RHEUMATOLOGY DOSSIER 2026

RHEUMATOLOGY DOSSIER

Updated & Reviewed 2026

Originally by: Noor Al-Huda Esam Al-Karaki
With contributions from: Dr. Ena'am Domi, Dr. Akram Oran, Dr. Mohammad Al-Abbadi, Dr. Soha Al-Ka'abneh, Dr. Mohammad Rabi, Dr. Sahem Otoom

Last Edited by: Dr. Marwan Herzallah

CONTENTS AT A GLANCE

1. INTRODUCTION & JOINT PAIN APPROACH

Key Definitions

- **Arthralgia:** Joint pain without inflammation
- **Arthritis:** Joint inflammation — cardinal features: pain, swelling (most important), redness, warmth, limitation of movement

Classification by Number of Joints

Type	Definition & Key Causes
Monoarticular (1 joint)	Trauma, Septic arthritis, Crystal-induced (gout/pseudogout), TB, Hemarthrosis Note: Oligo/polyarthritis can begin as monoarthritis
Oligoarticular (2–4 joints)	Seronegative arthritis — typically asymmetrical
Polyarticular (>4 joints)	RA (symmetrical, morning stiffness >1 h); SLE (symmetrical or asymmetrical)

Joint Pain History — 8 Key Questions

- 1. Which joints are involved, and how many?
- 2. Arthralgia or arthritis?
- 3. Symmetrical or asymmetrical?
- 4. Relation to movement: worse with movement → mechanical (OA); worse after rest → inflammatory
- 5. Morning stiffness present? (hallmark of inflammation)
- 6. Duration of morning stiffness: >30 min significant; >1 hour → think RA
- 7. Back symptoms? (SI joint, disc, epiphyseal involvement)
- 8. Systemic symptoms: fever, sweating, weight loss (systemic inflammation)

Patterns of Joint Involvement

Pattern	Description & Associations
Migratory	First joint resolves then another is affected. No pain-free interval. → Rheumatic fever, SLE
Additive	First joint stays inflamed as new joints added. → Rheumatoid Arthritis
Intermittent	Like migratory but WITH pain-free intervals. → Gout, Pseudogout

MNEMONIC: Arthritis History	
S	Swelling — is it present? Confirm with palpation
O	Onset — acute (hours = gout) vs. gradual (days/weeks = RA, septic)
A	Associated symptoms — rash, fever, uveitis, back pain
P	Pattern — migratory / additive / intermittent; number of joints

Seronegative Arthritis — Key Features

SERONEGATIVE SPONDYLOARTHROPATHY FEATURES

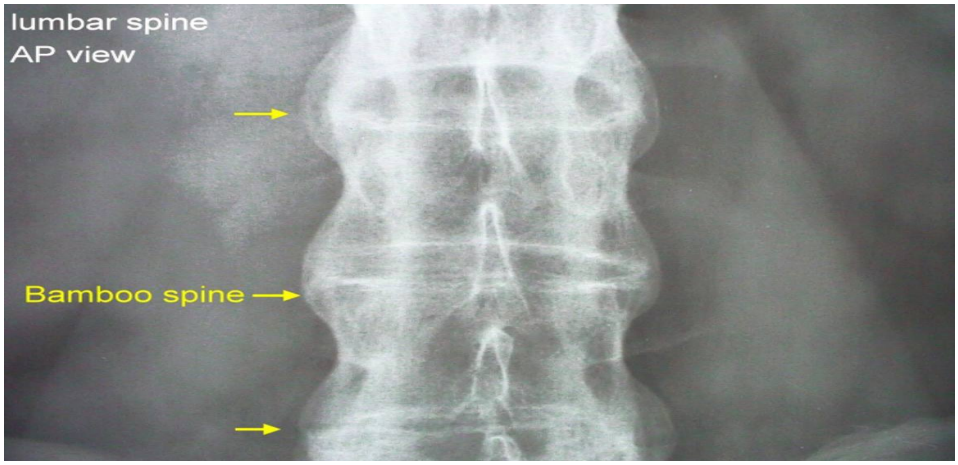
- **RF & Anti-CCP:** Both negative
- Autoimmune, chronic, inflammatory, systemic
- Oligoarthritis, large joints, lower limbs predominantly
- Asymmetrical distribution
- Axial involvement: Sacroiliac (SI) joint
- **Extra-articular:** Eyes (uveitis), heart, skin

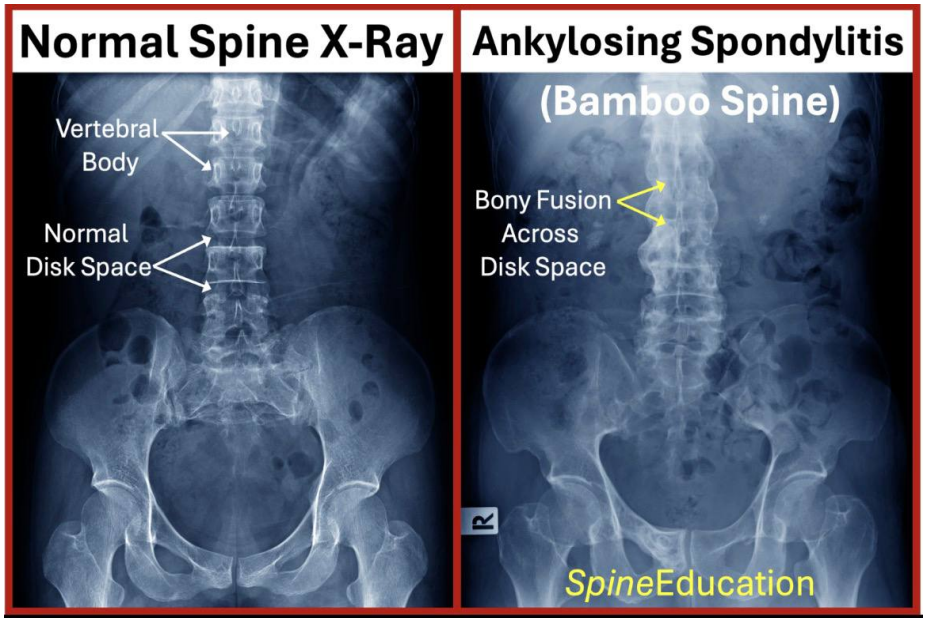
Types of Seronegative Arthritis

Type	Key Distinguishing Features
Ankylosing Spondylitis	Spine + SI joint, starts lower → ascends; apical lung fibrosis possible
Reactive Arthritis (Reiter's)	Follows URTI or GU/GI infection by ~2 weeks; triad of arthritis + urethritis + conjunctivitis (updated: not all 3 needed)
Psoriatic Arthritis	DIP joints, small joints; polyarthritis, asymmetric; nail pitting; psoriatic plaques
Enteropathic (IBD-related)	Associated with Crohn's disease or ulcerative colitis
Undifferentiated	Spinal arthropathy without other features

Treatment of Seronegative Arthritis:

- **Peripheral arthritis:** Treat as RA (NSAIDs, DMARDs)
- **Axial disease (SI joint):** Skip DMARDs/Methotrexate → go directly to biological agents (anti-TNF)





Investigations in Rheumatology

Test	Significance
Rheumatoid Factor (RF)	Antibody (IgM) against Fc portion of IgG — positive in ~2/3 of RA; also positive in SLE, Sjögren's, infections
Anti-CCP (ACPA)	Highly specific for RA; positive in ~2/3; predicts worse prognosis
ANA (Antinuclear Antibody)	Screening for SLE (sensitive ~95%); also positive in other CTDs
ANCA	C-ANCA (PR3): Granulomatosis with Polyangiitis (Wegener's); P-ANCA (MPO): Microscopic Polyangiitis
Complement (C3/C4)	↓ in active SLE nephritis (immune complex

	consumption)
Anti-dsDNA	Specific for SLE (~60–80%); used for disease monitoring (unlike ANA)
Anti-Smith (anti-Sm)	Highly specific for SLE (~30%); not used for monitoring
Uric acid	Elevated in gout (>7 mg/dL in males, >6 mg/dL in females)

2. RHEUMATOID ARTHRITIS (RA)

Chronic, inflammatory, systemic, autoimmune disease of unknown etiology. Affects joints symmetrically with extra-articular manifestations. Requires treatment (DMARDs) — does NOT remit spontaneously.

Epidemiology

- Age of onset: 30–55 years | Incidence: ~30/100,000 | F:M = 2–3:1
- **HLA association:** HLA-DR4 (most common); HLA-DRB1 = worse prognosis

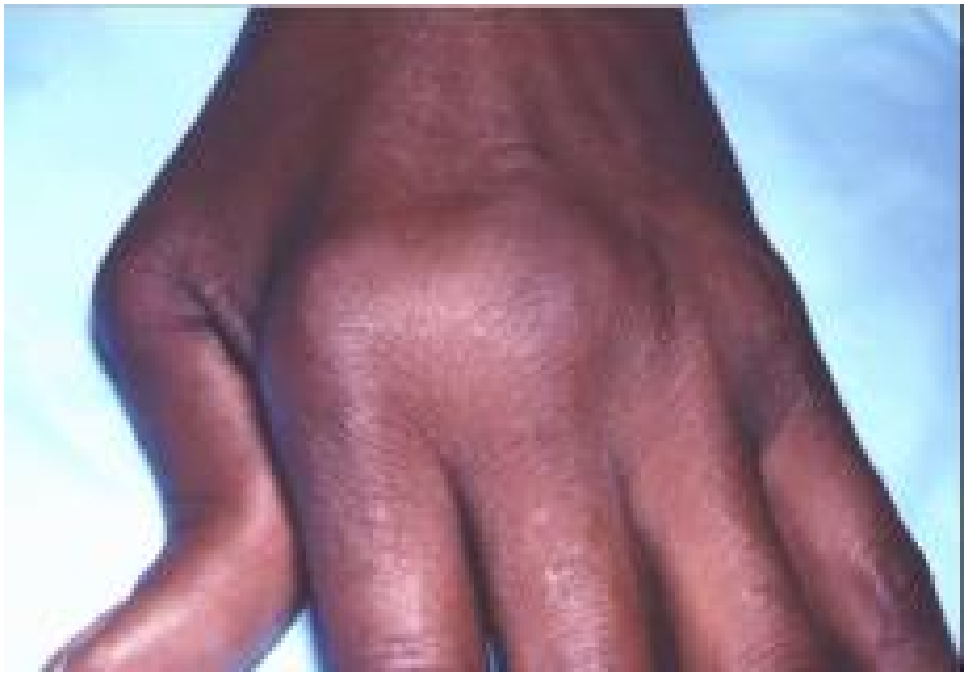


Figure: →NOTES : RA age (30-55), incidence : 30/100.000, F:M 2-3:1 : as patient younger think of SLE , as

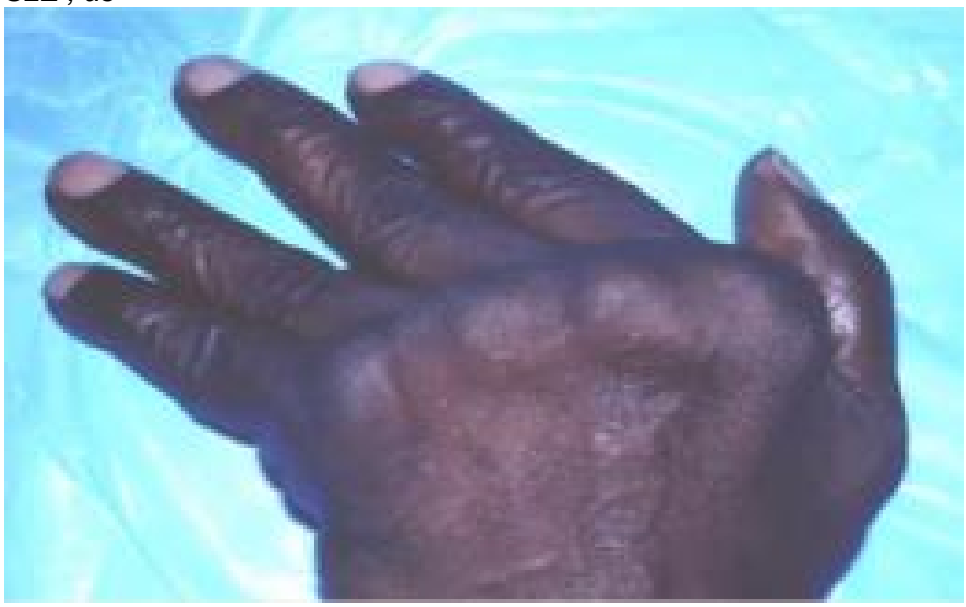


Figure: →NOTES : RA age (30-55), incidence : 30/100.000, F:M 2-3:1 : as patient younger think of SLE , as

- **Note:** Age <30 → think SLE first. Onset >65 → rule out TB and paraneoplastic syndrome

Joints Involved

- **Small joints primarily:** PIP, MCP, wrists, MTP, ankles, knees

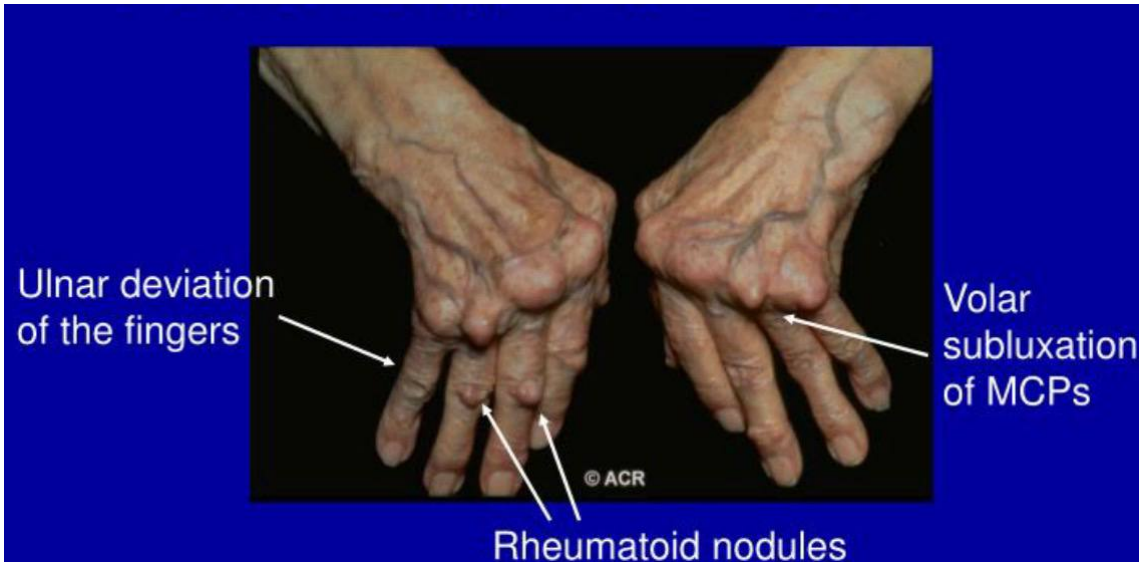
- **DIP joints NOT affected** (DIP involvement → OA or Psoriatic arthritis)
- Progresses distal → proximal: DIP → PIP → MCP → Wrist → Elbow → Shoulder
- **Symmetrical —** asymmetry argues against RA
- **Pattern: Additive** (joints accumulate, not migratory)
- Morning stiffness >1 hour (due to edema + high intra-articular pressure)

Deformities

Deformity	Description
Swan-neck	PIP hyperextension + DIP flexion
Boutonnière	PIP flexion + DIP extension
Ulnar deviation	MCP joints deviate ulnarly
Z-deformity (thumb)	MCP flexion + IP hyperextension
Volar subluxation	'Step sign' at MCP joints

⚠ KEY RULE: Deformity Reversibility

Fixed deformity → disease IN the joint (RA)
Reversible deformity → periarticular disease (SLE, Rheumatic Fever)



