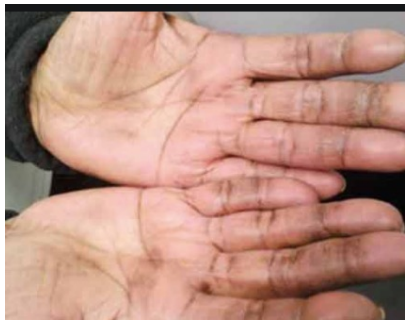
INTEGRATED RHEUMATOLOGY

Auto-Antibodies

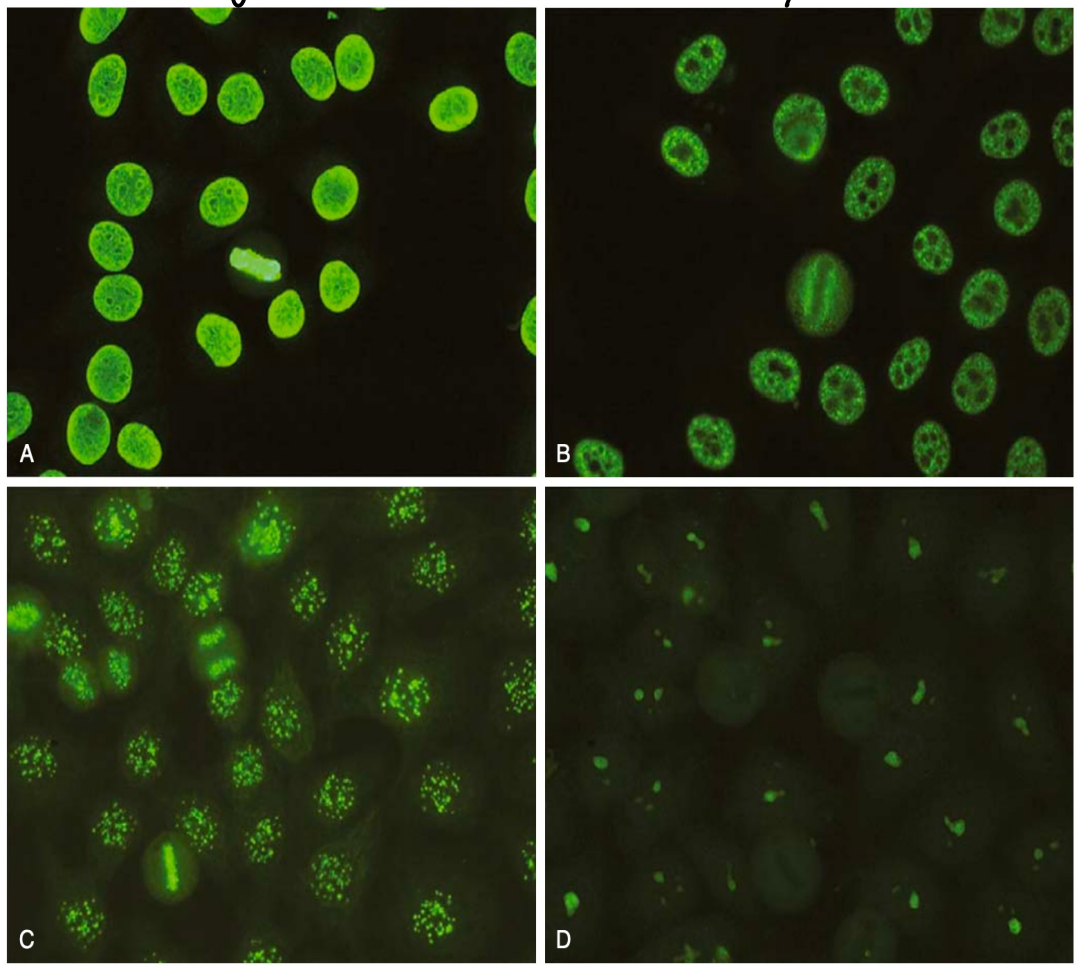
ANA - MC in SLE - entry criterion
Anti-C1q > Anti-dsDNA - disease activity / flares correlate
Anti-histone DRUG INDUCED LUPUS - SHIP → acetylⁿ
Anti-Sm - most specific SLE
Antineuronal Ab/ Antiglutamate receptor 2 - CNS Lupus
Anti-ribosomal P - psychiatric - SLE
Anti-U1 RNP → MCTD
Anti-Ro/SS-A } Sjogren's → neonatal lupus - ↑ cong ♡ block, ↓ lupus nephritis
Anti-La/SS-B }
Anti-Jo1 (Anti-synthetase) → Sx - Fever / ILD / Mechanic hands
Anti-Mi2 - good prognosis - DM
Anti-MDA-5 - bad " - DM
Anti-topoisomerase 1 / Anti-scl-70 → Diffuse scleroderma
Anti-centromere → CREST
p-ANCA - MPA / Churg strauss = EGPA / UC / PSC
c-ANCA = Wegener's granulomatosis = GPA
RF - IgM agnst Fc - IgG (anti-CCP - most sp RA)
Anti-endothelial cell Ab - Kawasaki
Anti-alpha-enolase Ab - Behcet Sx

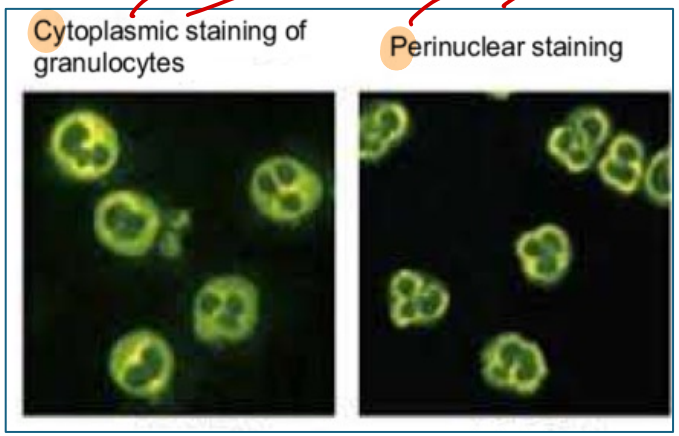


Auto-Antibodies-Fluorescence pattern

Homogeneous — anti dsDNA, anti-Histone

Speckled — anti Ro / La / Jo-1 / U1-RNP





PR-3 — MPO

ANCA

Peripheral
└ anti-SM

Centromere
↓
CREST

Nucleolar
└ SCL-70

New EULAR/ACR criteria-SLE

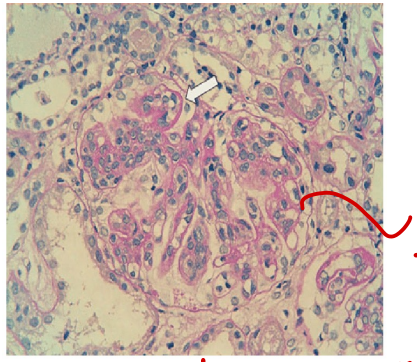
ANA + ≥10 pts

Clinical domains	Points	Immunologic domains	Points
Constitutional domain		*Antiphospholipid antibody domain*	
Fever	2	Anticardiolipin IgG > 40GPL or anti-B2GP1 IgG > 40 units or lupus anticoagulant	2
Cutaneous domain		*Complement proteins domain*	
Non-scarring alopecia	2	Low C3 or Low c4	3
Oral ulcer	2	Low C3 and Low c4	4
Subacute cutaneous or discoid lupus	4		
Acute cutaneous lupus	6		
Arthritis domain		*Highly specific antibodies domain*	
Synovitis tenderness in a at least 2 joints	6	Anti- dsDNA antibody ✓	6
		Anti- Sm antibody ✓	6
Neurologic domain			
Delirium	2		
Psychosis	3		
Seizure	5		
Serositis domain			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Hematologic domain			
Leukopenia	3		
Thrombocytopenia	4		
Autoimmune hemolysis	4		
Renal domain			
Proteinuria >0.5g/24hr	4		
Class II or V lupus nephritis	8		
Class III or IV lupusn nephritis	10		

- False- positive VDRL/RPR – anti-cardiolipin
- Prolonged PTT that is not corrected by the addition of normal platelet-free plasma

↳ Lupus anticoagulant

HLA-DR3 SLE
Early complement deficiency
TREX mutation (T-cell defect) – ve selection



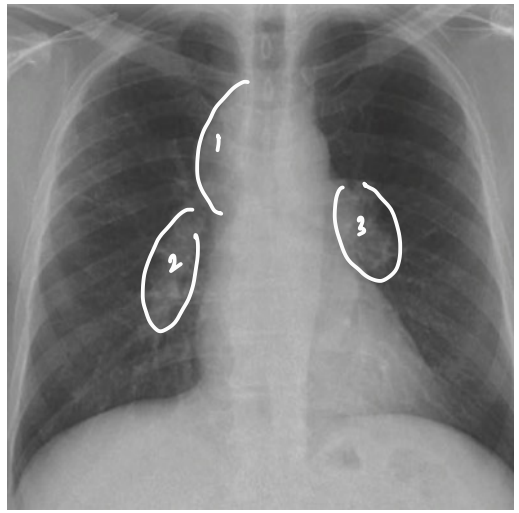
IF - Full-house effect:
IgG, IgM, IgA, C3, C1q

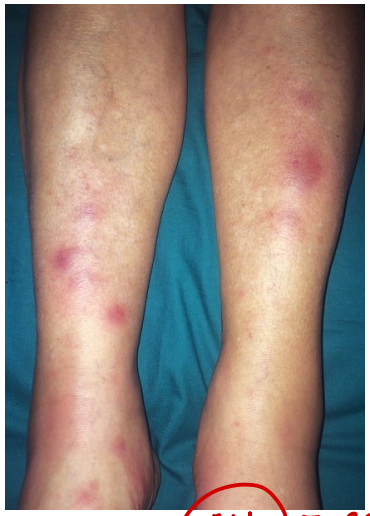
Lupus nephritis

Rx: Steroid +
Cyclophosphamide/ MMF
- Belimumab - BLys
- Anifrolumab INF type 1
- Voclosporin calcineurin

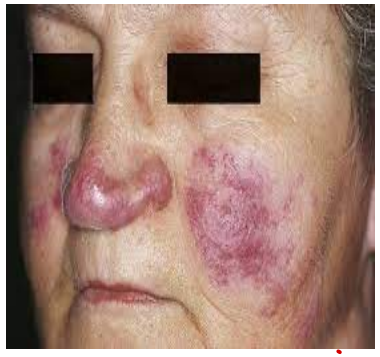
LUPUS NEPHRITIS	Histopathological Features
I-Minimal Mesangial	Deposition of immune complexes
II-Mesangial Proliferative	Mesangial hypercellularity on light microscopy.
III-Focal Lupus Nephritis	Glomerulonephritis involving **<50% of all glomeruli.**
IV-Diffuse Lupus Nephritis	**≥50% of all glomeruli.** Subendothelial diffuse immune deposits common.-Wire-loop
V-Membranous Lupus Nephritis	Global or segmental subepithelial immune deposition
VI-Advanced Sclerosing Lupus Nephritis	Terminal stage lupus nephritis with **≥90% of glomeruli** showing global sclerosis.

Sarcoidosis

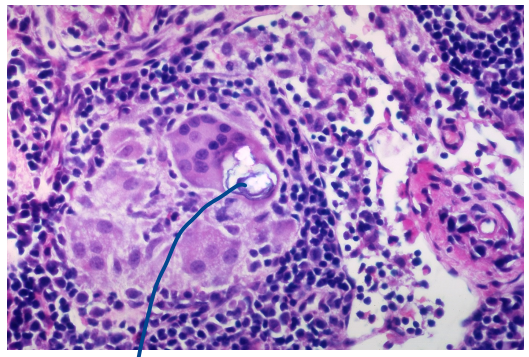




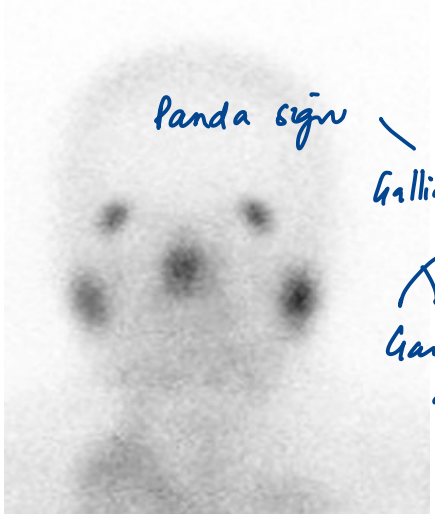
EN - septal panniculitis
tender / skin



LUPUS pernio
Lchronic skin



· NC granulomas
↳ 1α OH
↳ ↑Ca^{2+}
· Schaumann bodies
· Asteroid bodies



- alcoholic
- malnourished
- sialosis

Scadding staging

Stage	Radiographic Findings
Stage 1	Bilateral hilar LN
Stage 2	Hilar LN with pulmonary infiltration VL ↑
Stage 3	Pulmonary infiltration only
Stage 4	Pulmonary fibrosis

