoholism

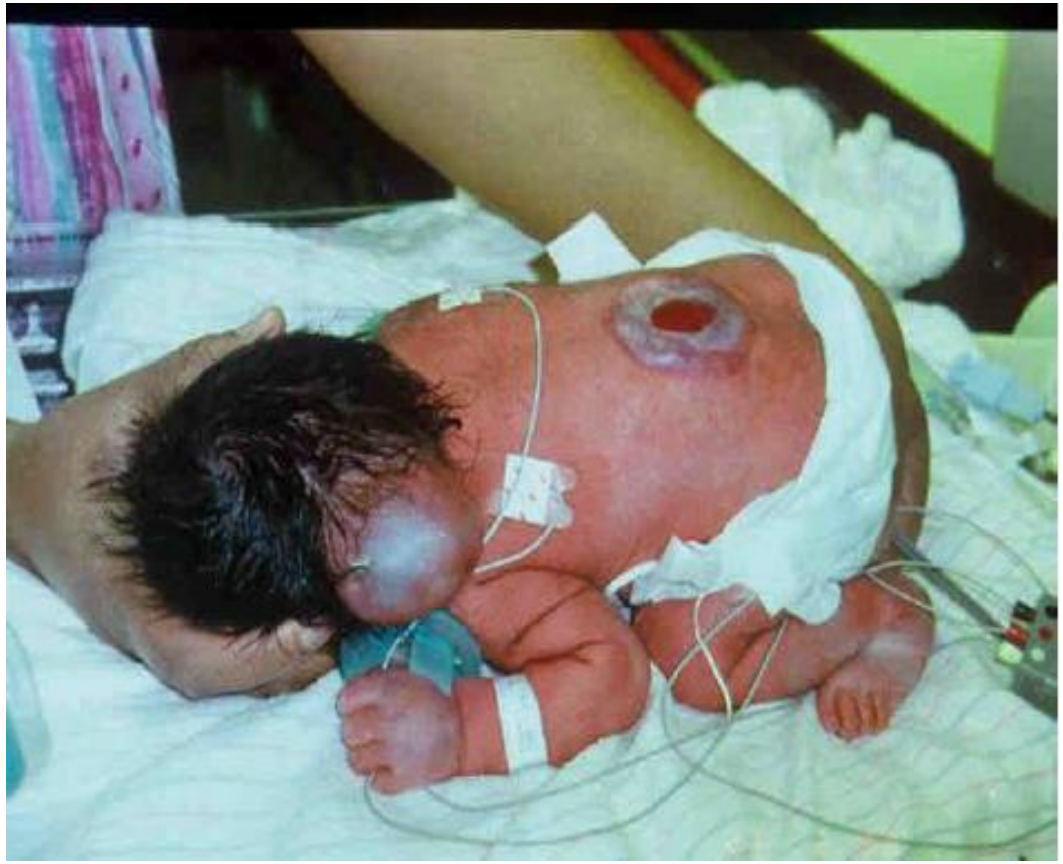
3. Increased requirements:

- pregnancy and lactation
- infancy
- chronic hemolysis
- **malignancy**
- hemodialysis

4. Defective utilisation

Drugs:folate antagonists(methotrexate, trimethoprim, triamteren), purine analogs (azathioprine), primidine analogs (zidovudine), RNA reductase inhibitor (hydroxyurea), miscellaneous (phenytoin, N_2)

CAUSES OF FOLIC ACID DEFICIENCY



NEURAL TUBE DEFECT

- Folic acid has a role in neural tube closure in fetus, a pregnant woman should have enough folate to protect her fetus from having Neural Tube Defects.

Case 2 B:
Treatment and follow-up

Treat the original Cause

Oral administration of folic 5 mg x2daily, for 3 months, and maintenance therapy if it is necessary.

Retics after 5-7 days.

Correction of anaemia after 2 months therapy.

TREATMENT AND FOLLOW-UP OF PERNICIOUS ANEMIA / FOLATE DEFICIENCY

- Always when you treat Folate Deficiency, make sure that Vit B12 isn't low.

Myelodysplastic Syndrome (MDS)

- A spectrum of Heterogenous malignant hematopoietic stem cells disorders (Clonal Hematopoietic proliferation of myeloid lineage) characterized by ineffective and dysplastic changes in bone marrow with Ineffective Hematopoiesis (dysmorphic cells in the blood) and Variable Cytopenia (frequent progression to AML).

- MDS may occur: 1- De novo: Primary MDS. 2- As a result of hematopoietic stem cell injury (Cytotoxic chemotherapy, Radiation, Previous Bone marrow disease – Myeloproliferative neoplasm, Polycythemia Vera, Essential thrombocytosis-): Secondary or Treatment-related MDS.

- Characterized by presence of Cytopenia and abnormal Bone marrow maturation feature (dysplastic feature).

- Hallmark: Pancytopenia + Dysplastic Feature + Macrocytosis + Megaloblastic Changes + Hypercellular Bone marrow.
- Associated with Higher Risk of Acute Myeloid Leukemia (AML).
- Lab Findings:

1- Low Hemoglobin.

2- High MCV.

3- Low WBC count.

4- Low Platelet count.

5- Low Corrected Reticulocyte count.

6- Normal LDH.

- Bone marrow biopsy: Ringed Sideroblasts (iron deposition around erythroblasts), Excess Blasts (Hypercellular).
- Cytogenetics: reveals FISH 11 q deletion.

PATHOGENESIS OF MDS

Pathogenesis

Poorly understood
Clonal process, thought to arise from single hematopoietic progenitor cell that acquired multiple mutations
Global hypomethylation with concomitant hypermethylation of gene-promoter regions.
Mutation in genes that encode enzymes, such as TET2, IDH1, IDH2
As role for immunosuppressive agents, suggest immune system implicated in myelosuppression and/or marrow hypocellularity

CLINICAL FEATURES IN MDS

- Leukopenia / Neutropenia → increased risk of infection.
- Thrombocytopenia → may cause bleeding.
- Dysplastic features of all lineages → bone marrow respond by increase production leading to hypercellular abnormally looking cells.
- Acute myeloid Leukemia in >20 %

Clinical features in MDS

- Anaemia
  - > 80% of patients with MDS are anaemic at diagnosis
  - Granulocytopenia
  - 50–70% of patients
  - predisposition for infections
- Thrombocytopenia in 30% of patients
- In MDS
  - chronically low Hb levels associated with cardiac remodelling and increased incidence of heart failure

Hemolytic Anemia

- Hemolysis means RBCs destruction → Shortened RBC survival with or without Anemia.
- Classification:

1- By sites of RBCs destruction: Intravascular (within vessels) Vs Extravascular (in the reticuloendothelial system) Vs Mixed (but one predominate).

2- Acquired (immune, Non-immune) Vs Congenital (Membrane defects: Hereditary Spherocytosis (HS) / Enzymopathies: G6PD deficiency, Pyruvate Kinase (PV) deficiency / Hemoglobinopathies: Thalassemia, Sickle cell disease.)

3- By mechanism of Red cell damage.

- Lab Findings:

1- Low Hemoglobin.

2- Slightly high WBC count.

3- Normal Platelet count.

4- High Corrected Reticulocyte count.

5- High LDH (increased in all cases of hemolysis).

6- High Indirect (unconjugated) Bilirubin

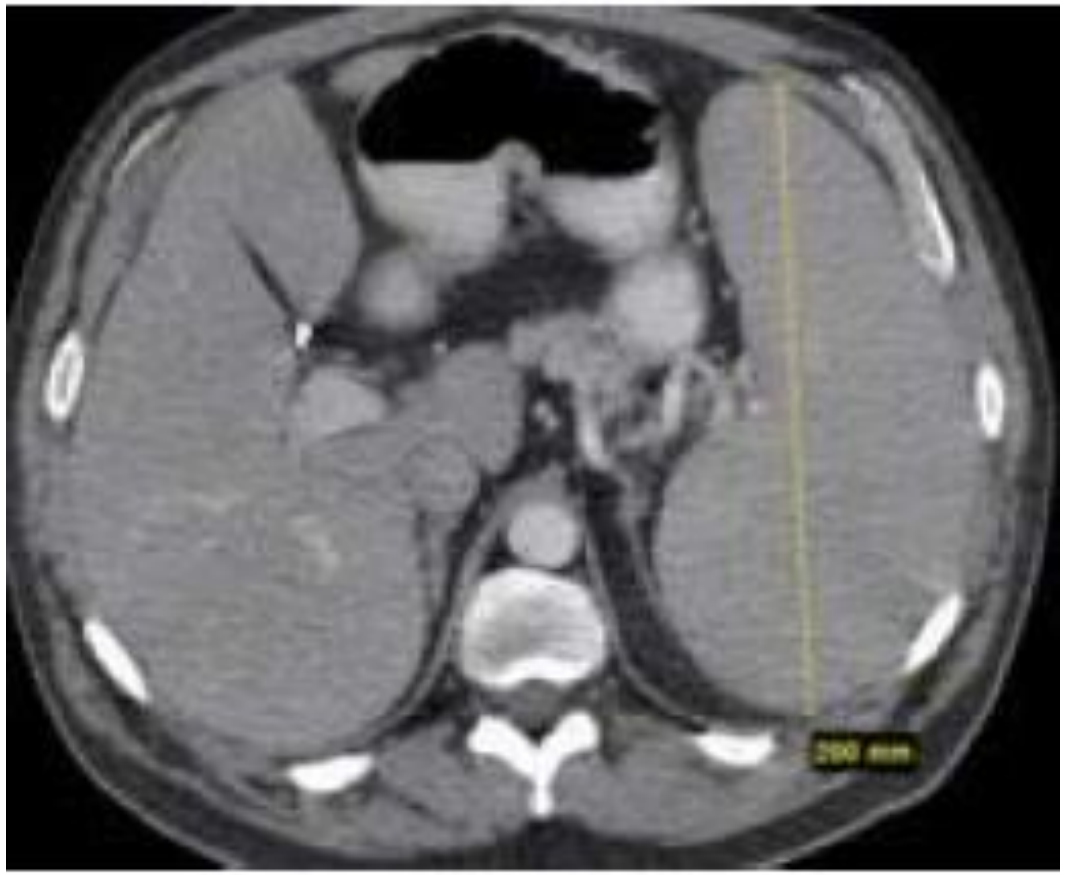
7- High Direct Bilirubin

- Blood Film: Spherocytosis (Rounded Spherical Shaped Red cells – not biconcave disk shape-) + Polychromasia (some RBCs appear bluish-gray when they're stained with a particular type of dye → indicating immature RBCs)
- The diagnosis is proven by Positive Coombs test (Direct Agglutination test DAT): Antibody directed against RBCs which decreases the life-span of RBCs

JAUNDICE

- One of the clinical features of Hemolytic Anemia.
- Other Clinical Features include:

1- Anemia Syndrome: SOB + Palpitations + Tachypnea.
2- Dark Urine (tea-colored or red): indicates intravascular hemolysis.
3- Patients may have chronic ankle ulcers.
4- Aplastic Crises associated with Parvovirus B19 (in the case of chronic hemolysis).
5- Increased requirement for Folate.

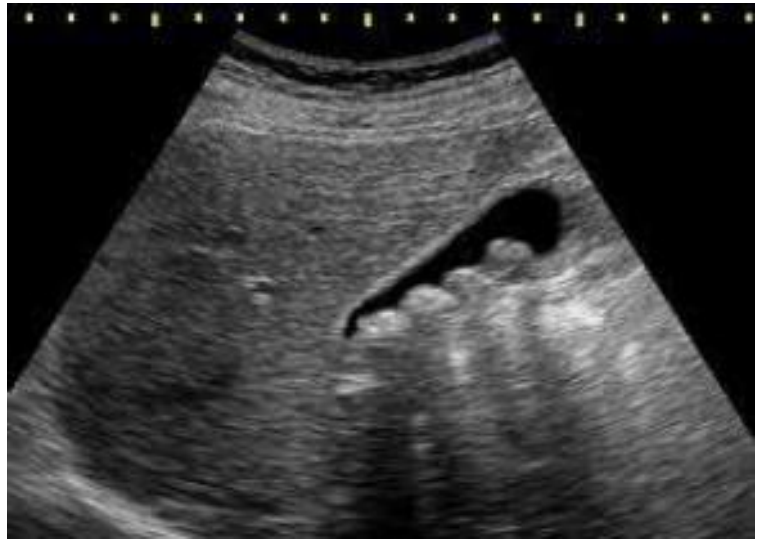


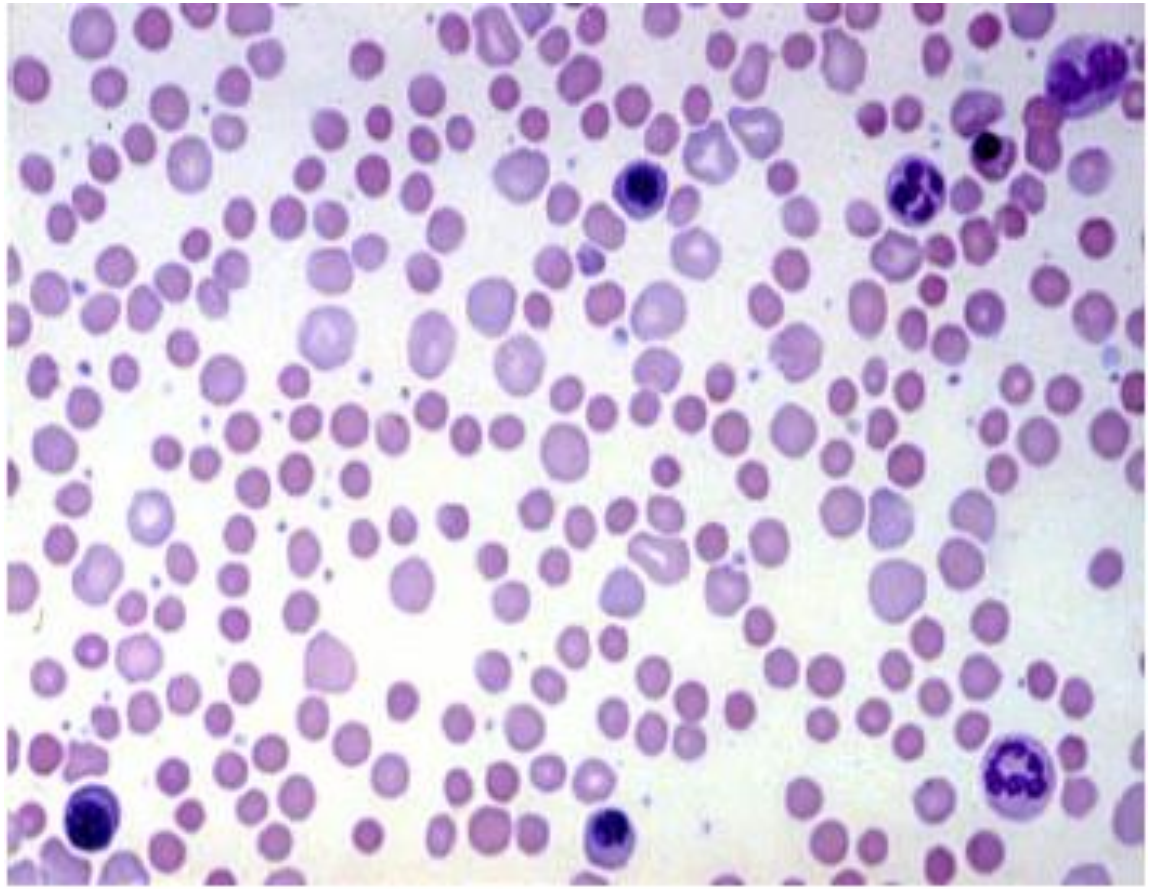
SPLENOMEGALY

- A CT scan showing Splenomegaly which is one of the clinical Features of Hemolytic Anemia

GALLBLADDER BILIRUBIN STONES

- The first image is an Abdominal Ultrasound Showing Gallbladder Bilirubin stones (biliary/pigmented) → indicating Extravascular Hemolysis.



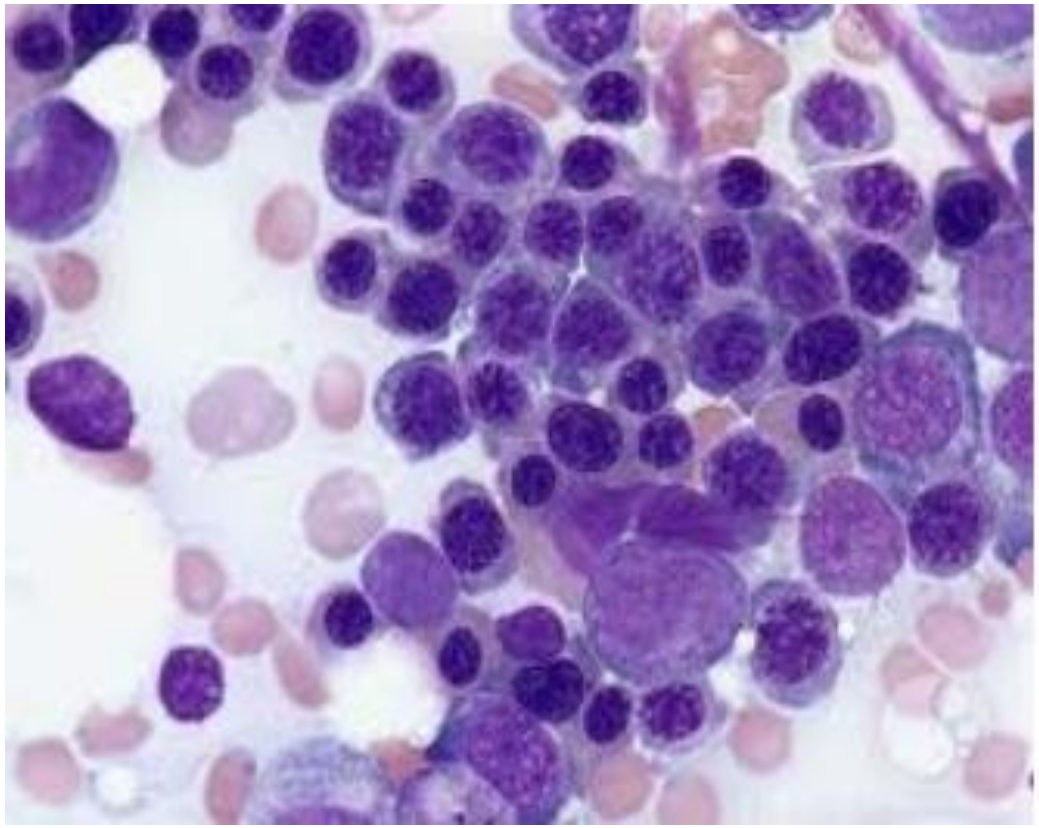


HEMOLYTIC ANEMIA

- A blood film showing Spherocytosis which are rounded spherical shaped RBCs (not biconcave disk shaped) indicating Hemolytic Anemia.

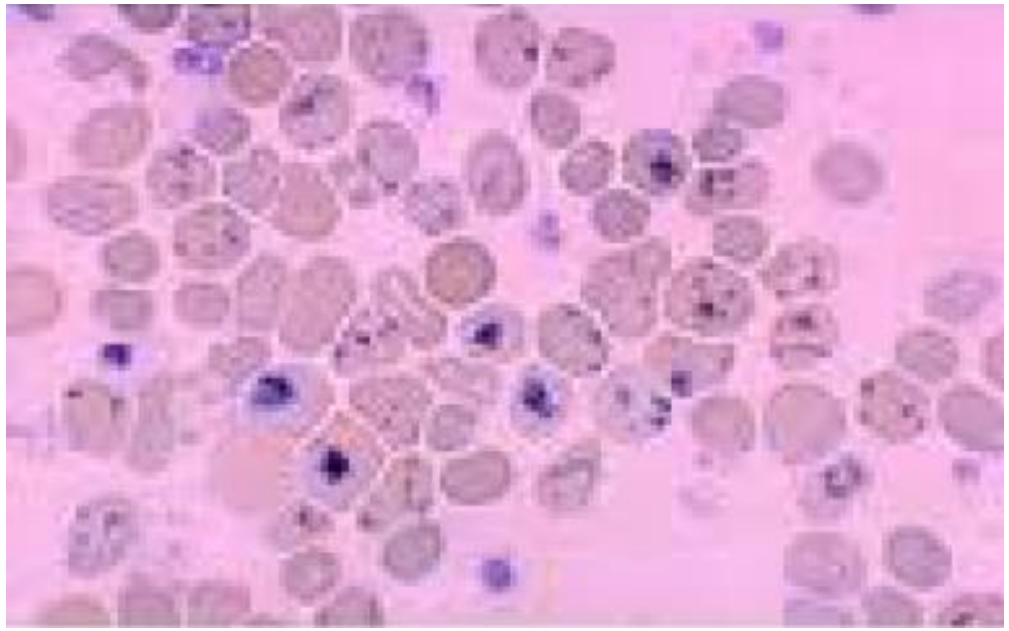
HEMOLYTIC ANEMIA

- Blood Smear from the Bone marrow, it shows Erythroid Hyperplasia with Megaloblastic Changes (due to Distressed Erythropoiesis).



HEMOLYTIC ANEMIA

- Blood Smear showing Polychromasia with Supravital Stain (indicating immature RBCs).
- One of the Features of Hemolytic Anemia.