Extra-articular Manifestations

Extra-articular Features of RA

- **Subcutaneous nodules:** Large, on extensor aspect of forearm, long duration (months–years) — present in ~30%
- **Scleritis / Scleromalacia:** Thinning of sclera → blue discoloration → risk of globe rupture and blindness
- **Pulmonary:** Interstitial fibrosis, nodules (bilateral reticular nodular shadow on CXR); finger clubbing signals fibrosis
- **Felty's syndrome:** RA + splenomegaly + neutropenia
- **Sjögren's (secondary):** Dry eyes + dry mouth (Sicca symptoms), parotid enlargement
- **Baker's cyst:** Posterior popliteal fluid collection; rupture mimics DVT
- **C1–C2 subluxation:** Electric shock-like pain on neck flexion → risk of quadriparesis. Always get cervical spine X-ray
- **Vasculitis:** Digital infarction, pinpoint lesions
- **Pericarditis, neuropathy**

Criterion	Definition
A patient is classified as RA if 4/7 criteria are satisfied. Criteria 1-4 must have been present for ≥6 weeks	
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least an hour before maximal improvement
2. Arthritis of ≥3 joints areas	≥3 joints areas simultaneously have had synovitis observed ay a physician
3. Arthritis of hand joints	At least 1 area swollen in a wrist, MCP or PIP joint
4. Symmetric arthritis	Simultaneous involvement of the same joint areas on both sides of the body
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, extensor surfaces or juxta-articular regions
6. Serum rheumatoid factor (RF)	Positive RF
7. Radiographic changes	Radiographic changes typical of RA in posteroanterior hand and wrist radiographs

1987 ACR Classification criteria for RA[3]

Target population: Patients who (i) have at least one joint with clinical synovitis, and (ii) the synovitis not better explained by another disease	Score
Add score of categories A-D, score of ≥6/10 needed to classify patient as having definite RA	
A. Joint involvement (tender/swollen)	
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology	
Negative RF /ACPA	0
Low-positive RF/low positive ACPA	2
High positive RF/high-positive ACPA	3
C. Acute phase reactants	
Normal CRP&ESR	0
Abnormal CRP/ESR	1
D. Duration of symptoms	
<6 weeks	0
≥6 weeks	1

2010 ACR/EULAR Classification criteria for RA[5]

Figure: New criteria for early diagnosis , in case of late diagnosis : deformities and erosions ↪

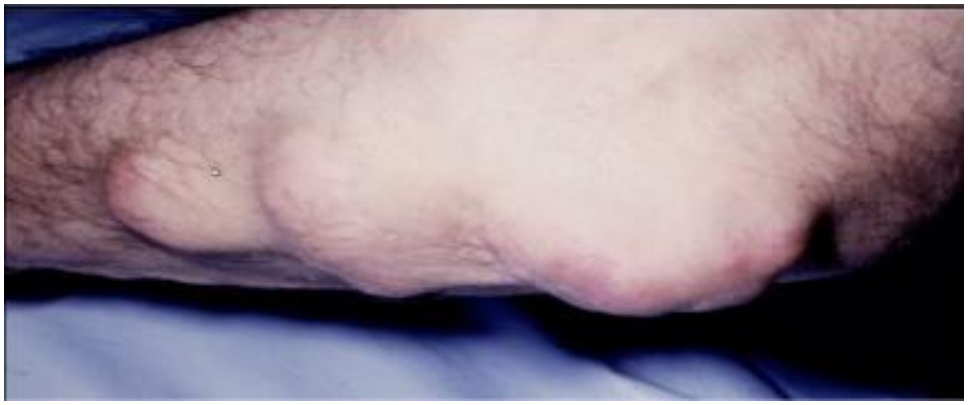


Figure: THE Difference between old and new criteria : (this points not found in new criteria) :

Diagnosis — Criteria

2010 ACR/EULAR Criteria (Current Standard)

Score ≥ 6/10 = Definite RA

Domain	Score
Joint involvement: 1 large joint	0
Joint involvement: 2–10 large joints	1
Joint involvement: 1–3 small joints (±large)	2
Joint involvement: 4–10 small joints (±large)	3
Joint involvement: >10 joints (at least 1 small)	5
Serology: Negative RF and Anti-CCP	0
Serology: Low-positive RF or Anti-CCP	2
Serology: High-positive RF or Anti-CCP	3
Acute phase reactants: Normal CRP and ESR	0
Acute phase reactants: Abnormal CRP or ESR	1
Duration of symptoms: <6 weeks	0
Duration of symptoms: ≥6 weeks	1

Key changes from 1987 criteria:

- Removed: Morning stiffness, symmetry, nodules, X-ray (not required for diagnosis now)
- Added: Scoring system with serology (Anti-CCP) and acute phase reactants
- Allows earlier diagnosis before erosions/deformities develop
- **2019 update:** Anti-CCP now graded high/low positive. Positive Anti-CCP = worse prognosis

Pathology

- Unknown trigger → T-cell activation → macrophage activation

- Cytokines released: TNF-α, IL-6, IL-1 → activate osteoclasts (bone destruction), chondrocytes (cartilage destruction), synoviocytes (Pannus formation)
- **Pannus:** Highly destructive granulation tissue invading cartilage and bone
- B-cells produce RF and Anti-CCP → immune complex deposition
- **RANK-RANKL pathway** → decreased OPG → osteoclast activation → bone erosion

X-ray Findings (in order of appearance)

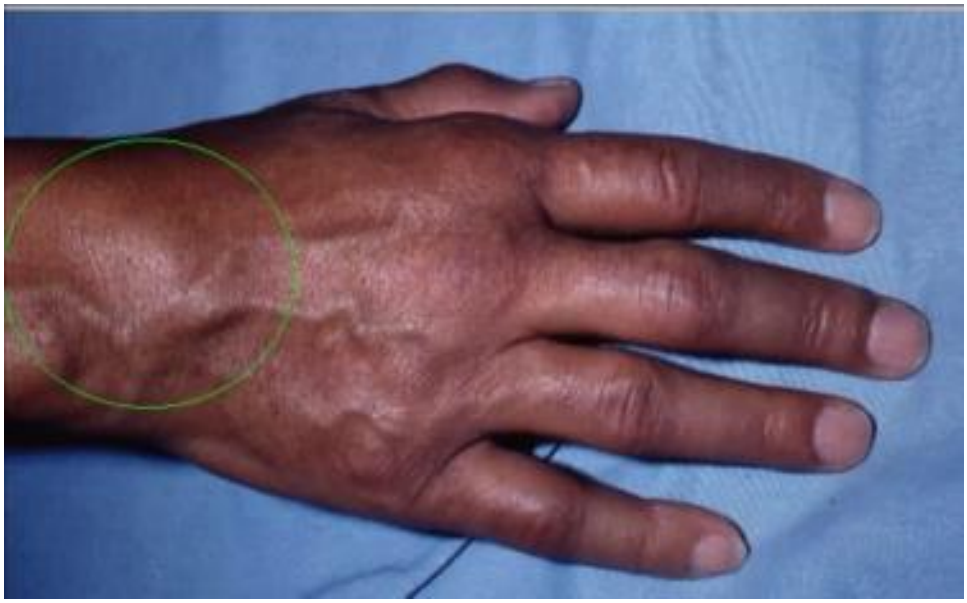


Figure: →Swelling in the wrist joint , Swelling in the PIP of 2nd, 3rd ,4th and 5th fingers, Swelling in the MCP of 2nd

1. **Soft tissue swelling**
2. **Peri-articular osteopenia**
3. **Joint space narrowing**
4. **Marginal erosions** (very important — 70% occur within first 2 years!)
5. **Joint destruction/deformity**

> ⚠ **X-ray valid for monitoring every 6–12 months**
> 70% of erosions occur in the FIRST 2 YEARS → early aggressive treatment is critical!

Poor Prognosis Factors

MNEMONIC: Poor Prognosis in RA	
P	Polyarticular joint disease (many joints)
R	RF and/or Anti-CCP positive
E	Extra-articular manifestations (nodules, vasculitis, lung)
M	Male sex (more aggressive disease)
I	Inflammatory markers persistently elevated

A	Age (elderly onset) + HLA-DRB1 positivity

Synovial Fluid Analysis

WBC Count	Interpretation
<200 cells/mm³	Normal
200–2,000 cells/mm³	Non-inflammatory (OA, trauma)
2,000–20,000 cells/mm³	Inflammatory (RA, Crystal arthritis)
>50,000–100,000 cells/mm³	Septic arthritis (pus = definitive septic)
200–2,000 (with RBCs)	Hemarthrosis

RA fluid: turbid (high inflammatory), high WBC, no crystals, sterile culture

Treatment

Non-pharmacological

- Patient education, physiotherapy, occupational therapy, rest and exercise balance

NSAIDs

- Pain control only — do NOT alter disease outcome
- **COX-2 selective (Coxibs):** fewer GI side effects, no platelet effects → BUT ↑ cardiovascular thrombosis risk
- **Avoid NSAIDs in renal disease and SLE (risk of interstitial nephritis)**

DMARDs — Disease-Modifying Antirheumatic Drugs

DMARDs

- **Methotrexate (MTX):** First-line DMARD. Slow-acting (6 weeks to effect). Use corticosteroids as bridge during this interval
- Monitor MTX with: LFTs (hepatitis risk), CBC (bone marrow suppression)
- **MTX Side Effects:** Bone marrow suppression, hepatitis, folate deficiency, interstitial pneumonitis, GI ulceration, TERATOGENIC (stop 3 months before conception)
- **Hydroxychloroquine:** Safer option — annual fundoscopy required (corneal/retinal toxicity)
- **Sulfasalazine, Leflunomide:** Alternative DMARDs

Corticosteroids

- Strong anti-inflammatory; short-term use (up to 3 months); can slow erosion progression
- Used: (1) Acute flares, (2) Bridging while MTX takes effect, (3) Vasculitis
- **NOT safe in pregnancy** — teratogenic

Biological Agents (Anti-TNF and others)

Biological Agents

- **Anti-TNF:** Etanercept (SC), Infliximab (IV), Adalimumab
- **Abatacept:** Blocks T-cell/APC interaction (B7-CD28)
- **Rituximab:** Anti-CD20 (anti-B cell)
- **IL-6 inhibitor:** Tocilizumab — useful when anti-TNF fails
- ⚠ **Risks:** Serious infections (especially TB reactivation — screen with Mantoux/IGRA before starting); Lymphoma; Very expensive
- ⚠ **Screen for TB before all biological agents!**

Pregnancy & RA

- **70% of RA patients improve** during pregnancy (placental steroids). Flares postpartum are common
- Stop MTX at least 3 months before conception (teratogenic)

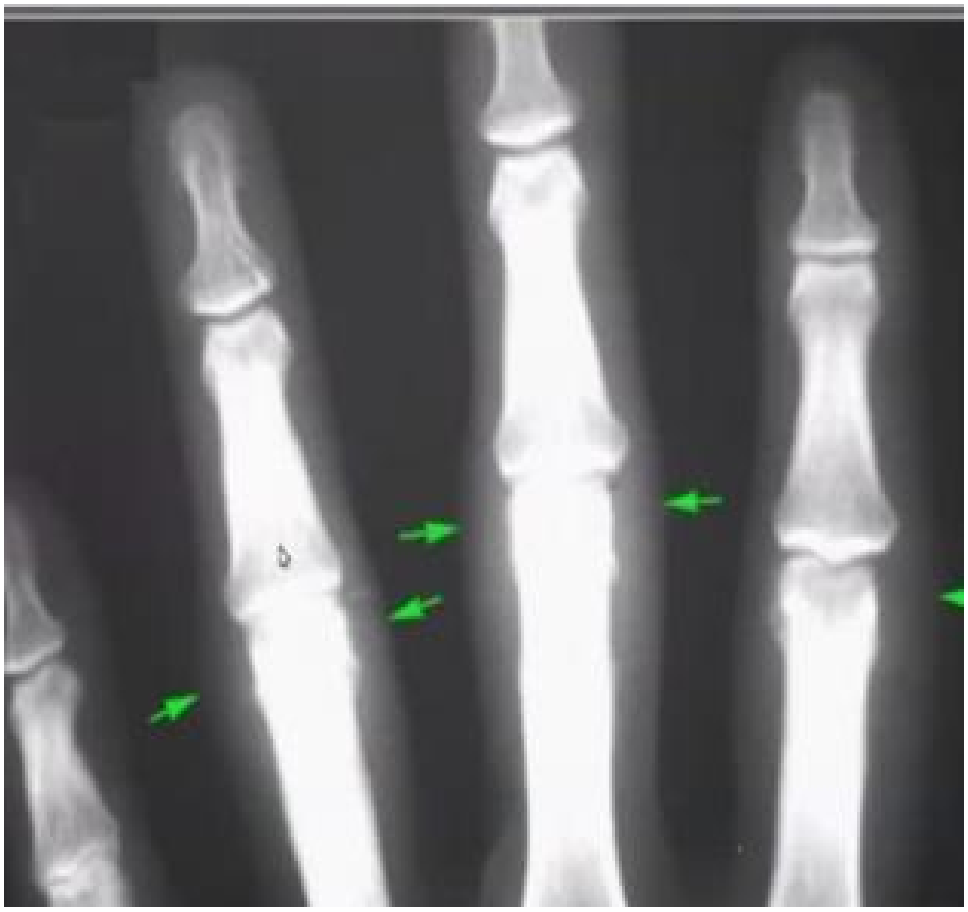
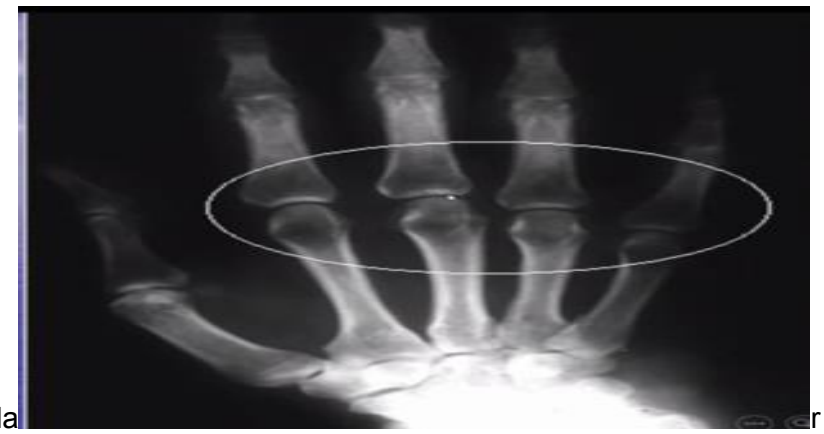
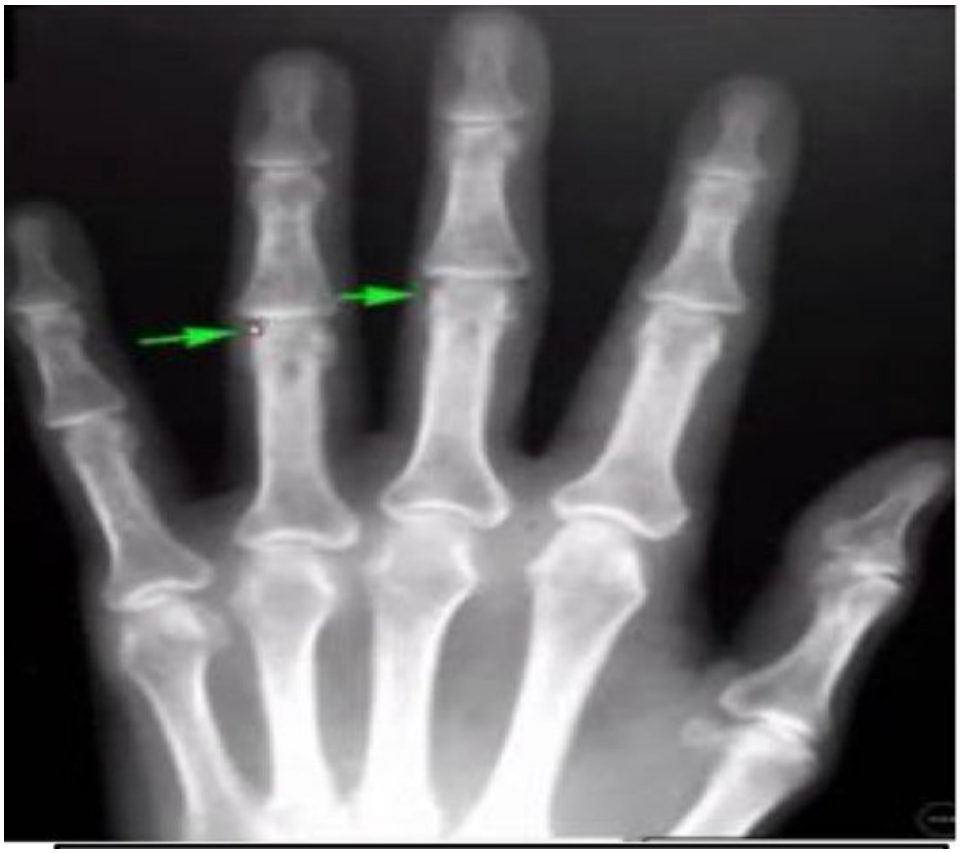


