Brigham and Women's Hospital
Founding Member, Mass General Brigham

Rheumatology Board Review

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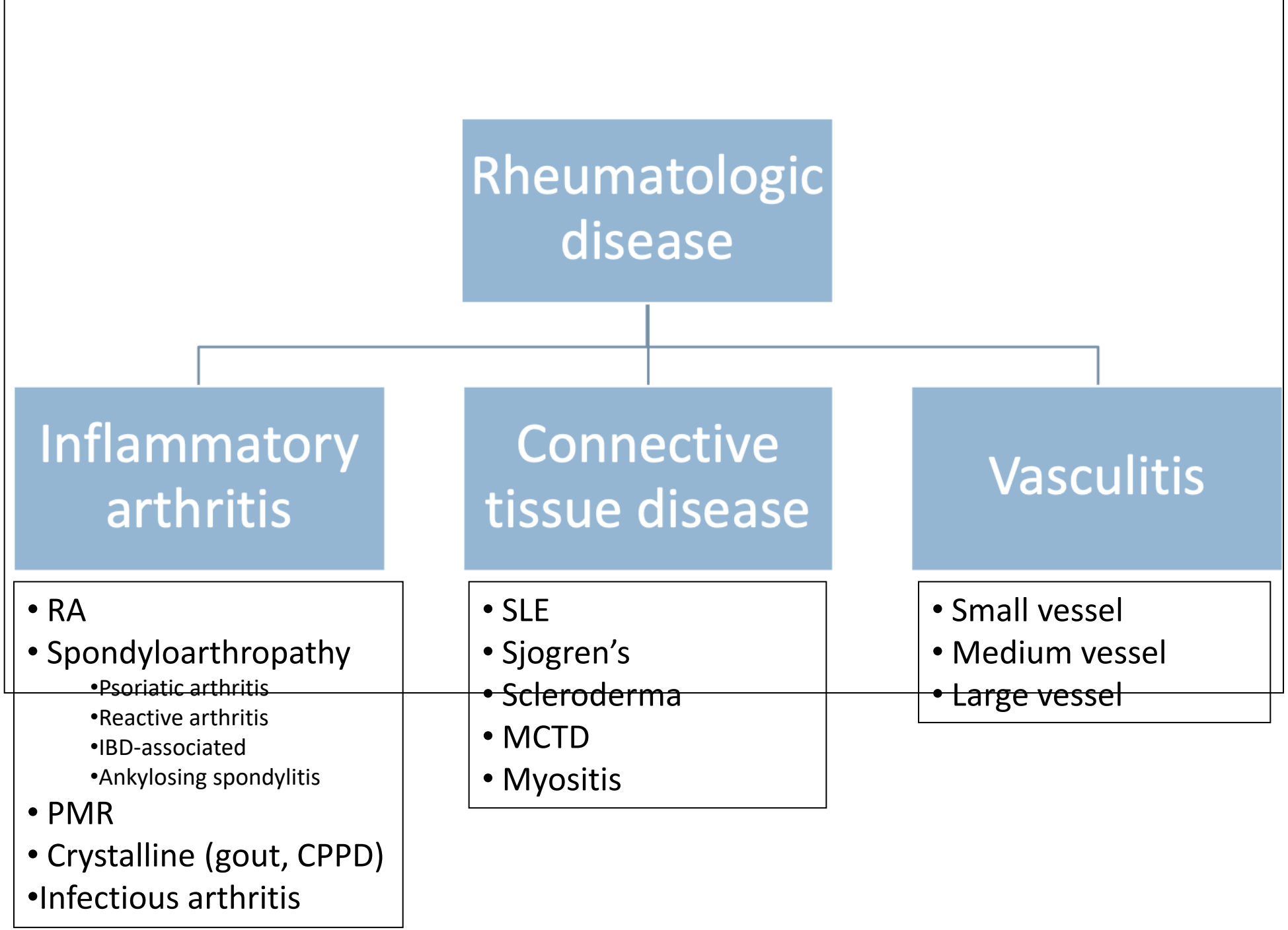
- Clinical focus: Vasculitis
- Research focus: Medical Education

DISCLOSURES

- None

OBJECTIVES

- Review and apply diagnostic and treatment strategies for the care of
  - Inflammatory arthritis
  - Connective tissue diseases
  - Vasculitis


Rheumatologic disease
Inflammatory arthritis
Connective tissue disease
Vasculitis
• RA
• Spondyloarthropathy
•Psoriatic arthritis
•Reactive arthritis
•IBD-associated
•Ankylosing spondylitis
• PMR
• Crystalline (gout, CPPD)
•Infectious arthritis
• SLE
• Sjogren's
• Scleroderma
• MCTD
• Myositis
• Small vessel
• Medium vessel
• Large vessel

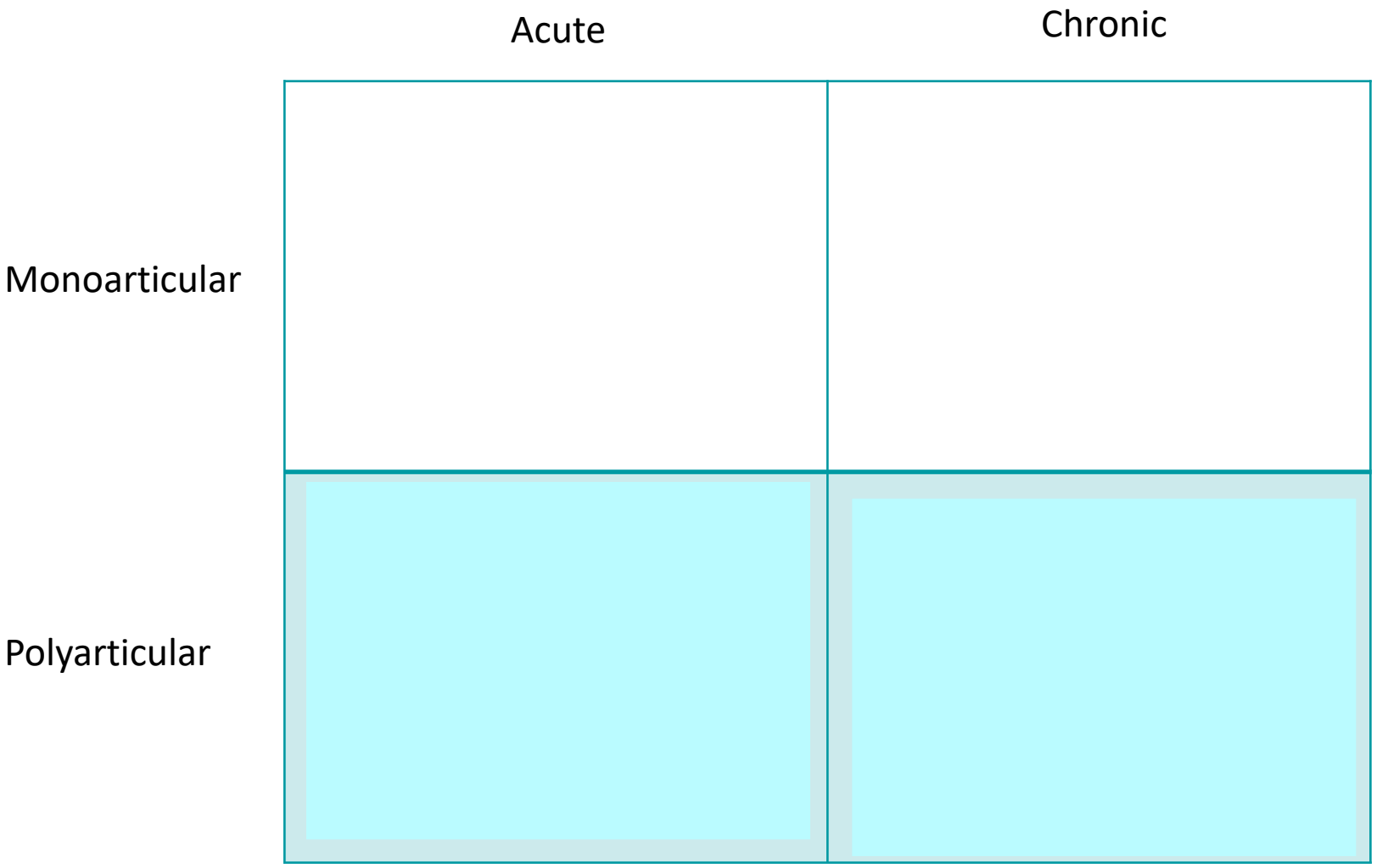
Case 1

- 52 yo M p/w R knee pain.
  - R knee pain has been present for 6 months. Worse with walking up the stairs, running and also bothersome at night. No AM stiffness.
  - Exam with mild pain with flexion, no swelling/warmth, no point tenderness.
- What is the most likely diagnosis?
  - Pseudogout
  - Osteoarthritis
  - Spondyloarthropathy
  - Bursitis