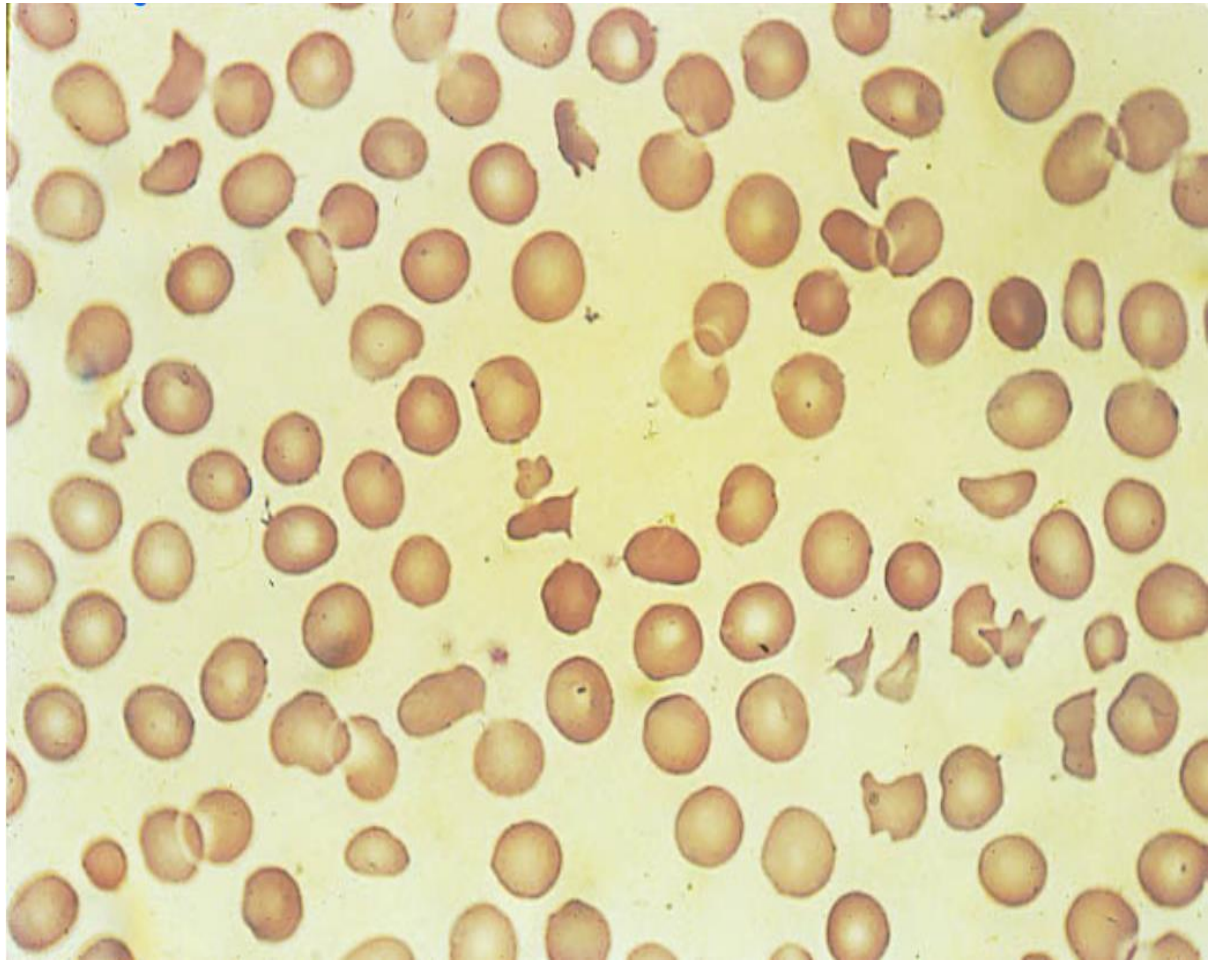
Notes on Hemolytic Anemia

If there is no Bone marrow Disease, then it's able to compensate and increase the production of RBCs.

Otherwise, there will be Non-compensated Hemolysis, since it's severe enough to cause Anemia, Reticulocytosis, Positive Hemolytic Markers (LDH, Unconjugated Bilirubin), Spherocytosis, and Polychromasia.

Anemia develop due to significant shortening of RBC life-span.

Hemolytic Anemia with intravascular Hemolysis (Acquired): 1- Mechanical Damage (Microangiopathic hemolytic anemia (Shistocytosis) due to mechanical heart valve, DIC, TTP). 2- Chemical Damage (Burns, Cytotoxin, Snake venom). 3- Infection (Malaria, Babesiosis). 4- Transfusion Reaction (ABO incompatibility).



SCHISTOCYTES

- This Blood Smear shows Fragmented RBCs, suggestive of RBC injury from damaged endothelium.
- A characteristic of Microangiopathic Hemolytic Anemia.
- It also shows some Polychromasia.

Differential Diagnosis of Microangiopathic Hemolytic Anemia

- Thrombotic thrombocytopenic purpura (TTP)
- Hemolytic uremic syndrome (HUS)
- Disseminated intravascular coagulation (DIC)
- Vasculitis
- Malignant hypertension
- Metastatic neoplasm with vascular invasion
- Preeclampsia/HELLP syndrome of pregnancy

DDX OF MICROANGIOPATHIC HEMOLYTIC ANEMIA

Treatment of Autoimmune Hemolytic Anemia (Warm Antibody type)

- Treat underlying disease if indicated

- Prednisone (1 mg/kg/day for two weeks, then taper)
- Splenectomy ??
- Other
  - Immunosuppressive agents
  - IVIG

TREATMENT OF AUTOIMMUNE HEMOLYTIC ANEMIA

- Prednisone is corticosteroid (immunosuppressive) → be cautious since high doses are used.

Aplastic Anemia

- A severe, Life-threatening syndrome in which production of Erythrocytes, WBCs, and Platelets has failed.
- It may occur in all age groups and in both genders.
- Characterized by Peripheral Pancytopenia and accompanied by a Hypocellular Bone marrow.
- The primary defect is a reduction in or depletion of hematopoietic precursor stem cells with decreased production of all cell lines (this may be due to Quantitative or Qualitative damage to the Pluripotential Stem cells, or in rare instances as a result of abnormal hormonal stimulation of stem cell proliferation, or the result of defective bone marrow microenvironment, or from cellular of humoral immunosuppression of hematopoiesis).
- Pathology: Dysregulation of T-cell hemostasis leading to hematopoietic stem cell injury → so treat by T-cell inhibition.
- When Anemia Syndrome (SOB, Palpitation, and Tachypnea) is seen with Fever and Early bruising → Think of Leukopenia and Thrombocytopenia (Pancytopenia).
- Fever with Pancytopenia → indicate the possibility of Neutropenic Fever (Medical Emergency).

Aplastic Anemia

Lab Findings:

1- Low Hemoglobin.

2- Low WBC count (Low Neutrophils Percentage, High Lymphocytes Percentage).

3- Low Corrected Reticulocyte count (**this is important to differentiate whether Pancytopenia is due to Bone marrow failure – low reticulocyte count- or due to peripheral destruction – High count-**).

4- High MCV (due to distressed erythropoiesis – the more premature red cells are, the larger their sizes-).

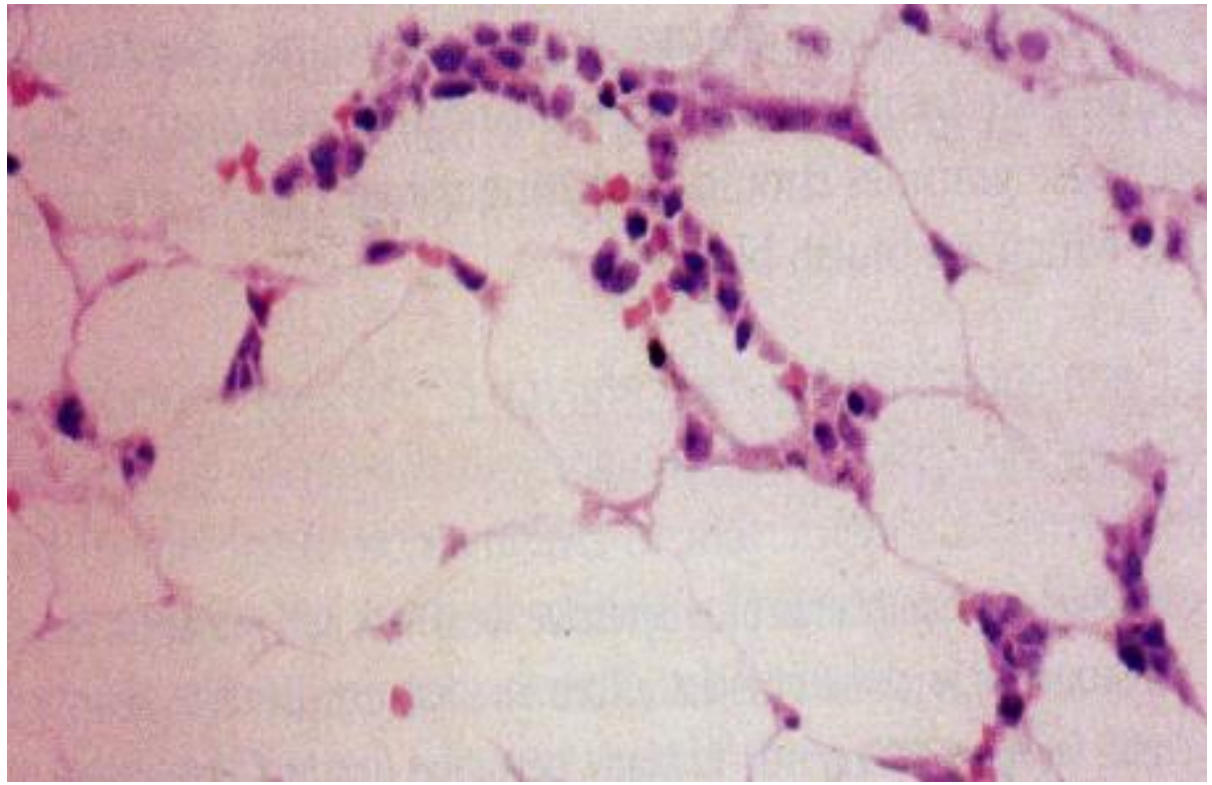
5- Low Platelet count (severe thrombocytopenia (<50K) which may cause spontaneous bleeding without challenge).

Bone marrow biopsy in Aplastic Anemia

- This biopsy shows Hypocellular Bone marrow + Hematopoiesis areas are Scant → indicating Bone marrow Failure (on lab tests there will be low corrected reticulocyte count).
- Causes of Bone marrow failure:

1- Acquired: Idiopathic, Paroxysmal nocturnal Hemoglobinuria (PNH), Secondary to Drugs, Radiation, and Viruses (Hepatitis).

2- Inherited (Symptoms at early age with family history): Fanconi Anemia, Diamond-Blackfan Anemia, Short Telomere length syndrome.



CLINICAL FEATURES OF APLASTIC ANEMIA

- Bleeding is the most common symptom

Clinical manifestations of AA

- »Anemia syndrome
- »Neutropenia syndrome
- »Thrombocytopenia syndrome
- »Combination of the above

Presenting Symptoms of Aplastic Anemia

Symptoms	Number of Patients
Bleeding	41
Anemia	27
Bleeding and anemia	14
Bleeding and infection	6
Infection	5
Routine examination	8
Total	101

CLASSIFICATION OF APLASTIC ANEMIA

- Classified based on Bone marrow cellularity and severity of peripheral neutropenia or cytopenia.
- Treatment depends on the classification.

Classification of aplastic anemia

Classification	Criteria
Severe	BM cellularity < 25% (or < 50% if < 30% of BM is hematopoietic cells) AND ≥ 2 of the following: • Peripheral blood neutrophil count < 0.5×10^9/L • Peripheral blood platelet count < 20×10^9/L • Peripheral blood reticulocyte count < 20×10^9/L
Very severe	As above, but peripheral blood neutrophil count must be < 0.2×10^9/L
Nonsevere	Hypocellular BM with peripheral blood values not meeting criteria for severe aplastic anemia

TREATMENT OF APLASTIC ANEMIA

Treatment of AA

» Remove causative agent, if known

» Supportive care

- RBC transfusions
- Treat infections
- Treat Bleeding

» **Bone marrow transplant**

» Immune suppression

- _ CSA
- _ ATG

Combination of the above

DISORDERS RELATED TO APLASTIC ANEMIA

1- Disorders in which there is peripheral pancytopenia, but the bone marrow is normocellular, hypercellular, or infiltrated with abnormal cellular elements (Myelopthesic anemia)

– replacement of bone marrow by fibrotic, granulomatous, or neoplastic cells

2- Pure red Cell aplasia

3- Myelodysplastic syndrome (MDS)

G6PD Deficiency

- The most common enzyme defect in RBCs leading to congenital Hemolysis.
- Hemolysis here is periodic and dependent on the type of stress found, so cell become less prone to tolerate the oxidative stress due to lacking quantitative / functional defect in G6PD (more than 150 mutations for G6PD leading to loss of function).
- The disease is most common in areas of Malaria.
- Pentose Phosphate Pathway: important to generate reduced NADPH, which is important for the regeneration of Glutathione to protect cells from O2 species.
- Due to the Inability to form glutathione, Stress Hemolysis starts as a result of certain triggers.
- Common precipitating factors: 1- Drugs (Primaquine, Methylene blue, Nalidixic acid, Sulpha drugs, Pyridium). 2- Infections. 3- Diabetic Ketoacidosis. 4- Favism: hemolysis after exposure to Fava Beans, occurs in G6PD Med Variant.
- The disease changes from completely asymptomatic to severe intravascular hemolysis upon exposure to oxidant stress.
- X-linked disease, affecting Males mainly.

CLINICAL SYNDROME OF G6PD DEFICIENCY

- The disease presents with acute periodic attacks of Hemolysis secondary to triggers.
- There is a need to resuscitate / support the patient by treating the underlying infection or dehydration, also blood transfusion + IV hydration + Observation.

1- **Neonatal Jaundice**: severe/ Kernicterus /, 1-3 day after birth.

2- **Favism**: acute intravascular Hemolysis after exposure to broad bean (Vicia fava), the offending agent is divicine, it produces free Oxygen radicals on autoxidation.

3-**Infection** which promote the formation of H_2O_2 following oxygen burst in neutrophils and macrophage may result in hemolysis

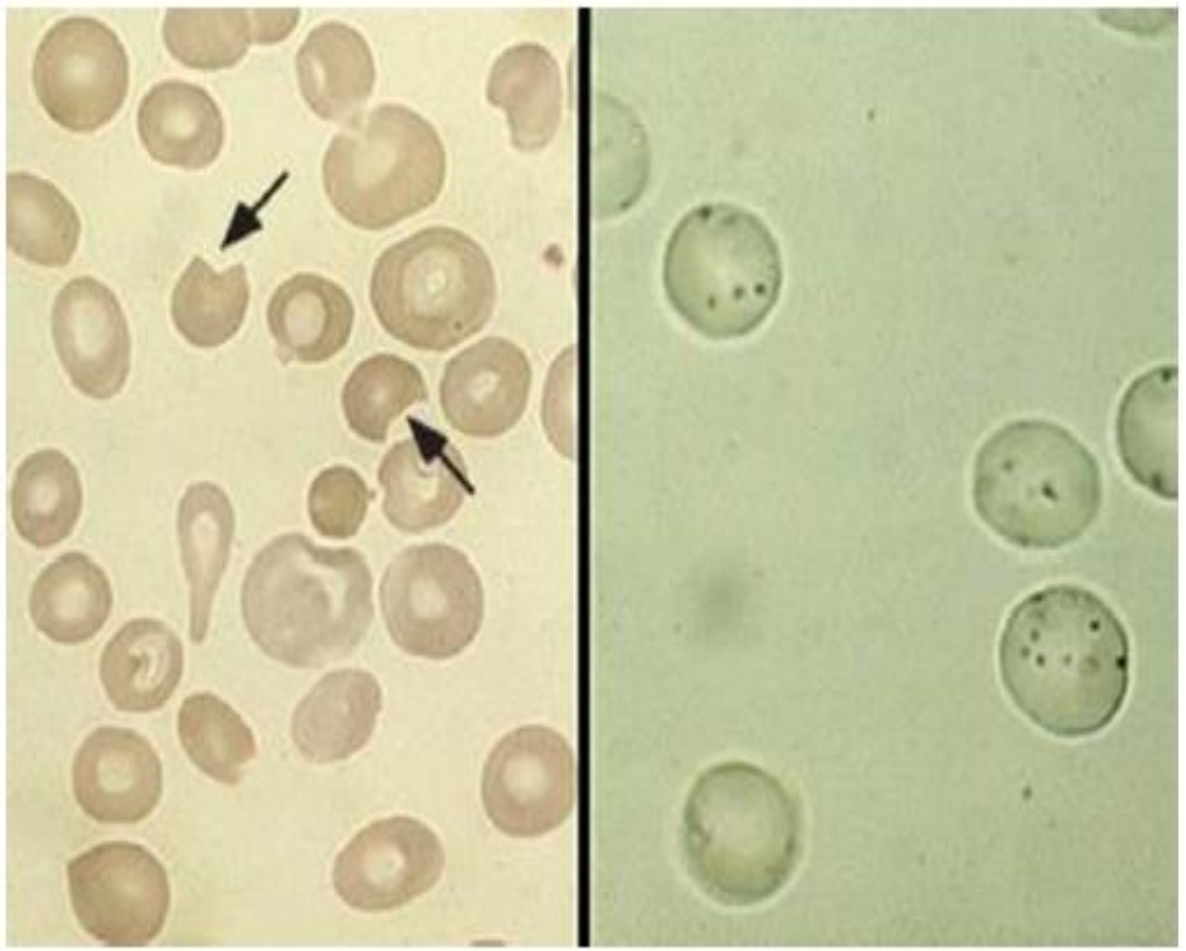
4- **Drug induced hemolysis**

DARK URINE (TEA-COLORED OR RED)

- Indicates Intravascular Hemolysis and Hemoglobinuria.
- Seen in Hemolytic Anemia (G6PD Deficiency).

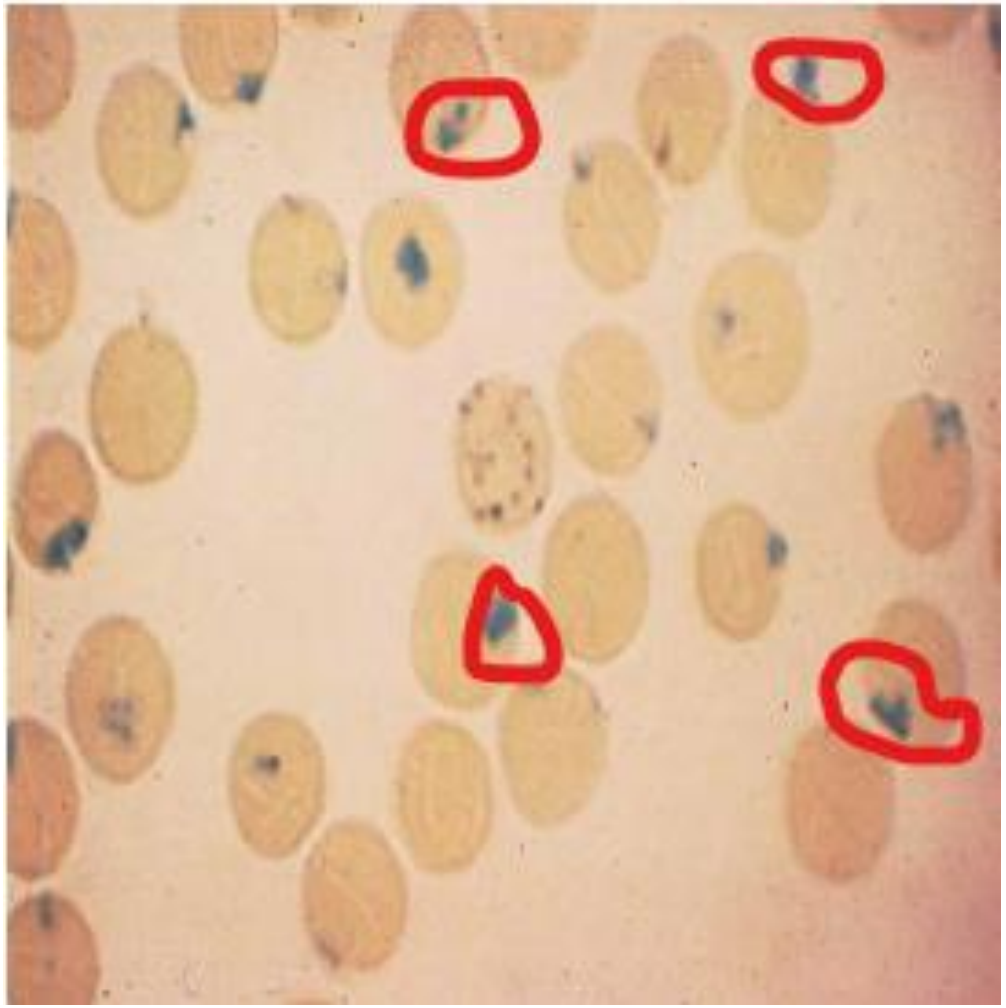
BITE CELLS

- Blood film showing abnormal RBCs- Bite Cells- (abnormally shaped mature RBCs with one or more semicircular portions removed from the cell margin).
- Seen in G6PD deficiency (Hemolytic Anemia).



HEINZ BODIES

- Clumps of damaged Hemoglobin attached to RBCs.
- They’re indicative of oxidative injury to erythrocytes.
- Seen in G6PD deficiency (Hemolytic Anemia) with Supravital stain.



TREATMENT OF G6PD DEFICIENCY

- Screen for the disease by testing G6PD activity.
- Don't test G6PD levels during acute hemolysis since it may give normal false value due to fresh immature RBC that has a more active enzyme than the older cells, so test enzyme levels only during steady states between attacks.
- G6PD deficiency is either Extravascular or Intravascular presentation (Mixed).

Therapy

- Avoid precipitating factors.
- Blood transfusion in severe hemolysis.
- Maintenance of good urine output during hemolytic episodes
- Folic acid.
- Exchange transfusion in newborn

Hereditary Spherocytosis

Autosomal Dominant disease.

Loss of the outer layer of RBCs with conservation of volume, thus forming Spherical shaped cells.

Caused by 1- Partial deficiency of Spectrin. 2- Combined deficiency of Spectrin and Ankyrin. 3- Molecular Defects (Mutations of Ankyrin – most common- , Mutations of Band 3 protein, Mutations of Protein 4.2).

Due to the loss of membrane elasticity in red cells by the vertical interaction between cytoskeleton and Lipid bilayer found in RBCs due to mutation in Ankyrin, Spectrin, Band 3/4, leading to different degree of deficiency in Alpha and Beta Spectrin, thus leading to loss of ability of RBCs to be elastic and squeezed, so now it can't move through tight places leading to increased risk of hemolysis.

Treatment of Choice: Splenectomy.

Sickle Cell Disease

More common in African population due to infection of malaria with trait (one copy of abnormal gene), so the consequence of infection is less severe, but mortality rate is high in case of 2 abnormal gene.

Inherited as Autosomal Recessive disease.

Caused by point mutation in beta globin gene (B6 Glu → Val).