Figure: Joint space narrowing

- **Relatively safe in pregnancy:** Hydroxychloroquine, Azathioprine, Sulfasalazine (with folic acid)

Figure: Peri-articular osteopenia 



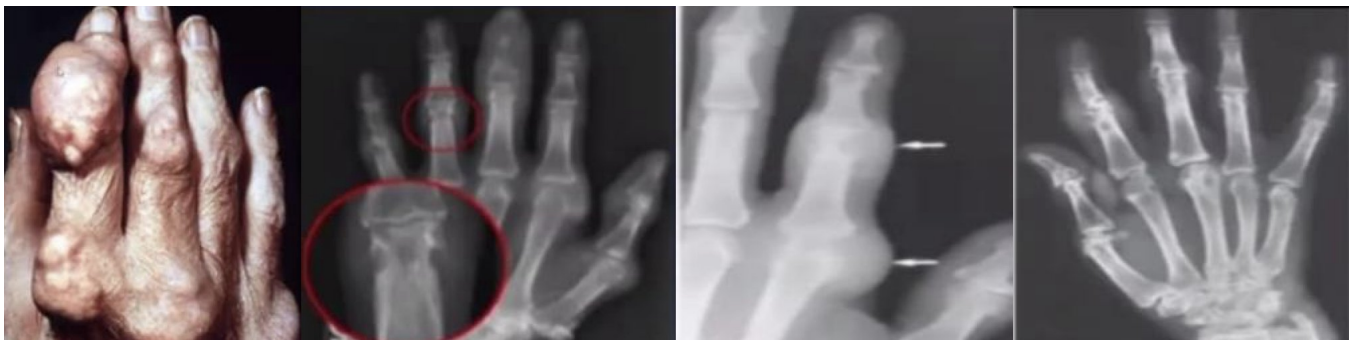


Figure: Crystal Induced Arthritis :

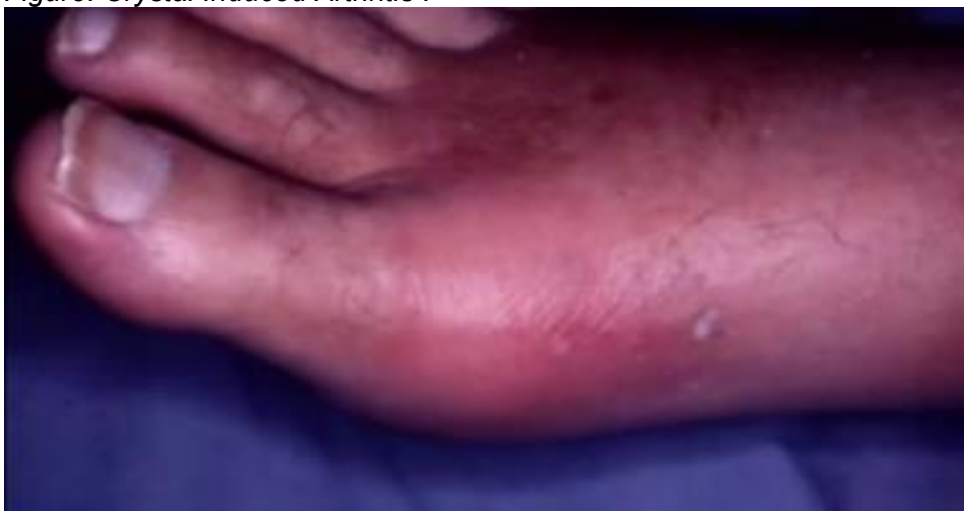
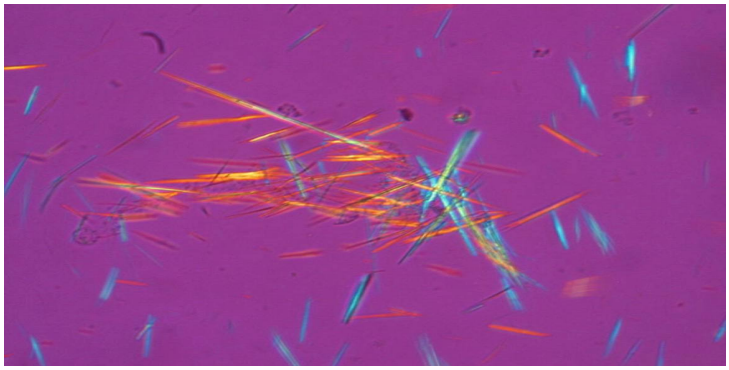


Figure: Crystal Induced Arthritis :

3. CRYSTAL-INDUCED ARTHRITIS

Crystal Type	Disease
Monosodium urate (MSU)	Gout
Calcium pyrophosphate dihydrate (CPPD)	Pseudogout / CPPD disease
Hydroxyapatite	Calcific periarthritis

- Monosodium urate crystals (MUC) using polarized light microscopy.



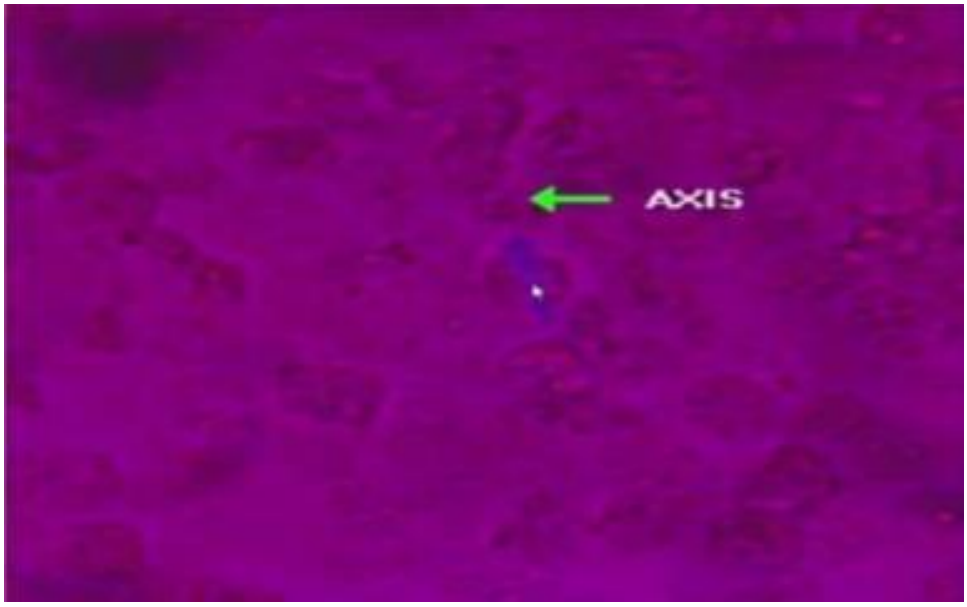
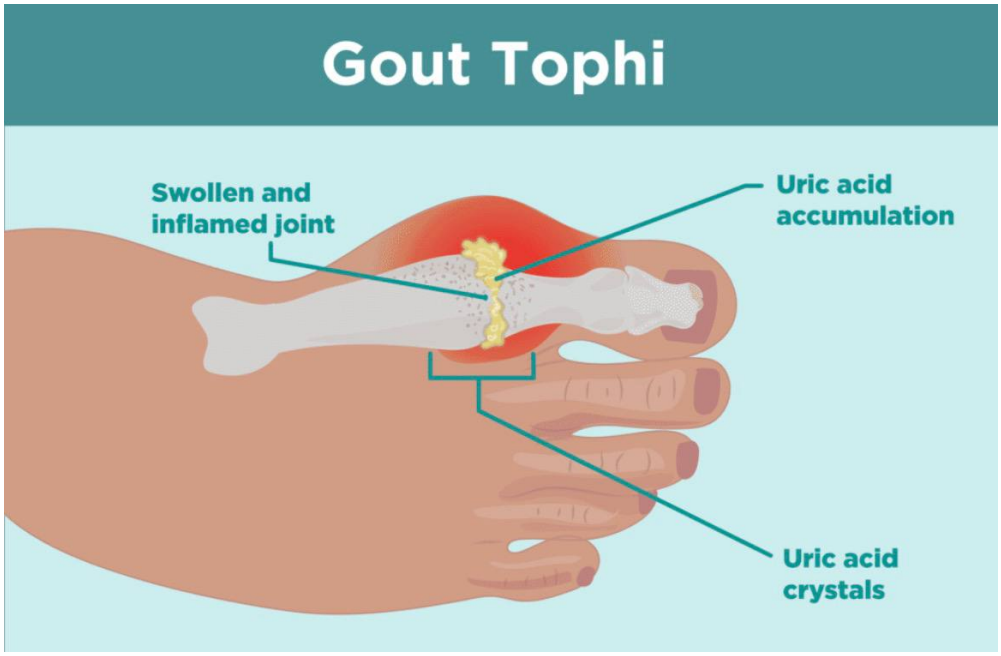


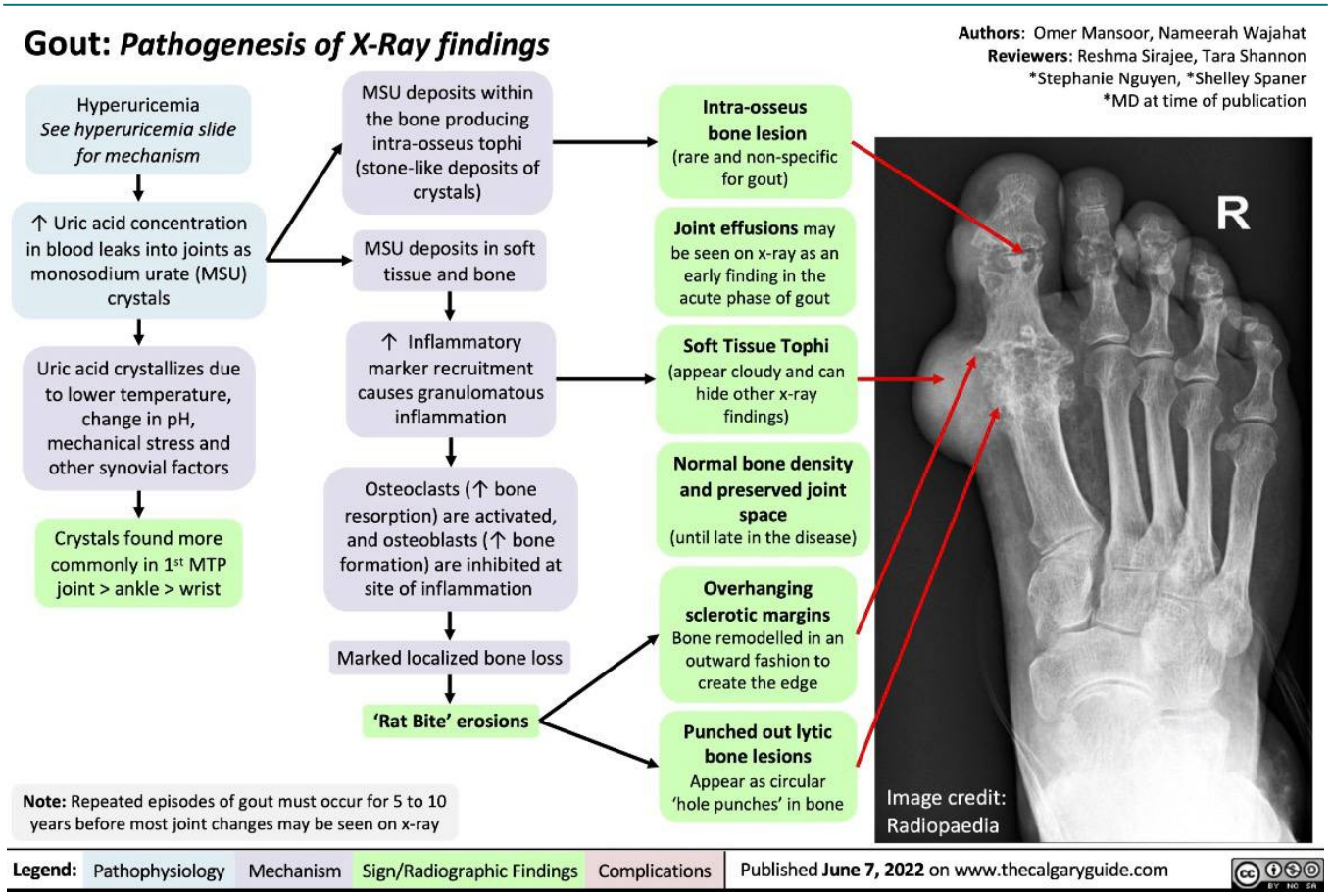
Figure: [Pseudo gout] : →Pseudo gout and CPPD aren't the same term ! , pseudo-gout is one

GOUT

Epidemiology & Key Facts

- Most common site: 1st Metatarsophalangeal (MTP) joint (podagra) — involved in 50% at first presentation, 90% over disease course
- Predominantly affects males; females usually postmenopausal (estrogen is uricosuric)
- Normal serum uric acid: up to 7 mg/dL in males, 6 mg/dL in females
- Onset typically at night (rapid onset within hours — key differentiator from septic arthritis)
- Attacks self-resolve in 1–3 weeks even without treatment





4 Phases of Gout

PHASES OF GOUT

1. Asymptomatic Hyperuricemia: High uric acid, no symptoms. Manage only if: urate >10 mg/dL (F) or >15 mg/dL (M), OR renal impairment/stones/tophi present

2. Acute Gouty Arthritis: Sudden onset (hours), often nocturnal. Monoarticular, lower limb, intensely painful. Lasts days–3 weeks. Precipitants: alcohol, diuretics (especially furosemide), trauma, surgery, IV heparin, cyclosporine

3. Intercritical Period: Asymptomatic interval between attacks. 50% have 2nd attack within 1 year. Don't treat unless high-risk

4. Tophaceous (Chronic) Gout: Appears ≥10 years after first attack. Tophi in joints, tendons, ear, subcutaneous tissue. Punched-out erosions with overhanging edges on X-ray