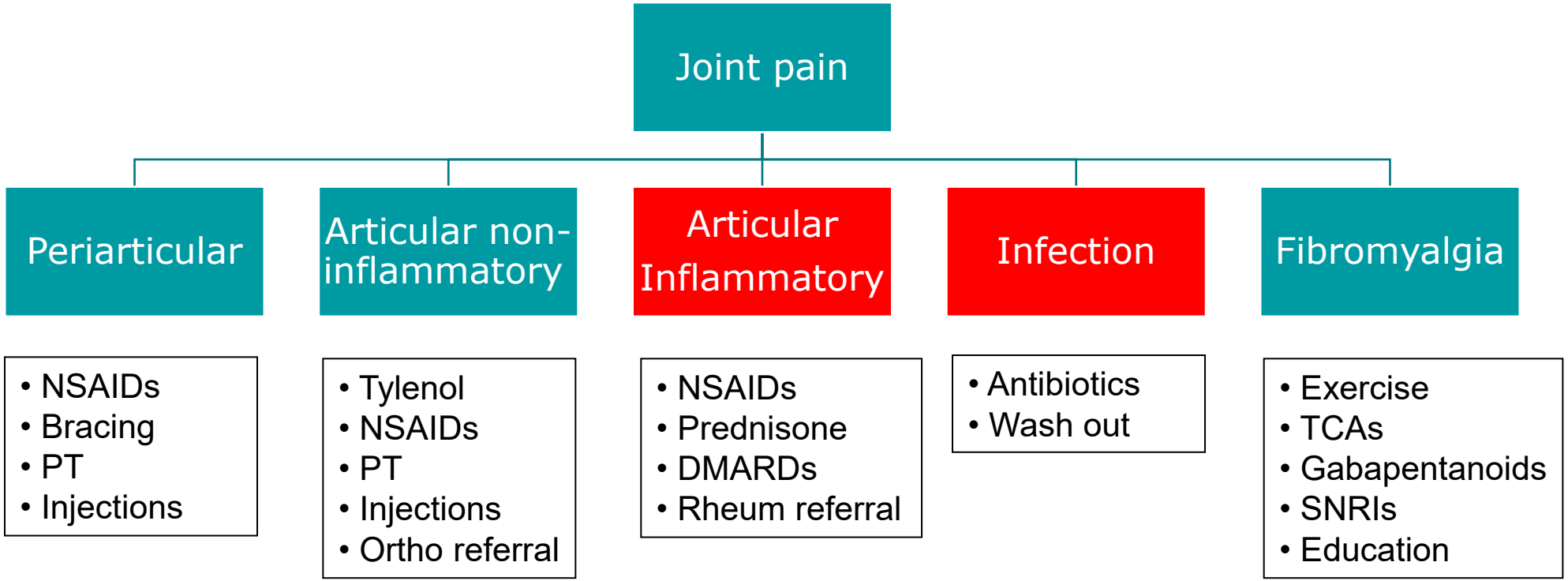
Case 2

- 65 yo F admitted for e.coli urosepsis. On hospital day 3 she develops acute R wrist pain and swelling.
  - Exam with swelling and markedly limited ROM
  - Labs with no leukocytosis, uric acid 3.4, ESR 80, CRP 129
- What is the most likely diagnosis?
  - Pseudogout
  - Gout
  - Osteoarthritis
  - Septic arthritis
  - Rheumatoid arthritis

Approach to joint pain



Categories of joint disease



Case 3

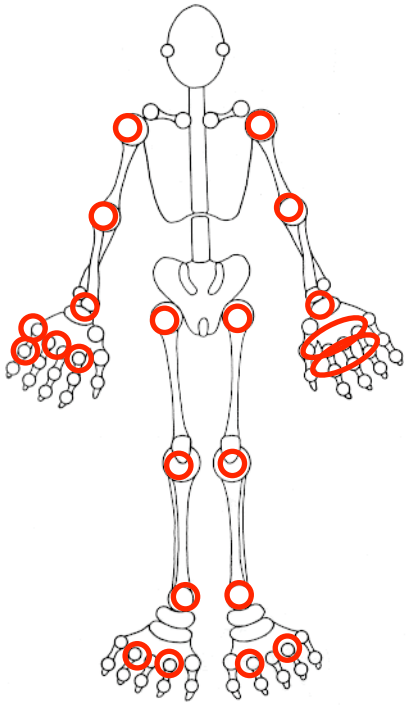
- 42 year old woman with hypothyroidism and obesity presents with pain and 45 minutes of AM stiffness in the PIPs and DIPs b/l x 6 months.
- Exam with pain and mild swelling of multiple PIPs and DIPs
- Inflammatory markers are normal
- Xrays with mild scattered DJD

What is the most likely diagnosis?

a. Osteoarthritis
b. Rheumatoid arthritis
c. Psoriatic arthritis
d. Reactive arthritis