Clinical Effects:

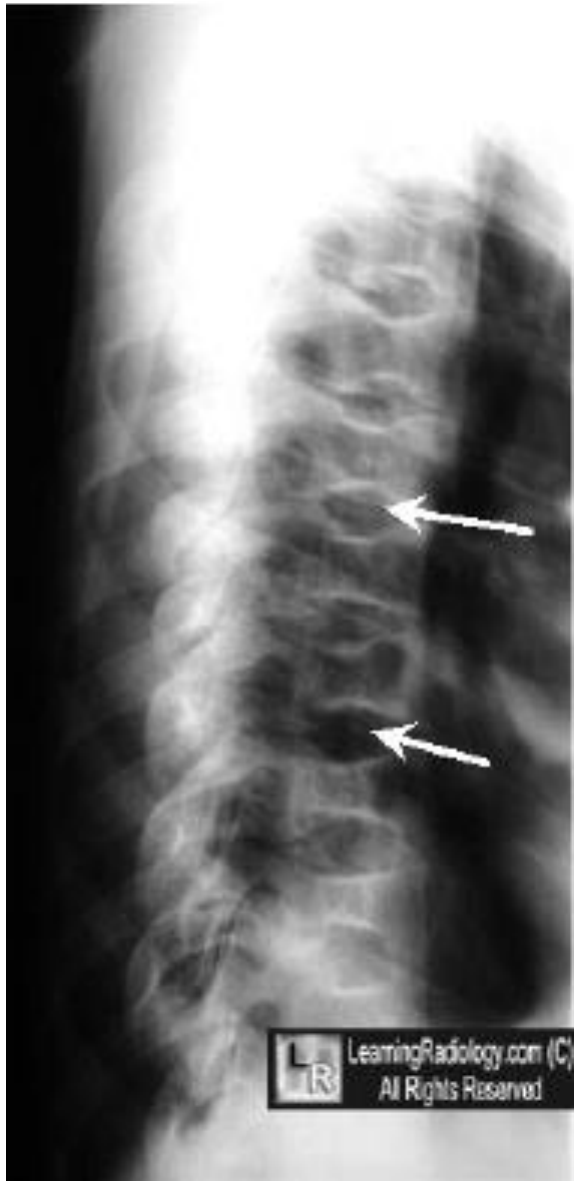
1- Chronic Hemolytic Anemia (Gallstones –bilirubin-, Risk of Red cell aplasia (Parvovirus), Decreased vascular tone).

2- Susceptible to infection (Functional Asplenia, Infarcted Tissue, Numerous manipulations).

3- Vaso-occlusion.

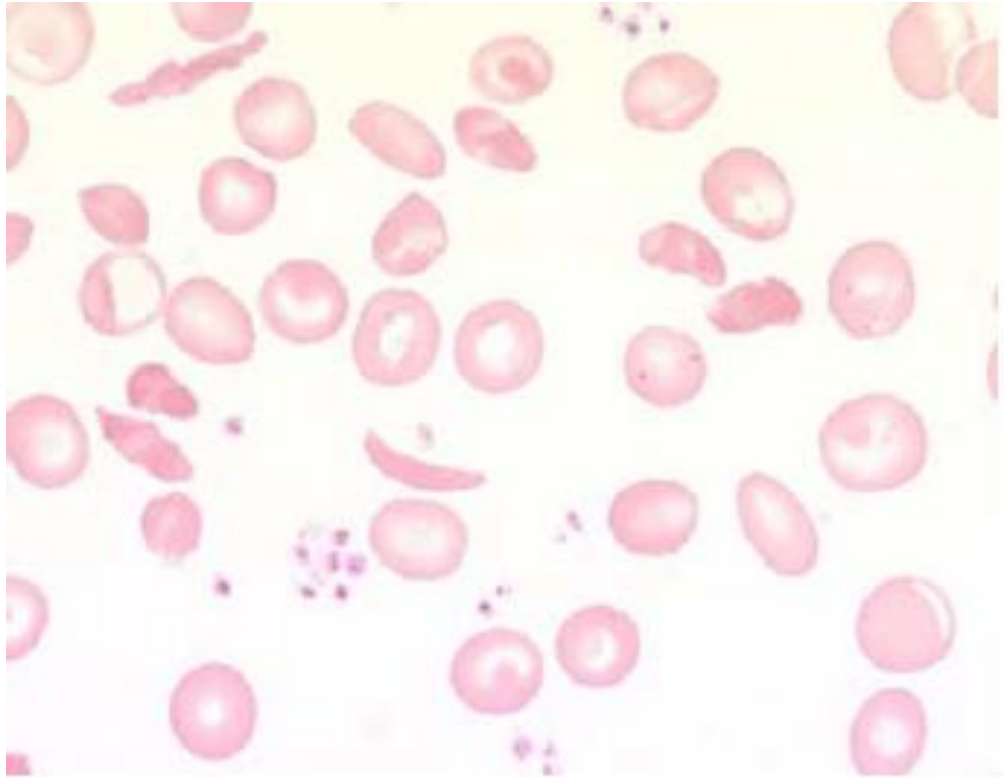
SICKLE CELL DISEASE / X-RAY FINDINGS

- Degeneration of Spinal column.
- You may also find Vascular necrosis in the hips.
- One of the clinical features of Sickle cell anemia (because defected cells got trapped in small blood vessels leading to blockage and necrosis).

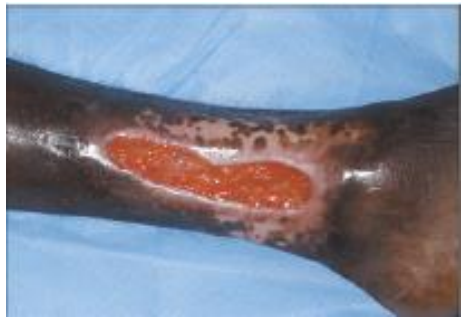


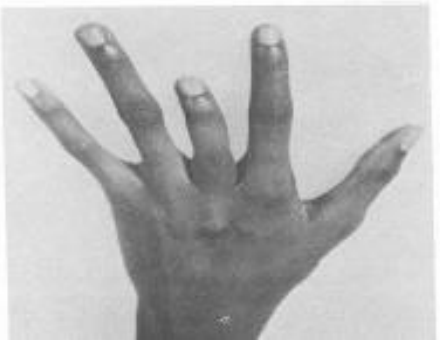
SICKLE CELL ANEMIA

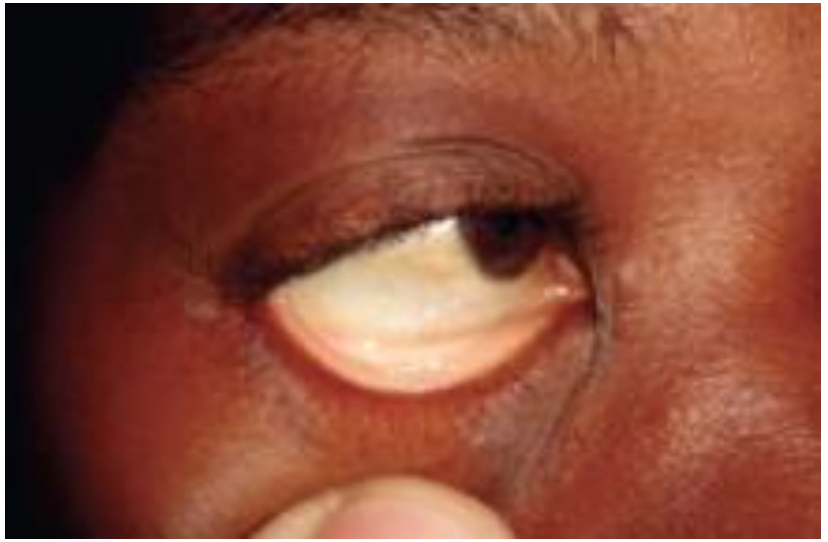
- Blood smear of a patient with Sickle cell disease, showing Sickle shaped cells.



CLINICAL FEATURES OF SICKLE CELL DISEASE



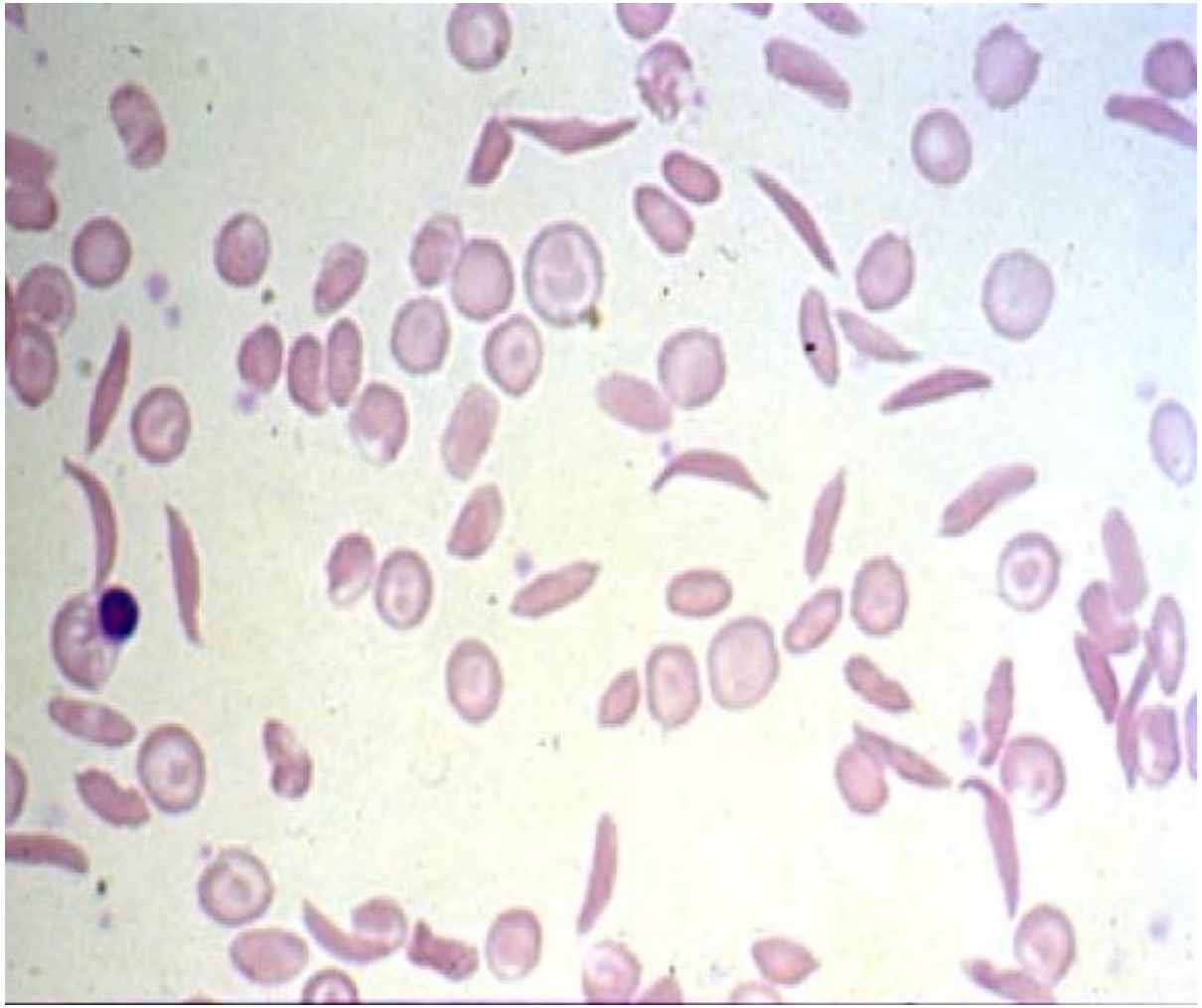




- The first image → Venous Ulcer.
- The second image → Dactylitis.
- The third image → Conjunctival pallor.

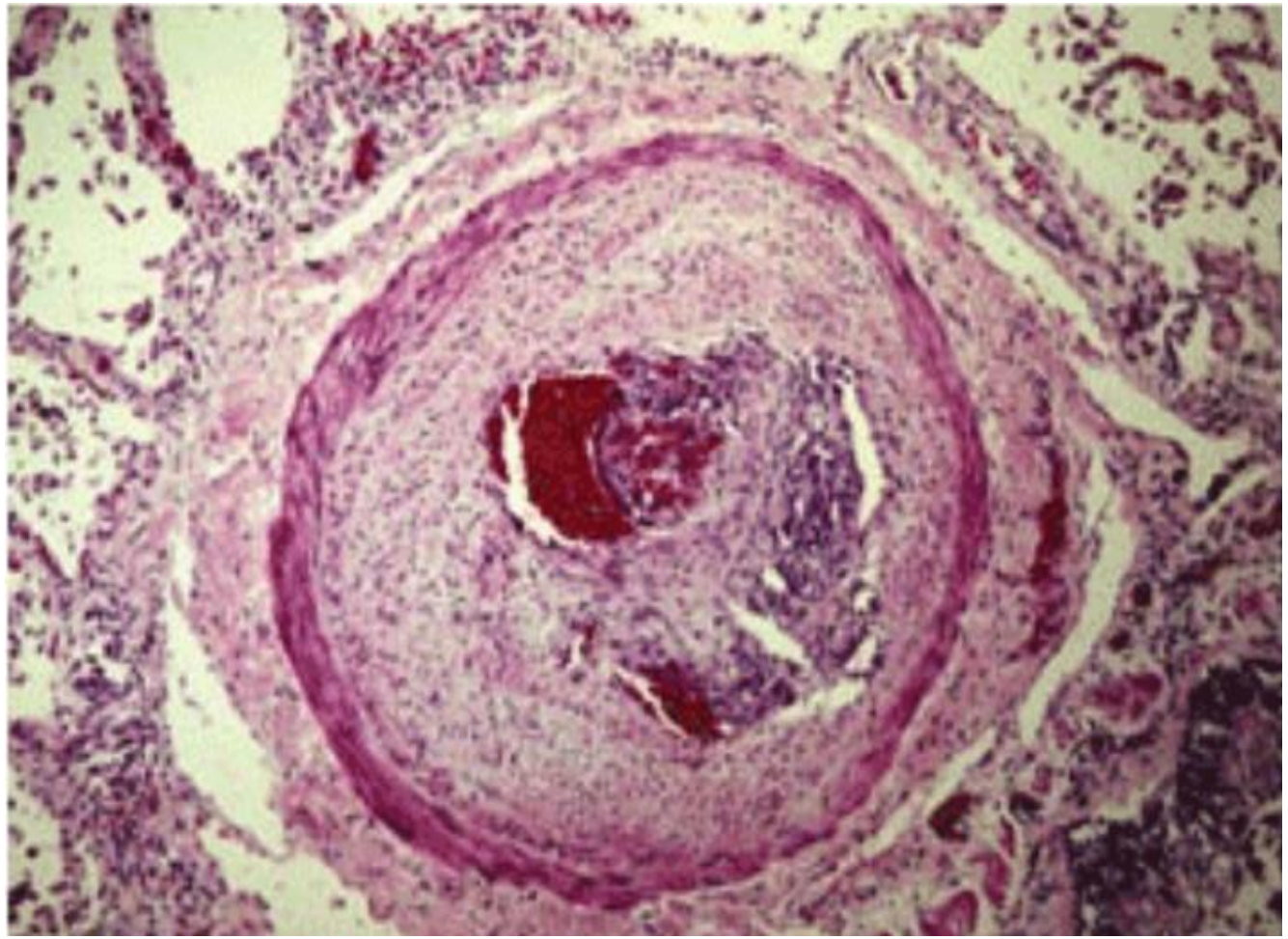
Blood Smear / Sickle Cell Disease

- Hemoglobin S induce membrane damage to RBCs leading to Ca+2 inflow and leading to cross link of membrane protein which activates channels that allow efflux of K+ and water leading to RBC dehydration and eventually sickling which occurs due to deoxygenation or tissue hypoxia.
- It may cause Vaso-occlusive crises if RBCs are obstructing and reducing blood flow to vital organs, leading to Ischemia, Necrosis, Pain, and repeated episodes in bone leads to infarction and necrosis and eventually Dactylitis (long bones are more affected).
- It may also cause Acute Chest Syndrome due to Sickling of Pulmonary vessels which is a medical emergency of sickle cell leading Acute chest syndrome, Hypoxia and lung damage, and infiltrate.
  - Stroke in brain.
  - Fat PE.
  - MI.
- Sequestration of the spleen (reducing spleen size and function causing Autosplenectomy / Afunctional splenia, thus increasing the risk of getting infected with encapsulated bacterial organisms like H.Influenza, N.Meningitidis, and Strep.Pneumonia.)



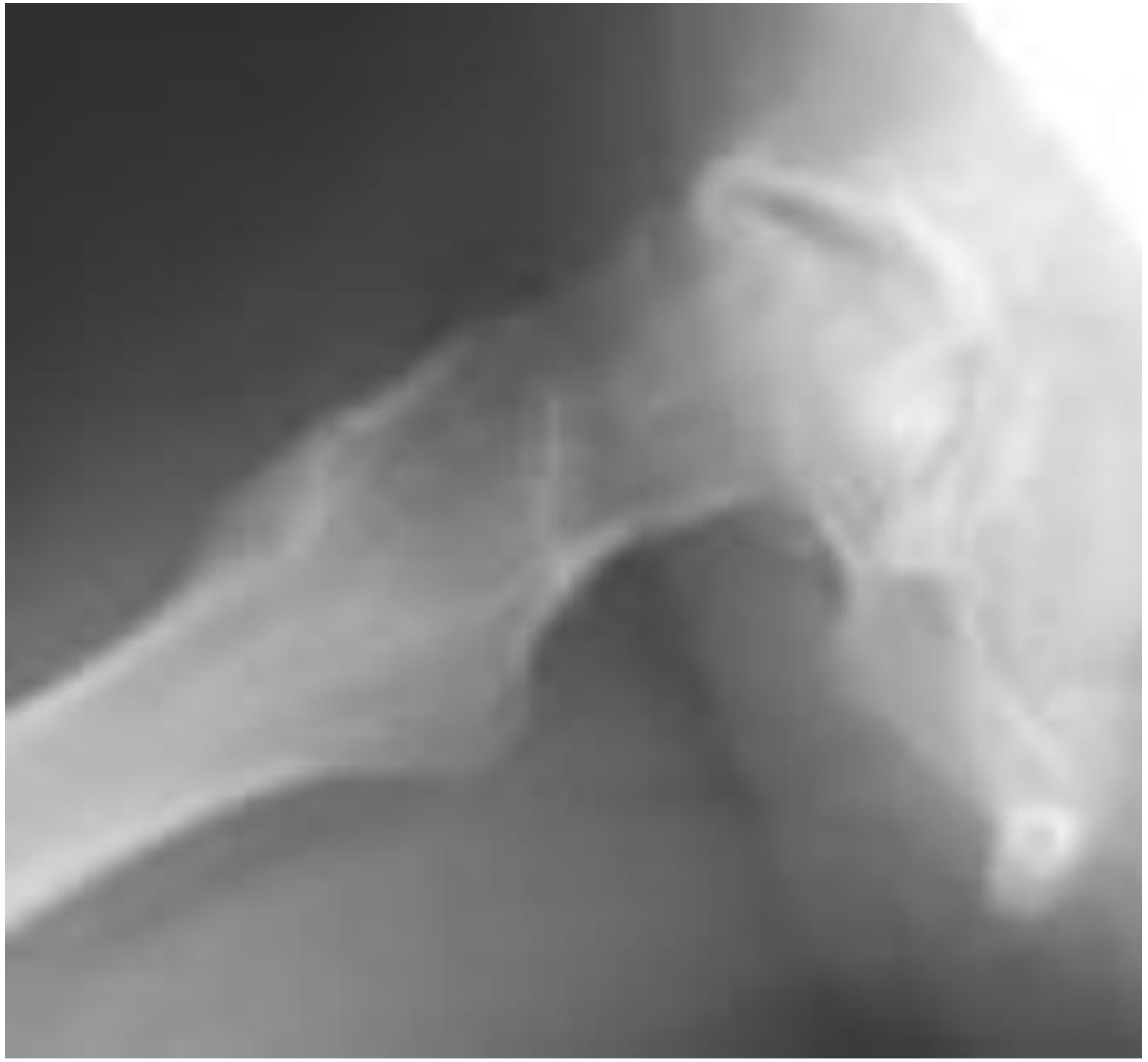
END-STAGE VASCULAR LUNG DISEASE

- Seen in Vaso-occlusive crises of Sickle Cell Disease.