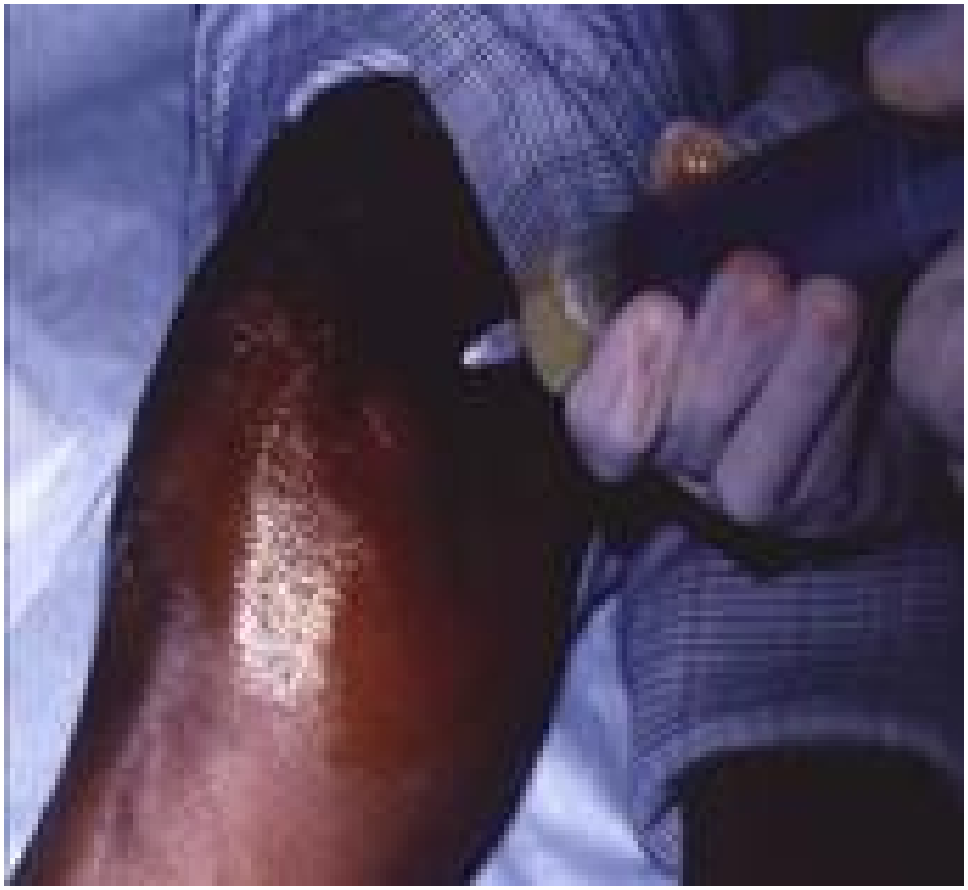


Figure: ☾ Pus from the joint coming out = septic arthritis

Figure: ☾ Pus from the joint coming out = septic arthritis

Gout vs. Septic Arthritis — Differentiation

Feature	Gout	Septic Arthritis
Onset	Hours (night)	Days (any time)
Gender/Age	Male, older / post-menopausal F	Any
Recurrence	Yes — resolves completely between attacks	No
Tophi	Present in chronic gout	Absent
Crystal on aspiration	Needle-shaped, -ve birefringent	Absent
Culture	Negative	Positive in ~95%
Glucose (fluid)	Normal	Low
Extension of inflammation	Extends beyond joint (within hours)	Slower spread (days–weeks)

Synovial Fluid & Crystal Microscopy

Crystal	Shape	Birefringence	Colour (parallel / perpendicular to axis)
Urate (Gout)	Needle-shaped	Negative	Yellow / Blue
CPPD (Pseudogout)	Rhomboid / brick-shaped	Positive (weak)	Blue / Yellow

Hyperuricemia & the Kidney

Figure: ⏛Hyperurcemia and Kidney :It causes chronic urate nephropathy [common] with renal

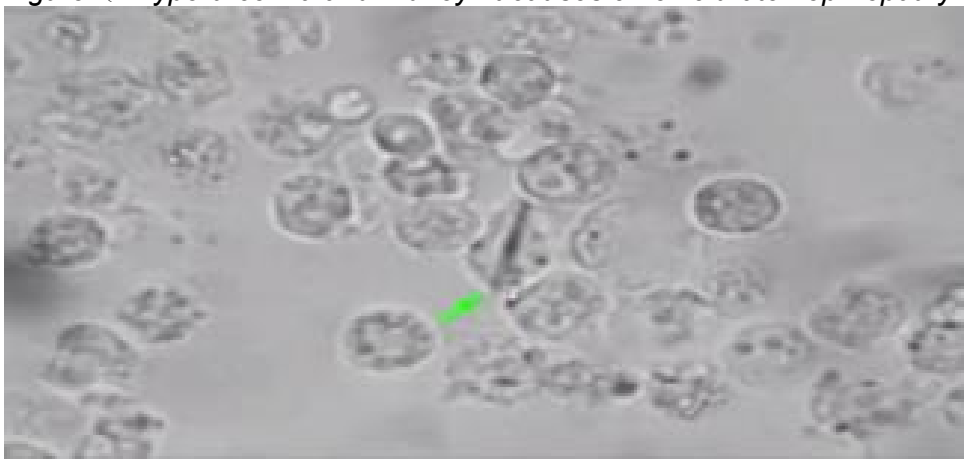


Figure: ⏛Hyperurcemia and Kidney :It causes chronic urate nephropathy [common] with renal

- **Chronic urate nephropathy:** Na-urate deposits in medullary interstitium → renal impairment (common)

- **Acute urate nephropathy:** Massive urate crystal precipitation in renal tubules — seen in Tumor Lysis Syndrome. Prevent with allopurinol + IV hydration BEFORE chemotherapy
- **Uric acid renal calculi:** Radiolucent on plain X-ray
- Underexcretion = 90% of cases (chronic RF, renal tubular defect). Overproduction = 10%

Management of Gout

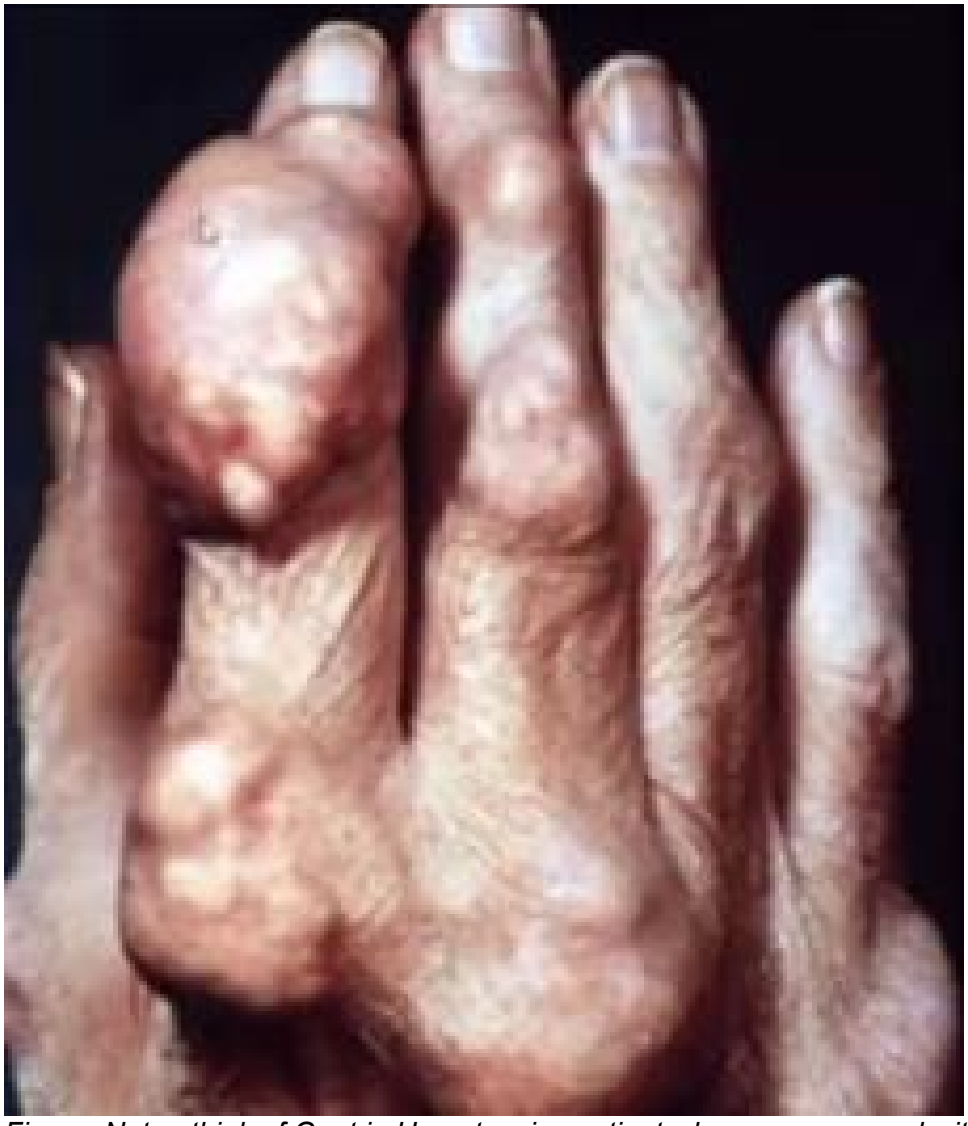


Figure: Note : think of Gout in Hypertensive patient who was managed with Thiazide .

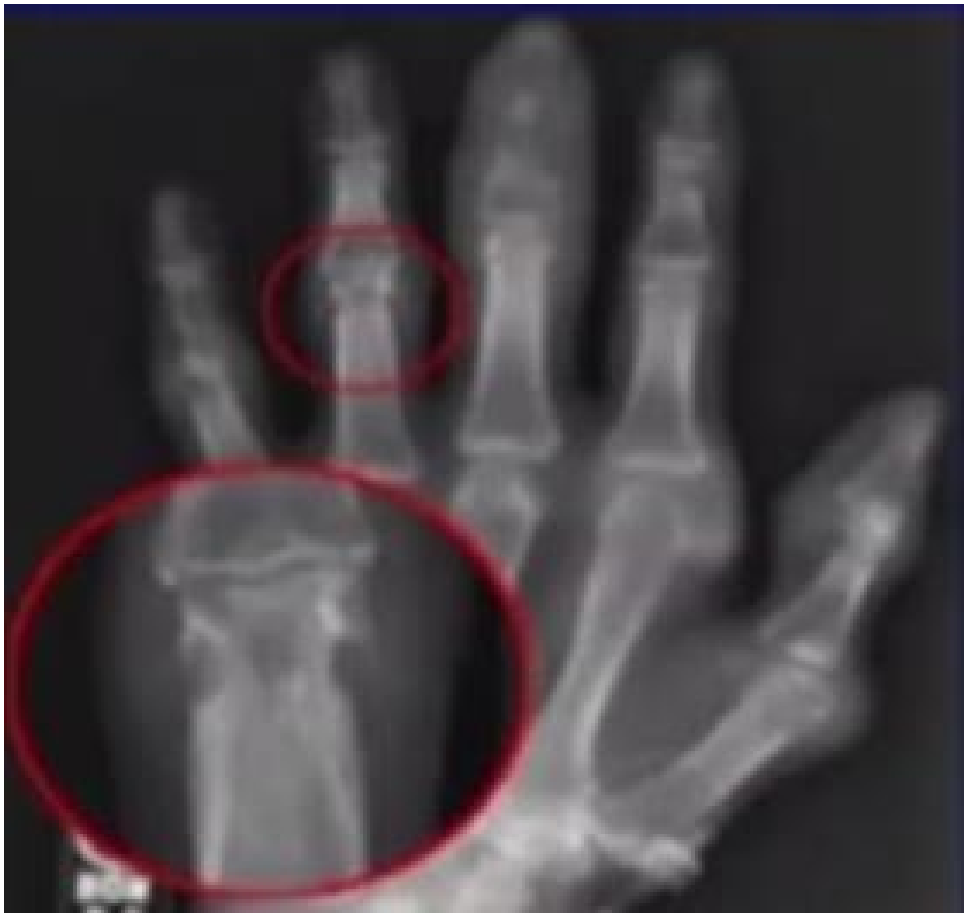


Figure: Note : think of Gout in Hypertensive patient who was managed with Thiazide .

Acute Attack

Acute Gout Treatment
• **NSAIDs** (e.g., indomethacin, diclofenac) — first-line if no renal impairment • **Colchicine** — alternative; start within 24 h of onset; low-dose preferred (0.5 mg BID) • **Intra-articular steroids** — preferred if monoarticular or contraindications to NSAIDs/colchicine • ⚠ **Do NOT combine NSAIDs + Colchicine** — severe GI toxicity • ⚠ **Do NOT start Allopurinol during acute attack** — prolongs or worsens the attack

Urate-Lowering Therapy (ULT) — Indications

MNEMONIC: Indications for Allopurinol	
C	Chronic/recurrent attacks (≥2 per year)
R	Renal impairment or uric acid kidney stones
E	Elevated urate causing damage (tophi)
S	Special situations (critical jobs: pilots, surgeons)
T	Tumor lysis syndrome prevention

- **Allopurinol:** Xanthine oxidase inhibitor. Start 4–6 weeks AFTER acute attack resolves. Target urate <6 mg/dL (<5 in tophaceous)
- **Febuxostat:** Alternative XO inhibitor. Use if allopurinol hypersensitivity (1/1000). Note: 2019 FDA warning — ↑ cardiovascular mortality vs. allopurinol; use with caution in CVD
- **Probenecid (uricosuric):** Increases renal urate excretion. Contraindicated in renal stones (worsens lithiasis)
- **Lifestyle:** Reduce (not eliminate) purine-rich foods, alcohol; increase hydration; weight loss

PSEUDOGOUT (CPPD)

- Calcium pyrophosphate crystal deposition in cartilage and synovium
- Typically elderly, more common in women
- **Most common joint: Knee** (also wrist, shoulder, pubic symphysis)
- **Chondrocalcinosis on X-ray:** Calcification of cartilage — pathognomonic; most patients asymptomatic
- Presentations: Asymptomatic (most common), Pseudo-rheumatoid, Pseudo-OA, Pseudo-neuropathic, Pseudogout attack
- **Treatment:** Same as gout (NSAIDs, colchicine, intra-articular steroids); no urate-lowering therapy needed