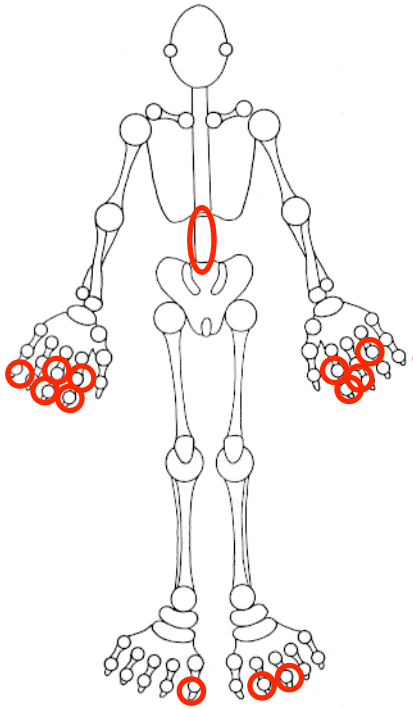
Joint involvement patterns

RA



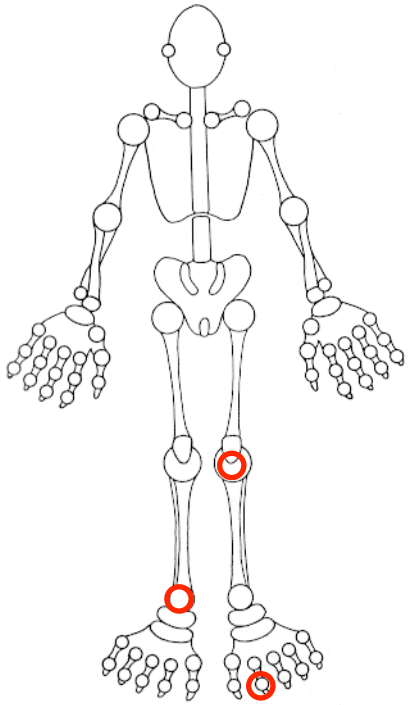
symmetric polyarthritis

PsA



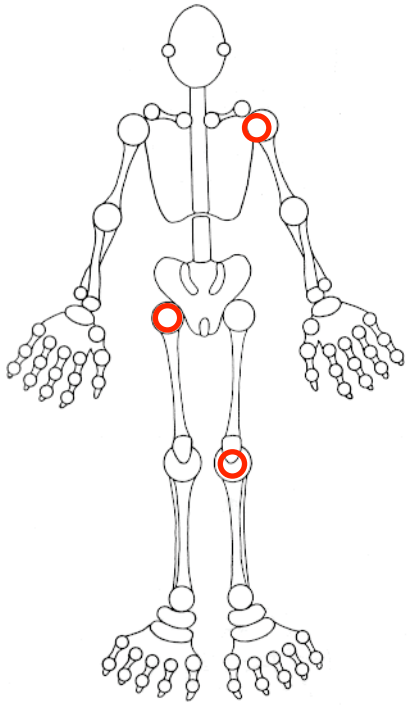
PIP, DIP arthritis

PsA



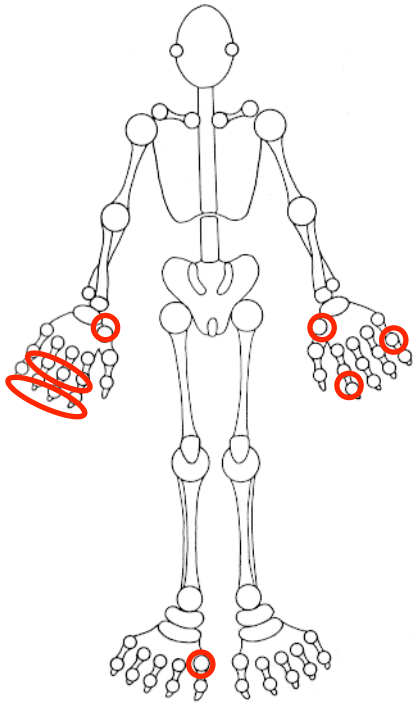
asymmetric oligoarthritis

OA



individual large joints (hip, knee)

OA



DIPs, PIPs CMC1, MTP1

Case 4

- A 28 yo kindergarten teacher presents with 1 week of pain, swelling and morning stiffness in her hands and knees.
- Exam: Mild swelling of several PIPs and MCPs. Minimally swollen + tender wrists and knees bilaterally.
- Labs: CBC wnl, ESR 40 mm/h, RF 24 IU (ref < 19), anti-CCP negative

- What is the most appropriate treatment?

A. Naproxen 500 mg BID
B. Hydroxychloroquine 300 mg daily
C. Methotrexate 15 mg weekly + folic acid 1 mg daily
D. Prednisone 15 mg daily
E. Doxycycline 100 mg BID for 10 days

Case 5

- 45 yo F with no PMH p/w joint pain
  - **L**ocation - b/l shoulder, ankle, foot (MTPs), wrist and multiple MCPs
  - **I**nflammatory features - 30 minutes of AM stiffness
  - **D**uration - 6 months
- ROS – negative
- Exam – L knee and R wrist swelling. Several MCPs, MTPs and b/l ankles are tender without synovitis
- Labs – CBC, BMP, TSH, U/A – normal
- Plain films – L knee with mild DJD

What is the most appropriate workup?

A. ANA, DsDNA, RF, Lyme, ESR/CRP
B. ANA, RF, CCP, ESR/CRP
C. ANA, DsDNA, Ro/La, Smith, RNP, RF, CCP, ESR/CRP
D. RF, CCP, uric acid, ESR/CRP
E. RF, ESR, CRP, Lyme

Case 5 (con't)

- RF – negative, Anti-CCP – negative
- ANA – 1:80 speckled
- ESR – 18 (< 20mm/hr), CRP – 6.8 (< 8mg/L)
- What is the most likely diagnosis?

A. Osteoarthritis
B. Rheumatoid Arthritis
C. Pseudogout
D. Seronegative spondyloarthropathy
E. Systemic Lupus Erythematosus

Inflammatory arthritis test characteristics

A. RF – 50-60% sensitive, 70% specific
B. CCP – 50-60% sensitive, 95% specific
C. ESR/CRP – normal in ~1/3 of patients

What doesn't fit?

A. OA – joint distribution, inflammatory features
B. RA – normal inflammatory markers, negative RF/CCP
C. Pseudogout – chronic symptoms, no xray findings
D. Seronegative spondyloarthropathy – no axial involvement or other features
E. SLE – low titer ANA, no other symptoms

RA Classification Criteria

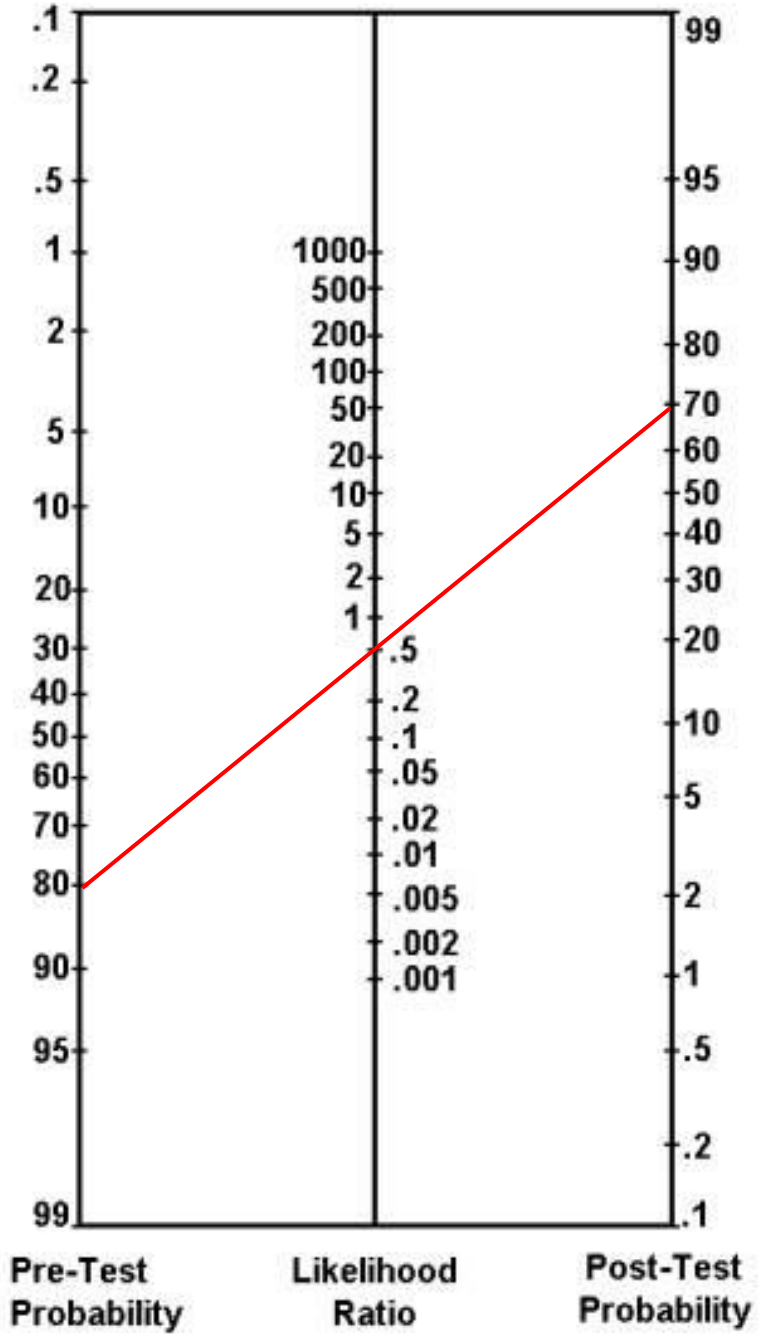
Joint involvement	Score
• 1 medium-large joint	0
• 2-10 medium-large joints	1
• 1-3 small joints	2
• 4-10 small joints	3
• More than 10 joints	5
Serology	
• RF (-) and anti-CCP (-)	0
• RF (+) or anti-CCP (+)	2
• High RF (+) or anti-CCP (+)	3
Duration of symptoms	
• < 6 weeks	0
• ≥ 6 weeks	1
Acute phase reactants	
• CRP and ESR within normal	0
• elevated CRP or ESR	1

- 6 out of 10 points needed for dx
- Need 1 swollen joint

LR+ = sensitivity / 1- specificity

LR- = 1- sensitivity / specificity

1-0.6 / .8 = 0.5



Case 6

- 60 year old woman with a history of hypertension presents with rapid onset of bilateral shoulder pain x 2 weeks. 2 hrs of AM stiffness
- Exam with limitation of abduction to 70 degrees b/l active and passive
- Xrays with bilateral glenohumeral joint arthritis
- ESR 40 (ULN 30), CRP 15 (ULN 10), RF and CCP negative