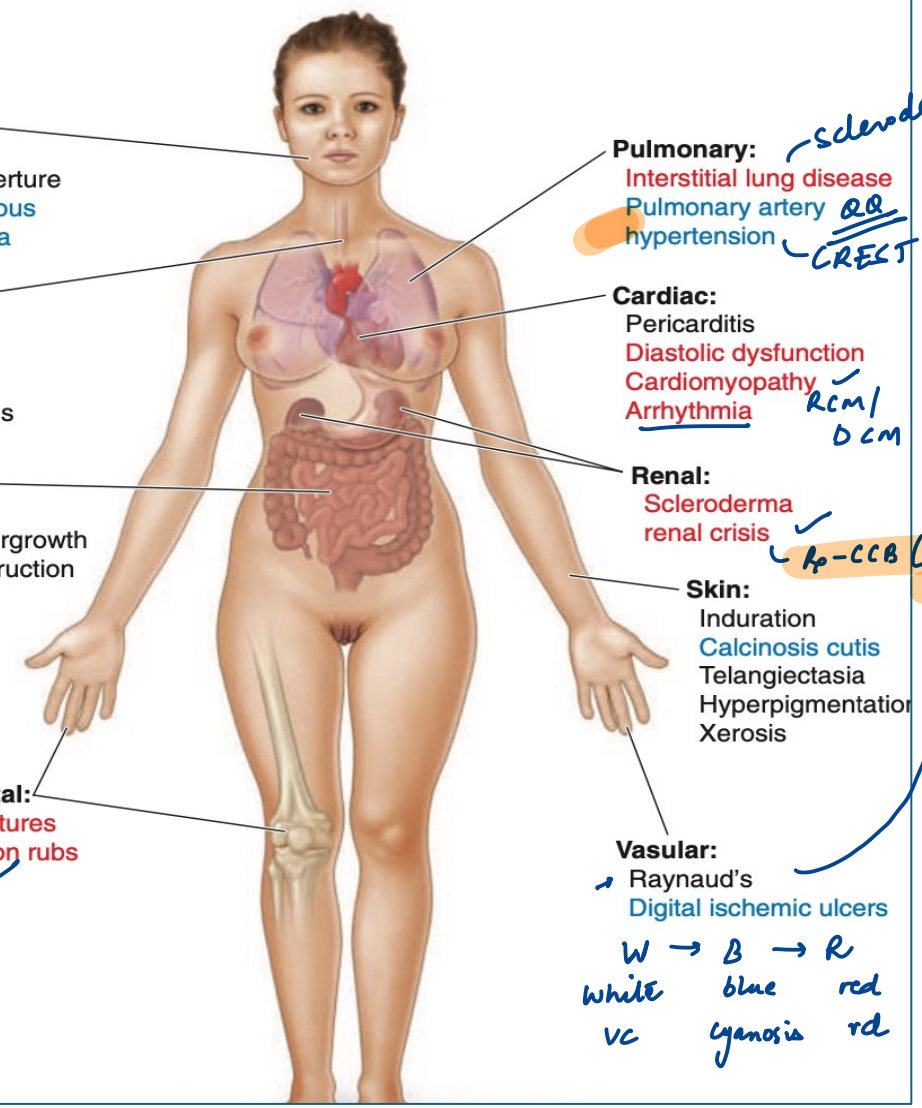
Lab:
ACE- (↑)
Calcium- (↑)
Lymphopenia
BAL: CD4 : CD8 3-5 : 1 (N) 2:1
Kweim test

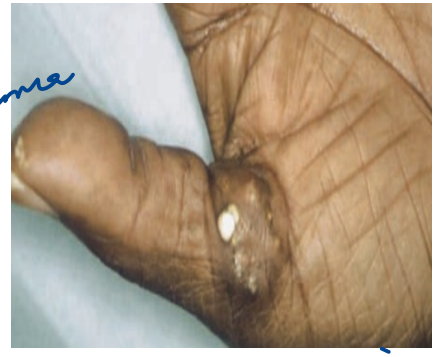
Lofgren syndrome: LN + EN
Heerfordt syndrome: uveoparotid fever → Bell's palsy

B/L Parotid swelling

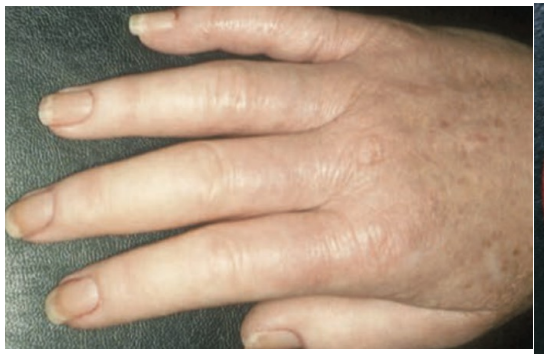
HIV INFECTION : BLEL	SJOGREN'S SYNDROME	SARCOIDOSIS
• Lymphoid infiltrate by CD8+ T lymphocyte • HIV +	• Lymphoid infiltrate by CD4+ T lymphocyte • Anto-Ro/La • R/o MALToma	Granulomas in salivary glands

Scleroderma-CREST

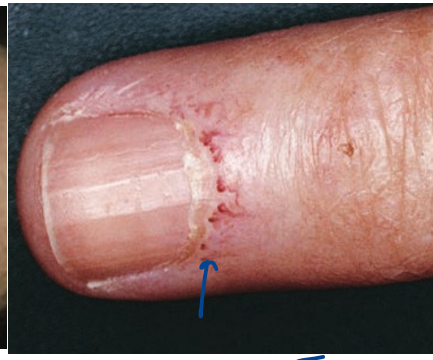




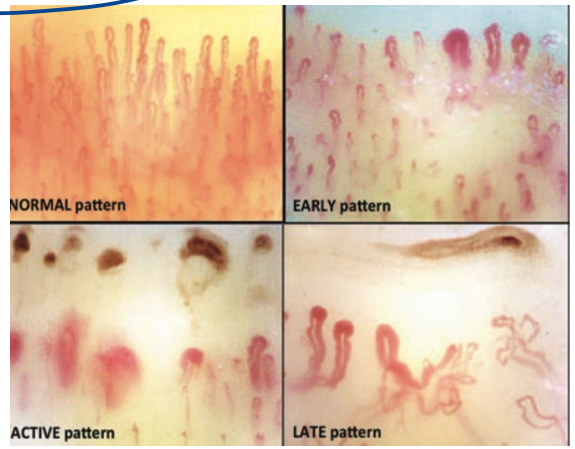
Calcinosis cutis



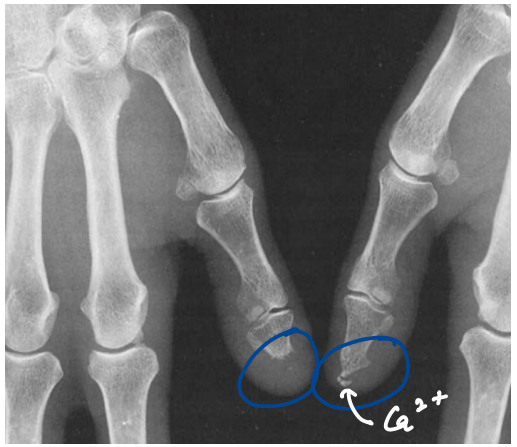
Sclerodactyly



Telangiectasias



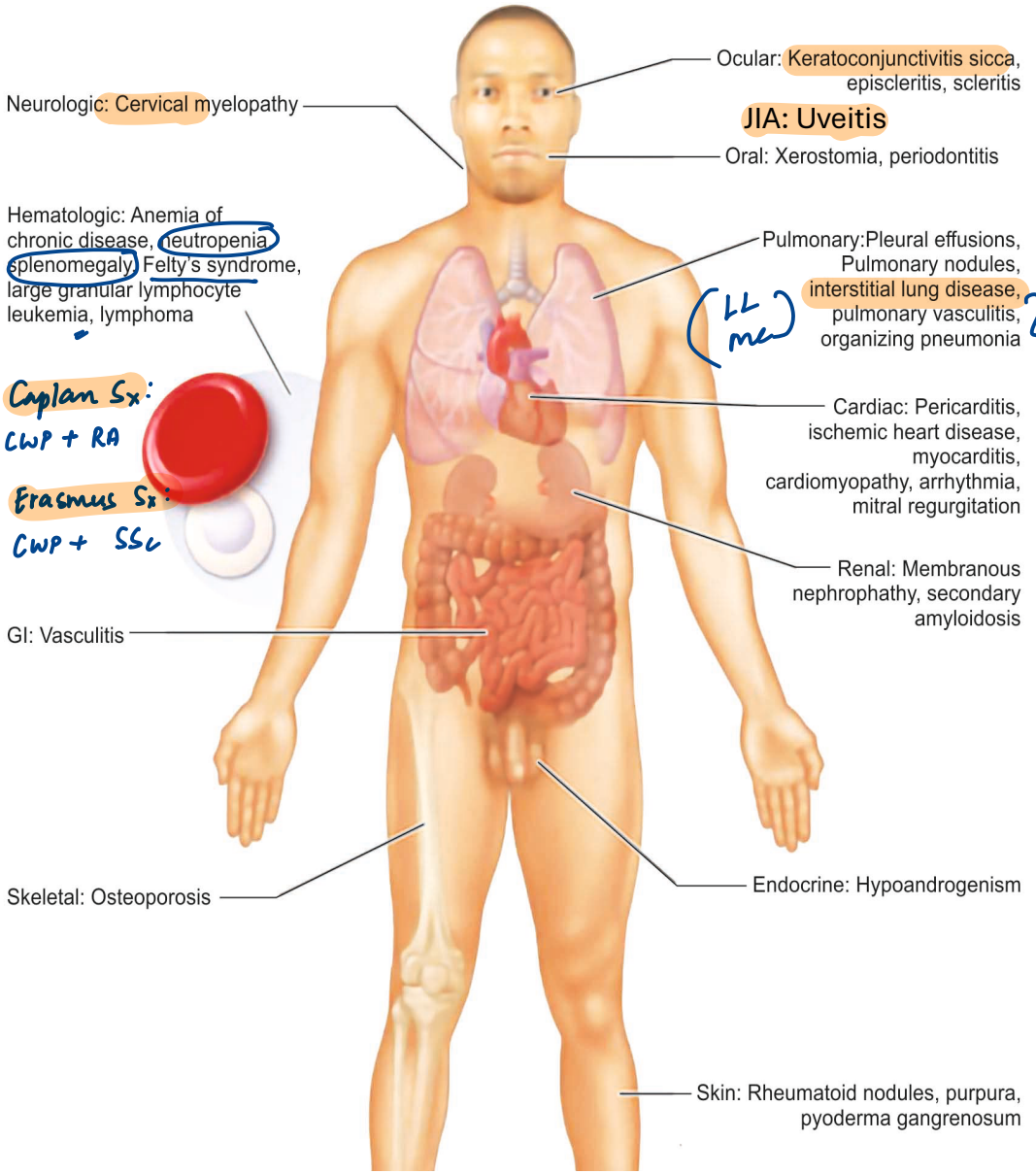
Capillaroscopy



Acro-osteolysis

Anti-fibrillarin / Anti-U3 RNP: ☹ – ILD / PAH / renal crises

Rheumatoid Arthritis



PANNUS → erosions

CTD: NSIP mc

(LL mc) → RA: UIP mc

Feature of RA	Most common
Involved joints	mc - MCP spared - DIP
Spine involvement	cervical - C1-C2 dislocn RA
Extra-articular manifestation	Subcut nodules
Cardiac manifestation	pericarditis
Valvular abnormality	MR
Pulmonary feature	pleural effusion
Hematological feature	AOCD
Ocular manifestation QQ	KCS > scleritis
Lymphoma	DLBCL
Cause of death	♡ - arrest.

JIA - mc: uveitis

Age < 16 years + arthritis (≥ 6 weeks)
MC type: OLIGO-A (≤ 4 jt)
Fever + Arthritis ≥ 2 wks/ salmon rash/HSM - Still's

Management

RA: NSAIDs → C-DMARDs → Biological-DMARDs

- Sulfasalazine
- HCQ
- Leflunomide

DOC: Mtx + folinic acid

Glucavipidase – toxicity – Pulm fibrosis / Hepatotoxicity

DOC in pregnancy:

HCQ: Irreversible retinal damage, cardiotoxicity (Ia) QT

Sulfasalazine: Male infertility, CI in G6PD

BIOLOGICALS in RA

TNF-apha inhibitors: S/e: SLE, TB, Hep B reaction (Rituximab)

Pregnancy? Biologicals safe >/T2 – safest in all + – certolizumab

- Adalimumab
- Certolizumab
- Etanercept
- Infliximab
- Golimumab

IL-1R Antagonist: Anakinra

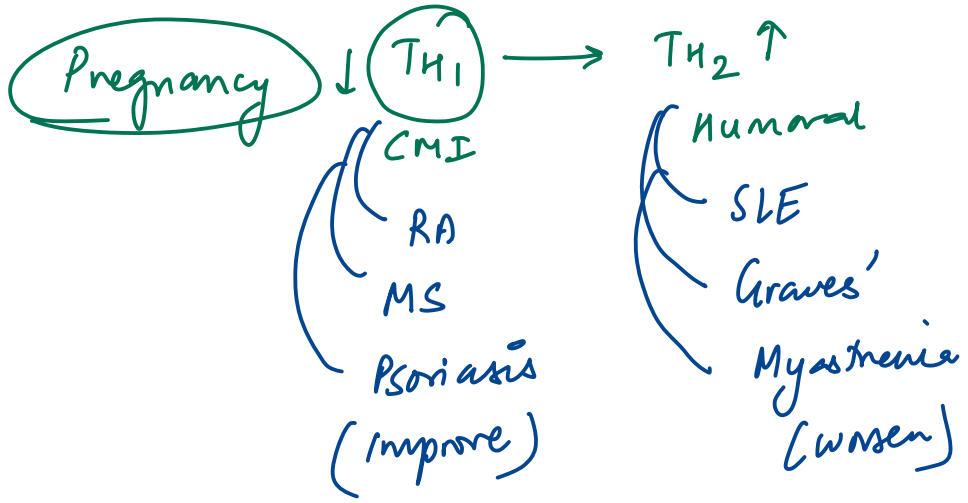
IL-6 inhibitor: Tocilizumab / Sarilimumab

B-cell depletor/CD20-: Rituximab

Co-stimulation inhibitor/CTLA4-: Abatacept

JAK inhibitors: Tofacitinib, Baricitinib, Upadacitinib

Ank spondylitis: (X) role of L-DMARDs
NSAIDs -> Biologicals



Acute arthritis

	Normal	OA	Inflammatory arthritis	Septic arthritis
Appearance	Clear	clear	turbid	turbid
Viscosity "stringing"	Normal	↓	↓	↓
WBCs	<200	200 - 5K	5K - 50K	>50K
PMNs	<25%	<25%	25 - 50 %	>50 %