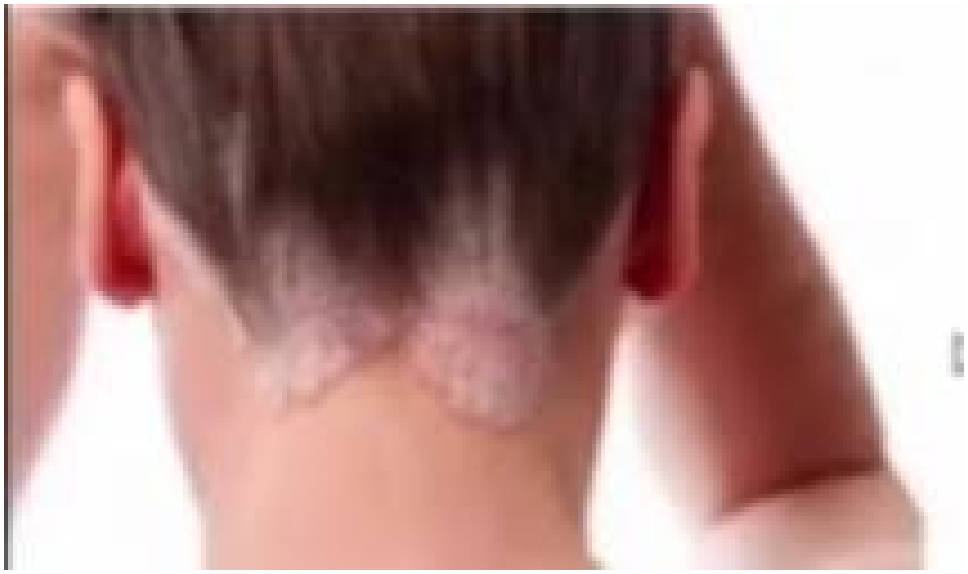


Figure: ARTHRITIS AND RASH

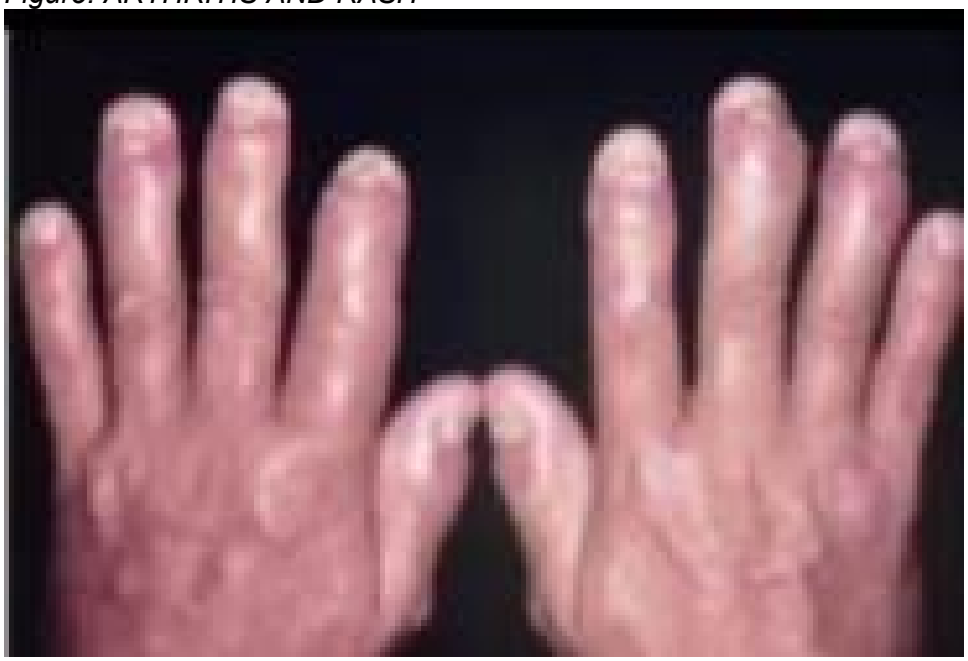


Figure: ARTHRITIS AND RASH

4. ARTHRITIS AND RASH

Condition	Key Rash Features
SLE	Malar (butterfly) rash — cheeks + nose bridge, spares nasolabial folds; photosensitive
Psoriatic Arthritis	Psoriatic plaques, nail pitting, onycholysis, DIP arthritis
Reactive Arthritis	Keratoderma blennorrhagica (palms/soles), circinate balanitis
Lyme Disease	Erythema chronicum migrans (bull's eye

	rash) — tick-borne Borrelia burgdorferi
Still's Disease / AOSD	Salmon-pink, non-itchy evanescent rash; comes and goes with fever
Henoch-Schönlein Purpura	Palpable purpura on buttocks and posterior thighs
Dermatomyositis	Heliotrope rash (eyelids) + Gottron's papules (knuckles)
Vasculitis	Palpable purpura, elevated, painful, on dependent areas
Behçet Disease	Erythema nodosum, pseudofolliculitis, oral/genital ulcers
Viral (EBV, Parvo B19)	Maculopapular rash; arthritis resolves in 1–2 weeks

Still's Disease (Adult-onset — AOSD)

Still's Disease

- **Triad:** Arthritis + Salmon-pink non-itchy rash (comes/goes with fever) + Quotidian fever (daily spikes)
- **Also:** Hepatosplenomegaly, leukocytosis, lymphadenopathy, serositis
- **Key marker:** Ferritin very high (often >10,000 ng/mL) — pathognomonic when extremely elevated
- **Serology:** RF, ANA, Anti-CCP all NEGATIVE
- **2022 update:** IL-18 is a key pathogenic cytokine; IL-1 and IL-6 inhibitors now used in refractory cases (anakinra, tocilizumab)

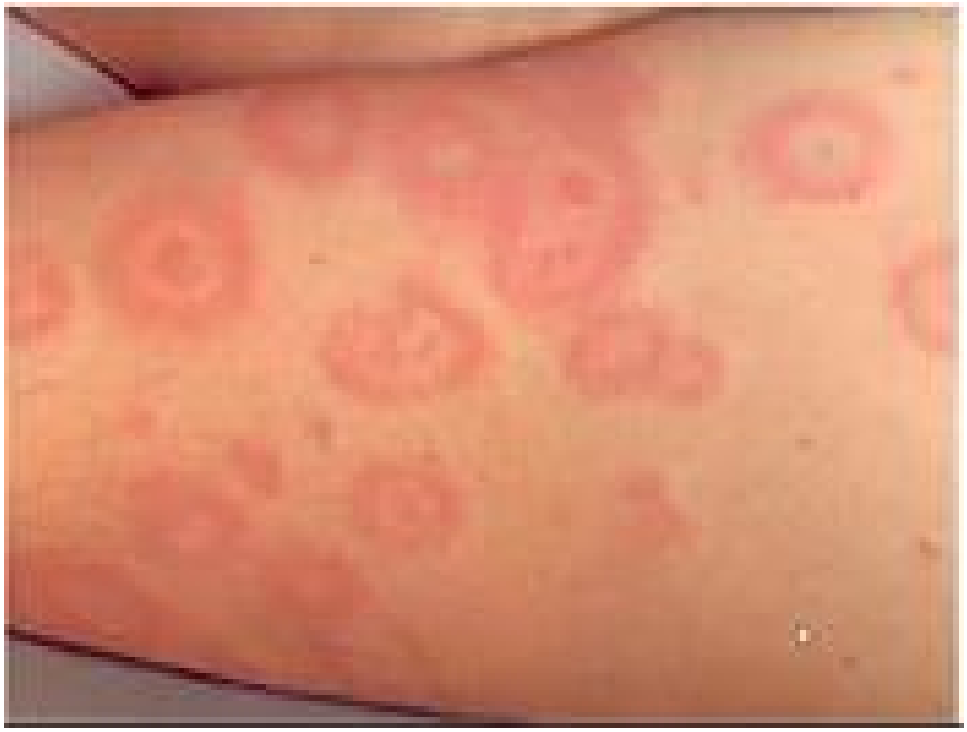


Figure: Erythema chronicum migrans (Bull's eye rash) DD: Lyme disease , Vasculitis.

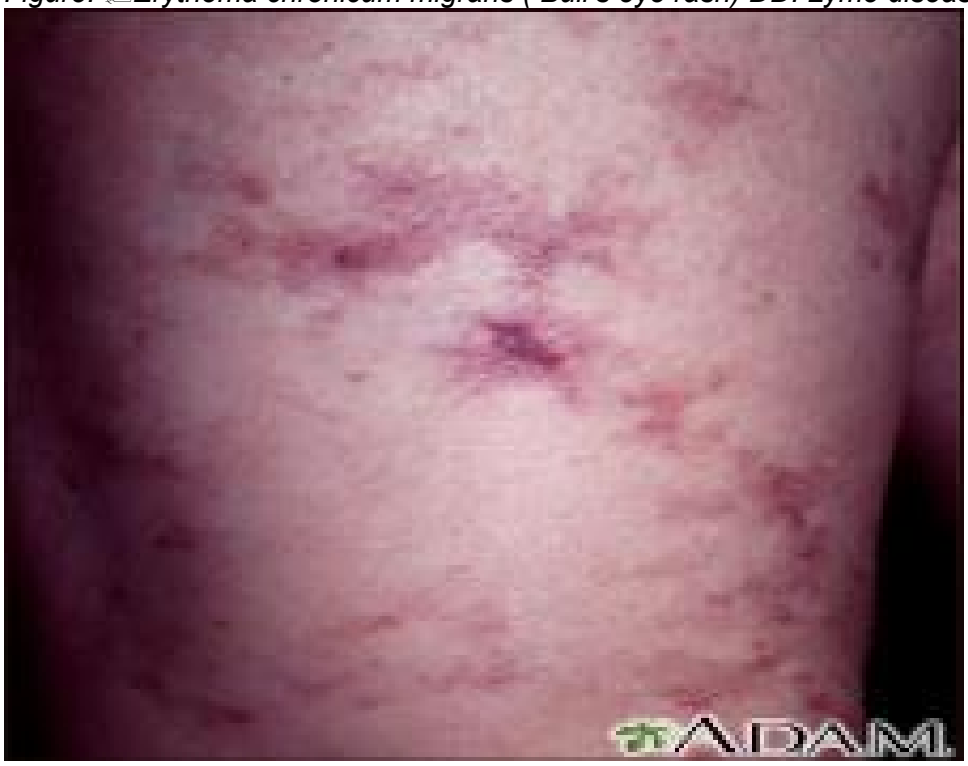


Figure: Erythema chronicum migrans (Bull's eye rash) DD: Lyme disease , Vasculitis.

Lyme Disease — Cardiac Involvement

- **Borrelia burgdorferi** (spirochete) transmitted by Ixodes tick
- ECG progression: 1st degree AV block → Mobitz I → Mobitz II → Complete (3rd degree) AV block
- 3rd degree block: bradycardia, syncope → may need temporary pacing

- **Treatment:** Doxycycline (early), IV ceftriaxone (cardiac/neurological)

5. SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Systemic = multi-organ | Lupus = wolf-like rash | Erythematosus = redness

Chronic, multisystemic, inflammatory autoimmune disease. Characterized by autoantibodies against self-antigens, immune complex formation, and immune dysregulation → damage to any organ.

Pathophysiology

- Defective apoptotic clearance → autoreactive B-cells survive → autoantibodies produced → immune complex deposition → complement activation → tissue damage
- **Key antibodies:** ANA (sensitive), anti-dsDNA (specific, monitors activity), anti-Sm (specific, not for monitoring), anti-Ro/SSA (neonatal SLE), anti-phospholipid (thrombosis)

Risk Factors

MNEMONIC: SLE Risk Factors	
F	Female sex (hormones — especially estrogen). F:M = 10–15:1 in reproductive age
I	Infections (especially viruses — possible trigger)
G	Genetics: HLA-DR2, HLA-DR3; Klinefelter (XXY) males at higher risk
S	Smoking (also worsens disease activity)
P	Pregnancy (can trigger or worsen flares)
V	UV radiation (triggers photosensitive rash and flares)

Clinical Features — SLE Criteria (2019 EULAR/ACR)

2019 EULAR/ACR Classification Criteria (Replaced 1997 ACR):

Entry criterion: ANA ≥1:80 at ANY time. Then domains below are scored. Score ≥10 = SLE.

Updated 2019: Fever now included as a criterion (not in 1997 criteria)

Domain / Feature	Notes
Malar (butterfly) rash	Fixed erythema over cheeks + nose bridge, spares nasolabial folds. No scarring
Discoid rash	Raised, scarring; follicular plugging; hypo/hyperpigmentation; treat like a vital organ
Photosensitivity	Rash worsens with UV exposure

Oral ulcers	Painless (unlike Behçet's which are painful); heal within days
Non-scarring alopecia	Hair loss >100 hairs/day
Arthritis	Non-erosive (reversible deformities); ≥2 joints; migratory/symmetrical; NO morning stiffness
Serositis	Pleuritis (knife-like, worsens with breathing) or pericarditis (worsens lying flat)
Renal	Proteinuria >500 mg/24h OR cellular casts. 50% of SLE have renal involvement
Neurological	Seizures, psychosis (2nd most common cause of morbidity after nephritis)
Hemolytic anemia	+ve Coombs; ↑ bilirubin, ↑ reticulocytes
Leukopenia/Lymphopenia	<4000/μL or <1500/μL lymphocytes
Thrombocytopenia	<100,000/μL (unlike RA where platelets are elevated)
Fever	Added in 2019 criteria update
Anti-dsDNA / Anti-Sm	Highly specific; anti-dsDNA used for monitoring activity
Antiphospholipid Ab	Anticardiolipin (IgG/IgM), Lupus anticoagulant — associated with thrombosis, miscarriage
Low complement (C3/C4)	↓ in active nephritis (immune complex consumption)

Renal Involvement — WHO/ISN Classification

Class	Histology	Clinical
I	Minimal mesangial	Normal urinalysis
II	Mesangial proliferative	Mild proteinuria/hematuria
III	Focal proliferative (<50% glomeruli)	Hematuria, proteinuria, mild renal impairment
IV	Diffuse proliferative (≥50% glomeruli)	MOST SEVERE — nephritic syndrome, RF, HTN. Requires aggressive immunosuppression
V	Membranous	Heavy proteinuria (nephrotic syndrome), preserved GFR
VI	Advanced sclerosing (>90% sclerosis)	Progressive renal failure; immunosuppression unlikely to help

⚠ **Important: Renal involvement is the #1 cause of morbidity and mortality in SLE**

- **Avoid NSAIDs in SLE renal disease** — cause interstitial nephritis (diagnosed by eosinophils in urine)
- Do urine dipstick + microscopy on ALL SLE patients — RBC casts = nephritis

SLE vs. RA — Key Differences

Feature	SLE	RA
Age	Younger (menarche–menopause)	30–55 years
Morning stiffness	Absent	Present >1 hour
Joint erosions	ABSENT (reversible deformities)	Present (fixed deformities)
Renal involvement	Common (50%)	Rare (Felty's, drugs)
Serology	ANA+, anti-dsDNA+	RF+, Anti-CCP+
Key drug to AVOID	NSAIDs (nephritis)	Gold (obsolete, nephrotoxic)

Antibody–Clinical Correlation

Antibody	Clinical Association
ANA	Sensitive screening test (95%); positive lifelong — for DIAGNOSIS only, not monitoring
Anti-dsDNA	Specific (60–80%), correlates with disease activity and nephritis — used for MONITORING
Anti-Sm	Highly specific (30%) — diagnostic but not for monitoring
Anti-Ro (SSA)	Neonatal lupus / congenital heart block; Sjögren's overlap
Anti-La (SSB)	Sjögren's overlap; associated with anti-Ro
Antiphospholipid Ab	Thrombosis (DVT, PE, stroke), recurrent miscarriage, thrombocytopenia
Anti-histone	Drug-induced lupus (positive; anti-dsDNA negative)

Drug-Induced Lupus

Drug-Induced Lupus

- **Drugs:** Hydralazine, Procainamide, Quinidine, Isoniazid, Methyldopa, Chlorpromazine, Minocycline

- **Features:** Equal M:F ratio, NO CNS or renal involvement, ANA positive, anti-dsDNA NEGATIVE, anti-histone positive
- **Treatment:** Stop offending drug → remission in 3–6 months
- **Prognosis: BETTER than SLE**

SLE & Pregnancy

- **SLE worsens during pregnancy** (opposite of RA which improves)
- Plan pregnancy only when stable ≥4–6 months; must be controlled at least 4 months prior
- Can cause preeclampsia, premature birth, neonatal lupus
- **Neonatal SLE:** Due to maternal anti-Ro/SSA antibodies crossing placenta → congenital AV block (bradycardia) — <1-2%
- **Hydroxychloroquine:** Safe in pregnancy — continue throughout
- **Avoid:** Methotrexate, Mycophenolate, Cyclophosphamide (all teratogenic)

Treatment of SLE

Organ Involved	Treatment
Malar rash	Sunscreen, topical steroids, hydroxychloroquine
Joints, skin, serositis (mild)	NSAIDs (if no renal disease), hydroxychloroquine, low-dose steroids
Serious organs (CNS, renal Class III–IV)	High-dose steroids + cyclophosphamide (induction) or mycophenolate mofetil (MMF)
Maintenance	Azathioprine or MMF (steroid-sparing)
Refractory	Belimumab (anti-BLyS — anti-B cell survival factor) — approved 2011, updated 2020 for active nephritis
Anti-phospholipid syndrome	Anticoagulation (warfarin/LMWH)

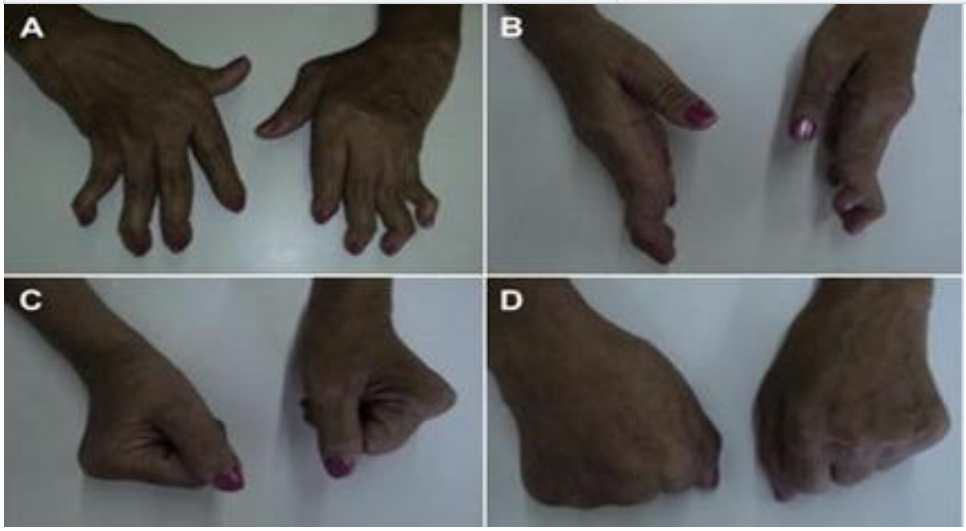


Figure: Final NOTE : methotrexate times of action is 6 weeks and we use corticosteroid in this interval to

- ⚠ **Do NOT use Methotrexate in SLE**
- **Vaccinations:** Annual influenza; Pneumovax every 5 years
- Monitor disease activity with: anti-dsDNA levels, complement (C3/C4), urine analysis, CBC, ESR/CRP

6. VASCULITIS

Inflammation of blood vessel walls by inflammatory cells. Autoimmune, can affect any vessel size and any organ → wide clinical manifestations. Can be primary or secondary (CTD, infection).