What is the most likely diagnosis?

a. Rotator cuff syndrome
b. Polymyalgia rheumatica
c. Osteoarthritis
d. Adhesive capsulitis

PMR classification criteria

Age at onset ≥ 50 years (required)
Bilateral shoulder aching (required)
Abnormal CRP and/or ESR (required)
Morning stiffness duration > 45 min (2 points)
Hip pain or limited range of motion (1 point)
Absence of RF or ACPA (2 points)
Absence of other joint involvement (1 point)
Required for classification: score of 4 or more

Dasgupta et al Ann Rheum Dis. 2012 Apr 1;71(4):484

Case 6 (con't)

- Started on prednisone 15mg with complete resolution of symptoms and normalization of inflammatory markers
- Return of shoulder pain at 10mg with rising ESR/CRP
- 5lb weight gain, insomnia, mood symptoms

What should you do next? (choose multiple)

a. Increase prednisone to 12.5mg
b. Start sarilumab
c. Start methotrexate
d. Start naproxen

Case 7

- 35 year old male presents for evaluation of low back pain
- Ongoing for 1 year, started insidiously
- 45 minutes of AM stiffness, improved with activity, worse with rest
- No improvement with NSAIDs, no nighttime awakening
- Exam without tenderness to palpation
- PT without improvement
- ESR, CRP normal
- SI joint and LS spine films normal

What is the best next step in management?

a. SI joint MRI
b. HLA-B27
c. No additional testing

Inflammatory back pain features

Table 2 Inflammatory back pain (IBP) parameters, according to experts

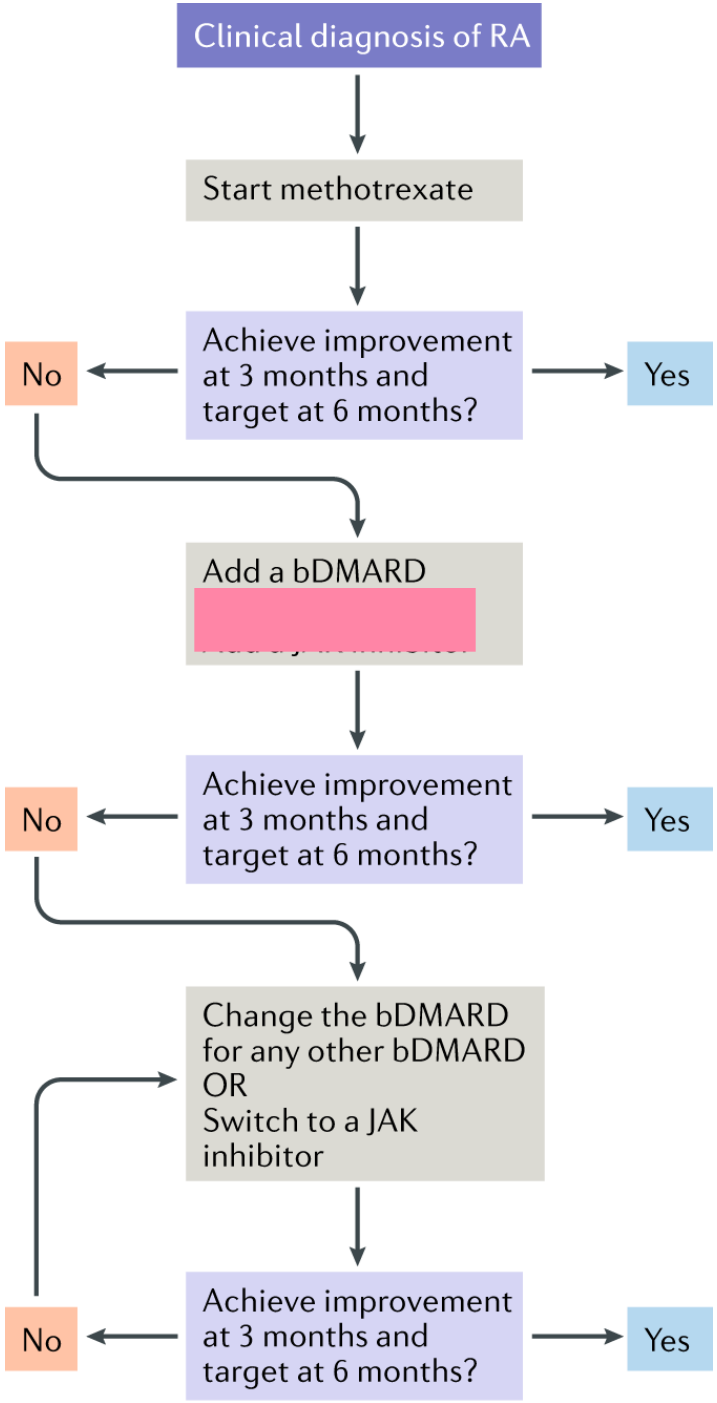
Parameter	Criteria
1	Age at onset <40 years
2	Insidious onset
3	Improvement with exercise
4	No improvement with rest
5	Pain at night (with improvement upon getting up)

Sensitivity 77.0% and specificity 91.7% if at least four out of five parameters are present. Note that sensitivity and specificity refer to the presence of IBP, not to diagnosis.

Annals of the Rheumatic Diseases 2009;**68:**784-788.

Case 8

- 59 yo M (he/him) with HTN, seropositive RA diagnosed 3 months ago and started on methotrexate 10mg and folic acid.
- Onset of symptoms in the MCPs, PIPs, wrists, knees, ankles, MTPs
- Now 30% improved but still difficulty with daily tasks
- Exam – several swollen MCPs, L wrist, R knee, b/l ankles
- Labs – ESR 30, CRP 12, LDL 160, TC 190 (10 yr risk of CVD 7%)
- What should you do today? (check multiple)
  - Increase methotrexate
  - Add prednisone
  - Start statin
  - Recommend discussing TNF inhibitor with rheumatologist



Van Vollenhoven, Nature Rev Rheumatology 2019

Rheumatic disease and CVD

- CVD mortality 59% higher in RA
  - Inflammation
  - Exercise
  - Medications – prednisone, NSAIDs, JAK inhibitors
  - Other risk factors
- RA pts less likely to report chest pain
- SLE CAD risk 2x general population
- Perfusion abnormalities 81% of symptomatic and 43% of asymptomatic pts with SLE (age 22-45)

Avina-Zubieta et al Arthritis Rheum. 2008;59(12):1690
Low et al. Ann Rheum Dis. 2017;76(4):654.
Del Rincon et al. Arthritis Rheumatol. 2014;66(2):264
Douglas et al Ann Rheum Dis. 2006;65(3):348
Sun et al Rheumatology (Oxford). 2001;40(10):1106

Summary

- RA → Symmetric, +6 weeks
- Spondyloarthropathy → Inflammatory back pain
  - Ankylosing spondylitis — Enthesitis
  - Psoriatic arthritis — Dactylitis
  - Reactive arthritis — DIP involvement
  - IBD associated arthropathy
- PMR → No distal involvement, prominent stiffness
- Crystal arthropathy → Episodic, wrist, MTP / lower extremity
- Infectious arthritis → Mono/oligo (except parvo), acute