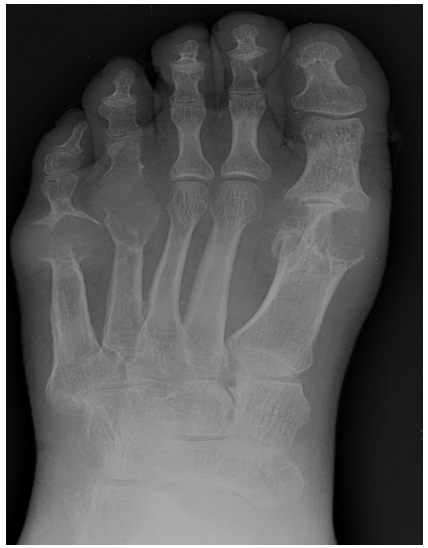
S.aureus → prosthetic jt

Acute Gout — except aspirin / PCM
- **NSAIDS** DOC → Indomethacin
- **Colchicine** - most effective - s/e - diarrhea, chemotaxis ⊖, UT ⊖
- **Chronic gout DOC:** ALLOPURINOL
- **MOA:** xanthine oxidase ⊖
- **HLA B5*801** → hysn / SJS / AIN
- **AVOID WITH:** 6MP / Azathioprine – XO
- **Rasburicase/Pegloticase** (Tumor lysis, Gout)

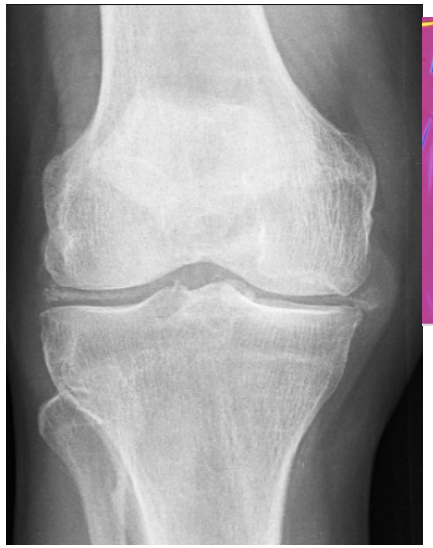
↑ r/o GOUT

Cyclosporine
Aspirin (low dose)
Niacin
Thiazide
Loop diuretic
Ethambutol
Alcohol
Pyrazinamide

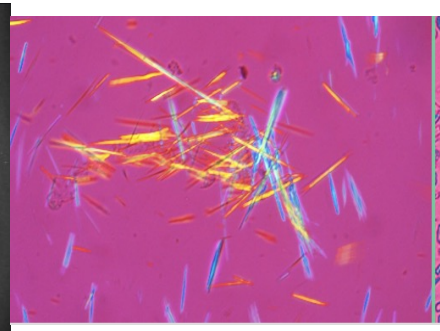
Z > E



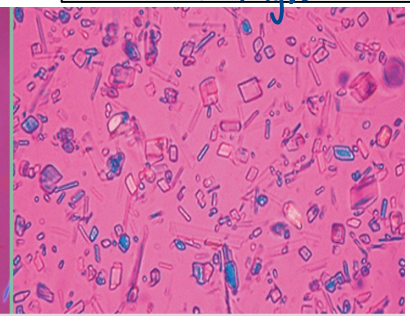
GOUT (MSU)
MC - 1st MTP
Martel G → overhanging margins
↳ Rat bite
TOPHI



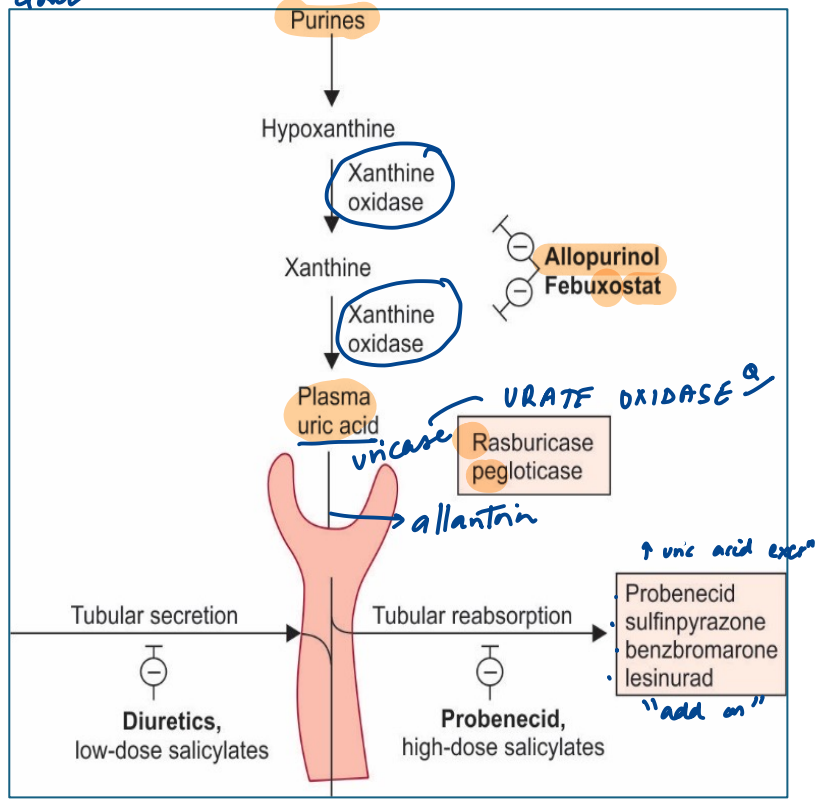
PSEUDOGOUT (CPPD)
. chondrocalcinosis
MC → knee
. HyperPTH . HyperMg
. Hypothyroid



needle - neg birefringent
↓
Uric acid



rhomboid
weakly positive
↓
CPPD



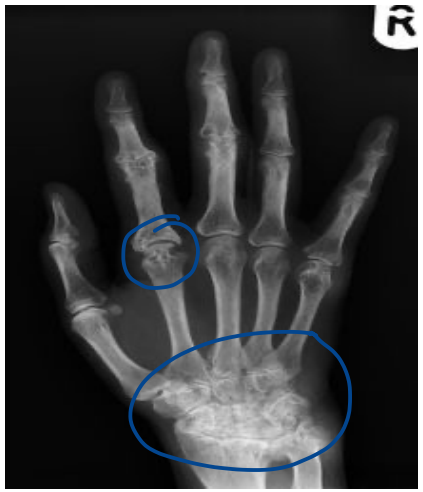
Hook shaped metacarpals:
. Hemochromatosis

Chronic Arthritis

Pain, swelling, Improves with activity, Morning stiffness

Inflammatory

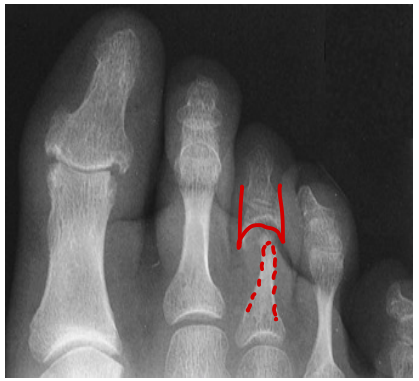
- HLA DR4 "Rheum" (RA)
- MC- MCP
- Sparing- DIP
- Symmetrical space reduction
- Osteopenia, Erosions - peripheral (Hallmark)
- PANNUS



Psoriatic arthritis

- MC joint- DIP
- MC type oligo-arthritis (≤4)
- Pencil-in-cup, telescoping of digits, Arthritis mutilans
- Skin and Nail changes

RF -ve



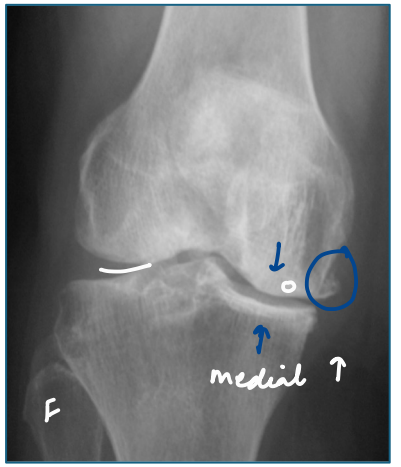
- No erosions
- Deformity +

Jaccoud's arthropathy (SLE)

Pain after weight bearing, improve with rest

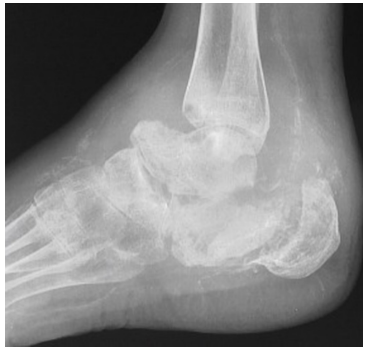
Non-inflammatory

- Hip, Knee, DIP, PIP, 1st CMC (OA)
- MCP sparing
- Asymmetric joint space reduction
- Osteophytes, Subchondral sclerosis, Geodes



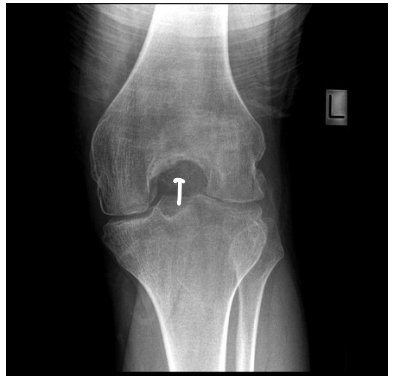
Neuropathic / Charcot foot

- 5Ds-Disorganisation, Density, Destruction, Debris, Distension
- Diabetes/ neuropathy
- Looks bad, doesn't feel bad



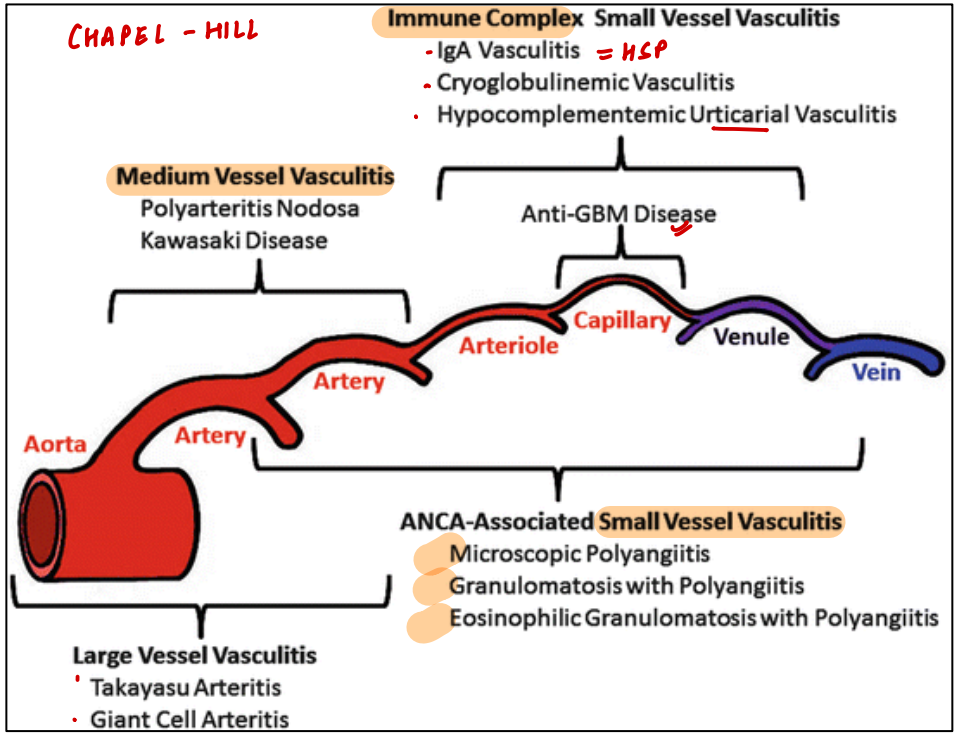
Hemophilic arthropathy

- Child
- Knee-Squared patella, Intercondylar notch widening
- Pseudotumor "hematoma muscle"



Vasculitis

Rx - steroids ± cyclophosphamide



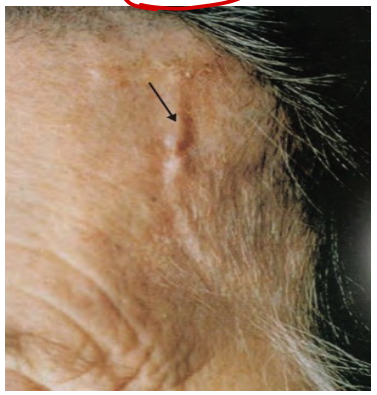
Granulomas

- GCA
- Takayasu
- GPA = WG
- EGPA = Churg Strauss

IMMUNE COMPLEX

H S P - C
/ \ \ \
HSP SLE PAN Cryoglobulinemia

GCA

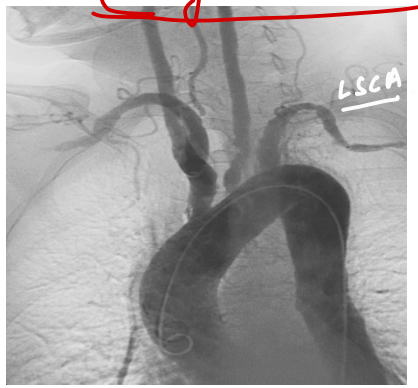


>50yr, Jaw claudication, PMR (-specific, skip lesions)