Classification by Vessel Size

Vessel Size	Conditions
Large vessel	Takayasu Arteritis, Giant Cell (Temporal) Arteritis
Medium vessel	Polyarteritis Nodosa (PAN), Kawasaki Disease
Small vessel (ANCA+)	Granulomatosis with Polyangiitis (GPA/Wegener's), Microscopic Polyangiitis (MPA), Eosinophilic GPA (Churg-Strauss)
Small vessel (Immune complex)	IgA Vasculitis (HSP), Cryoglobulinemic vasculitis, Goodpasture syndrome

Purpura — Diagnostic Approach

Purpura Approach

6. Low platelet count → thrombocytopenic purpura (ITP, SLE, TTP, HUS)
7. Normal platelet count → check platelet function (bleeding time)
8. Normal platelet count + normal function → Vasculitis

Vasculitic purpura: Palpable (elevated), painful, on dependent areas (lower legs)

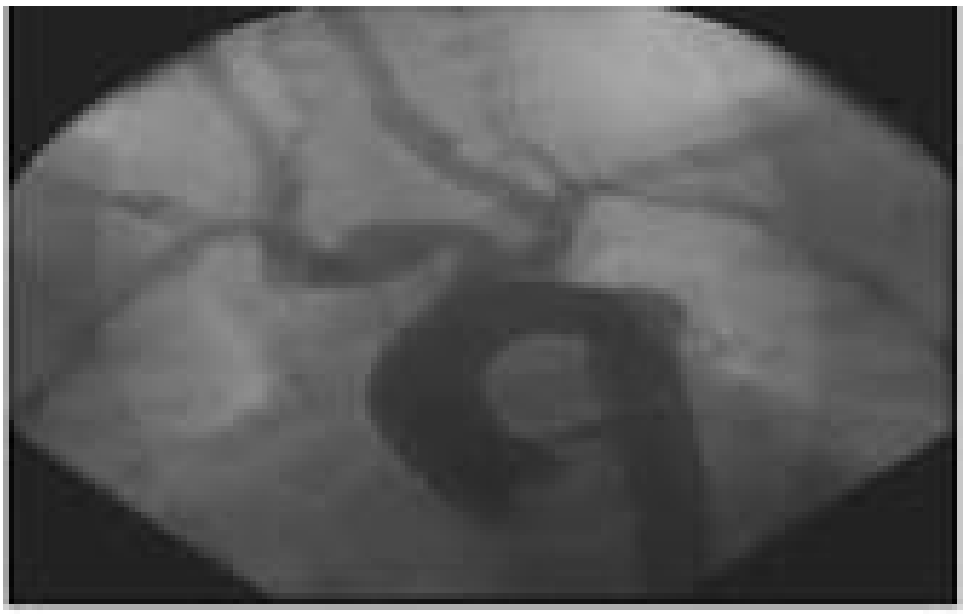


Figure: Takayasu Arteritis : 🎬

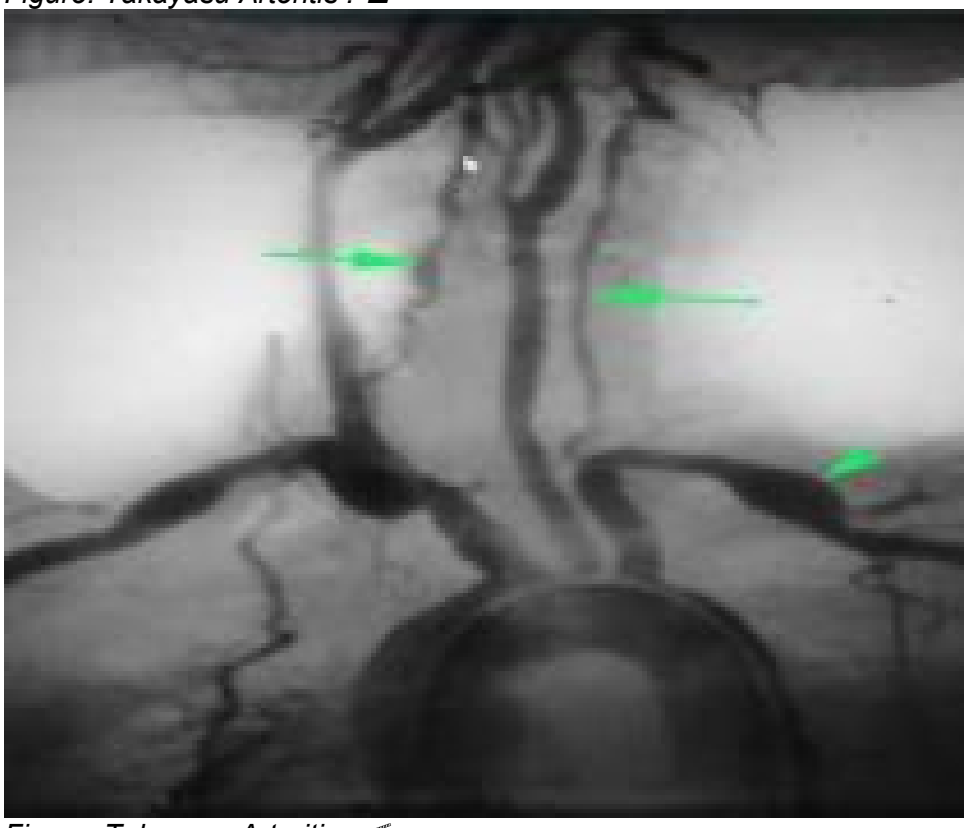


Figure: Takayasu Arteritis : 🎬

Takayasu Arteritis

Takayasu Arteritis
• **Age:** 10–40 years (if >40 → think atherosclerosis, not vasculitis) • **Demographics:** F:M = 10:1; More common in Japan, Asia, Middle East • **Vessels:** Aorta and major branches (subclavian, renal, carotid, vertebral, pulmonary)

Manifestations:

- Claudication of upper extremities, unequal/absent pulses, radio-radial or radio-femoral delay (>10 mmHg difference)
- **Pulse delay DDx:** Coarctation of aorta vs. Takayasu
- Renal artery involvement → renovascular HTN (50%)
- Subclavian steal syndrome — retrograde vertebral flow → syncope, dizziness
- Erythema nodosum (early inflammatory phase)
- Bruits over subclavian, brachial, abdominal aorta
- ⚠ **Biopsy of aorta is CONTRAINDICATED**

Diagnosis:

- Angiography (gold standard): aneurysms, beading, stenosis, collaterals in chronic disease
- MRI/MRA or CT angiography (non-invasive alternatives)
- PET scan: useful in inflammatory phase
- Labs: ↑ESR, ↑CRP, ↓albumin

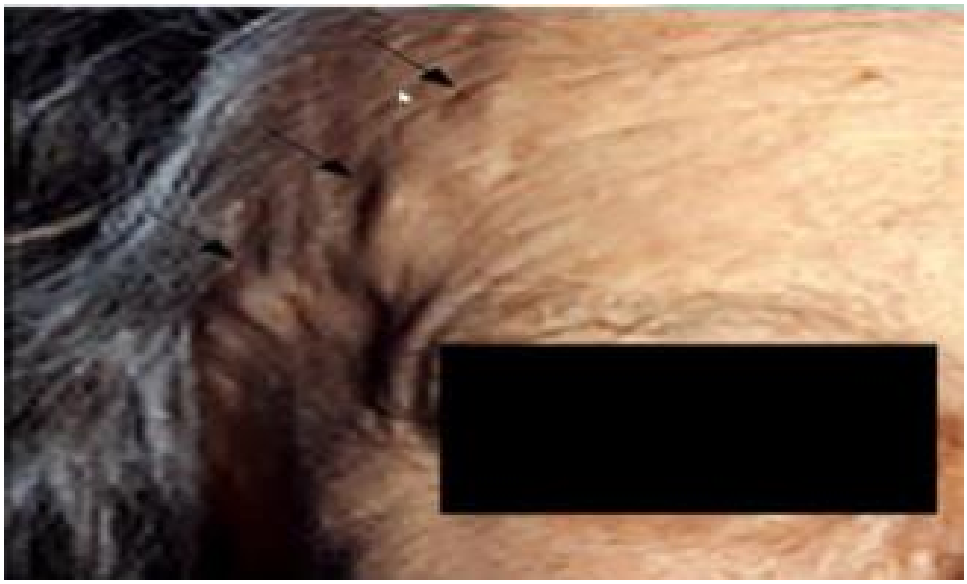


Figure: Temporal arteritis :

Giant Cell (Temporal) Arteritis

Giant Cell Arteritis — EMERGENCY RISK

- **Age: >50 years** (highest after 70). F:M = 3:1
- **Vessels:** Branches of external carotid (temporal, ophthalmic, posterior ciliary)

Classic Presentation:

- New-onset unilateral temporal headache (70%)
- Jaw/tongue claudication (50%) — pain with chewing/talking

- ⚠ **Sudden, irreversible blindness (12%)** — due to anterior ischemic optic neuropathy
- Fever of Unknown Origin (FUO) in elderly
- Scalp tenderness, thickened/nodular temporal artery — non-pulsatile, tender

Association: 50% have Polymyalgia Rheumatica (PMR) — pain/stiffness in shoulder/hip girdle, no weakness

15% of PMR patients have GCA

⚠ **DO NOT wait for biopsy before treating if blindness is suspected!**

Start high-dose steroids IMMEDIATELY → biopsy within 2 weeks (granulomatous changes persist)

Biopsy: ≥1.5 cm temporal artery (skip lesions → take long specimen)

First investigation: ESR (often >50 mm/hr, frequently >100)

MNEMONIC: Giant Cell Arteritis Features	
H	Headache (unilateral, temporal — 70%)
E	ESR elevated (>50, often >100) — first test to order
A	Age >50 (essentially never in younger patients)
D	Disease of the eye — abrupt blindness (ophthalmic artery)
S	Scalp tenderness + jaw claudication

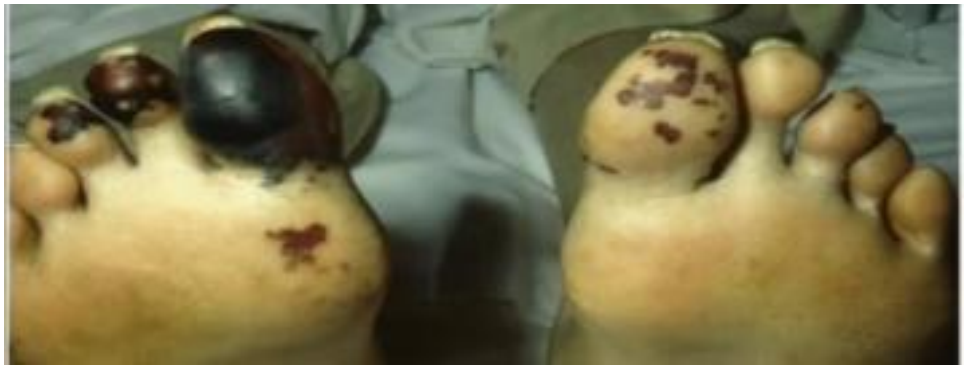


Figure: Polyarthritis nodosa (PAN) : systemic necrotizing

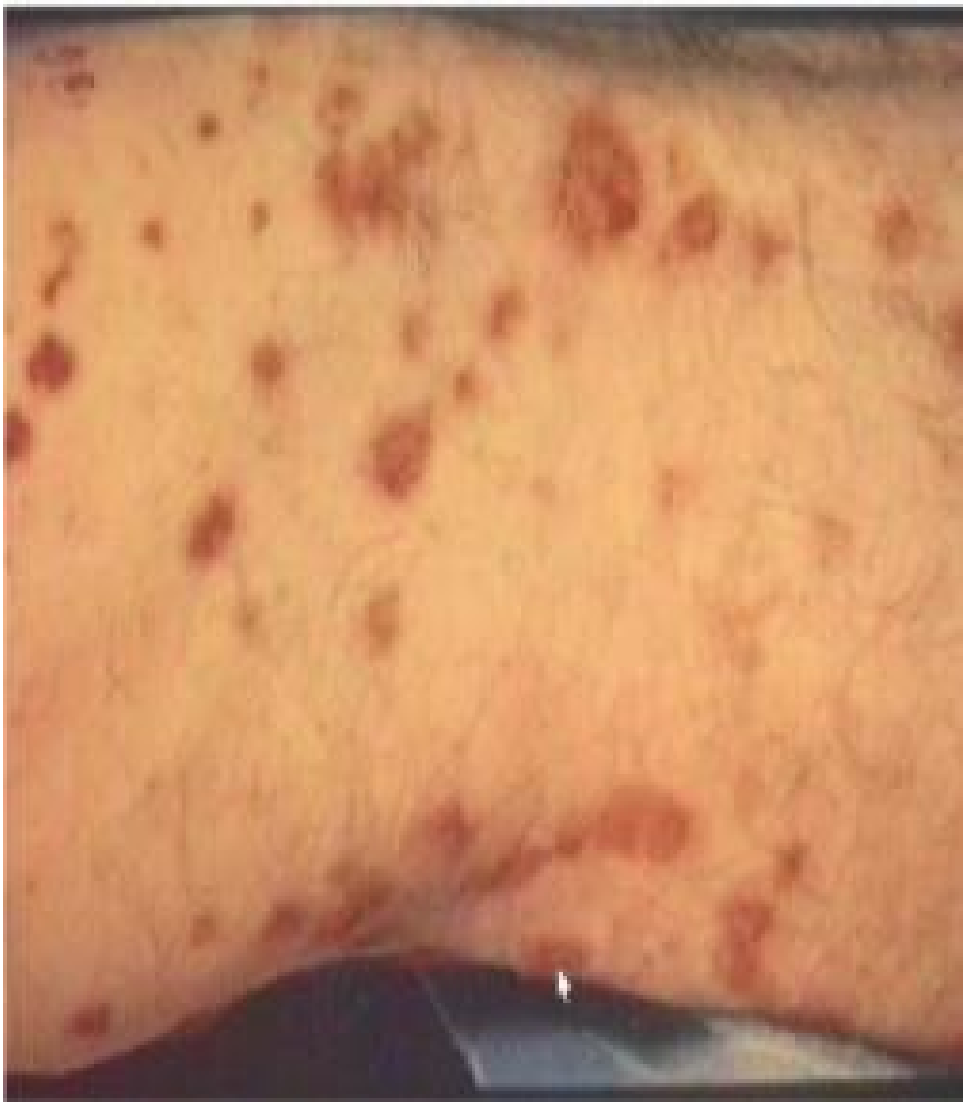
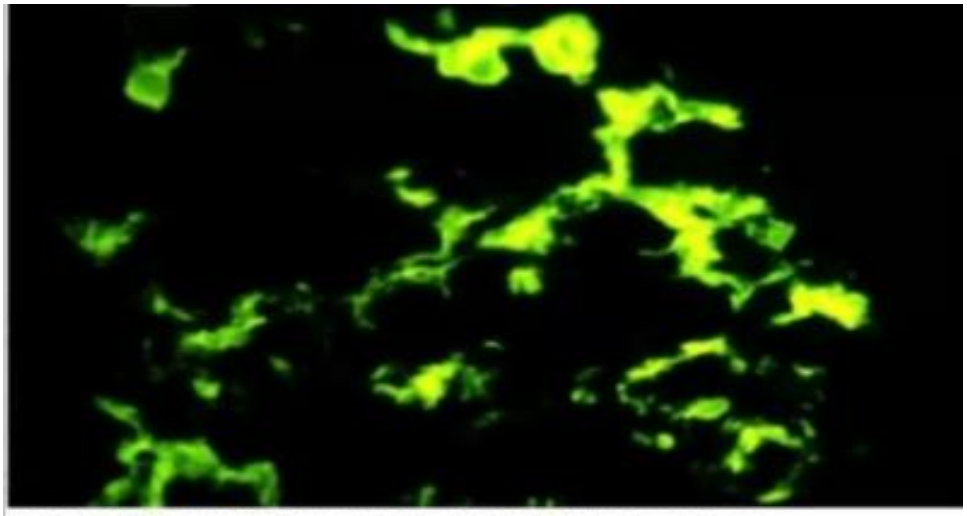