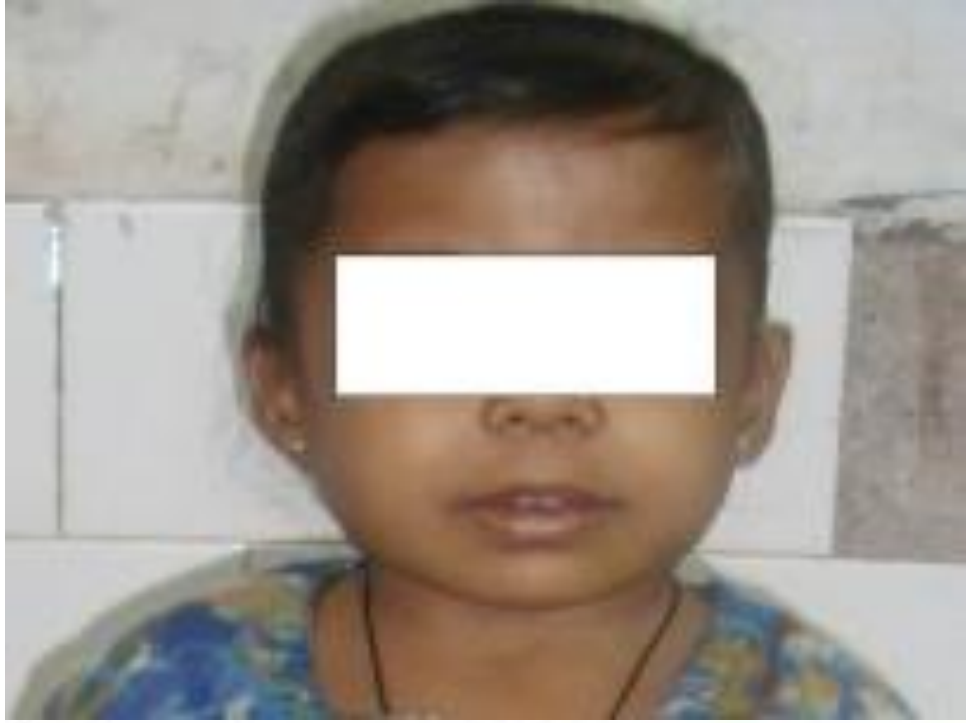
AVASCULAR NECROSIS OF THE HIP

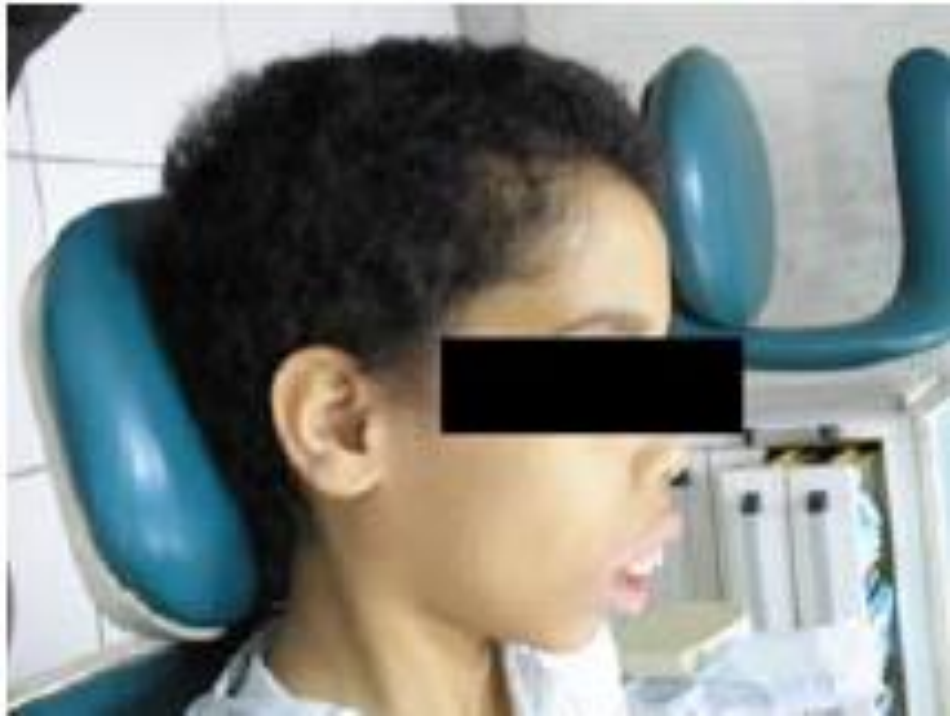
- Seen in Vaso-occlusive crises of Sickle Cell Disease.



CLINICAL FEATURES OF THALASSEMIA

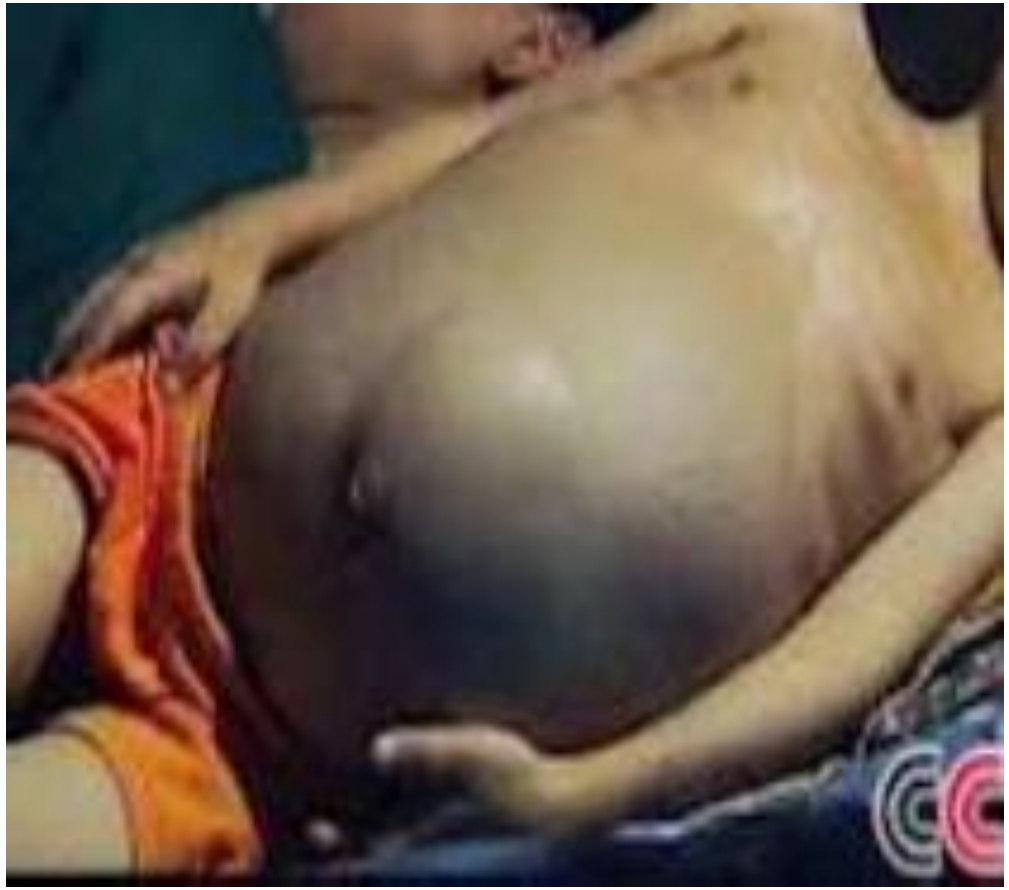
- The first figure shows Expansion of Hematopoiesis into the facial bones (Chipmunk Facies), due to massive Erythroid Hyperplasia.
- The second figure Shows Maxillary Prominence.





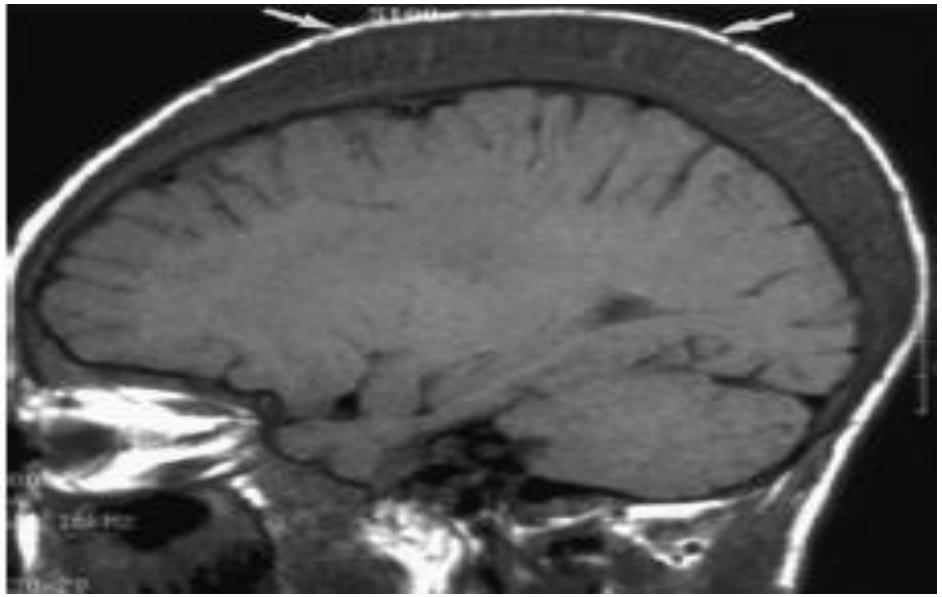
HEPATOSPLENOMEGALY IN THALASSEMIA

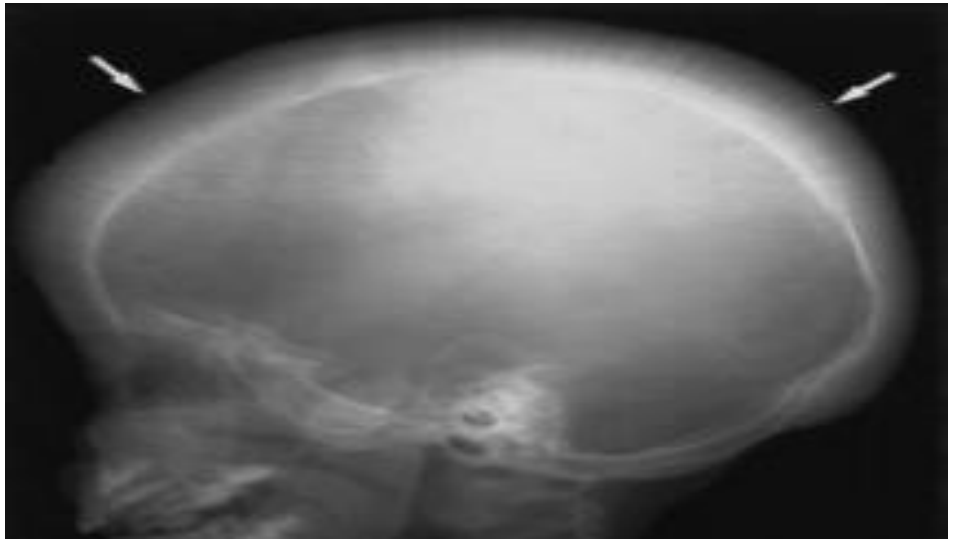
- Due to Extramedullary Hematopoiesis (formation of blood cells in organs outside of the bone marrow).



CREWCUT APPEARANCE IN THALASSEMIA

- Massive erythroid hyperplasia causing Expansion of Hematopoiesis into the skull and Reactive bone formation, leading to this appearance.





BLEEDING DISORDERS

Hemophilia A

- Inherited bleeding disorder, caused by deficiency in Coagulation Factor VIII.
- X-linked inheritance (more common in males).
- Severity is based on factor level / factor activity:

1- <1% → Severe → Spontaneous bleeding (requires treatment on regular basis).

2- 1-5% →Moderate → Bleeding with mild injury.

3- 5-25% → Mild → Bleeding with surgery or trauma.

- If Factor VIII turned out to be normal, we suspect Factor XI deficiency.
- Lab Findings:

1- Normal PT (prothrombin time).

2- Increased PTT (partial thromboplastin time).

3- Increased Mixing time.

4- Normal TT (Thrombin time).

5- Normal Platelets count.

6- Normal Bleeding Time.

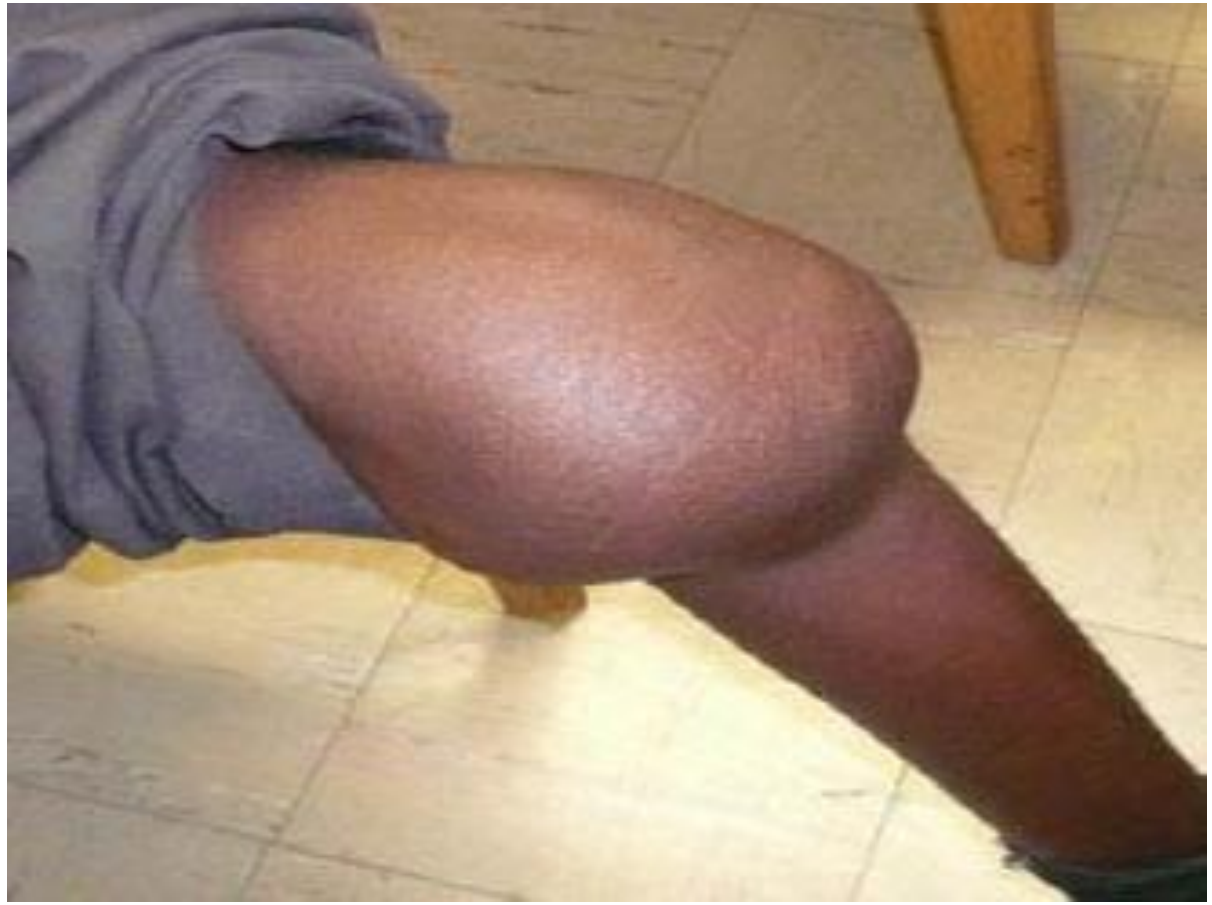
7- Low Factor VIII levels.

8- Normal Factor IX levels

⋆ When we donate normal plasma, PTT becomes normal (increased mixing time indicates Factor VIII deficiency)

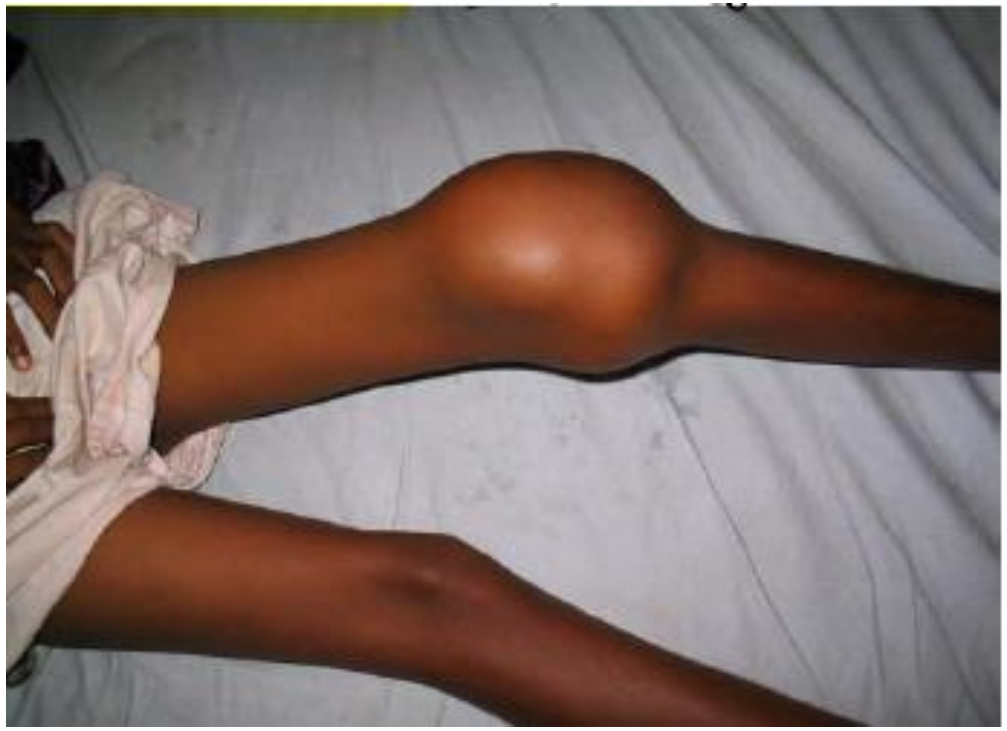
Hemarthrosis

- Bleeding into a joint and is an important cause of monoarticular joint pain and swelling.
- Mostly in knees in dependent limb, as well as other weight bearing joints including Ankle, Hip and Elbow.
    - It's a Feature of Hemophilia A.
    - Other clinical features include Recurrent episodes of destruction / inflammation in synovial tissue leading to continuous episodes of irritation of synovial structures → Destructive arthropathy, and Repeated attacks of bleeding (Enlarged joints + Painful swelling).
- Associated with: Male Sex (most commonly), Longstanding History (congenital), and Family history from maternal side.



DESTRUCTIVE ARTHROPATHY

- Recurrent episodes of destruction / inflammation in synovial tissue leading to continuous episodes of irritation of synovial structures.
- Seen in Hemophilia A.
- Treated by Raising Factor VIII levels (recombinant).



Management and follow-up for Hemophilia A

- We treat acute attacks with factor VIII TWICE daily because it has Short half-life (frequency depends on the T ½ of the product used).
- We must know the patient's weight and desired level, to indicate the baseline level and the target.
- Bleeding in large joints require Factor VIII to be 80% of the normal level for Surgery to be done (so in the case of destructive arthropathy consider Synovectomy or Joint replacement).
- Give prophylaxis after treating acute bleeding, give it regularly to keep the factor levels about 100% to prevent spontaneous bleeding in severe cases.
- Screen for inhibitors twice yearly, due to the risk of developing inhibitors in hemophilia which is a common complication

1- Treat acute attack: FVIII* 30u/kg/ IV q 12 hrs x 2 days, then daily until it subsides. + Analgesics.

2- Evaluate for ? Synovectomy (chemical or radio-isotope or surgical).Or Joint replacement.

3- Consider for long term prophylaxis 20u/kg x 2 per week indefinitely.

4- Education/ rehabilitation

5- genetic counseling.

6- Family screening and registration

7- Screen for inhibitors x 2 per yr since therapy is different.

***FVIII: recombinant or ?plasma derived**

A-Factor Replacement

1- On demand/hospital based

2- On demand/home based

3- Prophylactic/ home/ intermittent X 2 per week

B-Treatment of target joint

C- Physiotherapy/rehabilitation

D-Genetic counseling

E- Education

TREATMENT OF MODERATE / SEVERE HEMOPHILIA

- Factor replacement → to treat bleeding episode, then we give prophylaxis.
- Primary Vs Secondary Prophylaxis:

Primary prophylaxis → before any bleeding episodes,
Secondary prophylaxis → after the first or second episode to prevent subsequent episodes.

- **Formation of inhibitors** (antibodies)
  - 10-15% of severe hemophilia A patients
  - 1-2% of severe hemophilia B patients
- **Viral infections/ Transmissible disease (Plasma Derived)**

-Hepatitis B	-Human parvovirus
-Hepatitis C	-Hepatitis A
-HIV	-Others (Prion disease or BSE)

COMPLICATION OF HEMOPHILIA THERAPY

- Inhibitors: Factor specific neutralizing antibodies, they're more common in Hemophilia A, and they make treatment more difficult since it neutralizes the factor.
- Viral infections are common if we're using plasma derived factors for treatment.

vonWillebrands disease Type 1

- The most common Inherited bleeding disorder, characterized by primary hemostatic defect resulting in platelets dysfunction.
- Congenital primary hemostatic defect → mucocutaneous bleeding.
- Deficiency in VWF.
- Patients present with epistaxis, gum bleeding, and prolonged bleeding from wounds.
- Positive family history from paternal side with similar phenotypes.
- Impaired platelet aggregation to ristocetin indicates VWF deficiency.
- Factor VIII will be slightly low as well because it's stabilized by VWF so when VWF is deficient, factor VIII is low too but not low enough to cause clinical picture of hemophilia.
- Lab findings:

1- Low Hemoglobin.

2- High WBC count.

3- Normal Platelet count.

4- Normal PT.

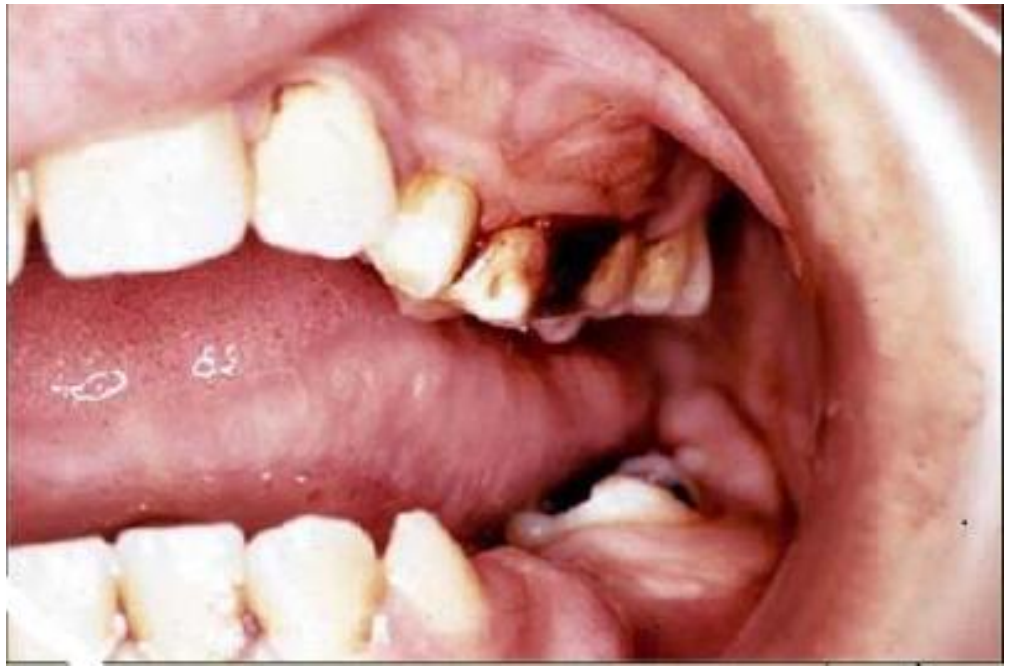
5- Slightly Elevated PTT (because factor VIII is low).

6- Normal TT.

7- Prolonged Bleeding time

GUM BLEEDING

- Indicative of VWD.



MANAGEMENT OF VWD

1- Cryoprecipitate 1 bag/ per 10 kg body weight x 2 day for 3-4 days then daily for 3 more days.