MC artery: STA
Next step: steroids
Gold standard: Biopsy (skip lesions)

most dreaded complication ↳ AION

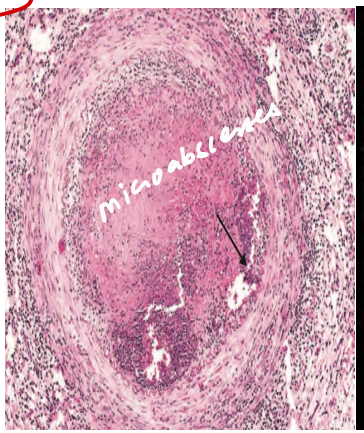
Takayasu arteritis

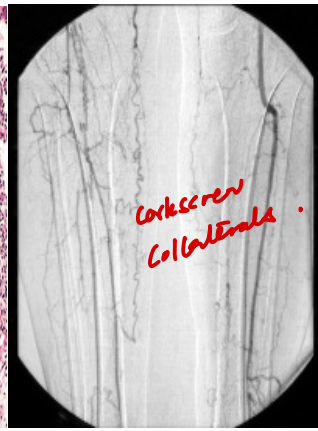


<40yr, BP difference between UL, RAS, MI

MC artery: Lt SCA

Mod. sharma classific

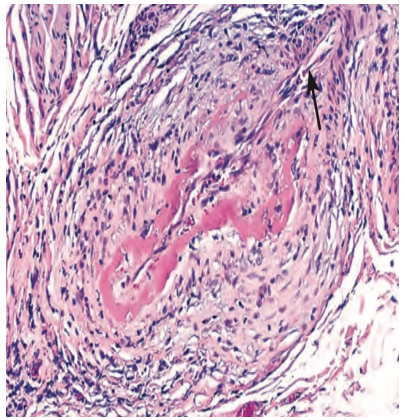




<35yr, smoker, severe limb pain - A/V/N

Thromboangiitis obliterans / BUERER'S D

radial / tibial A

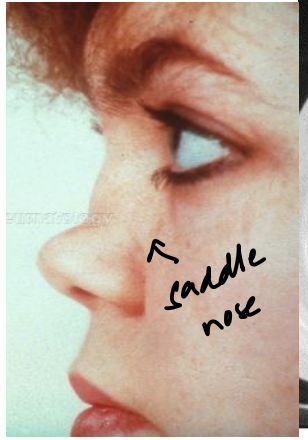


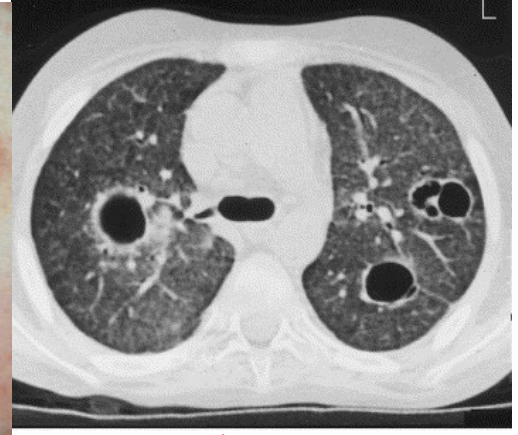
PAN

Hep B +(30%.) — renal A
Hypertension

Not involved: PA /glomerular
H/P: · fibrinoid necrosis
· skip areas
· transmural Inv

RA - aneurysm a
L D/D TSC
L PAN

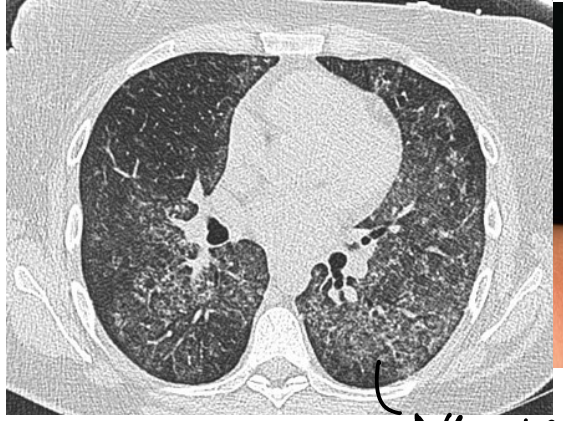




Wegener's = GPA

Triad: URT (sinusitis) +
LRT (cavity ++) +
RPGN (crescents)
↳ ⊛ granulomas

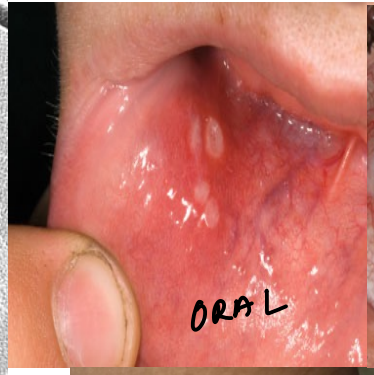
C ANCA

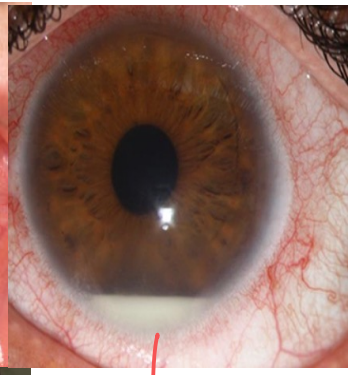


Diffuse nge

Hemoptysis + Hematuria
D/D: · Goodpasture · WG
· MPA
p-ANCA

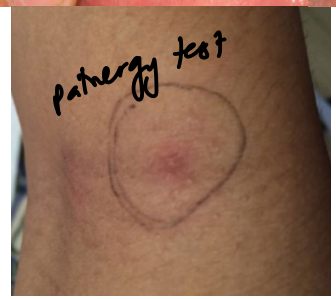
Churgg-Strauss / EGPA
eosinophilia asthma





uveitis

· GENITAL
MC - scrotum / labia

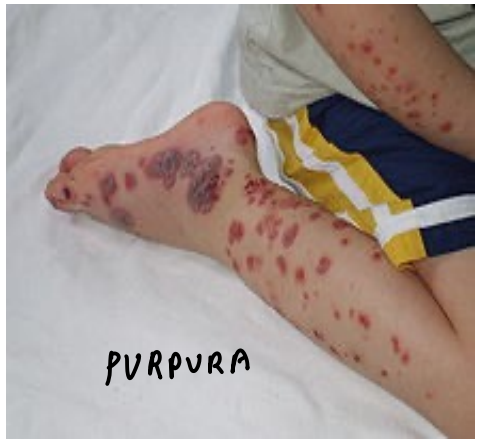


Diagnosis: Behcet's
HLA: B51
Ab: α-enolase
Biopsy: Neutrophilic

any vessel - s/m/l

Sweet Sx - dermatitis

Pannivins



HSP = IgA vasculitis

CRITERIA:

- Purpura with lower limb predominance ⊕
- Diffuse abdominal pain with acute onset – submucosal hematomas → intussusception
- H/P: leukocytoclastic vasculitis or proliferative glomerulonephritis with IgA deposits
- Arthritis or arthralgia of acute onset → cryoglobulinemia
- Renal involvement-proteinuria or haematuria

Rx: steroids (specific – GI bleed)

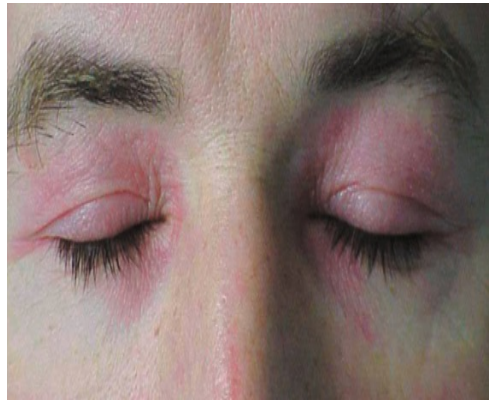
Cryoglobulinemia – Ig ppt in cold

Feature	Type I (10%)	Type II (65%) – Mixed	Type III (25%) – Mixed
Composition	Monoclonal IgM	Monoclonal IgM (RF)+ polyclonal IgG	Polyclonal IgM + polyclonal IgG
Associated conditions	Lymphoproliferative diseases	HCV (80–90%)	
Complement levels	Normal	Low C4	
Symptoms & signs	Raynaud phenomenon Livedo reticularis Hyperviscosity	Meltzer's triad: purpura, arthralgia, weakness Liver / lung/ Kidney (MPGN) involvement Peripheral neuropathy	

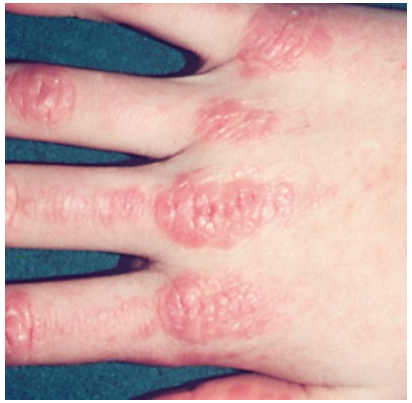
MM

Approach to myopathies

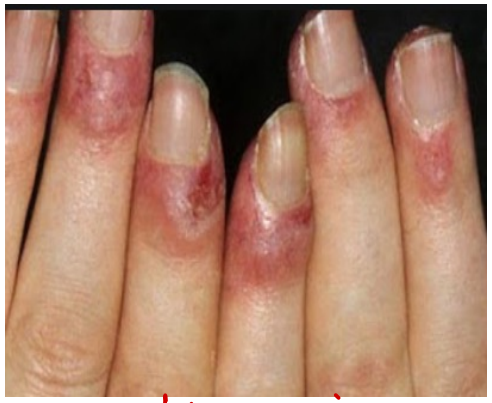
	Polymyalgia rheumatica	Inflammatory myopathy	Steroid myopathy	Statin myopathy	Hypothyroid
ESR	Raised	Raised	N	N	N
CK	N	Raised	N	Raised	Raised
	Shoulder, hip pain Morning Stiffness >50yrs GCA	Proximal pain and weakness	Proximal weakness No pain	Pain No weakness	Proximal Pain and weakness Delayed reflexes



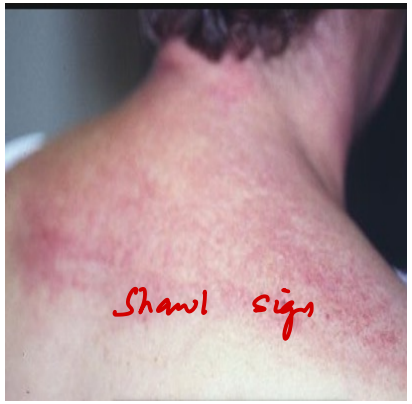
Heliotrope rash



Hallmark – Gottron papules

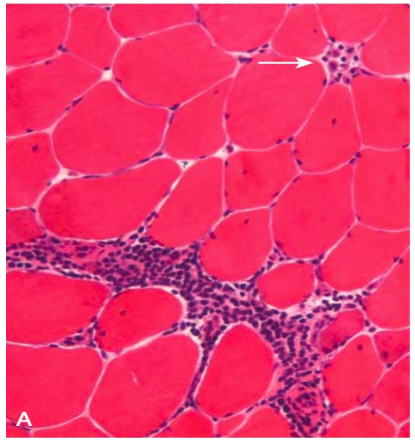


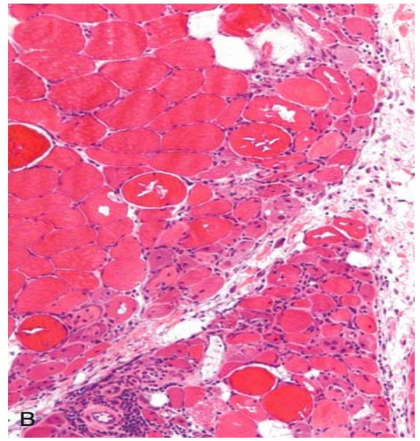
telengiectasia

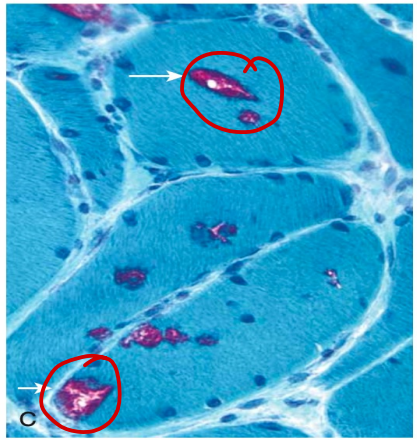


Holster sign – thighs

Dermatomyositis → paraneoplastic Cadeno







Endomysial inflammation → Polymyositis

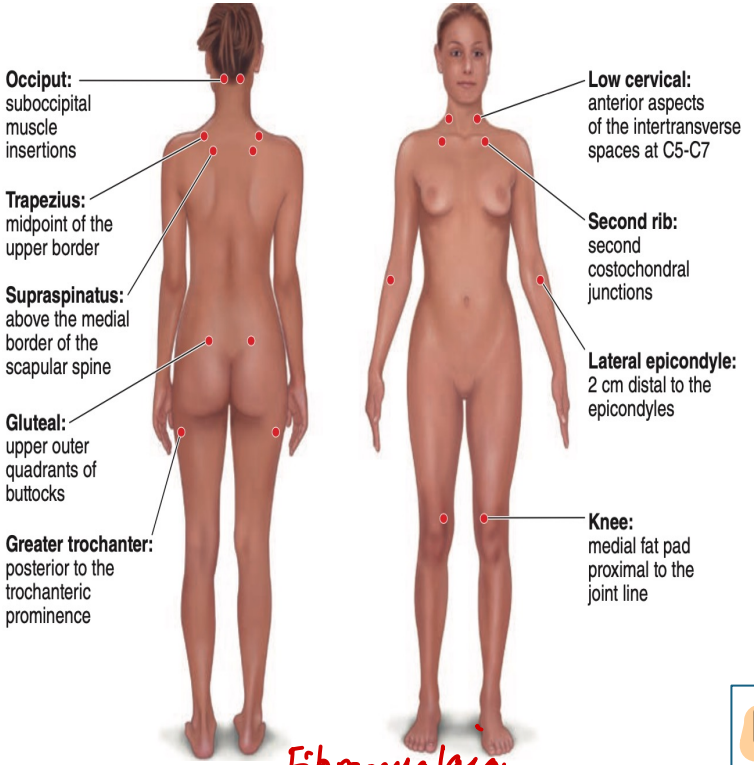
Perimysial Inflammation, Perifasicular atrophy → Dermatomyositis