Figure: How to approach vasculitis :

Polyarteritis Nodosa (PAN)

- **Medium vessel** systemic necrotizing vasculitis; spares lung
- **HBV association:** 25–40% are HBV surface Ag positive (screen all patients!)
- **ANCA negative** (key differentiator from MPA/GPA)
- Manifestations: Gangrene of digits, livedo reticularis, mononeuritis multiplex, renal artery stenosis (HTN), testicular pain
- **Diagnosis:** Angiography (multiple microaneurysms — pathognomonic)
- **Treatment:** Cyclophosphamide (not MTX); control HTN with CCB (NOT ACEi — renal artery stenosis contraindication); if HBV-related → antivirals + short-course steroids



Mesangial IgA deposits Immunofluorescence microscopy demonstrating large, globular mesangial IgA deposits that are diagnostic of IgA nephropathy or Henoch-Schönlein purpura. Note that the capillary walls are not outlined, since the deposits are primarily limited to the mesangium. Courtesy of Helmut Rennke, MD.

Figure: Wegener –granulomatosis : can be fatal ☹

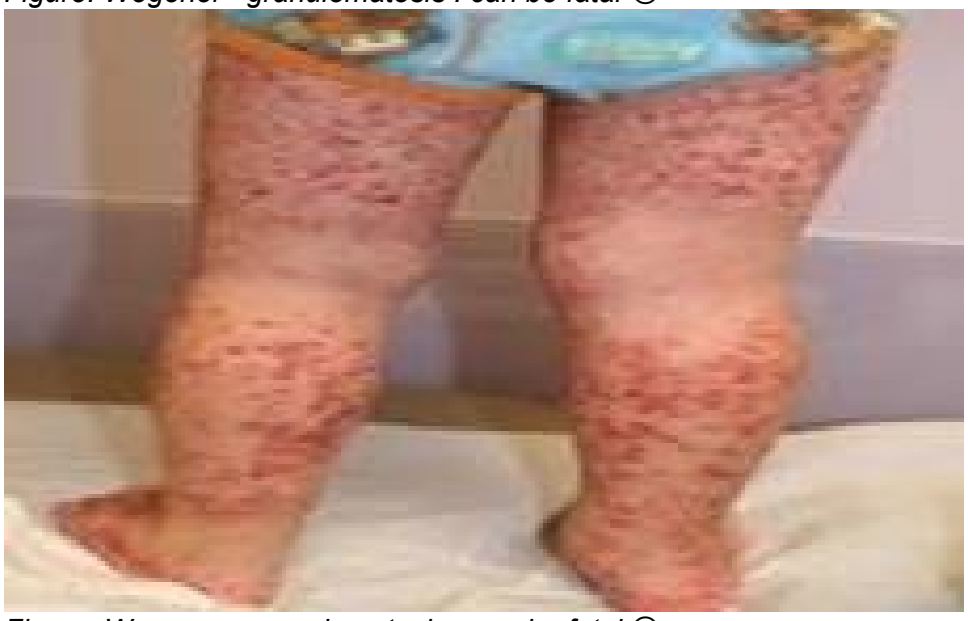


Figure: Wegener –granulomatosis : can be fatal ☹

Granulomatosis with Polyangiitis (GPA / Wegener's)

GPA (Wegener's)

- **Small/medium vessels;** upper + lower respiratory tract + kidneys (classic triad)
- Sinusitis, epistaxis, saddle-nose deformity (nasal septal destruction)
- **Saddle nose DDx:** Wegener's, SLE, Trauma, Syphilis, Relapsing polychondritis, Leprosy
- Lung: ring lesions, nodules, cavitation, alveolar hemorrhage
- **Serology: C-ANCA (PR3) positive**
- **Diagnosis:** Biopsy (granulomatous inflammation) + immunofluorescence

- **Treatment:** Rituximab (preferred) OR cyclophosphamide + steroids; maintenance with azathioprine or rituximab
- **2022 update:** Avacopan (complement C5a receptor inhibitor) now approved as adjunct — reduces steroid requirement

IgA Vasculitis (Henoch-Schönlein Purpura — HSP)

- **Predominantly children <14 years** (most common systemic vasculitis in children); follows URT infection
- **Tetrad:** Palpable purpura (buttocks/thighs, 100%) + Arthralgia (83%) + Abdominal pain (63%) + Renal involvement (40%)
- **Diagnosis:** Skin biopsy → IgA deposits
- **Treatment:** Steroids only if severe abdominal pain or nephritis (crescentic GN → add cyclophosphamide). Otherwise, supportive — most self-resolve

ANCA Reference

ANCA Type	Target Antigen	Associated Disease
C-ANCA	Proteinase 3 (PR3)	GPA (Wegener's) — primarily
P-ANCA	Myeloperoxidase (MPO)	Microscopic Polyangiitis (MPA), Eosinophilic GPA (Churg-Strauss)

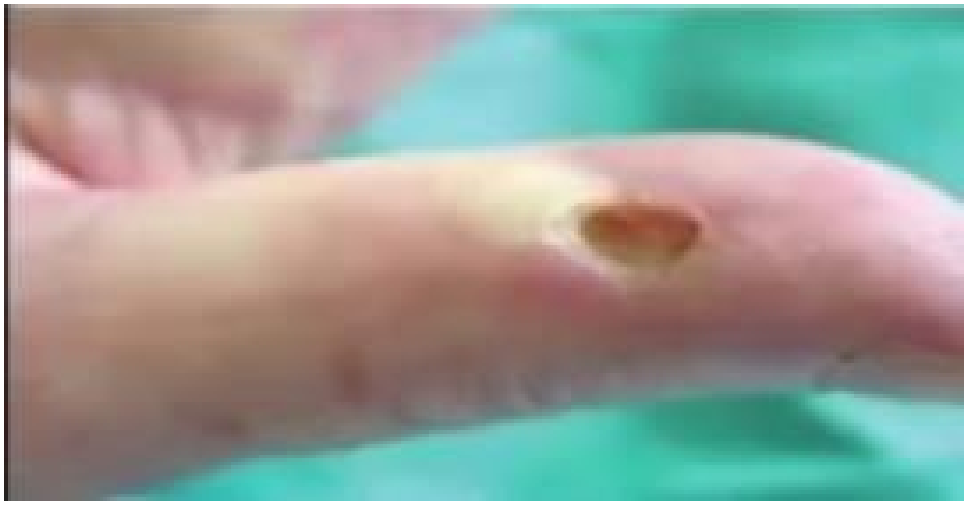


Figure: Scleroderma(systemic sclerosis):

7. SCLERODERMA (SYSTEMIC SCLEROSIS)

Rare connective tissue disorder characterized by: (1) Skin thickening/fibrosis, (2) Vasculopathy, (3) Autoantibodies. Diverse clinical picture — difficult to evaluate, treat, and monitor.

Types

Type	Limited (lcSSc)	Diffuse (dcSSc)
Skin involvement	Face + distal extremities only	Diffuse (trunk + extremities)
Key antibody	Anti-centromere (ACA)	Anti-topoisomerase I (Anti-Scl-70)
Raynaud's	Present, often years before other features	Present
Pulmonary HTN	More common (major cause of death)	Less common
Interstitial lung disease	Less common	More common
Renal crisis	Rare	More common (esp. with steroids)
Prognosis	Slower progression	Worse
Mnemonic	CREST syndrome	Diffuse

MNEMONIC: Limited Scleroderma Features	
C	Calcinosis (calcium deposits in soft tissues)
R	Raynaud's phenomenon (first symptom in many)

E	Esophageal dysmotility (GERD, dysphagia)
S	Sclerodactyly (tight, shiny skin of fingers)
T	Telangiectasia (dilated vessels on skin/mucosa)

Clinical Features

Organ Involvement

- **Skin (hallmark):** Tight, shiny, indurated skin. Salt-and-pepper pigmentation. Mask-like face, pursed mouth, peaked nose, loss of lateral eyebrows. Contractures of hands.
- **Raynaud's (95–99%):** White (vasospasm) → Blue (deoxygenation) → Red (hyperemia/pain). Bilateral Raynaud's → think Scleroderma first
- **GI (most common system — 95%):** Esophageal dysmotility, GERD, gastroparesis, bacterial overgrowth (diarrhea), fecal incontinence
- **Pulmonary HTN (limited form):** Silent killer. Screen with annual echo. Treat: Endothelin receptor antagonists (Bosentan, Macitentan), PDE-5 inhibitors (Sildenafil), Prostacyclins
- **ILD (diffuse form):** Bibasilar fibrosis on CXR/HRCT. Treat with Mycophenolate (MMF) or Nintedanib (2019 approval)
- **Renal crisis:** Hypertensive emergency, microangiopathic hemolytic anemia. Precipitated by steroids in diffuse SSc. TREATMENT: ACEi (captopril/enalapril) — drug of choice, even in renal crisis
- **Digital ulcers:** Painful, at fingertips. Bosentan reduces new digital ulcers
- **Heart:** Conduction defects, cardiomyopathy, pericarditis

Skin ↔ Internal organ correlation:
Severity of skin involvement predicts severity of internal organ involvement.
Skin softening may occur after 5+ years (immune adaptation).

Diagnosis

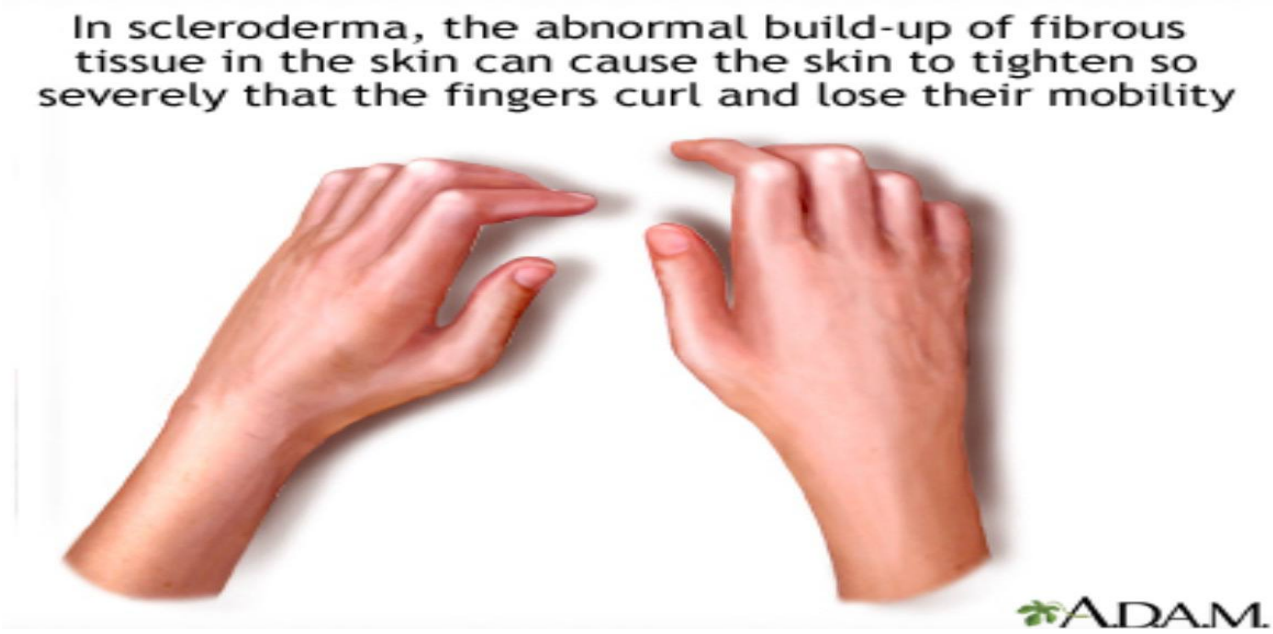
- **1 Major criterion:** Skin sclerosis proximal to MCPs (pathognomonic)
- **OR 2 of 3 minor criteria:** (1) Sclerodactyly, (2) Digital pitting scars/ulcers, (3) Bibasilar fibrosis
- ANA positive in 95%
- **Anti-centromere → limited; Anti-Scl-70 (anti-topoisomerase I) → diffuse**

Treatment

Problem	Treatment
Raynaud's	Calcium channel blockers (nifedipine), PDE-5 inhibitors, avoid cold/stress
Hypertension/Renal crisis	ACE inhibitors (drug of CHOICE — even in

	renal crisis)
GI symptoms	PPI (GERD), antibiotics (bacterial overgrowth), prokinetics
Skin (early diffuse)	Methotrexate (early disease), MMF
ILD	MMF (first-line); Nintedanib (2019); Cyclophosphamide (induction)
Pulmonary HTN	Bosentan (ERA), Sildenafil (PDE5i), Macitentan, Prostacyclins
Digital ulcers	Bosentan, vasodilators, wound care
Refractory disease	Rituximab (anti-CD20) — improves skin and lungs

⚠ **TNF inhibitors are USELESS in SSc skin/lung and may INCREASE mortality in ILD**
⚠ **Avoid high-dose steroids in diffuse SSc — precipitates renal crisis**



8. DERMATOMYOSITIS (& POLYMYOSITIS)

Inflammatory myopathy characterized by proximal muscle weakness + skin changes (in dermatomyositis). Both are autoimmune. Polymyositis = muscle only (no skin).