2- Dental consultation/ mouth hygiene & care.

3-Education and counseling.

4- Screening of family.

5- ?? DDAVP for therapy of mild bleeding

- Cryoprecipitate is very rich in VWF.
- Desmopressin is used when the disease is accompanied by other quantitative disorders.

CLINICAL FEATURES OF VWD

- von Willebrand factor
  - Synthesis in endothelium and megakaryocytes
  - Forms large multimer
  - Carrier of factor VIII
  - Anchors platelets to subendothelium
  - Bridge between platelets

  Von Willebrand Disease
- Inheritance - autosomal dominant
- Incidence - 1/10,000
- Clinical features - mucocutaneous bleeding, prolonged bleeding from wounds/cuts

Laboratory evaluation of von Willebrand disease

Classification

- Type 1 — Partial quantitative deficiency
- Type 2 — Qualitative deficiency
- Type 3 — Total quantitative deficiency

Diagnostic tests:

Von Willebrand type Assay	1	2	3
vWF antigen	⇓	Normal	⇓⇓
vWF activity	⇓	⇓	⇓⇓
Multimer analysis	Normal	Normal?abnormal	Absent

LABORATORY EVALUATION OF VWD

- Type 1 (autosomal dominant) and 3 (autosomal recessive with complete deficiency) are accompanied by quantitative deficiencies.
- In Type 2, Antigen quantity is normal.
- vWF antigen → Quantitative measure.
- vWF activity → Qualitative measure.

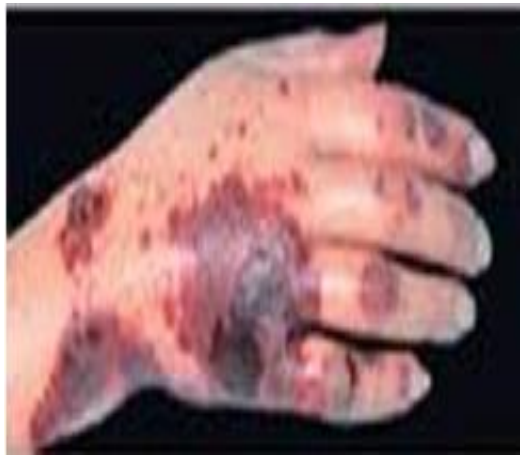
Disseminated Intravascular Coagulation (DIC)

- Acquired bleeding disorder, caused by exaggerated generation of fibrin leading to consumption of coagulation factors and microvascular thrombi in various organs, associated with various organ damage and dysfunction and sometimes arterial or venous thrombosis (uncontrolled activation of coagulation system leading to consumption of platelets and clotting factors).
- Bleeding from puncture sites and bruising is a characteristic of DIC.
- Patients present Febrile (High temperature) + Hypotensive / in shock + Tachycardic.
- Lab Findings:

1- Low Hemoglobin (Hemolytic Anemia).
2- High Corrected Reticulocyte count.
3- High Bilirubin.
4- High WBC count (due to sepsis).
5- Low Platelet count (Thrombocytopenia).
6- High PT.
7- High PTT.
8- High TT.
9- Positive D-Dimer.
10- High Creatinine.
11- Low Fibrinogen.

CLINICAL FEATURES OF DIC

- A + B → Bruising.
- C → Conjunctival Hemorrhage.
- D → Petechial rash



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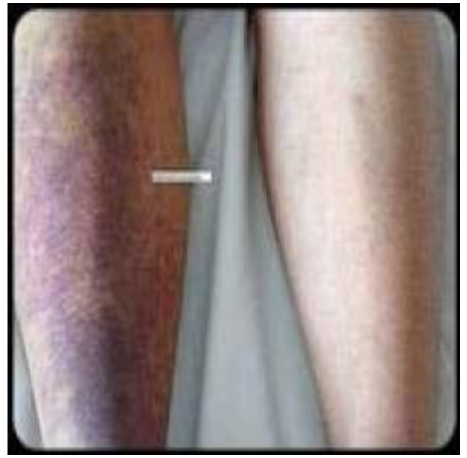

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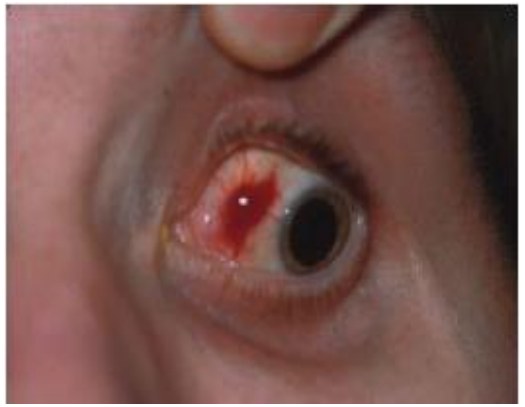

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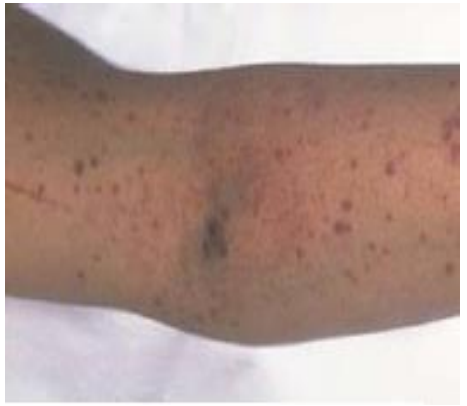
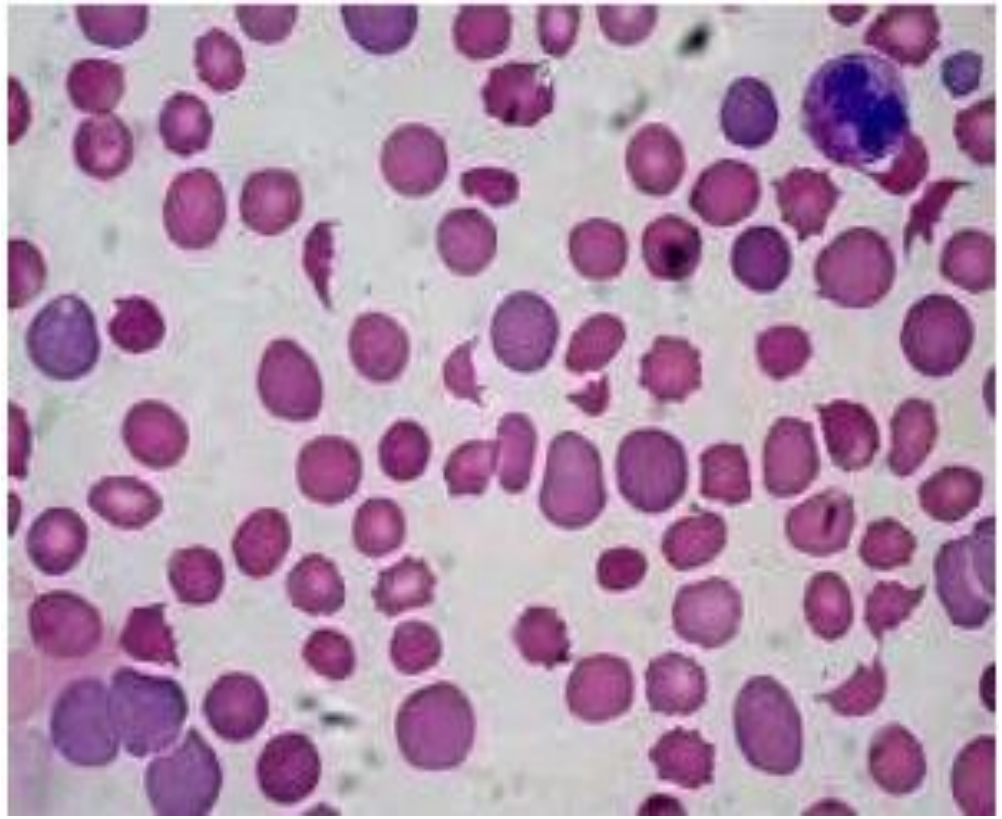


D

SHISTOCYTOSIS

- Fragmented RBCs.
- A Characteristic of DIC and Microangiopathic Hemolytic Anemia.



MANAGEMENT AND FOLLOW UP OF DIC

- We start with treatment of the underlying cause with broad spectrum antibiotics.
- Replace missing clotting factors with Fresh Frozen Plasma if the patient is bleeding ONLY, if not bleeding don't give FFP due to the risk of thrombus formation.
- Fresh Frozen Plasma only contains deficient clotting factors (doesn't contain platelets) so we need to give additional platelets and Vit K.

1- Treat vigorously with IV antibiotics after blood, urine culture and septic work-up

2- Hydrate and ensure adequate urine output

3- ? ICU care

4- Replace missing clotting factors: FFP 10 ml/kg frequency to be determined as needed

5-Plt replacement

6- Monitor PT, PTT, D-Dimer and fbgn, Plt count

7- Investigate cause of uro-sepsis.

8- TTP can easily be excluded.

TREATMENT APPROACHES TO DIC

- Treatment of underlying disorder
- Platelet transfusion
- Fresh frozen plasma
- Coagulation inhibitor concentrate (ATIII)

Glanzmann thrombasthenia (GT)

- Inherited condition of Platelet dysfunction, seen more in populations where there is high prevalence of consanguinity (autosomal recessive).
- Characterized by absent Platelet aggregation to all agonists except Ristocetin (since ristocetin mediates platelet function by another receptor (GP1b) thus inducing platelet aggregation even in GT).
- Confirm diagnosis by demonstrating GP by flowcytometry.
- Patients present with Pallor, Abdominal Pain, and Gum bleeding (long standing – congenital-).
- Congenital Platelet disorder → Platelet qualitative defect.
- Lab Findings:

1- Low Hemoglobin.

2- Low MCV.

3- Normal Corrected Reticulocyte count.

4- High WBC count.

5- Normal Platelet count.

6- Normal PT, PTT, TT.

7- Prolonged Bleeding time (consistent with primary hemolytic disorder).

8- Normal vWF.

9- Absent or Impaired Clot reaction (a measure of the function of Fibrin and its interaction with platelets).

10- Absent or Reduced Platelet Fibrinogen.

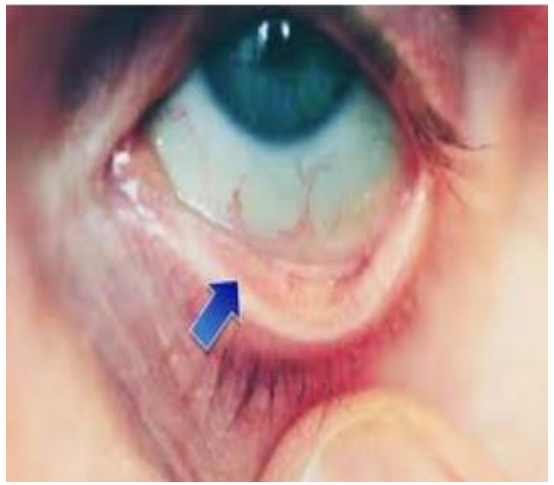
11- Absent or Reduced GPIIB-IIIa

- Non-Specific screening tests is a non-specific suggestive of primary hemostatic defect: prolonged bleeding time + Normal PT, PTT, TT → could be vWD or GT
- Changes of iron deficiency are seen due to bleeding for long time.

CLINICAL FEATURES OF GT

- A → Conjunctival Pallor.
- B → Gum Bleeding (lifelong mucosal bleeding).
- C → Bruising.
- Other Clinical Manifestations:

1- Prolonged bleeding from cuts / wounds.
2- Ovarian Bleeding.
3- Critical Bleeding.



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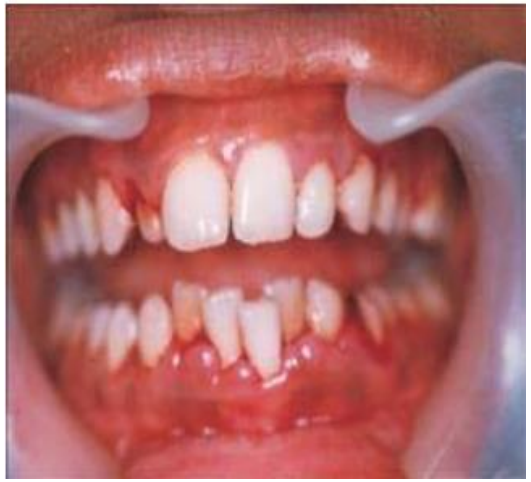

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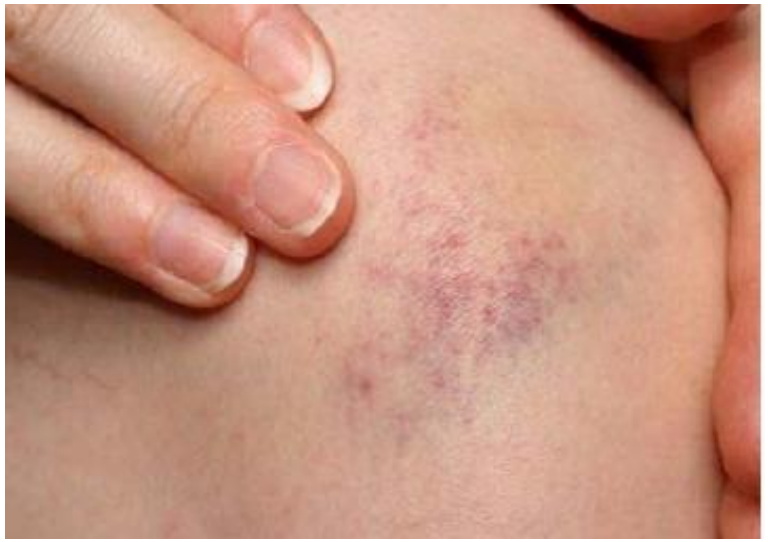

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Management and follow up for GT

- Blood Transfusion: since the patient is severely Anemic due to bleeding, so always start with blood transfusion.
- IV Tranexamic acid: Anti fibrinolytic agent to stabilize the clot (used in the case of Platelet dysfunction and Hemophilia).
- For platelet transfusion, we give functional platelets from a donor.
- Platelet transfusion is associated with alloantibodies formation and decrease platelets response, so first we need to test for these antibodies, and we give platelets only if antibodies are negative.
- If antibodies are positive, we use recombinant Factor VIIa.

1- Bld TX: Packed RBC or washed RBC

2- Local dental measures

3- Iv Tranexemic acid (Cyclokapron) 1g X3 daily 3-4 days

4- Symptomatic for the ovarian cyst

5- If bleeding is not controlled: Plt TX if antibodies are -ve, if antibodies are +ve, use recombinant factor VIIa (Novoseven) 150-200µg/kg iv hr: 0, 3 and 8hrly until bleeding stops.

7- Long term contraceptives.

6- Education and counseling.

Immue Thrombocytopenic Purpura (ITP)

- An immune disorder in which platelets become coated with antibodies against certain antigens on platelet membrane, resulting in splenic destruction and phagocytosis.
  - Normal platelet lifespan is 7-10 days → in ITP it's significantly shorter.
  - Bone marrow Megakaryopoiesis will compensate.
- Low platelet count in peripheral blood but they're larger in size than usual since they are released prematurely into the circulation.
  - Treated with immunosuppression using Steroids.
  - Patients present with Purpuric skin rash, Bleeding, and easy bruising.
  - Lab findings:

1- Low Hemoglobin.

2- Normal WBC count.

3- Low Platelet count.

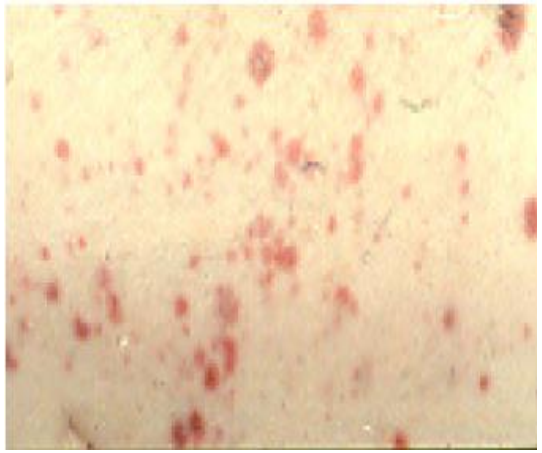
4- Normal PT, PTT, TT.

5- Negative Direct Antiglobulin Test (DAT).

- Check for other associated hematological / autoimmune diseases (Lupus, RA) / infection / liver disease.
- Summary: Low platelet count + Bleeding symptoms + No other suggestive symptoms + No splenomegaly + No lymphadenopathy + No systemic symptoms (Fever, Night Sweats, Weight Loss).

CLINICAL FEATURES OF ITP

- A → Thrombocytopenic Rash.
- B → Petechial rash in soft palate.
- C → Blood film showing no platelets.
- D → Bruises due to rupture of small veins.



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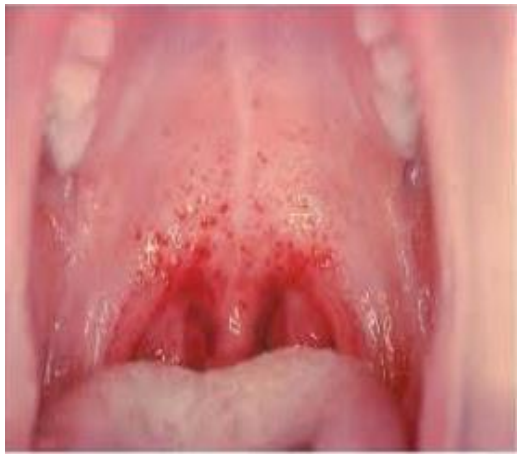

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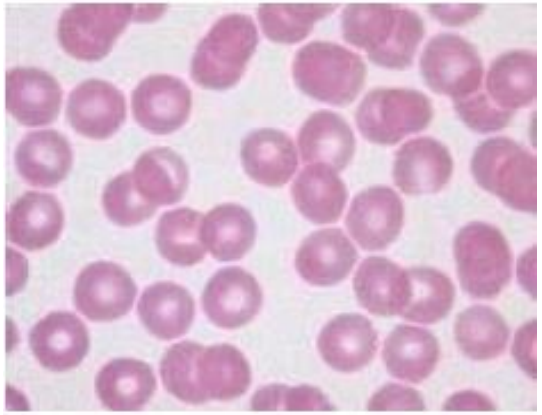

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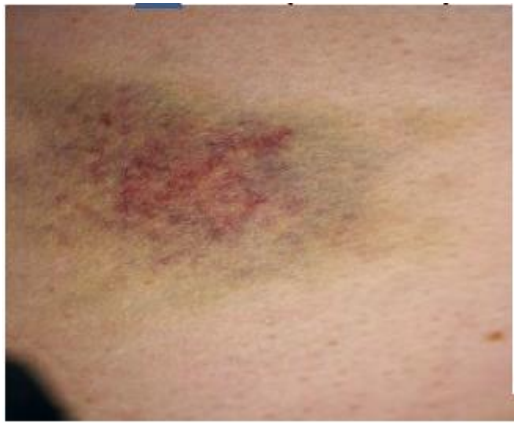

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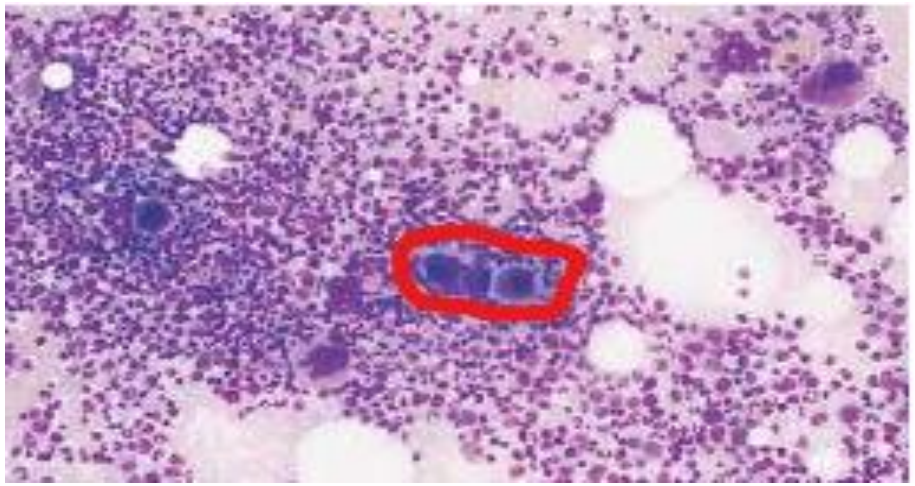
Bone Marrow Biopsy in ITP



- This Biopsy shows that Megakaryocytes are normal in term of quantity and quality → thus the low number of platelets is due to peripheral destruction rather than Bone marrow disorder.

MANAGEMENT AND FOLLOW UP OF ITP

- The first line treatment is oral prednisolone; we start with high doses for 2 weeks then we taper them off.

1- Start oral Prednisolone 1mg/kg daily.Aim at ± 4 wks, then taper. If no response or relapse: IVG, Other immune suppressors. New TPO agonists, ???splenectomy.

2- Follow up for additional immune disease (SLE, APS) or lympho-proliferative neoplasms.

3- Careful monitoring during pregnancy & delivery (post delivery care of the baby).

- Increased platelet destruction mediated by autoantibodies
- Auto-antibodies that react with major membrane glycoproteins can be identified in ~80% of patients

- Antibody concentrations diminish with effective treatment and increase with relapse
- Decreased production despite the increase in megakaryocytes in BM

PATHOGENESIS OF ITP

- Disease is diagnosed by exclusion with bone marrow test.
- Disease outcome differ according to age group:

1- Pediatric → Self limiting disease (Subclinical), no bleeding, treat only if symptomatic regardless of platelet count.

2- Adults → most patients don't recover completely, persistent ITP for 3 months.

Treatment of ITP

- Treat when Platelets count <30K.
- Treat Symptomatic Patients.
- Target higher platelet count based on patient's activity, like Field workers and military due to high risk of bleeding.
- Regarding treatment with steroids, we have 2 types of patients:

1- Steroid dependent: Patients respond initially then platelet count drop after you taper dose.

2- Steroid refractory: Patients don't respond to steroid.

★ Those patients account for 30-40% of all patients and we treat them with second line treatments like thrombopoietin receptor agonist (responsible for stimulating Megakaryopoiesis process), Rituximab, Splenectomy.