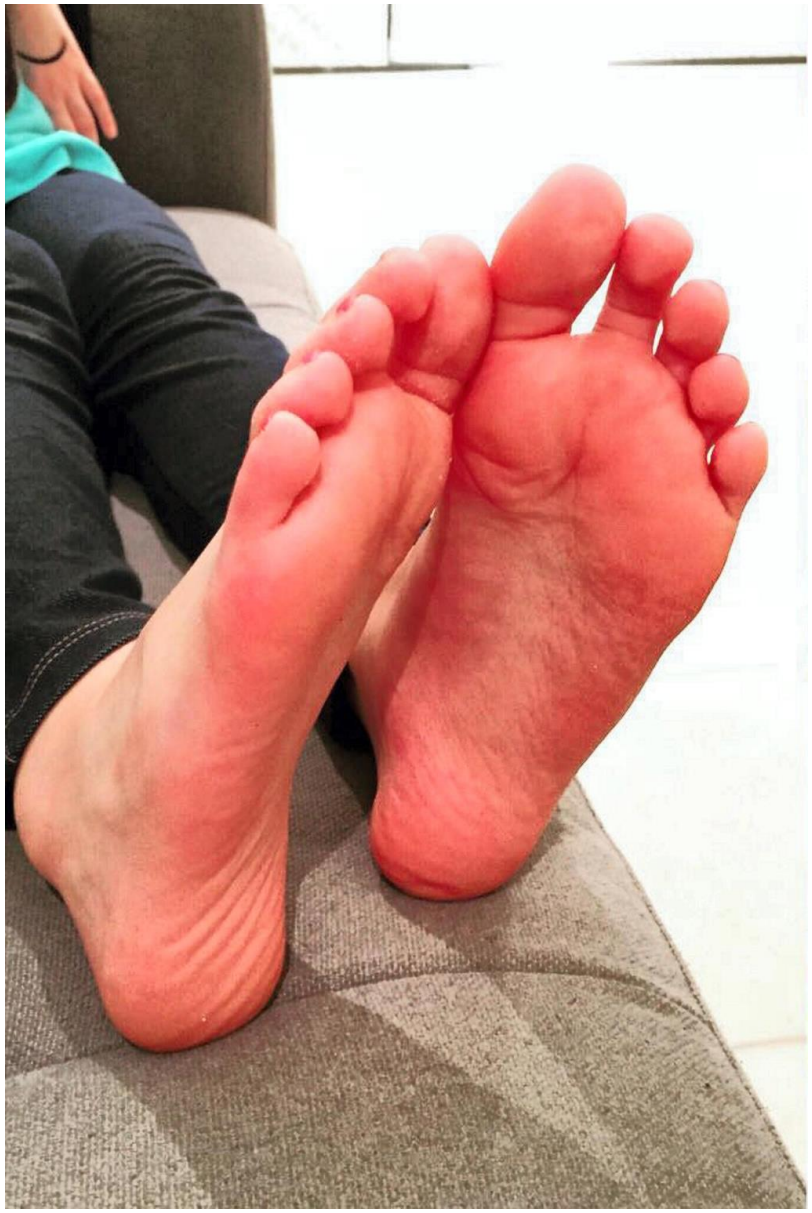
Case 9

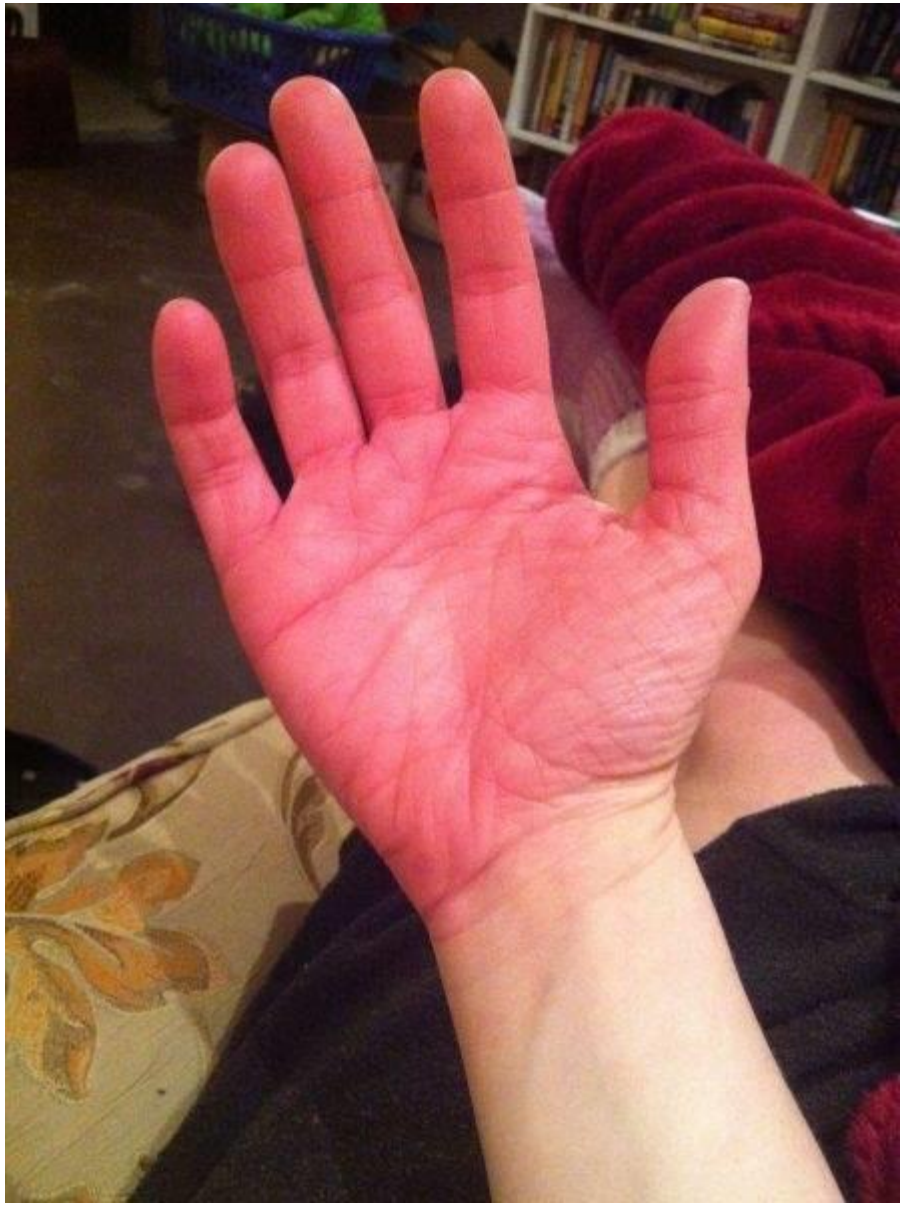
- 45 year old female presents with multiple symptoms ongoing for 2 years
  - Daytime fatigue
  - Diffuse pain described as burning involving the face, arms, legs
  - Hands turn red at end of day and after hot showers
  - Orthostasis
  - Intermittent diarrhea – dx as IBS
- Exam with diffuse tenderness, no synovitis
- ESR/CRP, ANA, TSH, SPEP, A1c, B12/folate – wnl
- EMG without abnormalities

What is the next best step in management?

a. Start nortriptyline
b. Trial of prednisone
c. Refer to neurology for skin biopsy