- young
- proximal PP

Rimmed vacuoles → Inclusion body myositis

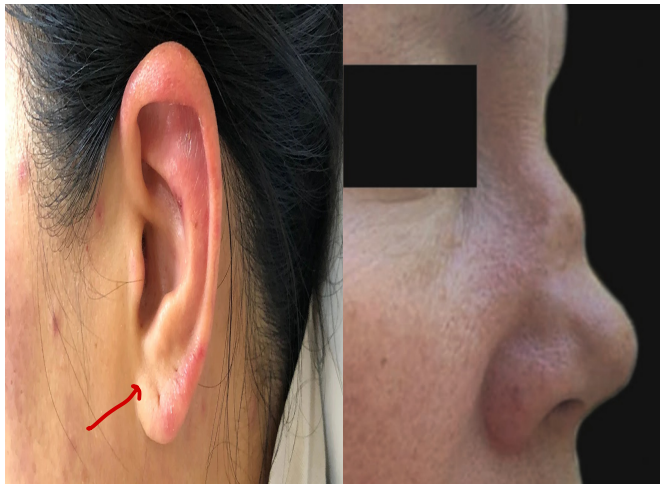
- elderly
- distal / proximal

Miscellaneous



Fibromyalgia

Fatigue / Sleep dysfunction
Tension headache
ESR: (N)
>11/18 tender points
TOC: CBT
FDA-approved drugs:
Duloxetine (SNRI), Milnacipran, Pregabalin

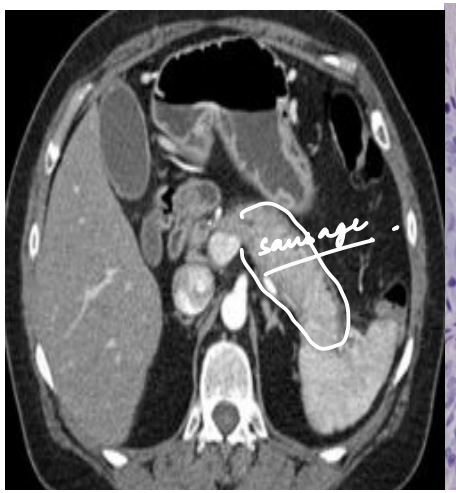


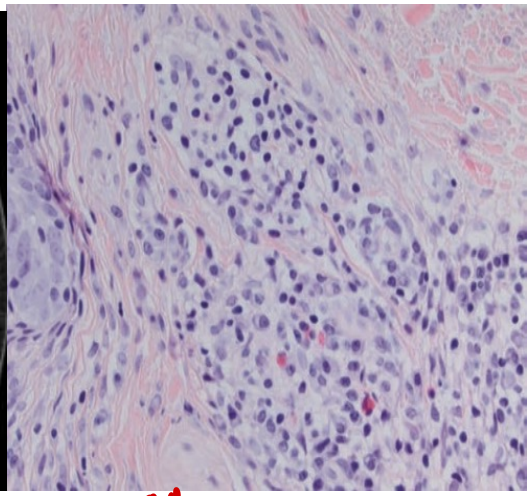
Relapsing polychondritis
Pinna
Nose
tracheal cartilage

MAGIC syndrome
(Mouth And Genital ulcers with Inflamed Cartilage)

Familial mediterranean fever

MEFC gene → Pyrin IL-1 / IL-6 ↑↑
Periodic fever (1-3 days)
Recurrent serositis
Arthritis
Rx-Colchicine





IgG4RD ad

CRITERIA: Mayo
Histology - Lymphoplasmatic + storiform fibrosis
Imaging of Pancreas (mc) - AIP
Serology: IgG4 (>140mg/dL)
Other Organ Involvement 2nd - bile duct stricture
Response to Steroid Therapy

INTEGRATED **RHEUMATOLOGY**

BTR 3.0

Auto-Antibodies

Associated with **SLE**

1. **ANA (Anti Nuclear Antibody) :** most sensitive *(entry criterion for diagnosis)*
2. **Anti C1q** > **Anti ds-DNA :** Corresponds to disease activity in SLE *(Flares)*
3. **Anti histone :** drug induced SLE *(SHIP drugs)*
4. **Anti Smith** : most specific antibody in SLE
5. **Anti neuronal Ab/ Anti glutamate receptor 2 :** CNS Lupus
6. **Anti ribosomal P :** Psychiatric manifestations in SLE

Anti-Ro (SSA) **antibodies**

In the fetus / neonate

- Associated with **neonatal lupus**
- Can cause **congenital heart block** (CHB)

In the mother

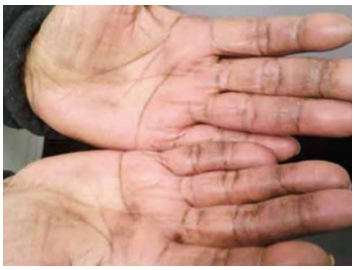
- **Lower incidence of Lupus Nephritis**

Associated with other **Connective tissue disorders**

1. **Anti-U1 RNP :** Mixed connective tissue disorder (MCTD)
2. **Anti-Ro** (SS-A) / **Anti-La** (SS-B) **:** Sjogren's Syndrome

Associated with **Dermatomyositis**

1. **Anti-Jo1 :** Anti Synthetase Syndrome *(Mechanic's hands + ILD + Myositis + Fever)*
2. **Anti-Mi2** : Good prognosis in Dermatomyositis "***MI-2 was a good movie***"
3. **Anti MDA-5** : Bad prognosis in Dermatomyositis



Mechanic's hands

Seen in Antisynthetase syndrome

Associated with **Scleroderma**

1. **Anti-topoisomerase 1** / **Anti-scl-70 :** Diffuse cutaneous systemic sclerosis
2. **Anti-centromere :** Limited cutaneous systemic sclerosis *(CREST Syndrome)*

Anti-Neutrophil Cytoplasmic Antibodies (ANCA)

1. **P-ANCA** :
   - Microscopic polyangiitis (MPA)
   - Eosinophilic granulomatosis with polyangiitis (*formerly called Churg Strauss syndrome*)
   - Ulcerative colitis & Primary sclerosing cholangitis
2. **C-ANCA** : Wegner's Granulomatosis with Poly Angiitis (WGPA)

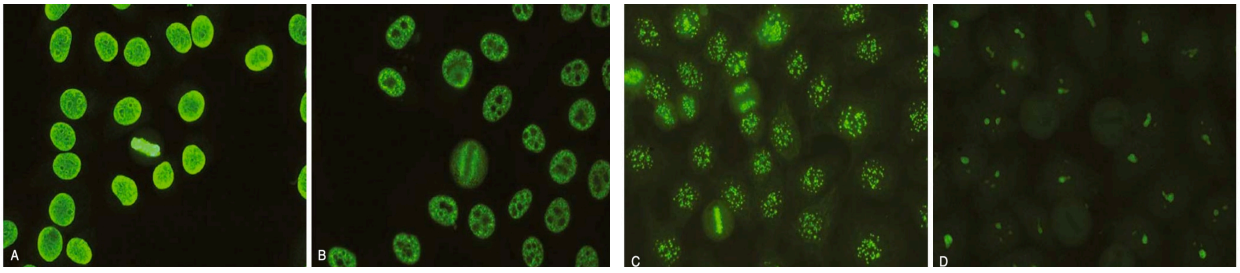
Associated with **Rheumatoid arthritis**

1. **Rheumatoid factor : IgM** antibody against **Fc** portion of **IgG**
2. **Anti CCP antibody** : Most specific antibody in Rheumatoid arthritis

Other auto-antibodies

1. **Anti-endothelial cell Ab** : Kawasaki disease (*medium vessel vasculitis*)
2. **Anti-alpha-enolase Ab** : Behcet's disease *(variable vessel vasculitis)*

Auto Antibodies - Fluorescence pattern



Homogeneous pattern
- Anti-**dsDNA**
- Anti-**histone**

Speckled pattern
- Anti-**Ro**, Anti-**La**
- Anti-**U1 RNP**
- Anti-**Jo-1**

Centromere pattern

Anti-centromere in CREST syndrome

Nucleolar pattern

Anti-Scl-70 in Diffuse Systemic Sclerosis

Cytoplasmic pattern : C-ANCA
- Target antigen: **Proteinase-3** (PR3)
- Seen in Wegener's GPA

Peri-nuclear pattern : P-ANCA
- Target antigen: **Myeloperoxidase** (MPO)
- Seen in MPA, EGPA, UC, PSC

EULAR/ACR Criteria - SLE

- ANA ≥ **1:80** *by immunofluorescence*, is entry criterion (*without this - no SLE classification*)
- Additive weighted scoring system (**clinical** + **immunological** domains)
- **Only highest score** per domain is counted, total score ≥ **10** : classify as SLE

Clinical Domain

Constitutional
- Fever (2)

Mucocutaneous
- Non-scarring alopecia (2)
- Oral ulcers (2)
- Subacute cutaneous / Discoid lupus (4)
- Acute cutaneous lupus (6)

Musculoskeletal
- Synovitis in ≥2 joints (6)

Neuropsychiatric
- Delirium (2)
- Psychosis (3)
- Seizure (5)

Serosal
- Pleural / Pericardial effusion (5)
- Acute pericarditis (6)

Shrinking lung syndrome seen with SLE (decreased lung volume)

Hematologic
- Leukopenia (3)
- Thrombocytopenia (4)
- Autoimmune hemolytic anemia (4)

Renal
- Proteinuria >0.5 g/24 hr (4)
- Class II / V lupus nephritis (8)
- Class **III** / **IV** lupus nephritis (10)

Immunological Domain

Antiphospholipid Abs
- aCL / anti-β2GP1 / Lupus anticoagulant (2)

Laboratory effects :
- **Anti Cardiolipin** : **False-positive VDRL / RPR**
- **Lupus anticoagulant** : ↑ **aPTT** (*not corrected on mixing study*)

Complement proteins
- Low C3 **or** C4 (3)
- Low C3 **AND** C4 (4)

SLE-specific Abs
- Anti-dsDNA (6)
- Anti-Sm (6)

ISN/RPS Classification of Lupus Nephritis

Class	Type	Key Features
I	Minimal **mesangial**	Mesangial immune deposits
II	**Mesangial** proliferative	Mesangial **hypercellularity** + deposits
III	**Focal** Lupus Nephritis	<50% glomeruli involved
IV	**Diffuse** Lupus Nephritis (m/c type in SLE)	≥50% glomeruli; **subendothelial deposits**; **wire-loop lesions**
V	**Membranous** LN	**Subepithelial** deposits
VI	**Advanced sclerosing**	≥90% globally sclerosed; **ESRD**

Treatment of Lupus Nephritis

Induction therapy :
- **Steroids** + Cyclophosphamide or Mycophenolate mofetil (MMF)

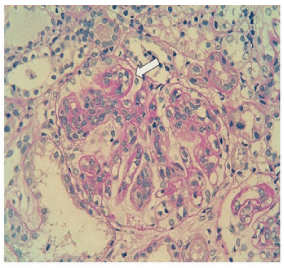
Biologics / targeted therapy
- **Belimumab** : inhibits **B-lymphocyte stimulator** (BLyS)
- **Anifrolumab :** inhibits **type I interferon** receptor

Newer agent
- **Voclosporin** : calcineurin inhibitor

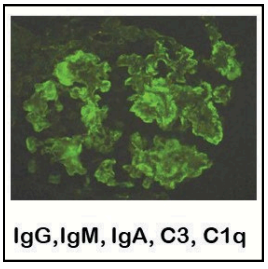
Definitive : **Renal transplantation** *(low recurrence post-transplant)*

Pathophysiology

Defective clearance of apoptotic debris and DNA leads to **immune complex formation** (type 3 Hypersensitivity)
- HLA-**DR3** : genetic susceptibility to SLE
- **Early complement deficiency** (C1q, C2, C4) due to **impaired immune complex** clearance in SLE
- **TREX1 mutation** : causes defective DNA clearance

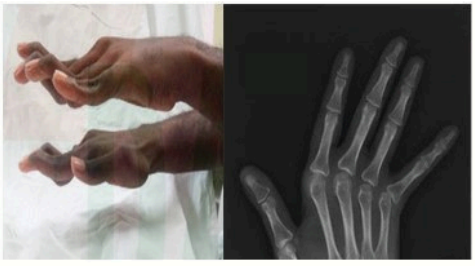


Wire loop deposits *on light microscopy*



Full house effect *on immunofluorescence*

- "**Symmetrical**" small joint polyarticular arthritis (***most common clinical feature*** *of SLE*
- **Jaccoud arthropathy** : Deformity present but erosions absent (d/d of RA)

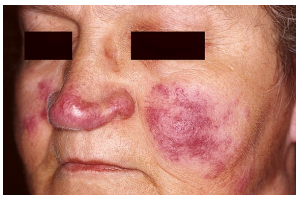


Jaccoud Arthropathy

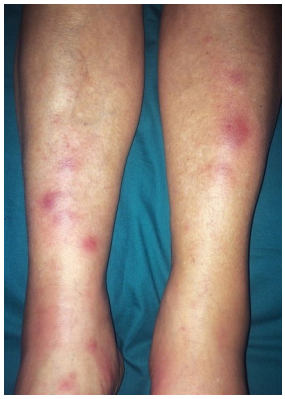
Sarcoidosis

Fever + Cough + hilar lymphadenopathy = TB or Sarcoidosis

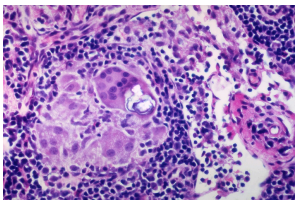
- Sarcoidosis is a **multisystem granulomatous** disorder
- Histology**: non-caseating granulomas**
- Granulomas contain **1-α hydroxylase : extra-renal calcitriol production**
  - Leads to **hypervitaminosis D** and **hypercalcemia**
- **Erythema nodosum**: a panniculitis *(inflammation of subcutaneous adipose tissue)* characterised by red, painful nodules.
- **Lupus pernio**: a violaceous, nodular rash distributed over the nose and cheeks *(pathognomonic but rare)*



Lupus Pernio
(seen in chronic sarcoidosis)

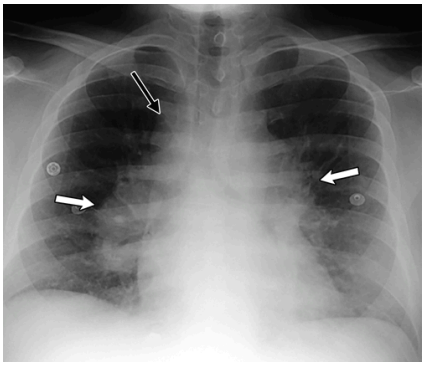


Erythema nodosum
(septal panniculitis)