Initial treatment	Glucocorticoids IVIG
Curative therapy	Glucocorticoids Splenectomy Rituximab
Rescue therapy	High dose glucocorticoids IVIG
Chronic therapy	Many agents **Thrombopoietin receptor agonists**

Heparin Induced Thrombocytopenia (HIT)

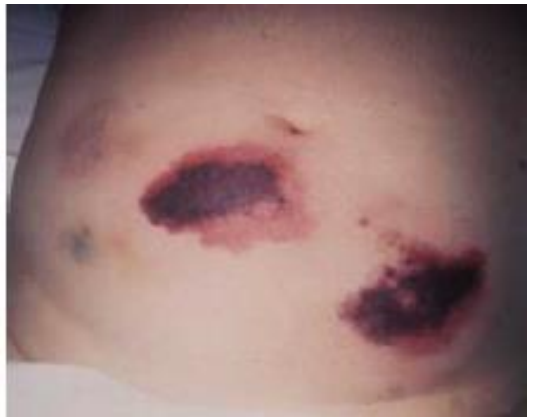
- Occurs in patients taking Unfractionated Heparin due to its higher molecular weight.
- Antibodies develop against a complex formed between Platelet factor IV and Heparin → this process doesn't happen immediately; it happens between days 4 and 14 of starting heparin.
- Binding of antibodies to the complex causes thrombosis (it causes platelet activation by cross-linking receptors thus increase the release of surface expression → positive feedback and further activation of more platelets.
- So, despite low platelet count, there is increased risk of thrombosis leading to limb ischemia, critical ischemia, and skin ischemia that may require amputation.
- We should stop heparin once suspected, and use am alternative anti-coagulation that works immediately on factor X.
- Don't give warfarin until platelet count is normalized.
- Don't give platelet transfusion.
- Look for thrombosis by Doppler ultrasound of the lower limb and skin necrosis.
- Confirm by PF4 antibody (>90% sensitivity).
- Lab findings:

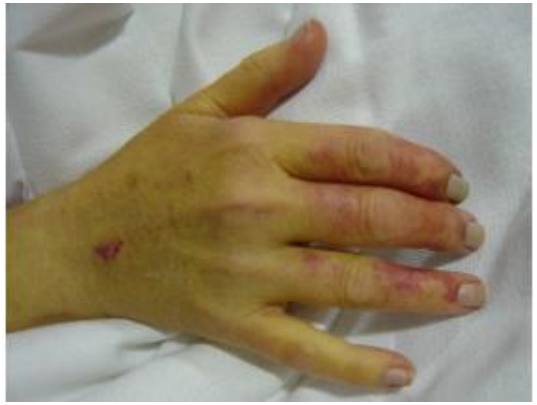
1- Low Platelet count.

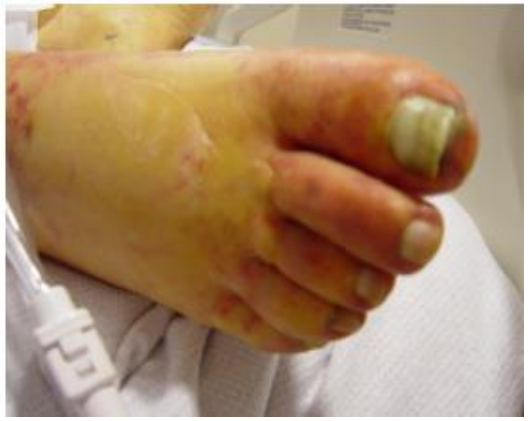
2- High PT.

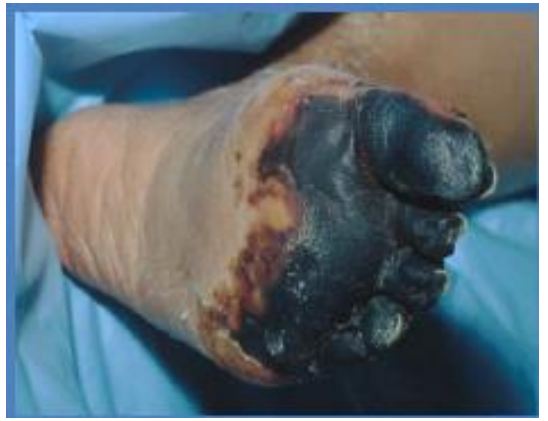
3- High PTT (prolonged due to heparin use).

CLINICAL FEATURES OF HIT









Thrombotic Thrombocytopenic Purpura (TTP)

- Acquired defect.
- Characterized by deficiency of the enzyme ADAMTS13 (vWF cleaving protease): this enzyme processes a large protein which is vWF that is involved in the last step of blood clotting at the site of injury.
- Patients present with Fever, Neurological symptoms, Hemolysis, Thrombocytopenia, and Renal Failure.
- Low Platelet count + Microangiopathic Hemolytic Anemia (High LDH, Corrected Reticulocyte count, Indirect Bilirubin).
- Schistocytes are seen in blood film.
- Abrupt onset.
- Start treatment immediately without waiting for lab results since mortality rate is high.
- Lab Findings:

1- Low Hemoglobin.

2- High Corrected Reticulocyte count.

3- High Bilirubin.

4- High WBC count.

5- Low Platelet count.

6- High LDH.

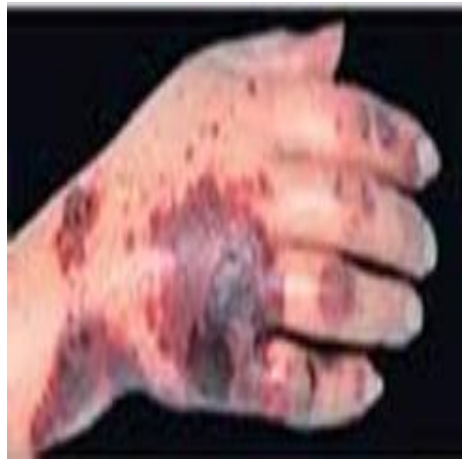
7- High PT, PTT, TT.

8- High Creatinine.

9- Low Fibrinogen.

CLINICAL FEATURES OF TTP

- A → Skin necrosis.
- B → Ecchymosis.
- C → Conjunctival Hemorrhage.
- D → Thrombocytopenic Rash.



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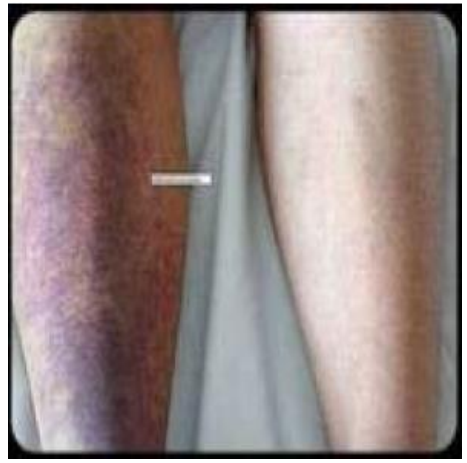

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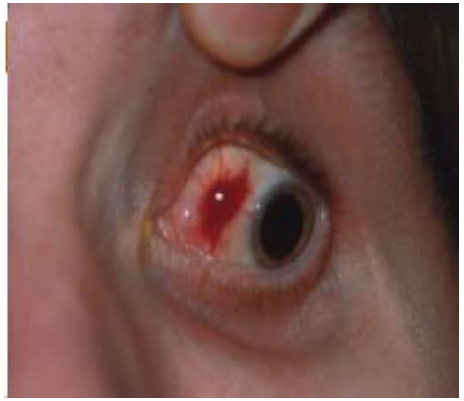

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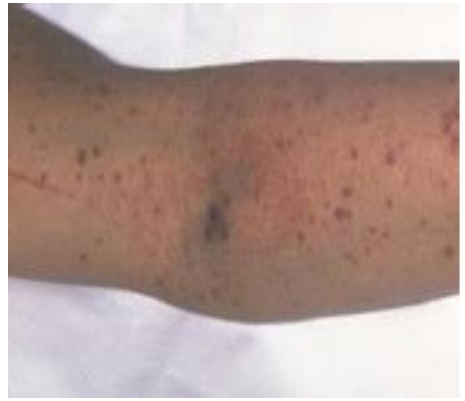

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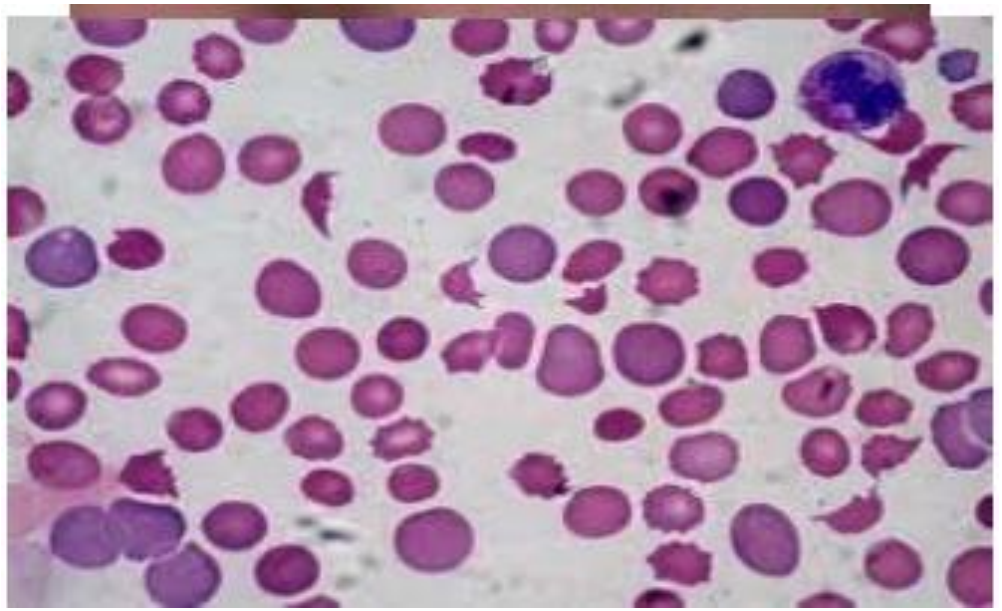
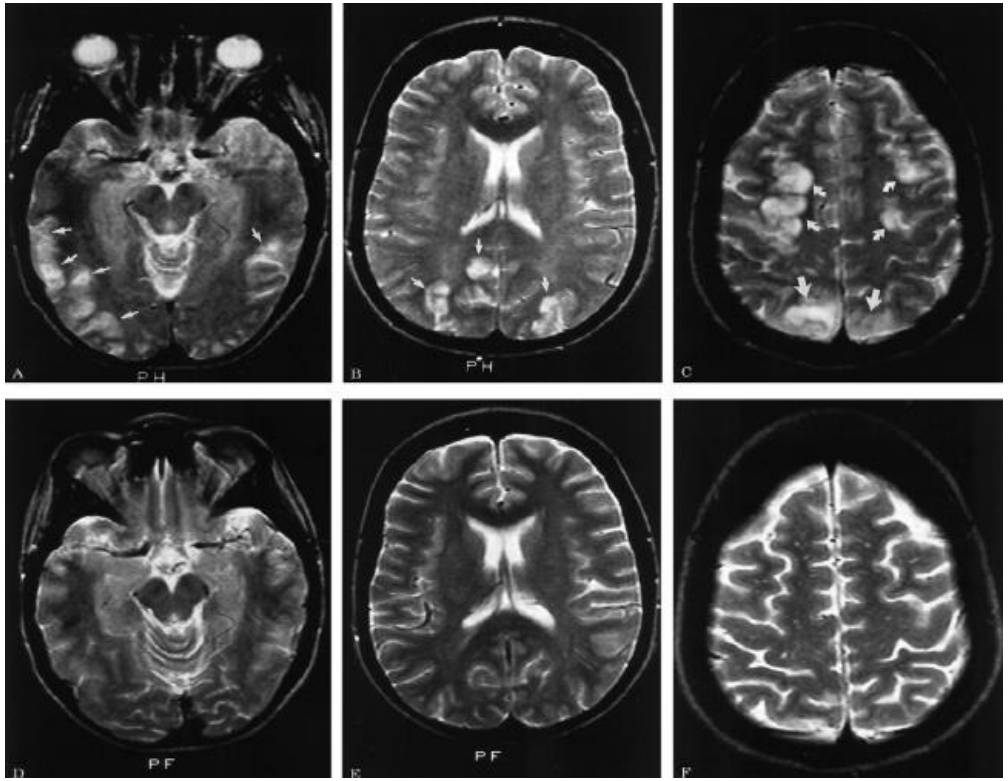
A BLOOD FILM OF A PATIENT WITH TTP

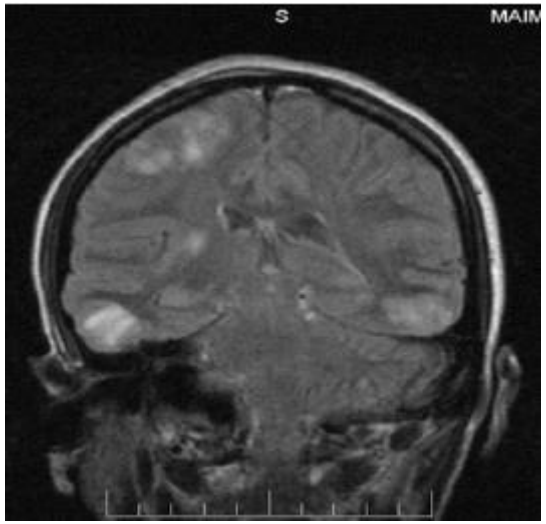
- Schistocytes are seen on blood smear.



BRAIN MRI OF TTP

- MRI shows Leukoencephalopathy and Brain infarcts + Reversible cerebral edema.





MANAGEMENT AND FOLLOW UP OF TTP

1- Plasma exchange daily until recovery

2- Monitor LDH, Plt count and clinical status

3- Monitor ADAM TS 13

4- Careful follow-up post recovery for ?relapse

TREATMENT OF TTP

- Initial treatment:
  - Plasma exchange (plasmapheresis) daily
- Relapsed or refractory disease:
  - Plasmapheresis ± Rituximab immunosuppressive therapy
  - Other (Vincristine; Splenectomy)
- Adjunctive therapy (unproven role)
  - Glucocorticoids
  - Aspirin

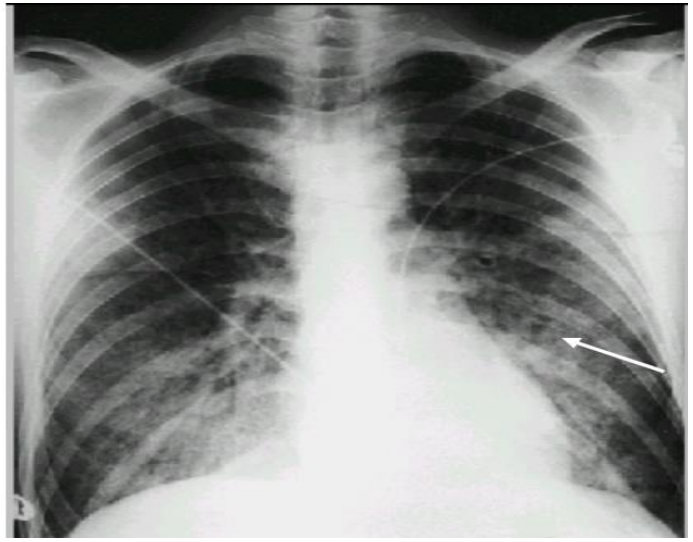
BLOOD TRANSFUSION

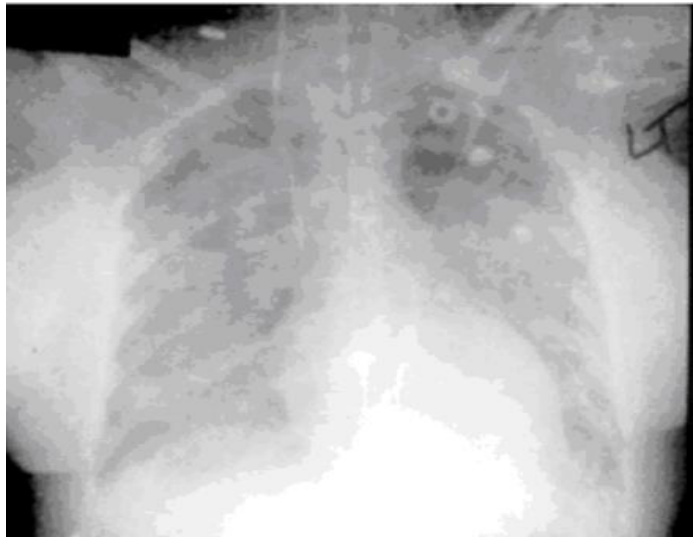
Transfusion Related Acute Lung Injury (TRALI)

- Suspected in patients taking Fresh Frozen Plasma.
- Not Rare but underdiagnosed (1 in 5000).
- A potentially fatal condition.
- Presents as pulmonary edema.
- Occurs within 1-4 hours of starting transfusions.
- Seen in unwell patients admitted with infection, increased cytokine release and tissue inflammation, surgery and burns.
- Patients present with respiratory symptoms following transfusion: 1- Acute respiratory distress. 2- Fever with chills. 3- Non-productive cough. 4- Cyanosis. 5- Hypotension. 6- Chest pain. 7- Bilateral pulmonary edema. 8- CXR reveals bilateral pulmonary infiltrates in the hilar region.
- Pathogenesis (Classical Theory – immune TRALI-): Donor Antibodies react with the patient's neutrophils (doesn't happen in all cases since recipient must be in a certain clinical condition that would activate pulmonary endothelium) → Neutrophils sequestrate in pulmonary vasculature → Complement and Cytokines Liberated → Damage to endothelium → Pulmonary Edema.
- Pathogenesis (Two Hit Theory – non-immune TRALI-): Predisposing conditions (Sepsis, Surgery, Hematological malignancies, Trauma) → Pulmonary endothelial activation and neutrophil sequestration → Lipids and WBC antibodies activate neutrophils which then causes endothelial damage.

CXR IN TRALI

- The X-ray shows bilateral pulmonary infiltrate in the hilar region, which progressed into diffuse infiltrates after few hours (the second Image).





MANAGEMENT OF TRALI

- Supportive treatment: supplement with O2, maintain BP (by hydration, vasopressor, and monitor urine output), maintain perfusion, and vital organs.

- No specific treatment
- Largely supportive
- Respiratory support with O_2
- Most cases require mechanical ventilation
- Steroids
- Clinical staff who administer transfusions must be aware how to diagnose & manage promptly

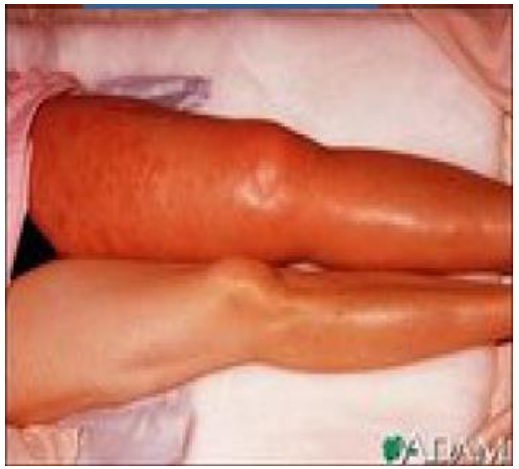
VENOUS THROMBOEMBOLISM

Venous Thromboembolism

- Clot within the venous system → DVT, Pulmonary embolism.
- Thrombosis may occur in superficial veins, but the treatment differ from thrombosis of deep veins.
  - Distal DVT → thrombus formed beyond popliteal vein.
  - Upper limb DVT is always VTE, Superficial are not VTE.
- Venous thrombosis at rare sites → Retinal vein, Sinuses of the brain, Abdominal, Mesenteric, and portal vein → considered VTE.
- Diagnosis: Duplex ultrasound + Willis's criteria (to check the likelihood of DVT depending on the risk factors like Active cancer, history of paralysis, immobilization, swelling, pitting edema and signs of venous insufficiency and possible alternative diagnosis.
- Diagnosis is confirmed by imaging: Lower limb → Doppler ultrasound to assess blood flow inside the vein and show if the vein is occluded or non-compressible (due to thrombus / no blood flow).
- Physiologic process to prevent thrombosis → Anti-coagulation and Fibrinolysis (they work together).
  - Thrombin activates Protein C which binds Protein S to inhibit Factor VIII and V.

CLINICAL FEATURES OF VTE

- A → Painful swelling, redness and hotness of the leg (DVT).
- B → CT scan showing Pulmonary Embolism.
- C → Doppler US showing DVT within the common femoral vein.