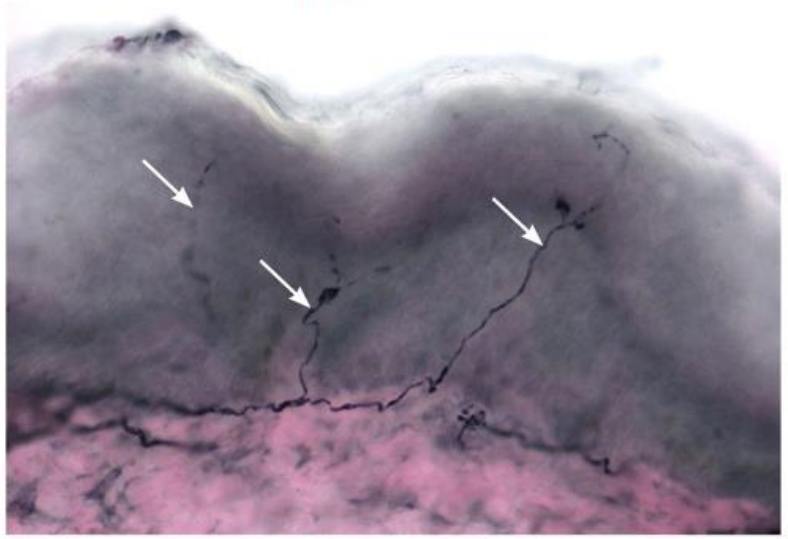
Erythromelalgia





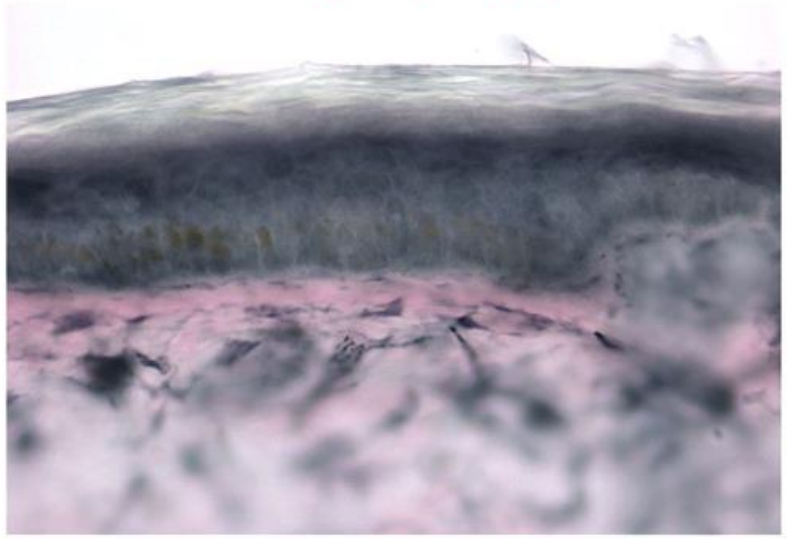
Small fiber polyneuropathy

Normal skin biopsy



Normal innervation with small nerve fibers seen in the epidermis (arrows). Skin biopsy specimens with protein gene product 9.5 immunostaining.

Small fiber neuropathy biopsy



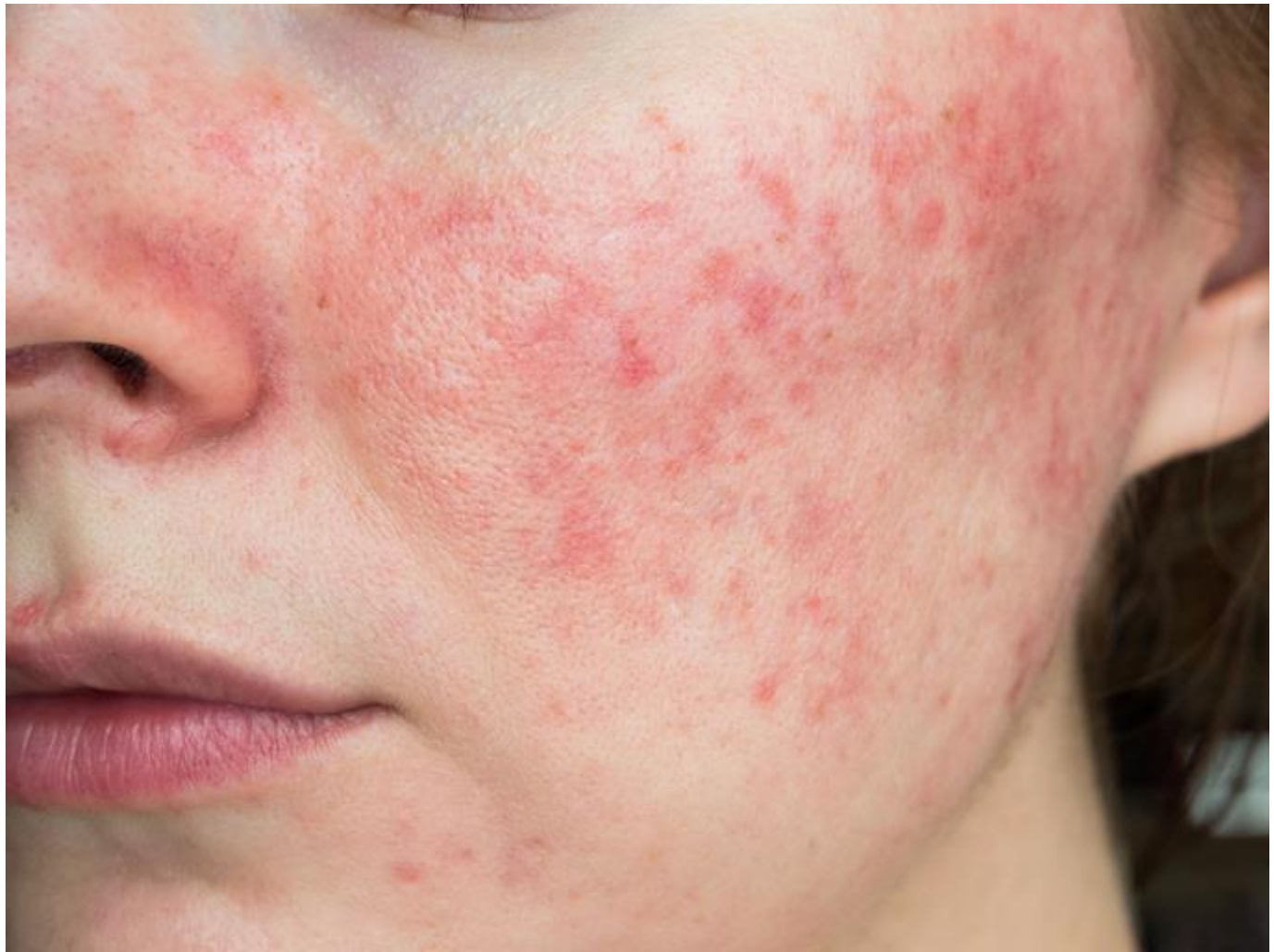
A specimen from a patient with small fiber neuropathy shows denervation with no small nerve fibers seen in the epidermis.

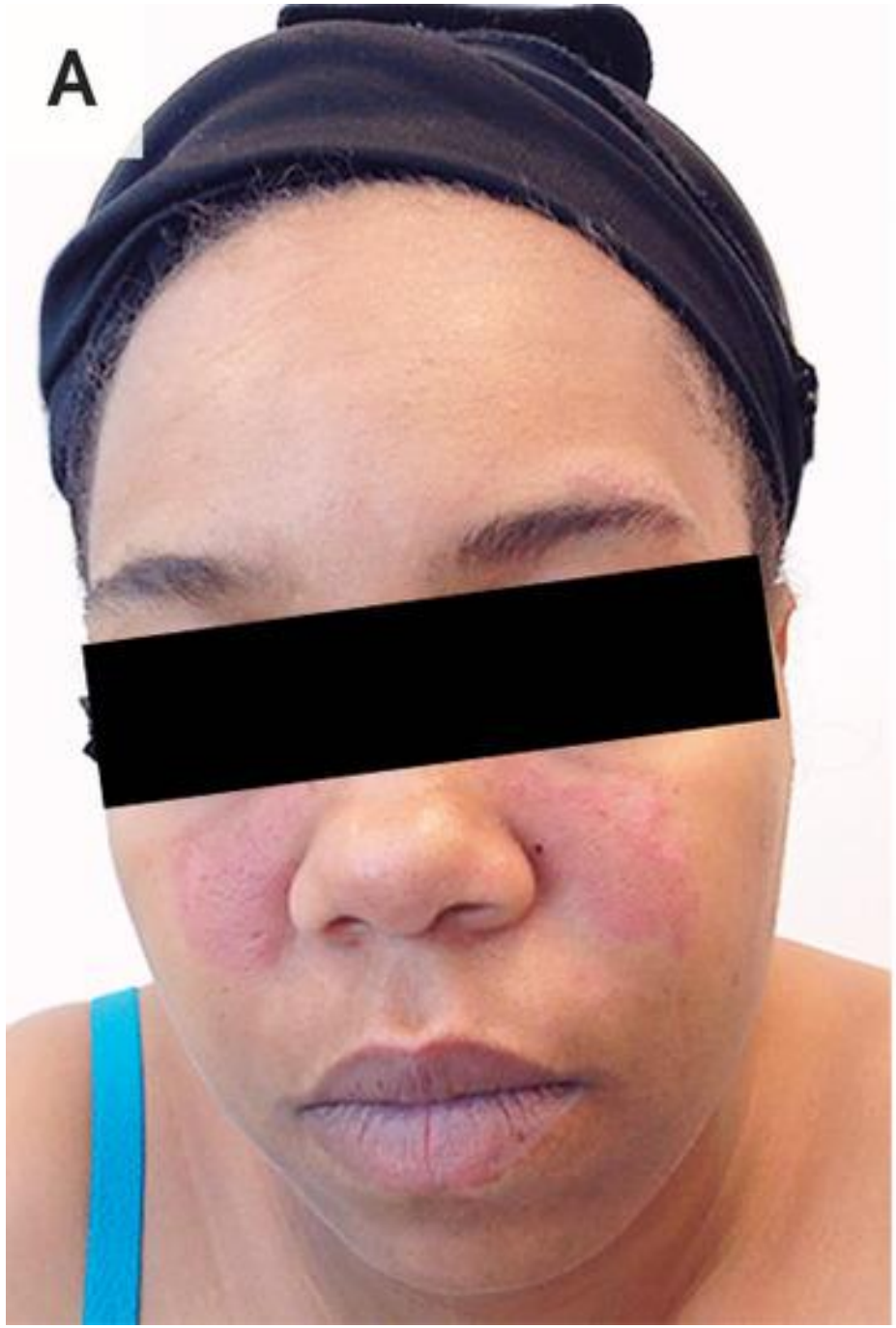
Tavee and Zhou, http://hepatitiscnewdrugs.blogspot.com/2010/11/small-fiber-neuropathy-burning-problem.html