Non caseating Granulomas

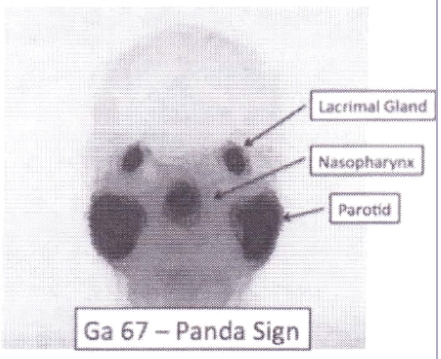
- **Schumann bodies :** calcium + protein inclusions
- **Asteroid bodies :** star-shaped eosinophilic inclusions



Bilateral hilar and mediastinal lymphadenopathy

Scadding staging based on CXR findings

Stage 1 : **Bilateral hilar lymphadeno.** (BHL)
Stage 2 : BHL + **pulmonary infiltrates**
Stage 3 : Pulmonary infiltrates only
Stage 4 : Pulmonary **fibrosis**



Panda sign on **Gallium 67** scan

- Increased uptake in **bilateral parotid** and **lacrimal glands** gives the Panda appearance
- **Lambda** (Garland) **sign**: uptake in **bilateral hilar** + **right paratracheal lymph nodes** forming **λ pattern**

Clinical Syndromes in Sarcoidosis

Heerfordt Waldenstorms's syndrome

- **Uveitis**, **Parotitis** (*aka uveoparotid fever*)
- **7th CN** palsy *(facial nerve)*

Lofgren's Syndrome

- **Hilar Lymphadenopathy**
- **Erythema Nodosum**
- **Migratory polyarthritis**

Lab features in Sarcoidosis

1. **Serum ACE** *(angiotensin converting enzyme)* raised
2. **Calcium** elevated *(extra-renal 1α-hydroxylase causes increased calcitriol)*
3. **Lymphopenia :** Because lymphocytes (T cells) are sequestered in granulomas
4. Bronchoalveolar lavage : **CD4/CD8 ratio > 3.5** *(normal CD4/CD8 is 2 : 1)*
5. **Kveim test** = Diagnostic skin test *(obsolete now*

Differentials of Bilateral Parotid Swelling

HIV infection	Sjogren's syndrome	Sarcoidosis
CD8+ T-cell infiltrate	**CD4**+ T-cell infiltrate	**Granulomatous** inflammation
HIV positive	Anti-Ro , Anti-La	**↑ ACE**, hypercalcemia
	Risk of **MALT lymphoma**	

Sialosis : painless, non-inflammatory bilateral parotid enlargement seen in **Alcoholism**, **malnutrition**, and **Diabetes Mellitus**

Scleroderma-CREST

- **Immune-mediated damage** to vascular structures (e.g. blood vessels) and **excessive synthesis and deposition** of extracellular matrix structures (e.g collagen). This leads to chronic fibrosis, scarring and damage to organs
- Further divided into 2 subtypes :

Limited Cutaneous systemic sclerosis

*anti **centromere** Ab*

- **CREST** Syndrome
- Long standing history of Raynaud's
- Internal organ involvement is **very late**
- **PAH** > ILD

Diffuse cutaneous systemic sclerosis

*anti **topoisomerase** Ab/ anti **SCL 70** Ab*

- Sudden onset of Raynaud's
- **Rapidly progressive** course
- **ILD** > PAH
- Scleroderma **renal crisis**
- **Cardiomyopathy** (RCM/DCM)

For **screening** of systemic sclerosis :

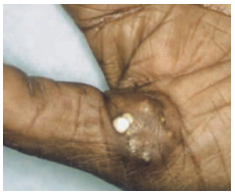
- **ANA** testing is done *(ANA is positive in >95% cases)*
- **Most sensitive** for both limited and diffuse type

For **confirmation**

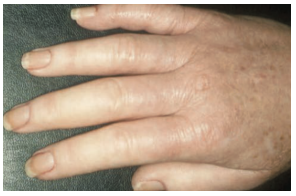
- **Limited cut. :** Anti **centromere** Ab
- **Diffuse cut. :** Anti **Topoisomerase/** Anti **SCL 70** Ab

CREST syndrome

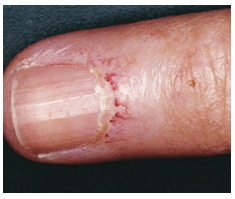
C - **Calcinosis cutis** : calcium deposits in the skin
R - **Raynaud's phenomenon** *(white-blue-red)*
E - **Esophageal dysmotility** : swallowing difficulty
S - **Sclerodactyly** : skin thickening of fingers and toes
T - **Telangiectasia** : dilated capillaries.



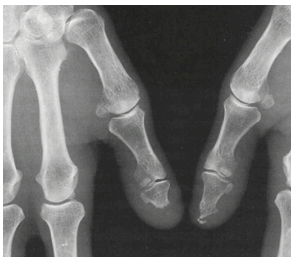
Calcinosis cutis



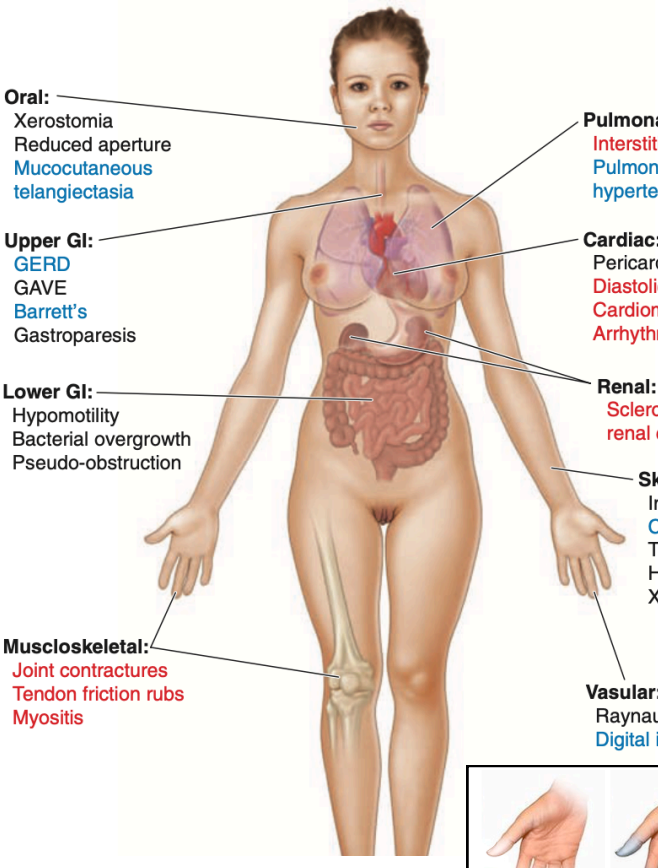
Sclerodactyly
(Sausage fingers)

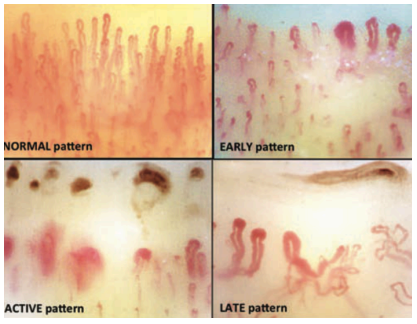


Telangiectasia



Acro-osteolysis
(secondary to ischemia)

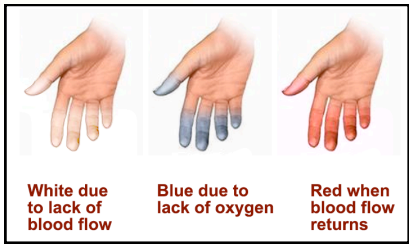




Nail bed capillaroscopy
Non-invasive test to examine microcirculation at nailfold

Anti-fibrillarin (Anti–U3 RNP)

- Prognostic marker in **diffuse systemic sclerosis**
- Associated with **severe disease**, especially **pulmonary hypertension** and **visceral involvement**



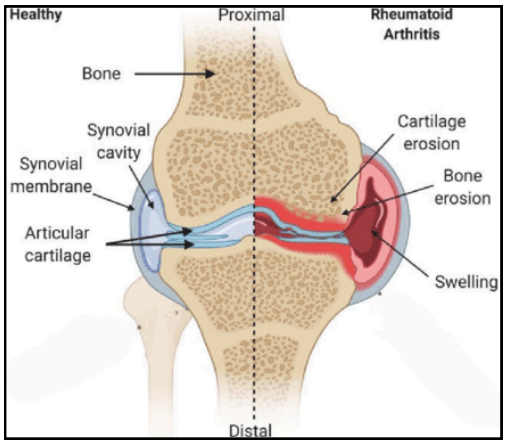
Raynauds Phenomenon

- Attacks usually happen when patient is **cold** or **feeling stressed**.
- DOC : **DHP CCBs**

Rheumatoid Arthritis

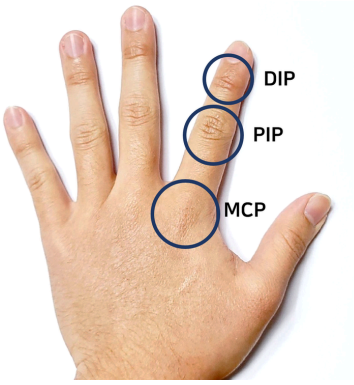
Pathophysiology

- Synovitis - synovial hyperplasia - pannus formation - **erosion**
- **Pannus :** Hyperplastic, inflamed synovium that invades and destroys cartilage and bone in Rheumatoid arthritis



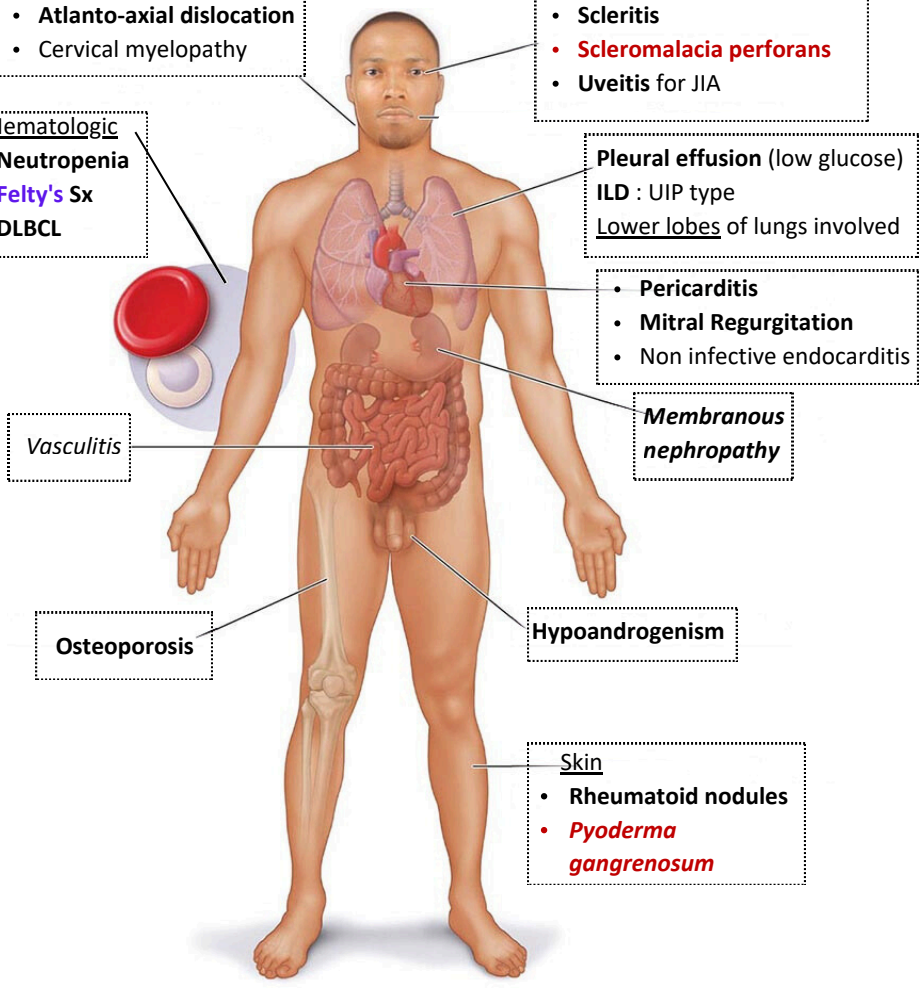
Rheumatoid Arthritis - Most common features

- Joints involved : **MCP** & **PIP**; DIP spared
- Spine involvement: **C1–C2** (atlanto-axial) **subluxation**
- Extra-articular : **Subcutaneous nodules**
- Cardiac manifestation : **Pericarditis**
- Valvular lesion : **Mitral regurgitation** (MR)
- Pulmonary : **Pleural effusion**
- Hematological : **Anemia of chronic disease** (AOCD)
- Ocular : **Keratoconjunctivitis sicca** (KCS) > **scleritis**
- Lymphoma : **Diffuse large B-cell lymphoma** (DLBCL)
- MCC of death: **Cardiovascular disease** - cardiac arrest



Juvenile Idiopathic Arthritis (JIA)

- Definition: Age <**16 years** + arthritis ≥**6** weeks
- Most common type: **Oligoarticular JIA** (≤4 joints)
- Systemic JIA (aka Still's disease): Least common type of JIA
  - **Fever** + **arthritis +** Inflammatory markers raised
  - **Salmon-pink evanescent** rash
  - **Hepatosplenomegaly** (HSM)



Felty Syndrome:
RA **+ splenomegaly + neutropenia**

Caplan Syndrome
RA + **Coal worker pneumoconiosis**

Erasmus Syndrome :
Silicosis + Systemic sclerosis

Rheumatoid Arthritis - Management

Symptomatic RA → **NSAIDs** *± short-term glucocorticoids* → Conventional **DMARDS** (Disease-modifying antirheumatic drugs) → **Biologics** (Targeted Therapy)