Clinical Features

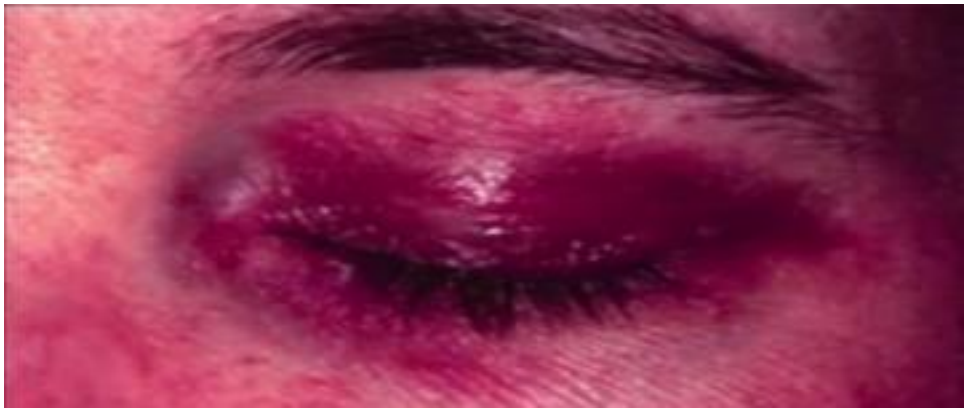


Figure: Dermatomyositis: inflammatory proximal

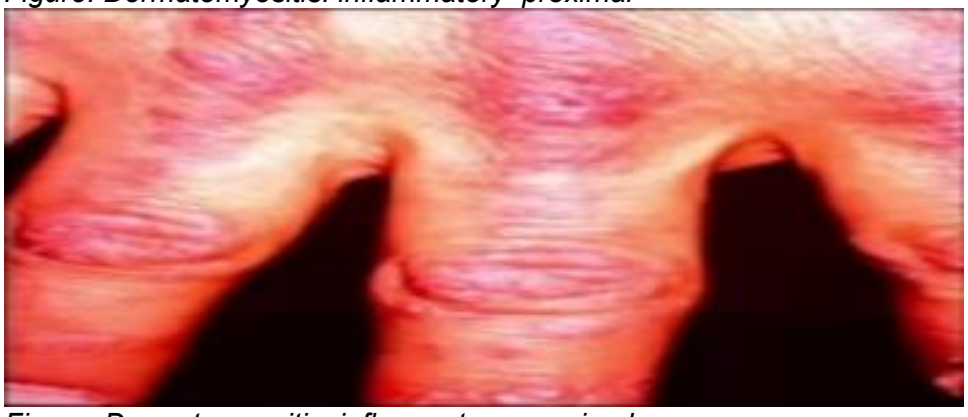


Figure: Dermatomyositis: inflammatory proximal

Muscle Weakness — Proximal

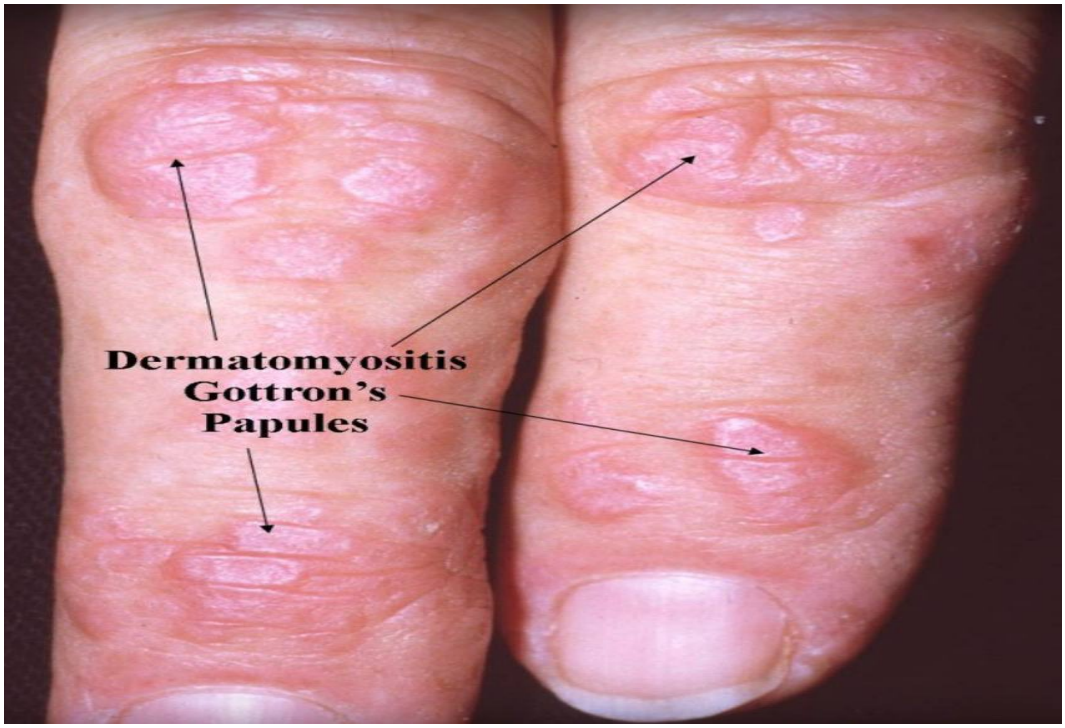
- **Upper limbs:** Cannot comb hair, cannot raise arms above head
- **Lower limbs:** Cannot rise from chair, difficulty climbing stairs
- **Gower's sign:** Patient climbs up their own legs to rise from floor (proximal weakness)

Figure: Skin is very important organ to detect scleroderma:

Figure: Skin is very important organ to detect scleroderma:

Skin Changes (Dermatomyositis only)

- **Heliotrope rash:** Violet/purple discoloration of eyelids ± periorbital edema
- **Gottron's papules:** Raised erythematous papules over dorsal knuckles (PIP/MCP/DIP joints)
- **Gottron's sign:** Erythema only (not raised) over same areas
- V-sign (chest), Shawl sign (shoulders/upper back), Mechanic's hands (cracked skin on lateral fingers)



⚠ MALIGNANCY ASSOCIATION

⚠ New-onset dermatomyositis in adults >40 years = SCREEN FOR MALIGNANCY

Associated cancers: lung, ovary, colon, lymphoma (Lambert-Eaton paraneoplastic syndrome). Screen with CT chest/abdomen/pelvis + appropriate cancer markers.

2019 update: Anti-TIF1γ antibody strongly associated with cancer-associated DM (especially in older adults)

Diagnosis

- **Muscle enzymes:** ↑ CK (most sensitive), ↑ aldolase, ↑ LDH, ↑ AST/ALT
- **EMG:** Fibrillation potentials, myopathic changes (small, polyphasic motor unit potentials)
- **MRI:** Shows muscle inflammation — guides biopsy site

Figure: Reentry via US without biopsy .

Figure: Reentry via US without biopsy .

- **Muscle biopsy:** Gold standard — perimysial inflammation (DM) vs. endomysial (PM)
- **Autoantibodies:** Anti-Jo-1 (anti-synthetase syndrome — ILD, Raynaud's, mechanic's hands, arthritis); Anti-MDA5 (rapidly progressive ILD, amyopathic DM)

Treatment

9. **High-dose steroids:** Initial treatment (prednisone 1 mg/kg/day × 4–6 weeks, then taper)
10. **Steroid-sparing DMARDs:** Methotrexate OR Azathioprine (start alongside steroids)
11. **IVIG:** For severe or refractory disease (especially dermatomyositis)
12. **Rituximab:** For cases failing conventional therapy
13. **2020 update:** JAK inhibitors (tofacitinib, ruxolitinib) show promise in refractory DM

9. BEHÇET DISEASE

Systemic vasculitis affecting arteries and veins of ALL sizes. Immune complex deposition. Prevalent along the ancient Silk Road (Turkey → Japan). HLA-B51 strongly associated.

Peak incidence: 20–40 years

MNEMONIC: Behçet Disease Features	
P	Pathergy test positive (papule/pustule 24–48h after needle prick)
A	Aphthous mouth ulcers — PAINFUL, recurrent, ≥3x/year (100% of cases) — INITIAL symptom
T	Thrombosis (arterial AND venous — veins not just arteries, unlike other vasculitides)
H	Hemoptysis (pulmonary artery aneurysm — rare but serious)
E	Eye lesions — uveitis (bilateral), retinal vasculitis — occurs 2–3 years after oral/genital ulcers
R	Recurrent genital ulcers (60–90%) — painful, scar-forming (unlike SLE oral ulcers which are painless)
G	GI involvement — ileocecal ulceration, diarrhea, GI bleeding
Y	Young patients (3rd decade peak)

Diagnostic Criteria (International Study Group)

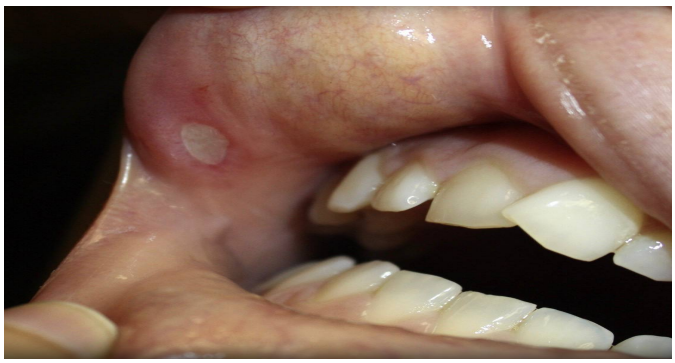
Diagnostic Criteria

Required: Recurrent oral ulcers ≥3 times in 12 months

PLUS ≥2 of:

- Recurrent genital ulcers
- Eye lesions (uveitis, retinal vasculitis)
- Skin lesions (erythema nodosum, pseudofolliculitis)
- Positive pathergy test

Note: ANA, ANCA, RF usually ABSENT — negative serology in a vasculitis is a clue for Behçet

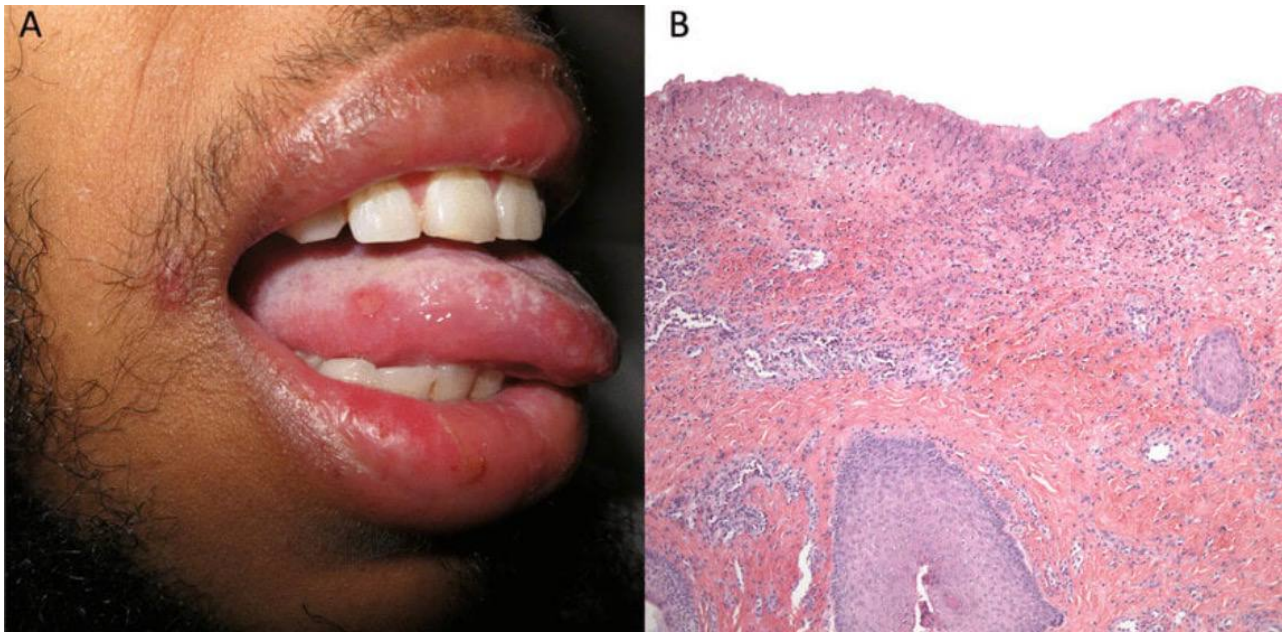


Key Distinctions

Feature	Behçet	SLE	Reactive Arthritis
Oral ulcers	PAINFUL, recurrent	Painless	Usually absent
Genital ulcers	Painful, scarring	Rare	Circinate balanitis
Serology	All negative	ANA+, dsDNA+	HLA-B27+
Pathergy	Positive	Negative	Negative
Thrombosis	Arterial + Venous	Arterial (APS)	Absent

Treatment

Manifestation	Treatment
Oral/Genital ulcers	Topical corticosteroids, topical lidocaine (pain), colchicine (recurrence prevention)
Skin lesions	Colchicine (erythema nodosum), topical acne treatment (pseudofolliculitis)
Arthritis	Colchicine, NSAIDs, low-dose steroids
Ocular disease	Systemic steroids + azathioprine or cyclosporine; anti-TNF (infliximab) for refractory
CNS / Severe vascular	High-dose steroids + cyclophosphamide or azathioprine; anticoagulation for thrombosis
Refractory disease	Apremilast (2020 approval for oral ulcers); Secukinumab (IL-17A inhibitor) — emerging evidence



QUICK REFERENCE SUMMARY

Antibodies at a Glance

Antibody	Disease Association
RF (IgM anti-IgG)	RA (~66%), also SLE, Sjögren's, infections, elderly normal
Anti-CCP (ACPA)	RA (specific ~95%); positive = worse prognosis
ANA	SLE (sensitive), Sjögren's, Scleroderma, DM, drug-induced lupus
Anti-dsDNA	SLE (specific, monitors activity)
Anti-Sm	SLE (highly specific, diagnostic)
Anti-Ro (SSA)	SLE + Sjögren's, neonatal lupus, congenital AV block
Anti-La (SSB)	Sjögren's, SLE
Anti-histone	Drug-induced lupus
Anti-Scl-70 (topoisomerase I)	Diffuse Scleroderma (poor prognosis)
Anti-centromere	Limited Scleroderma (CREST syndrome)
Anti-Jo-1	Antisynthetase syndrome (DM/PM + ILD + Raynaud's)
Anti-MDA5	Amyopathic DM + rapidly progressive ILD
Anti-TIF1γ	Cancer-associated dermatomyositis
C-ANCA (PR3)	GPA (Wegener's)
P-ANCA (MPO)	MPA, Eosinophilic GPA (Churg-Strauss)
Antiphospholipid Ab	APS — thrombosis, recurrent miscarriage, thrombocytopenia

Drug Dangers — Know These!

⚠ Drug Safety Summary

Drug/Agent	Key Danger / Note
Methotrexate	Teratogenic, hepatotoxic, bone marrow suppression; stop 3 months pre-conception; add folic acid
Hydroxychloroquine	Retinal toxicity → annual fundoscopy; safe in pregnancy
NSAIDs in SLE	Interstitial nephritis → avoid in renal SLE
Steroids in diffuse SSc	Precipitate renal crisis → avoid high doses

Allopurinol in acute gout	Prolongs/worsens acute attack → wait 4–6 weeks
ACEi in PAN	Renal artery stenosis → avoid ACEi/ARB → use CCB
Anti-TNF	TB reactivation → screen with IGRA/Mantoux before starting; useless/harmful in SSc ILD
Colchicine + NSAIDs	Severe GI toxicity → never combine
Cyclophosphamide	PAN, GPA severe — hemorrhagic cystitis, infertility, malignancy

Erosive vs. Non-erosive Arthritis

Erosive	Non-Erosive
Rheumatoid Arthritis (marginal erosions)	SLE (reversible deformities, no erosions)
Gout (punched-out with overhanging edges)	Rheumatic Fever (migratory, short-lived)
Psoriatic Arthritis (pencil-in-cup deformity)	Reactive Arthritis
Ankylosing Spondylitis (SI joint erosions)	Behçet (non-erosive oligoarthritis)

Document prepared for educational purposes in Rheumatology.

Last edited by: Marwan Herzallah | 2026