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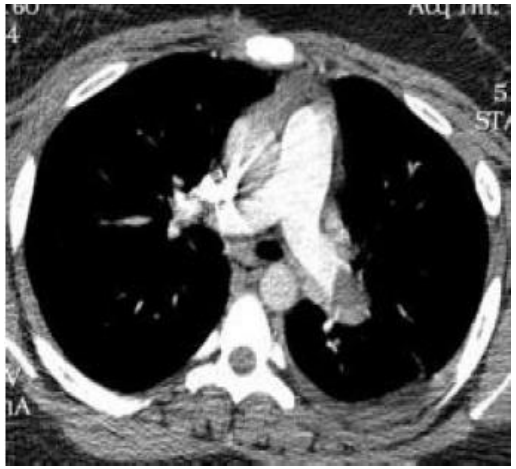

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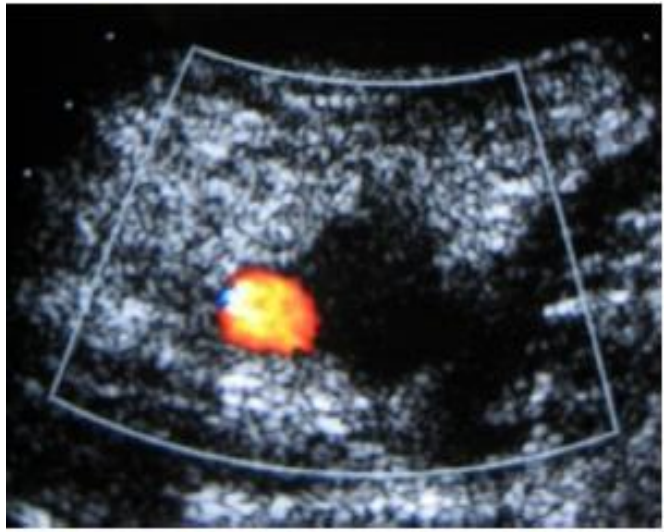
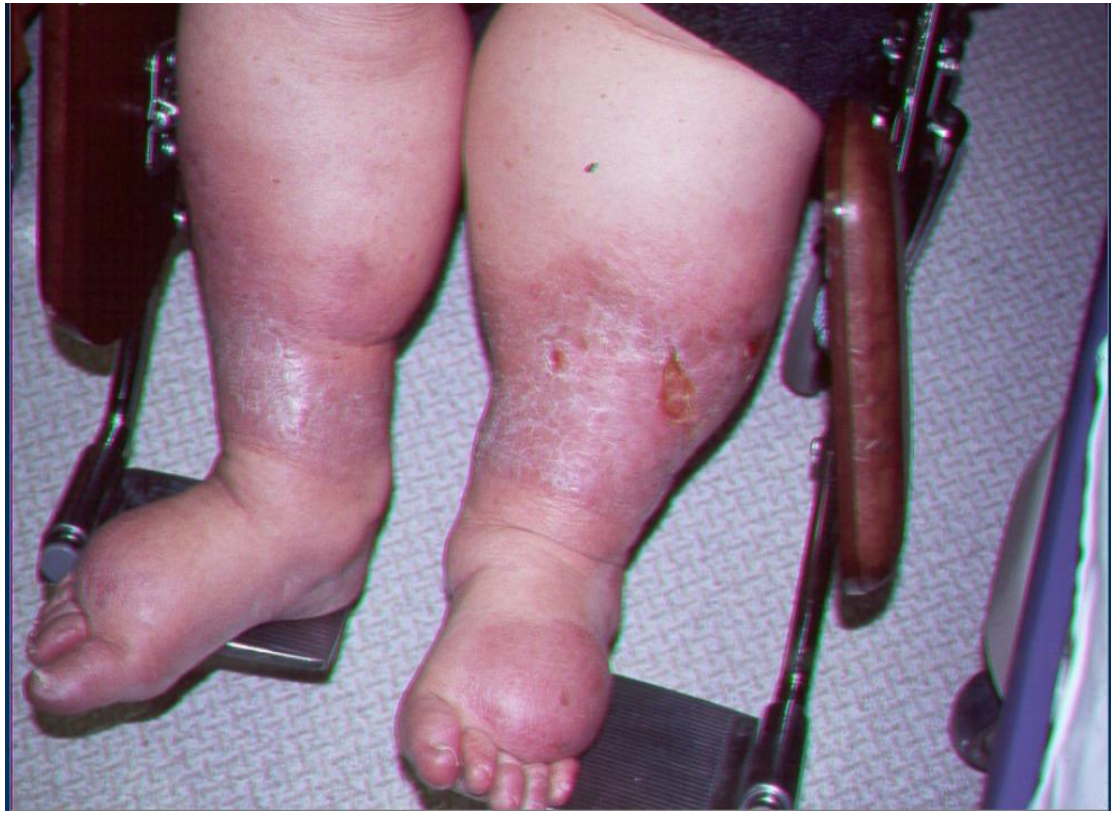


C

VENOUS STASIS / POST DVT SYNDROME

- A lifelong condition in which patients feel heaviness in their legs along with Itching, Tingling, leg pain that's worse with standing (better after resting and raising the leg), widening of leg veins, swelling of the leg, Darkening or redness of the skin around the leg.

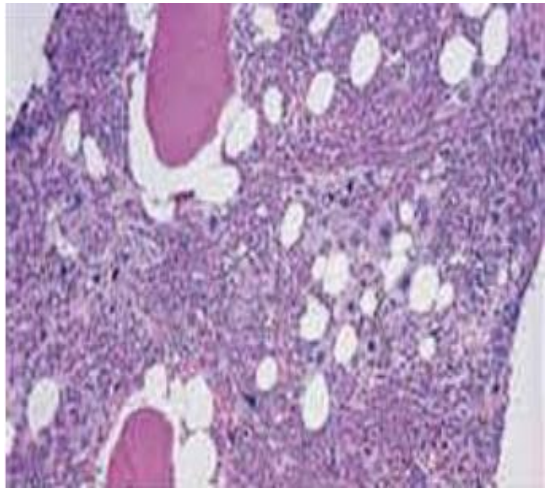


Polycythemia Rubra Vera

- Myeloproliferative disorder, caused by clonal abnormality in the bone marrow, in which the bone marrow makes too many blood cells.
  - It increases the risk of Arterial / Venous Thrombosis.
- If the clonal abnormality was in Granulocyte precursors → Chronic Myeloid Leukemia CML (affects tyrosine kinase activity due to translocation).
- If the clonal abnormality was in Red Cell precursors → Polycythemia Rubra Vera PRV (Lesion in JAK2 → Hypersensitivity response for erythropoietin leading to continuous activation regardless whether EPO is present or not).
- If the clonal abnormality was in Megakaryocytes → Essential Thrombocytosis ET (Lesion in JAK2 → Hypersensitivity response for erythropoietin leading to continuous activation regardless whether EPO is present or not).
- If the clonal abnormality was in Megakaryocytes and was associated with Reactive Fibrosis → Myelofibrosis.
  - If JAK2 is positive → increased risk for thrombosis.

CLINICAL FEATURES OF POLYCYTHEMIA RUBRA VERA

- A → Hypercellular Bone marrow.
- B → Redness and Hotness of the face.
- C → Severe acute pain in the big toe (Gouty attack)



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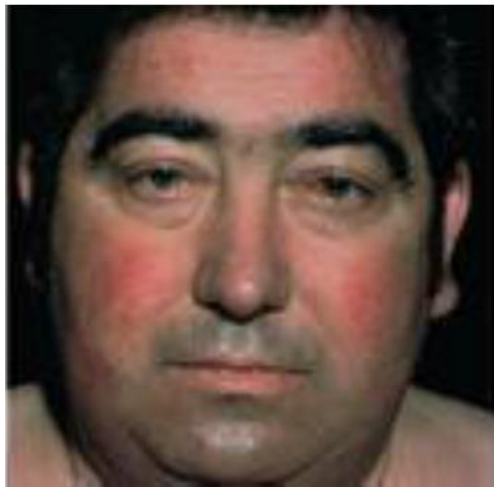

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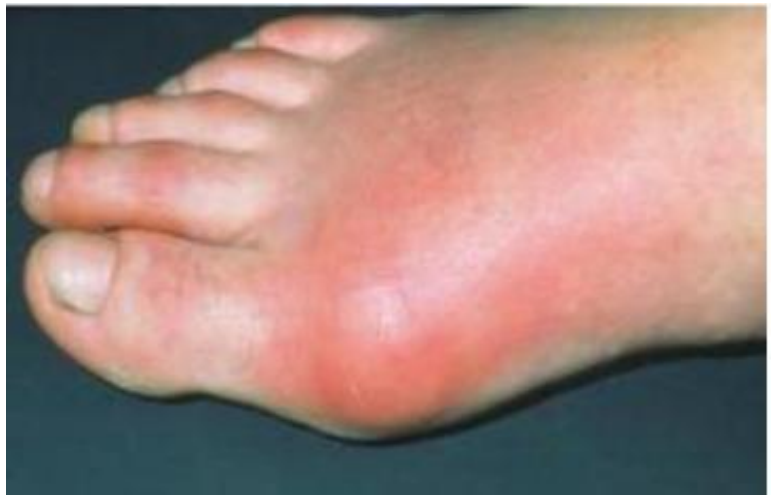
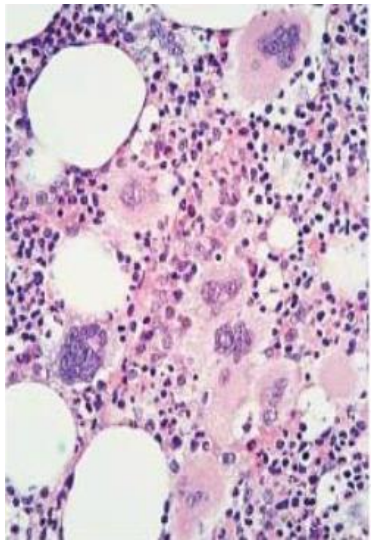


C

ESSENTIAL THROMBOCYTHEMIA

- Bone marrow biopsy in ET showing Hypercellular Bone marrow with marked Megakaryocytic hyperplasia.
- A → Bone marrow biopsy with Hematoxylin and Eosin stain.
- B → Bone marrow biopsy with Reticulin stain.
- Diagnostic criteria:

1- Platelet count >=450K
2- JAK2V617F+ or No evidence of reactive thrombocytosis.
3- Not meeting WHO criteria for other MPNs.
4- Megakaryocyte proliferation with large and mature morphology.



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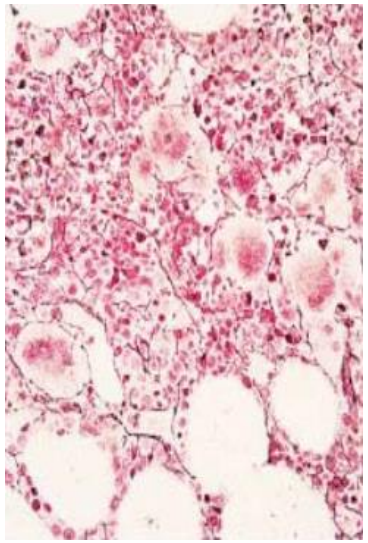


B

ACUTE LEUKEMIA

Acute Leukemia

- Symptoms of bone marrow failure → Thrombocytopenia resulting in bleeding symptoms like gum bleeding, lower limb bruises, epistaxis, and fever due to leukopenia / functional neutropenia + symptoms of anemia.
- Lab Findings:

1- Low Hemoglobin.

2- High WBC count (although high count but these cells are non-functional – Premature → Leukopenia → increased risk of infection -).

3- High Blast count.

4- Low Platelets count.

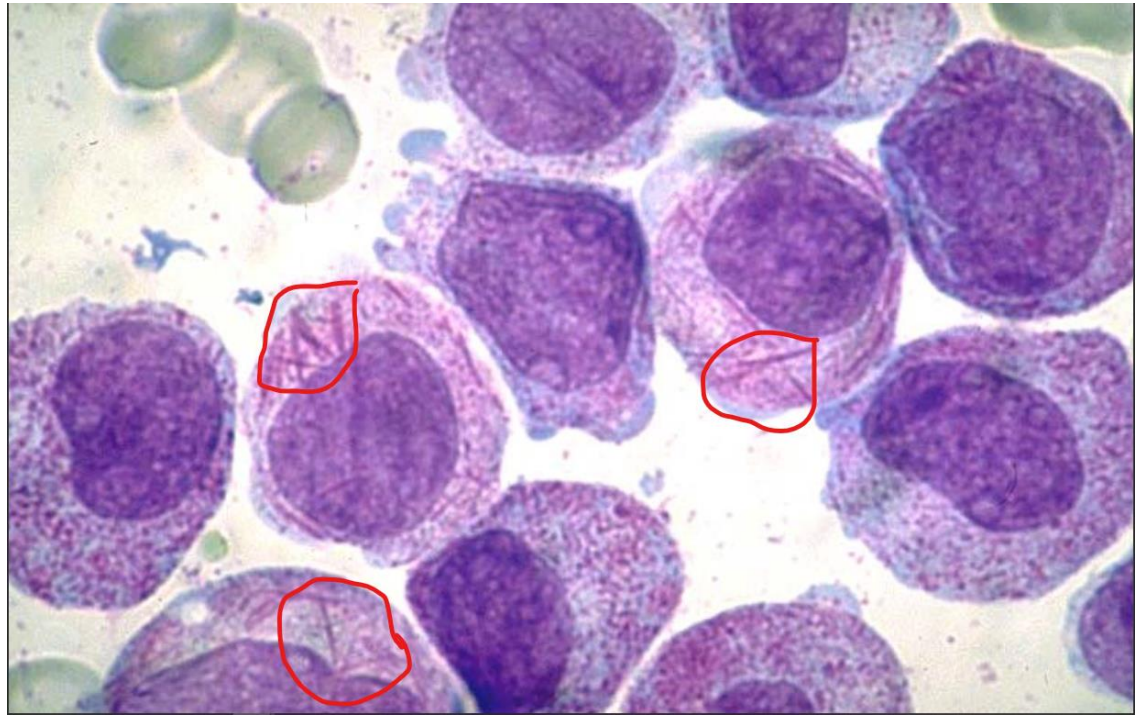
5- High PT, PTT.

6- Hematuria.

7- High WBC in urine.

8- Bacteria in urine

9- Urine culture: Positive E.Coli.



Auer Rods

- Pink or Red-stained needle-shaped structures, seen in the cytoplasm of myeloid cells, containing agglomeration of azurophilic granules containing enzymes such ad acid phosphatase, Myeloperoxidase, and esterase.
- Seen only in Acute Myeloid Leukemia.
- AML occur due to a major genetic changes in Hematopoietic precursor cells which alter normal differentiation and growth of multipotent stem cell resulting in accumulation of large number of abnormal immature myeloid cells (Myeloblasts).
- In AML → >20% of Myeloblasts in bone marrow / peripheral blood.
- Risk factors for AML: Previous bone marrow disease (secondary AML), Chemical exposure (pesticides, Herbicides, Benzene, chemotherapy with alkylating agents or topoisomerase inhibitors), Syndromes (Down syndrome, neurofibromatosis).

Acute Lymphoblastic Leukemia (ALL)

- Bone marrow biopsy shows increased number of Lymphoblasts (the large purple cells are lymphoblasts).
- Common Manifestations:

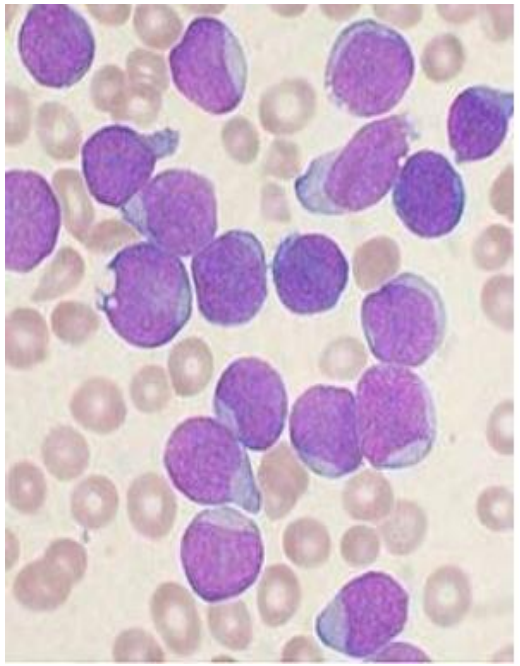
1- Manifestations of Bone marrow replacement (Anemia, Thrombocytopenia, Neutropenia).

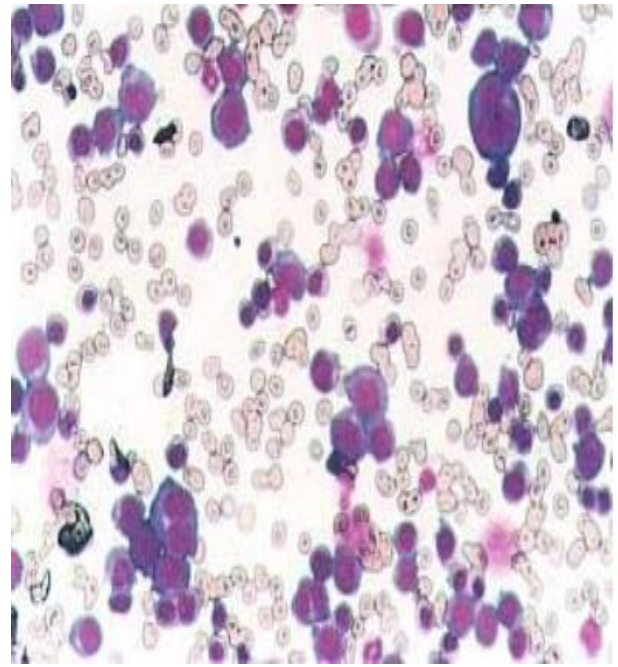
2- Infiltration of extra bone marrow tissues (Lymph nodes, Gums, Skin, CNS).

3- Release of granules / metabolites (DIC, Gout, ARF).

4- Hyperviscosity.

- Differentiate the disease by CD markers and Flowcytometry.





CHRONIC LEUKEMIA

Chronic Lymphoblastic Leukemia (CLL)

- The most common leukemia in adults.
- Mainly a disease of elderly (median age 70-74 years).
- Slight male predominance.
- Autoimmune Hemolysis → Lymphoproliferative disease with immune destruction of red cells (if found you must check if CLL is present or not).
- Polychromia may be seen in the case of Autoimmune hemolysis.
- >5000 abnormal lymphocytes must be found in peripheral blood for diagnosis.
- Expansion of the disease may be found in bone marrow or in all secondary lymphoid tissues.
- Small lymphocytic lymphoma is a term used for CLL when disease is mainly involving the lymph nodes only without bone marrow or blood.
- CLL is used in case of Bone marrow or Blood involvement.
- Initial Stages are diagnosed due to incidental blood tests (lymphadenopathy).
- As disease progresses and Lymphocyte's count predominate and involve the bone marrow more → Expect symptoms of Anemia, Thrombocytopenia, and immune dysfunction (Infection and Bleeding Symptoms).
- Lab Findings:

1- Low Hemoglobin.

2- Normal MCV.

3- High Corrected Reticulocyte count.

4- High LDH.

5- High WBC count.

6- Low Platelet count.

7- Positive DAT.

8- High Bilirubin.

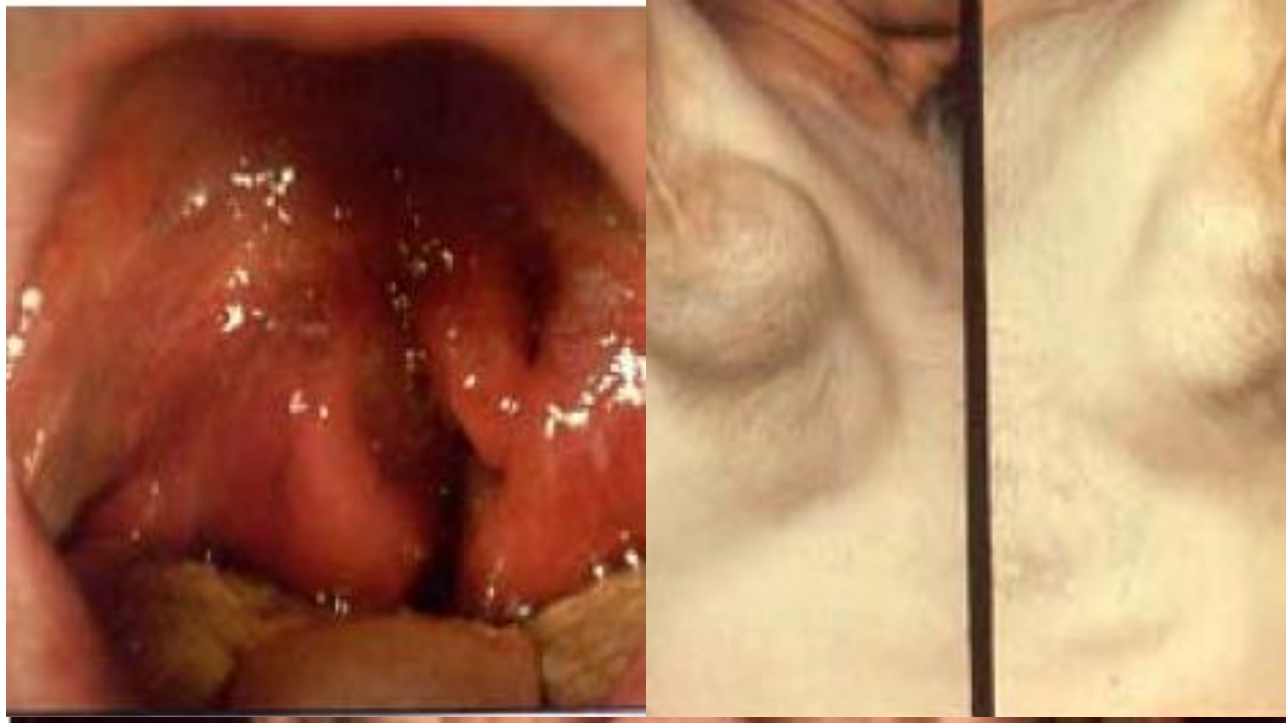
Clinical Features of CLL

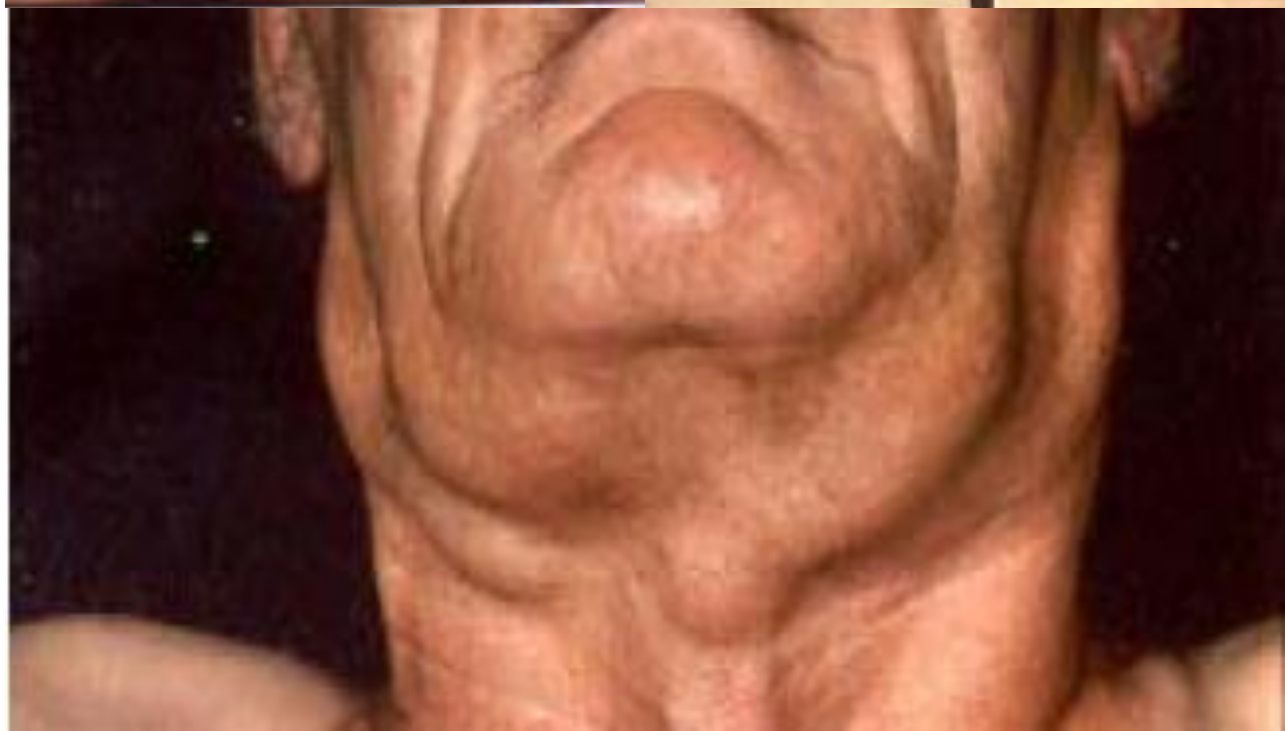
- Cervical and Axillary Swelling (for several months) → Lymphadenopathy.
- Associated with recurrent Fever, and Productive cough.
- Other clinical features:

1- Lymphocytosis (Morphologically mature, Immunologically immature, Accumulation in Peripheral blood, Bone marrow, and lymphatic tissue).