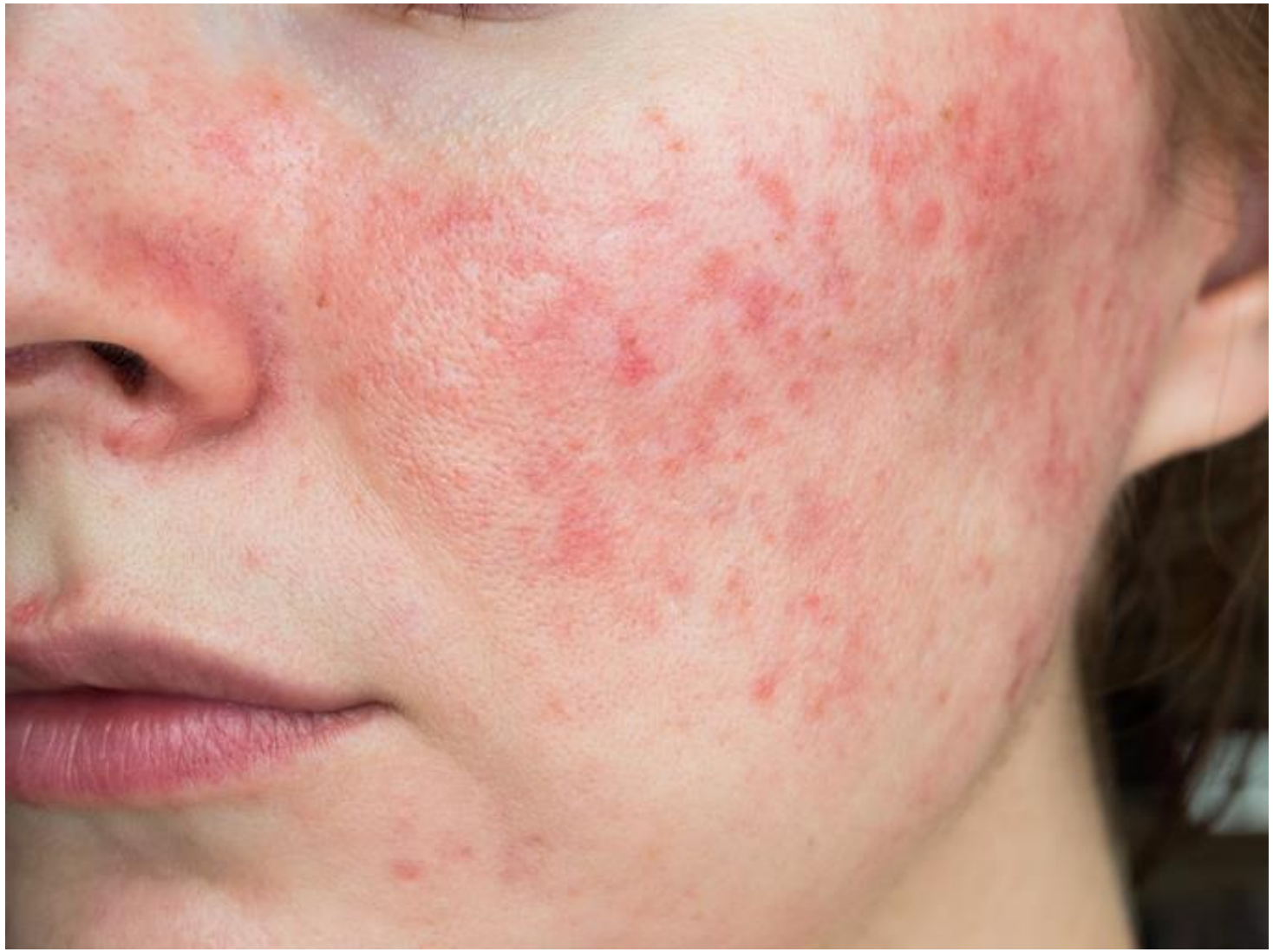
Case 10

- 45 yo F presents with:
  - Raynaud's – started at age 16
  - Chronic fatigue
  - Facial rash
  - Normal CBC, CMP, TSH, ESR, CRP

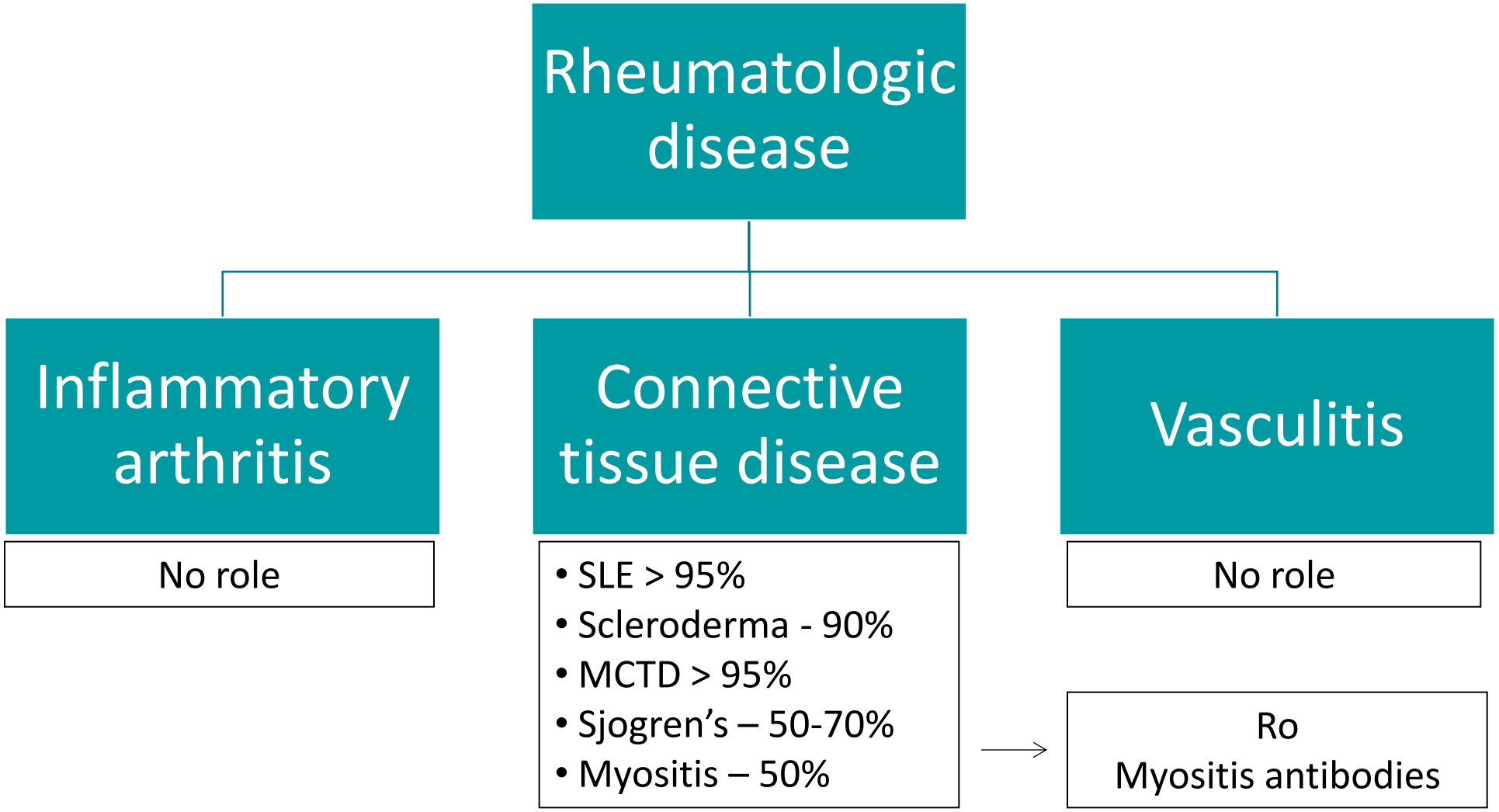
- What is the pretest probability of a CTD?
  - Low
  - Moderate
  - High