Methotrexate (MTX) with Folic acid

- **DMARD of choice** and has to be started early
- Failure to respond : **DMARD "step up"** *(another DMARD is added for combination therapy)*
- S/E: **Hepatotoxicity**, **pulm. fibrosis**, **myelosuppression**
- Antidote in toxicity: **Leucovorin** (folinic acid)
- **Glucarpidase** : Used in **severe toxicity** with renal failure (*Hydrolyzes MTX into non-toxic compounds*)

Others

1. **Sulfasalazine**
2. **Hydroxychloroquine** (HCQ)
3. **Leflunomide**

Biologics

- Used as **second-line** in combination with DMARDs
- Initial therapy in patients with **severely active** and **progressive disease**

TNF-α inhibitors : ***ACE-I ki GOLI***

A	**A**dalimumab
C	**C**ertolizumab
E	**E**tanercept
I	**I**nfliximab
Goli	**Goli**mumab

Other Biologics

- **Interleukin 1R** antagonist : **Anakinra**
- **Interleukin 6** inhibitor : **Tocilizumab, Sarilumab**
- **B cell** (**CD 20**) inhibitor : **Rituximab**
- **CTLA-4** (T cell co-stimulator) inhibitor : **Abatacept**
- **JAK** inhibitor *(small mol inhibitor)* : **Tofacitinib, Baricitinib, Upadacitinib**

Side effects of Biologics

- **TNF-α inhibitors** : **TB reactivation** (*IGRA done to rule out TB*), Drug induced SLE
- **Rituximab** : **Hep B reactivation**

Pregnancy & autoimmune shift

Th1 to **Th2** shift : ↓ **cell-mediated immunity**, ↑ **humoral immunity**

- Improve in pregnancy: **RA**, **Multiple sclerosis**, **psoriasis**
- Worsen in pregnancy: **SLE**, **Graves disease**, **Myasthenia gravis**

Drugs for RA in pregnancy

- Safe : **Hydroxychloroquine**, **Sulfasalazine** (+ folic acid)
  - **HCQ**: Retinal toxicity (bull's eye maculopathy), cardiotoxicity
  - **Sulfasalazine**: Reversible male infertility, CI in G6PD deficiency
- Avoid: **Methotrexate**, **Leflunomide**

Biologics in pregnancy

- All biologics are **safe in later pregnancy** (*after 2nd trimester*)
- Safest overall**: Certolizumab**

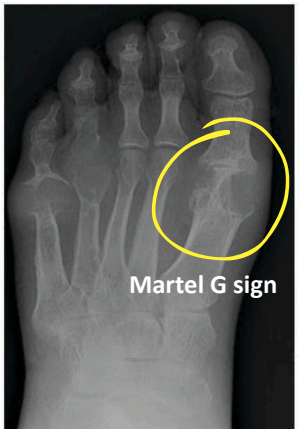
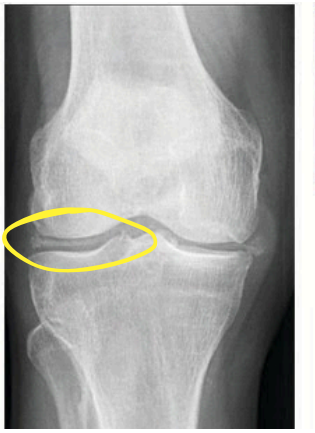
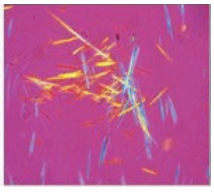
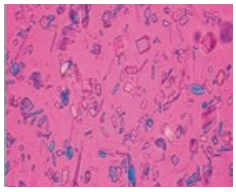
In Ankylosing spondylitis : *No role of conventional DMARDs*

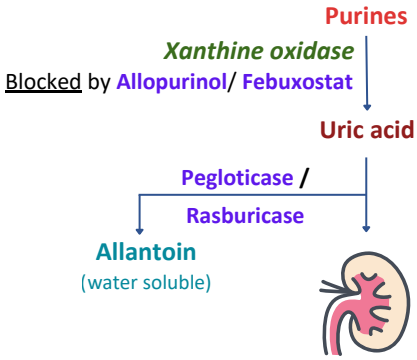
- **NSAIDs** → directly to **biologics**

Acute Arthritis

Feature	Normal	Osteoarthritis (OA)	Inflammatory arthritis	Septic arthritis
Appearance	Clear	Clear	Turbid	Turbid
Viscosity "Stringing"	**High** *Stringing Positive*	**Decreased** *Stringing Negative*	**Decreased** *Stringing Negative*	**Decreased** *Stringing Negative*
WBC count (/mm³)	<200	200–5000	5,000–50,000	>**50,000**
PMN %	<25%	<25%	25–50%	>**50**%

Acute Arthritis - Crystal Arthropathies

Gout	Pseudo-Gout
	
• Deposition of **uric acid crystals** in the joints • **1st MTP** joint m/c affected (*aka Podagra*) • Acute red great toe • Elderly/Alcoholic • Deposition of **monosodium urate** crystals • **Erosions** present *(rat bite erosions)*	• **Calcification** in joint cartilage *(aka chondrocalcinosis)* • m/c joint : **Knee** • Deposition of **calcium pyrophosphate** crystals Important associations 1. **Hemochromatosis :** classic hook-shaped MCPs on X-ray 2. **Hyper-parathyroidism** 3. **Hyper-magnesemia** 4. **Hypo-thyroidism**
 ***Negatively birefringent*** **Monosodium Urate** crystals in gout (*needle shaped*)	 ***Positively birefringent*** **Calcium pyrophos.** crystals (rhomboid) in pseudogout



Management of Gout

Acute Gout Attack

- First-line: **NSAIDs**
  - **Indomethacin** preferred
  - **Avoid aspirin** (*low dose aspirin reduce uric acid excretion and worsen gout*)
  - **Avoid Paracetamol** (*only pain relief, no anti-inflammatory effect*)
- Alternative: **Colchicine** *(most effective for acute gout)*
  - MOA: **Blocks microtubules** - inhibits neutrophil **chemotaxis** and inflammation
  - Limitations: **Refractory Diarrhea**, **bone marrow suppression** (hence, not used as 1st line)
- **Steroids**: Used if NSAIDs/colchicine contraindicated

Chronic Gout :

Goal: Lower serum uric acid <**6** mg/dL
(prevent attacks & tophi)

- DOC : **Allopurinol** (*xanthine oxidase inhibitor*)
  - S/E: **Hypersensitivity**, **Stevens-Johnson syndrome** (SJS), **allergic interstitial nephritis** (AIN)
  - Drug interactions: Avoid with **azathioprine** or **6-mercaptopurine** (*metabolized by XO*)
- Alternative: **Febuxostat** (XO inhibitor)

Recombinant uricase

(***Urate oxidase*** *- converts uric acid to allantoin)*

- **Pegloticase :** Used in severe gout
- **Rasburicase** : Used mainly for hyperuricemia associated with tumor lysis syndrome

Drugs that precipitate Gout

'CANT LEAP'

C	**C**yclosporine & cancer drugs
A	**A**spirin *(low dose)*
N	**N**iacin
T	**T**hiazide (m/c/c)
L	**L**asix (furosemide)
E	**E**thambutol
A	**A**lcohol
P	**P**yrazinamide (*more than ethambutol*)

Diuretics *are the most common precipitating drugs for gout*
Thiazide *> Loop Diuretics*

Chronic Arthritis

Chronic Arthritis (> 6 weeks)

Inflammatory arthritis

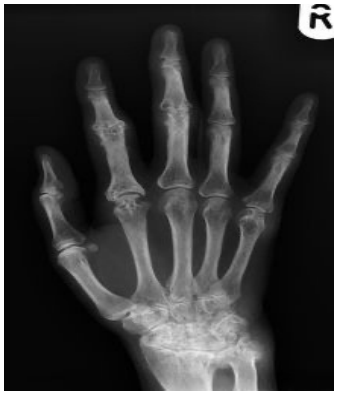
- Pain: **Worse at rest**, improves with activity
- Swelling: **Present**
- Stiffness: Morning stiffness **>30 minutes**
- Examples: **Rheumatoid arthritis**, **Psoriatic arthritis**, **Ankylosing spondylitis**, **SLE arthritis**

Non - Inflammatory arthritis

- Pain: **Worse with activity**, improves with rest
- Swelling: **Usually absent** or **minimal**
- Stiffness: Brief (**<30 minutes**), mainly mechanical
- Examples: **Osteoarthritis**

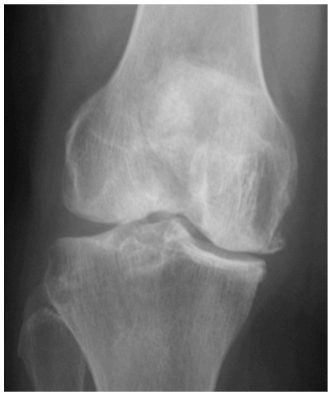
Rheumatoid Arthritis

- Genetics: **HLA-DR4** "***Room has 4 walls***"
- Joints: **MCP** (m/c)**, PIP**
- Joint spared : **DIP**
- X-ray hallmark:
  a. **Symmetrical** joint space narrowing
  b. **Periarticular osteopenia**
  c. Peripheral **erosions**



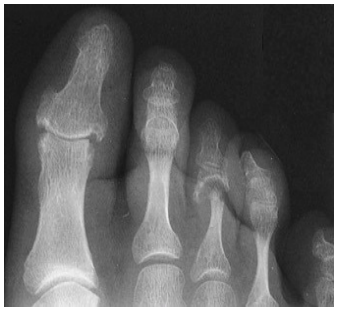
Osteo-Arthritis

- Joints: **Hip**, **knee**, **DIP**, **PIP**, **1st CMC** (*specific*)
- Joint spared : **MCP**
- X-ray features:
  - **Asymmetric** joint space reduction
  - **Osteophytes**
  - Subchondral **sclerosis**
  - **Geodes** (subchondral cysts)



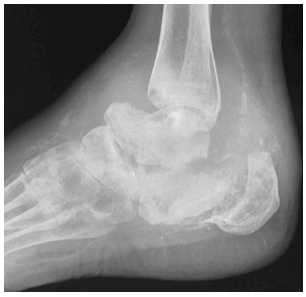
Psoriatic Arthritis

- MC joint: **DIP**
- MC type: **Oligoarthritis** *(<4 joints)*
- X-ray:
  a. **Pencil-in-cup** deformity
  b. **Telescoping digits** (*arthritis mutilans*)
- Clinical: Skin and nail changes



Neuropathic Joint (Charcot)

- Causes: **Diabetes**, **neuropathy**, **syringomyelia**
- Mnemonic: **5 D's**
  - **D**isorganization
  - **D**ensity
  - **D**estruction
  - **D**ebris
  - **D**istension
- *Looks very destructive,* ***but pain often minimal***

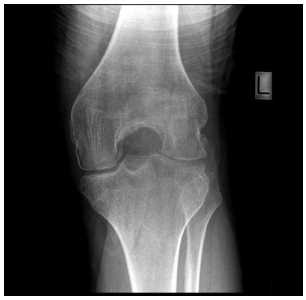


SLE-associated Arthritis

- Features: **Non-erosive**
- Deformities: **Jaccoud's arthropathy** (*ulnar deviation, swan-neck, correctable*)
- X-ray: **Usually normal** or **mild joint space narrowing**, no erosions

Hemophilic Arthropathy

- Seen in **Children**, *(often* ***knees****)*
- X-ray:
  a. **Squared patella**
  b. **Widened intercondylar notch**
- Complication: *Pseudotumor*



Vasculitis

Vasculitis
(Chapel Hill Classification)

Large Vessel
1. **Giant cell** arteritis
2. **Takayasu** arteritis

Both affect Aorta and its branches

Medium Vessel
1. **Kawasaki** disease
   *Affects **coronary** arteries*
2. **Poly arteritis nodosa**
   *Affects **renal** arteries*

Small Vessel

ANCA associated
1. Eosinophilic GPA - **P ANCA**
2. Microscopic poly-angitis (MPA) - **P ANCA**
3. Wegener's GPA - **C ANCA**

Immune complex associated
1. **HSP** *(IgA Vasculitis)*
2. **Cryoglobulinemia**

Variable
1. Behcet's Syndrome
2. Cogan's Syndrome

Most common
- Vasculitis in adults : **GCA**
- Vasculitis in children : **HSP** *(Kawasaki in Asia)*

*Vasculitis based on **pathophysiology***

Granulomatous Vasculitis
- **Giant cell arteritis**
- **Takayasu arteritis**
- **Wegner's** GPA
- **Eosinophilic** GPA *(Churg Strauss Sx)*

ANCA associated

C-ANCA
Wegener's GPA

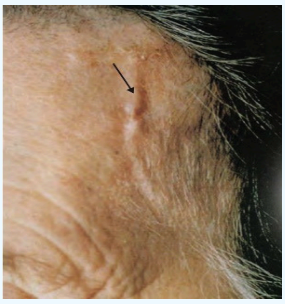
P-ANCA
aka MPO ANCA
- ***Eosinophilic GPA***
- ***Microscopic poly-angitis*** *(MPA)*

Immune complex associated
1. **HSP** *(IgA Vasculitis)*
2. **SLE**
3. **PAN** *(a/w **Hep B**)*
4. **Cryoglobulinemia** *(a/w **Hep C**)*

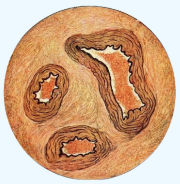
ANCA associated diseases involve **Lungs** *(pulmonary haemorrhage)* and **Kidney** *(glomerulonephritis)*

Giant Cell Arteritis

- Also called **Temporal Arteritis**
- Type: **Granulomatous large-vessel vasculitis** (Type IV hypersensitivity)
- Age: >**50** years
- Association: **Polymyalgia Rheumatica** (stiffness of bilateral shoulders, neck, hips, and pelvic girdle)
- Symptoms: **Jaw claudication** (*classic*), Unilateral headache, Scalp tenderness
- Most commonly affected : **Superficial temporal artery**
- Medical emergency: **Risk of permanent blindness** if **ophthalmic artery** gets involved (causes AION) → *start steroids immediately on clinical suspicion*
- Diagnosis: **Temporal artery biopsy** (**VVG stain**)
  long segment biopsy preferred because of skip lesions



Superficial Temporal artery thickening

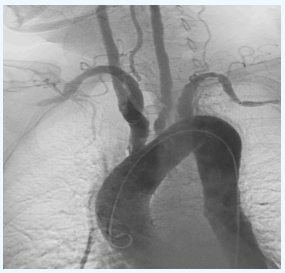


VVG staining *(stains elastic fibers)*

Vasculitis continued

Takayasu Arteritis

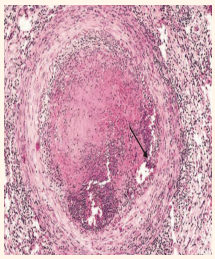
- aka "**pulse-less disease**" and "**aortic arch syndrome**"
- **Granulomatous** - **Large vessel** - **vasculitis** *(type 4 hypersensitivity reaction)*
- **BP difference between upper limbs**
- Affects younger adults **< 40yrs**
- Affects **woman** (>80%) and *Asian ethnicity*
- Affects the **aorta and its major branches** (m/c is **left Subclavian artery**)
- Associated with **renal artery stenosis** and **Myocardial infarction**
- Diagnosis is usually made on **imaging**.