2- Splenomegaly.

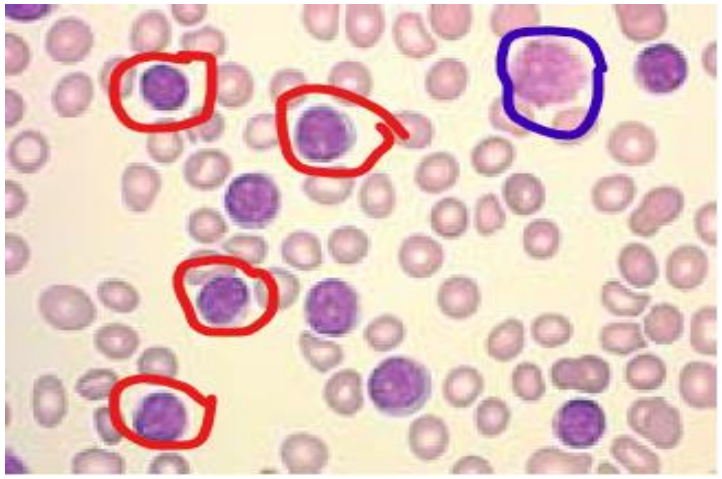
3- Hypogammaglobulinemia.

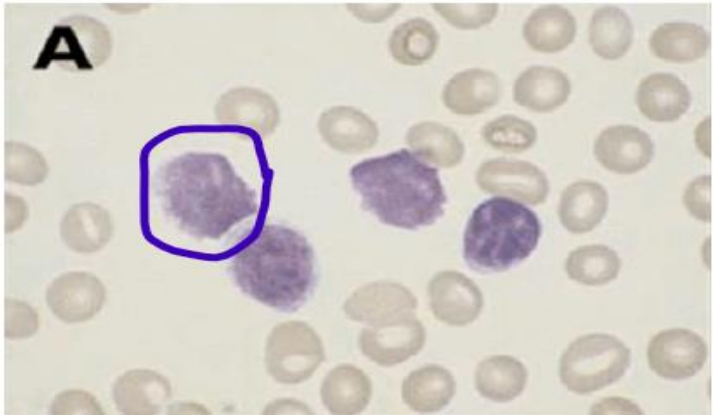




Blood Smear of CLL

- This blood film shows Lymphocytosis (High number of lymphocytes).
  - Red Circles → B-Lymphocytes.
  - Blue Circles → Smudge cells.
- B-Lymphocytes look mature but they're malignant and clonal B-cells (they arrest intermediately between the stage of Pre-B Cells and Mature B-Cells).
- B-Lymphocytes carry CD19, CD20, and CD5 Positive, but Negative CD10.
- Also, the blood film shows Smudge cells (Lymphocytes that got destructed during preparation of the slide → Fragile Lymphocytes).





Chronic Myelogenous Leukemia (CML)

- Clonal expansion of a hematopoietic stem cell possessing a reciprocal translocation between chromosome 9 and 22.
- Fusion of BCR region on chromosome 22 with ABL (oncogene) gene from chromosome 9.
- The disease has 3 phases: 1- Chronic phase (lasts 2-4 years, mostly patients are diagnosed during it with symptoms of weakness and fatigue, blood test reveals Leukocytosis (granulocytes at different stages of maturation), with Splenomegaly without Lymphadenopathy). 2- Accelerated phase. 3-Blast Crises.
- Confirm diagnosis detecting Philadelphia Chromosome.
- Pathophysiology: BCR/ABL gene product plays central role. BCR/ABL fusion proteins (with strong tyrosine kinase activity) p210 bcr/abl and p230 bcr/abl can transform hematopoietic progenitor cells in vitro.
- Test for CML by cytogenetic analysis (Karyotyping / FISH technique).
- Symptoms are similar to CLL but without Lymphadenopathy.
- Lab findings:

1- Normal Hemoglobin.

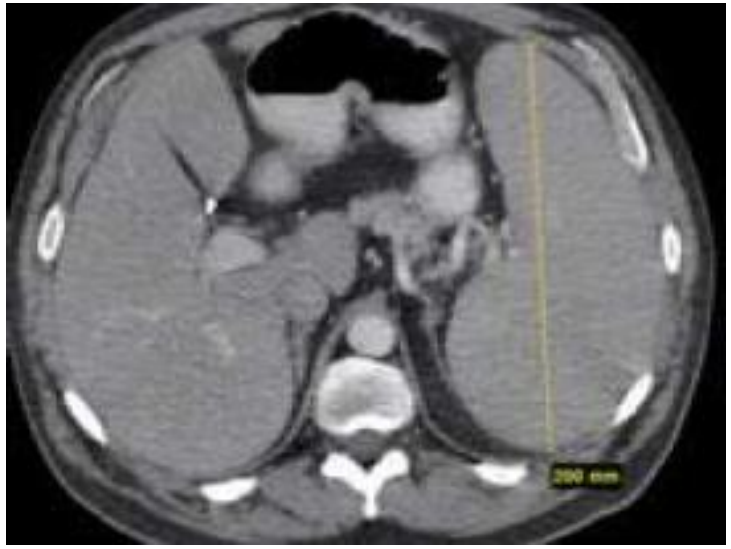
2- Normal MCV.

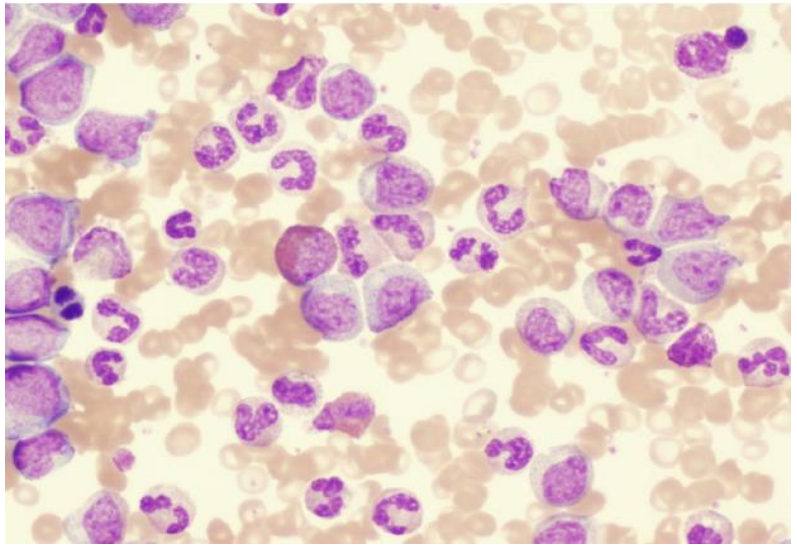
3- Normal Corrected Reticulocyte count.

4- High Platelet count.

5- High WBC count.

6- High Serum Uric Acid.





Clinical Features of CML

- The first figure is an Abdominal CT showing Splenomegaly.
- The second figure shows Abnormal Blood Film: Granulocytes at different stages of maturation (since in CML cells have abnormal proliferation but still carry on their capacity to differentiate), in addition to granulocyte hyperplasia (Eosinophilia and Basophilia are seen as well).

- Other clinical manifestations: Fatigue, malaise, weight loss, Infections, thrombosis, bleeding, Gout (due to rapid cell turnover leading to hyperuricemia).

LYMPHOMAS

Non-Hodgkin / Hodgkin Lymphoma (NHL/HL)

- NHL is more common than HL.
- They differ in age presentation: NHL (65-70 years) / HL (30-34/ 55 years).
- Extranodal involvement is more common in NHL.
- Each has different histology types.
- To differentiate between the two, we need to do Lymph node biopsy.
- 85% of NHL are of B-cell origin, the rest are T-cell or null.
- Etiology of NHL: 1- Idiopathic. 2- Immune suppression (Congenital – Wiskott-Aldrich-, Organ Transplant (cyclosporine), AIDs, Increasing age). 3- DNA repair defects (Ataxia Telangiectasia, Xeroderma Pigmentosum). 4- Chronic inflammation and Antigenetic Stimulation (H.Pylori inflammation of the stomach, C.Psittaci inflammation of ocular adnexal tissues, Sjogren's Syndrome). 5- Viral Causes (EBV and Burkitt's lymphoma, HTLV-I and T-cell leukemia lymphoma, HTLV-V and cutaneous T-cell lymphoma, Hepatitis C).
- Lab findings:

1- Low Hemoglobin.

2- Normal MCV.

3- High WBC count.

4- Normal Platelet count.

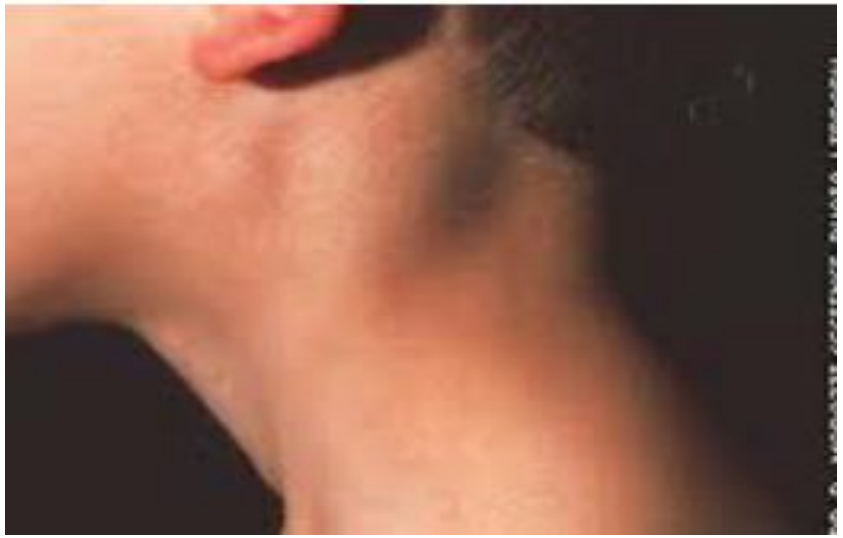
5- High LDH.

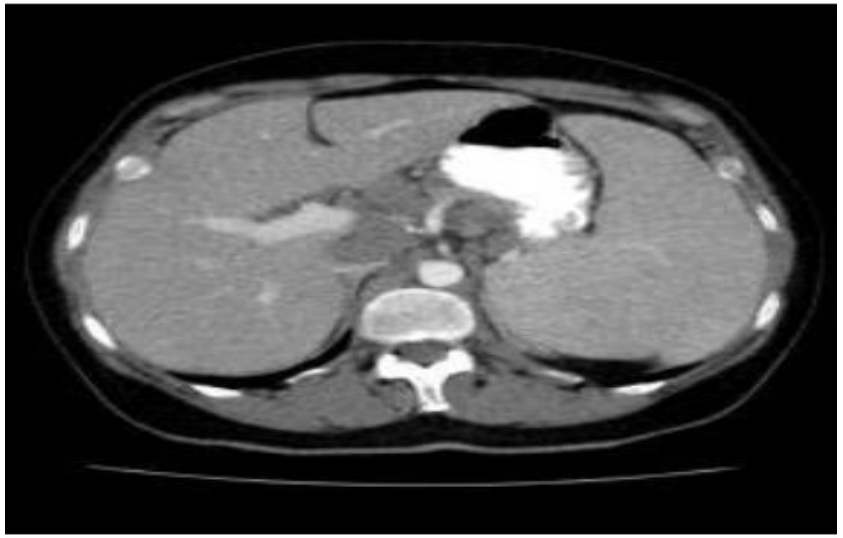
6- High Serum uric acid.

7- Normal Creatinine, Ca, PO4.

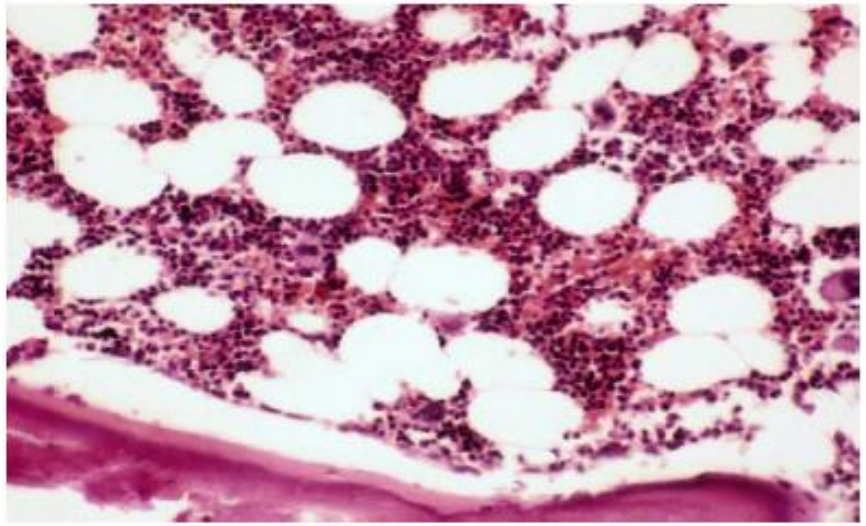
CLINICAL FEATURES OF NHL

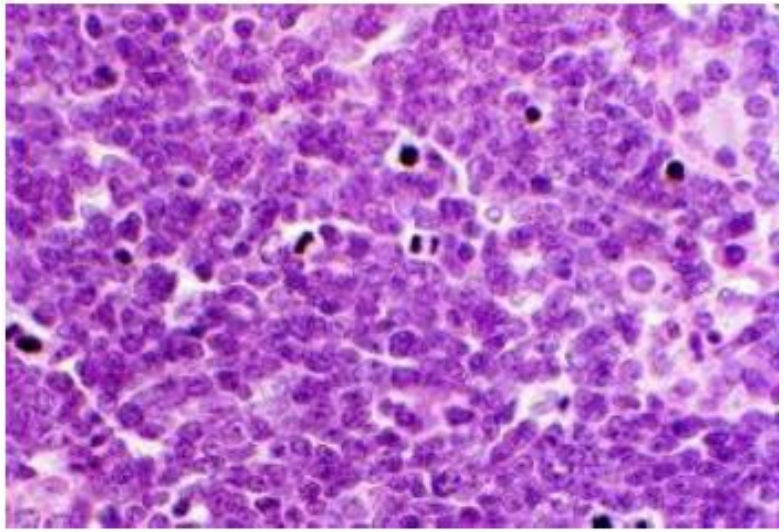
- Enlarged Tonsils.
- Hepato-Splenomegaly.
- Other Features: Generalized Lymphadenopathy.





LYMPH NODE BIOPSY IN NHL





Multiple Myeloma

- Typical age of onset: 68-70 years.
- Males > Females.
- Patients present with symptoms related to bone marrow infiltration including bone pain, osteolytic lesions and fractures, Anemia, and Hypercalcemia + Secretion of abnormal proteins (Renal and neurological or visceral manifestations + Hyperviscosity syndrome + Recurrent infections + Amyloidosis.
- The first step in diagnosis is Serum protein Electrophoresis (SPEP)
- Lab findings:

1- Low Hemoglobin (normocytic normochromic RBCs).

2- Normal WBC count.

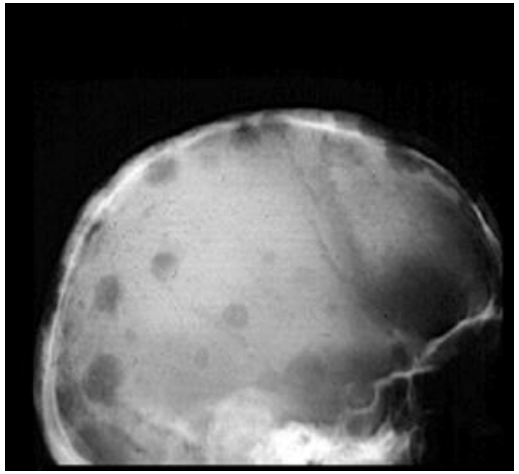
3- Normal Platelet count.

4- Elevated ESR.

5- Elevated Beta 2 macroglobulin in blood.

6- Low Serum Albumin.

CLINICAL FEATURES OF MULTIPLE MYELOMA



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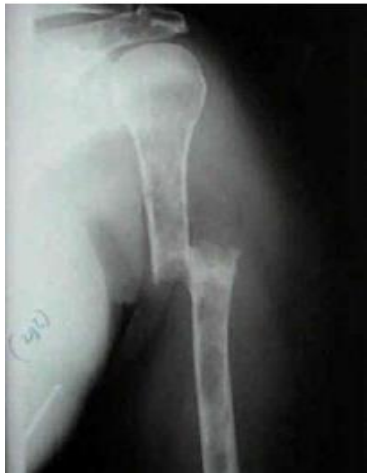
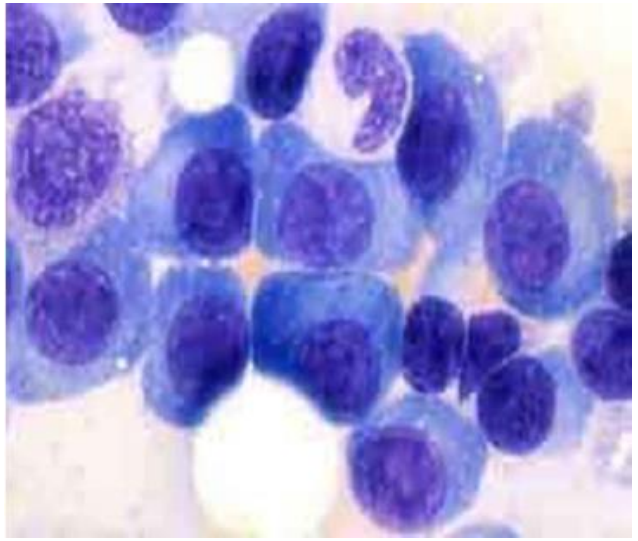


B

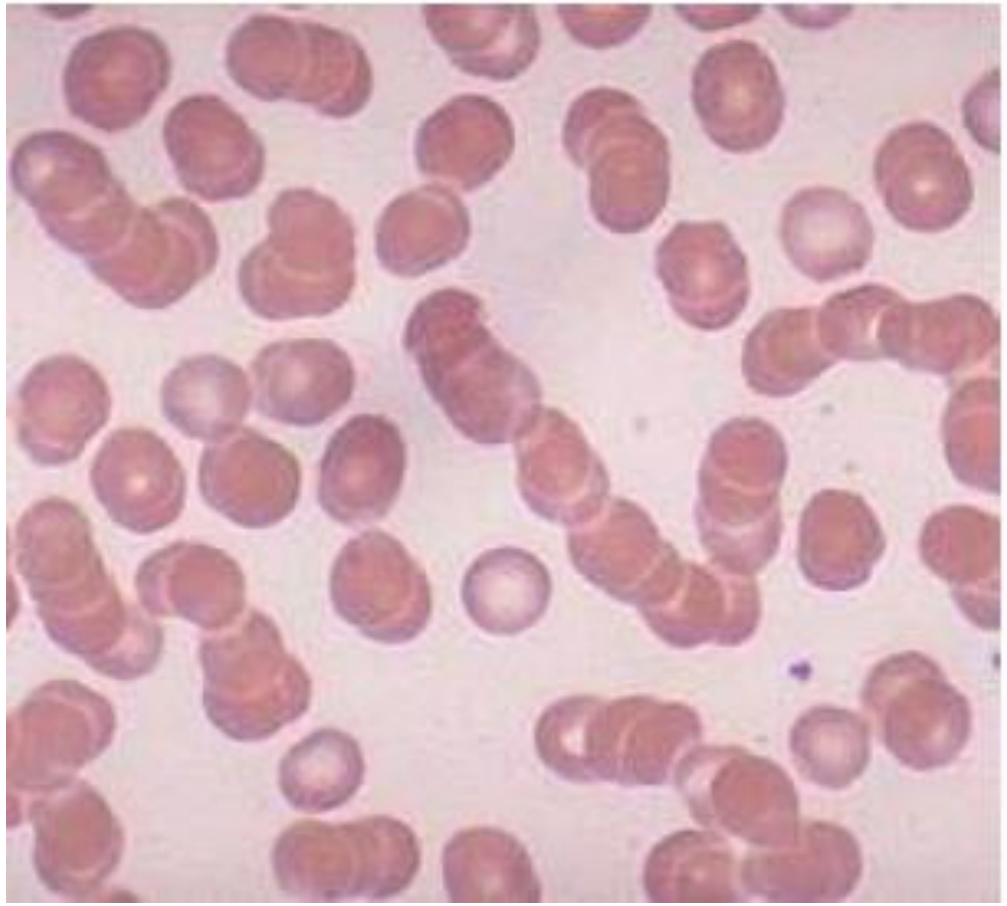
- A → Lytic Lesions (spots of bone damage that results from cancerous plasma cells building up in your bone marrow).
- B → Fracture.
- C → Bone marrow biopsy: it shows high amount of plasma cells that have Fried egg appearance caused by Ig overexpression.



C

BLOOD FILM OF MULTIPLE MYELOMA

- This blood film shows Rouleaux formation (the linking of RBCs into chains resembling stacks of coins).
- Seen in association with Infection, Multiple Myeloma, Inflammatory and connective tissue diseases, and Cancers.



HOPEFULLY, EVERYTHING WAS CLEAR
BEST OF LUCK ♡
WAIT FOR PART 2 😜