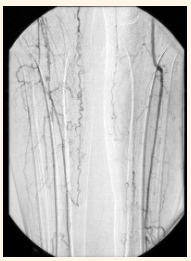
***DSA** showing **left subclavian artery** involvement*

Thrombo-angitis Obliterans
(Buerger's Disease)

- Affects **artery**, **veins** and **nerves** *(spares lymphatics)*
- Young adult **< 35 years**
- **Smoker -** strong association
- **Severe limb pain**
- M/c artery : **Radial/Tibial**
- *Corkscrew collaterals* seen on **DSA**
- T/t : **Stop smoking** *(surgery has no role)*



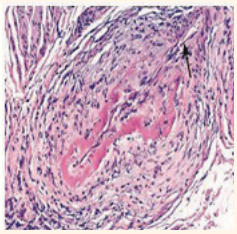
Thrombotic Micro-abscess in the vessel



Corkscrew Collaterals on DSA

Poly-arteritis nodosa

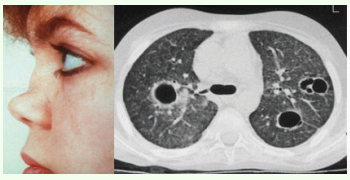
- **Medium** vessel vasculitis ***(immune complex** mediated)*
- Associated with **Hepatitis B** in **30**%
- Segmental**,** transmural **"necrotizing"** inflammation of arteries *(fibrinoid necrosis)*
- **Renal artery** involved : **Secondary Hypertension**
- Differentials for **renal artery micro-aneurysms : PAN** or **Tuberous Sclerosis**
- It **never affects** the **pulmonary system** or the **glomeruli** ***(PAN** - Pulmonary artery never-involved)*



Fibrinoid necrosis

Wegner's GPA

- ANCA asso. **granulomatous necrotising** vasculitis **(C-ANCA)**
- **URTI + LRTI + Glomerulonephritis**
- **Cavitatory lung lesions**
- **Crescentic RPGN** - No granulomas



Saddle nose and Cavitations in lung

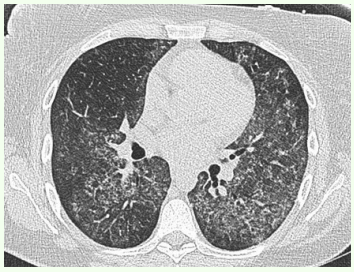
Eosinophilic GPA

- aka *Churg Strauss Syndrome*
- ANCA asso. **granulomatous** vasculitis **(P-ANCA)**
- **Asthma** and **Eosinophilia**

Mono-neuritis complex is associated with all small vessel vasculitis

Microscopic polyangitis

- ANCA asso. vasculitis **(P-ANCA)**
- Clinical features similar to PAN
- **Glomerulonephritis** with rapid progression to renal failure



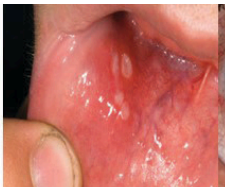
Pulmonary Hemorrhage

Differentials for **Hemoptysis** + **Hematuria**

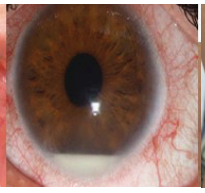
1. **Good Pasteur Sx**
2. **Wegner's GPA**
3. **Microscopic Polyangiitis**

Behcet's Disease

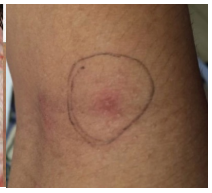
- Variable vessel vasculitis *(small, medium, large)*
- Aka **Oculo-oro-genital** syndrome :
  - **Uveitis** + **painful oral** & **genital ulcers**
- Oral ulcers: **painful**, **recurrent**, heal without scarring
- Genital ulcers: **painful**, heal with scarring - *glans usually spared*
- Biopsy: **neutrophilic vasculitis**
- **Pathergy test**: positive
- **HLA-B51** association, **α-enolase** antibody (*non specific*)
- Associated with **neutrophilic dermatosis** (e.g., *Sweet's Sx*) and **Erythema Nodosum**



Oral ulcers



Uveitis

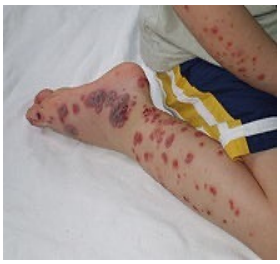


Pathergy Test

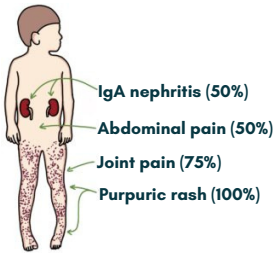
Vasculitis continued

IgA Vasculitis

- Formerly called **Henoch–Schönlein purpura** (HSP)
- **IgA-mediated** small vessel vasculitis - commonly presents in **childhood**
  - **Palpable purpura** (*lower limb predominance*)
  - **Abdominal pain** : due to intussusception
  - **Arthralgia/arthritis** (*acute onset*)
  - **Renal involvement** : **hematuria** ± **proteinuria** (*IgA nephropathy-like*)
- Histopathology : **Leukocytoclastic vasculitis** with IgA deposition
- Kidney: **mesangial proliferative GN** with **IgA deposits**
- **Steroids** are used in **severe abdominal pain / renal involvement**



Palpable purpura



Cryoglobulinemia

- Cryoglobulins are **immunoglobulins** that **precipitate in cold (<37º)** and dissolve upon rewarming.
- Associated with **Hepatitis C**
- Histopathology : **Leukocytoclastic vasculitis**

Feature	Type I (10%)	Type II (65%) – Mixed	Type III (25%) – Mixed
Composition	Monoclonal IgM	Monoclonal IgM (RF)+ Polyclonal IgG	Polyclonal **IgM** + **IgG**
Association	Lymphoproliferative disorders	**Hepatitis C (80–90%)**	Autoimmune diseases
Complement	Normal	↓ C4	↓ C4
Key features	**Raynaud**, **livedo reticularis**, **hyperviscosity**	**Meltzer triad** (purpura, arthralgia, weakness), **MPGN**, Liver/Lung inv, **Peripheral neuropathy**	

Approach to Myopathies

Feature	Polymyalgia rheumatica	Inflammatory Myopathies	Steroid Myopathy	Statin induced myopathy	Hypothyroid myopathy
ESR	**Raised**	**Raised**	Normal	Normal	Normal
CK	Normal	**Raised**	Normal	**Raised**	**Raised**
Key features	**Shoulder/hip** pain, **morning stiffness**, age **>50** Associated with **GCA**	**Proximal pain + weakness**	**Proximal weakness**, no pain	**Pain,** no weakness	**Proximal pain** + **weakness**, **delayed reflexes**

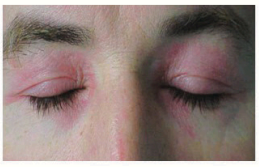
Inflammatory Myopathies

Inflammatory myopathy

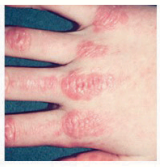
- **Proximal** weakness
- **Younger** patients

Dermato-myositis

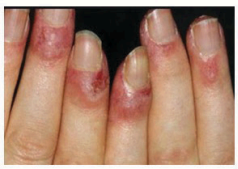
- **Characteristic rash** along with **muscle weakness**
- **Proximal Esophageal weakness** *(distal weakness seen in CREST Syndrome)*
- Can be a **paraneoplastic syndrome** with **adenocarcinomas**
- ***Peri-fascicular atrophy***



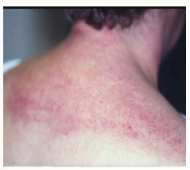
Heliotrope eyelid rash



Gottron's Papules (Hallmark)



Nail-fold telangiectasia



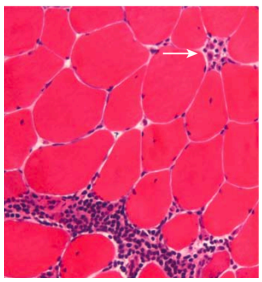
Shawl Sign on thigh it's known as **Holster sign**

Poly-myositis

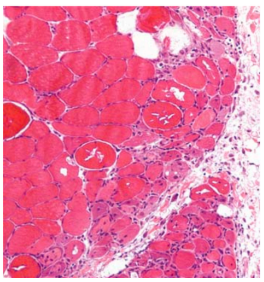
- Only muscle weakness and **no rash**
- Associated with **other auto-immune conditions**

- **Proximal** as well as **distal weakness**
- **Elderly** patients

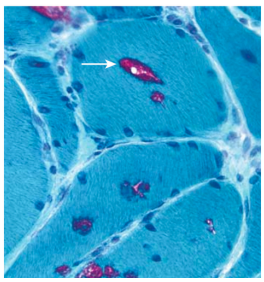
Inclusion body myositis



Endomysial inflammation
Polymyositis



Peri-fascicular atrophy
Dermatomyositis

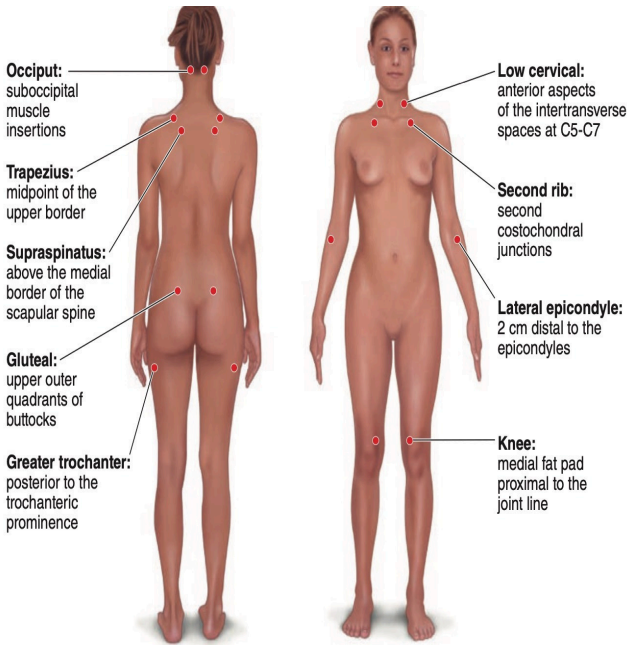


Rimmed vacuoles
Inclusion body myositis

Miscellaneous

Fibromyalgia

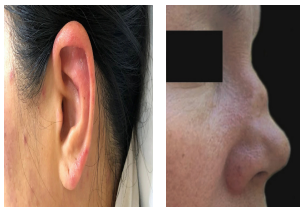
- Symptoms:
  - Chronic widespread pain
  - Fatigue + sleep dysfunction
  - Tension-type headache
- Investigations:
  - **ESR: Normal**
- Diagnostic clue:
  - **≥11/18** tender points *(classical criteria)*
- Treatment of choice (TOC):
  - **Cognitive Behavioral Therapy (CBT)**
- FDA-approved drugs:
  - **Duloxetine** (SNRI)
  - **Milnacipran** (SNRI)
  - **Pregabalin**



Miscellaneous continued

Relapsing Polychondritis

- Inflammation of **cartilaginous structures**
  a. **Auricular chondritis** : inflamed pinna (ear lobule spared)
  b. **Saddle nose deformity**
  c. Respiratory cartilage involvement : **tracheomalacia**
- Can mimic **Wegener's GPA**

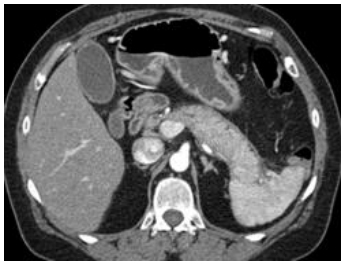


MAGIC syndrome

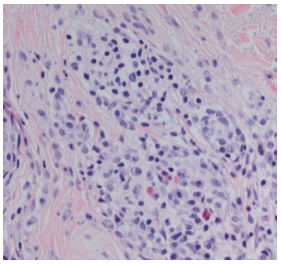
- **Mouth** And **Genital ulcers** with **Inflamed Cartilage**
- Can mimic **Behçet's disease**

Familial Mediterranean fever

- Gene: **MEFV**
- Protein: **Pyrin** (regulates **IL-1** mediated inflammation)
- Episodes: **periodic fever** lasting **1–3** days
- Features
  - Recurrent serositis (*peritonitis, pleuritis*)
  - Arthritis
- Major complication: **AA amyloidosis**
- Treatment: **Colchicine**



Sausage Shaped Pancreas on CT in IgG4 related disease



Lymphoplasmacytic infiltrate, storiform fibrosis in IgG4 related disease

IgG4-Related Disease

Mayo Clinic **HISORt** Criteria

Component	Feature
H – Histology	**Lymphoplasmacytic infiltrate**, **storiform fibrosis**, obliterative phlebitis
I – Imaging	**Tumor-like organ enlargement** (e.g., *sausage-shaped pancreas*)
S – Serology	**IgG4 >140 mg/dL**
O – Other organs	**Bile duct strictures**, salivary glands, retroperitoneum, **Riedel thyroiditis**
Rt – Response to therapy	**Rapid steroid response**