A



ANA sensitivity



Case 11

- 32 yo F presents with:
  - Inflammatory arthritis, pericarditis, oral ulcers
  - ANA – 1:640 speckled
  - CBC, CMP – nl
- What labs would you order? (select all)
  - RF/CCP
  - DsDNA, Smith
  - Ro/La
  - RNP
  - C3, C4
  - Antiphospholipid antibodies
  - Scl 70
  - Jo-1
  - Urinalysis

- SLE
- Sjogren's
- Scleroderma
- MCTD
- Myositis
- Undifferentiated CTD

CTD – non-differentiators

- Raynaud's
- Sicca
- Oral ulcers
- Inflammatory arthritis
- Serositis

Approach to CTD Ddx

- SLE

Is there sicca? → • Sjogren's

Is there Raynaud's? → • Scleroderma

Is there elevated CK or ILD? → • Myositis

Approach to labs

- SLE → DsDNA, Smith
  → C3, C4, antiphospholipid antibodies
- Sjogren's → Ro, La
- Scleroderma → centromere *limited*
  → Scl70, RNApol3 *diffuse*
- MCTD → RNP
- Myositis → CK, aldolase, myositis panel, Jo-1

Antibody	%
DsDNA	60%
Smith	30%
Ro	40%
RNP	50%
↓C3/C4	50%
APLAs	30%

Case 12

- 25F with no PMH presents with
  - Joint pain in the wrists, MCPs, PIPs with 45 min of AM stiffness x 3 mos
  - Intermittent oral ulcers x 1 year
  - Exam with tenderness but no synovitis
  - Labs with ANA 1:320, nl CBC, inflammatory markers, +RF, -anti-CCP
  - C3/C4, DsDNA, Smith, Ro/La, RNP negative

What should you do next?

a. Diagnose SLE and start hydroxychloroquine
b. Diagnose RA and start methotrexate
c. Check urinalysis
d. Start naproxen and observe

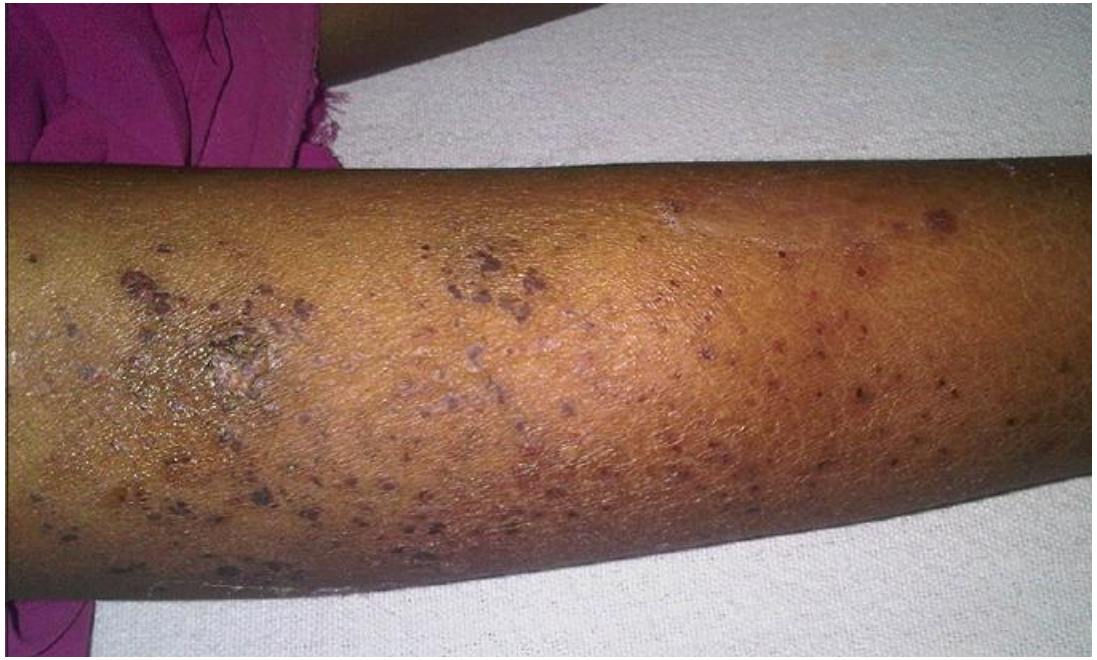
Case 13

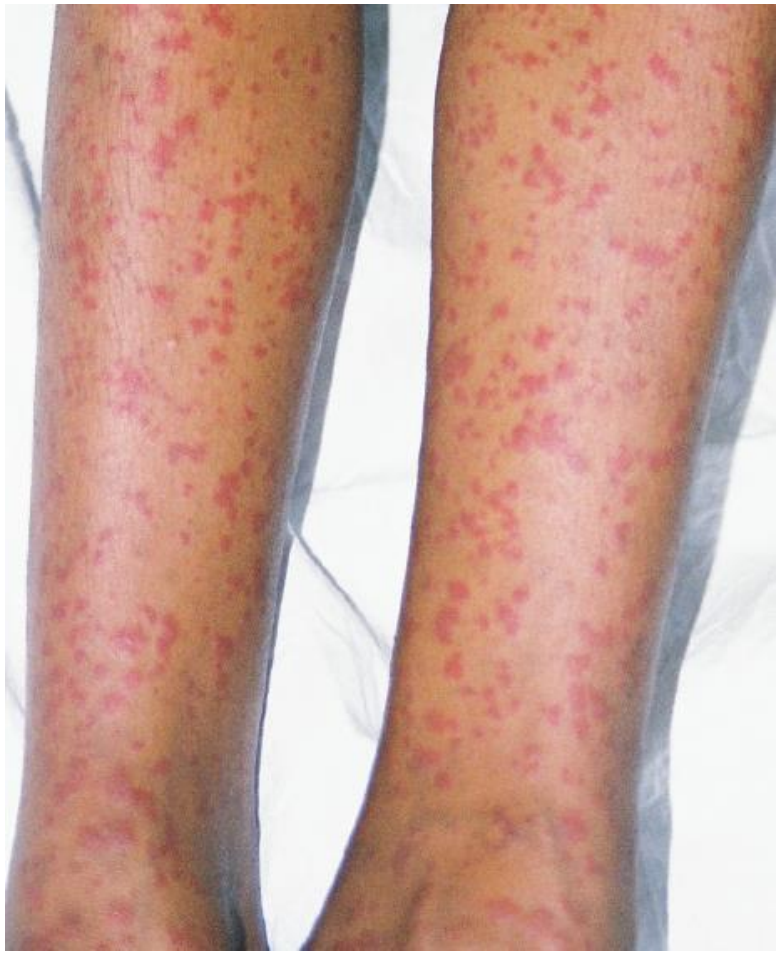
- 52 yo M p/w Raynaud's, AKI, hemolytic anemia, thrombocytopenia, found to have new HTN (190/100)
  - ANA 1:1280
  - Urinalysis normal
  - Smear - schistocytes

- What findings is this patient most likely to have? (select all)
  - DsDNA
  - Scl 70
  - Malar rash
  - Skin thickening above the elbows
  - Myositis
  - Palpable purpura

Case 14

- 55 yo M treated with amoxicillin for bronchitis presents with the rash pictured.
- ROS – no joint pain or other symptoms
- CBC w/diff/CMP – normal



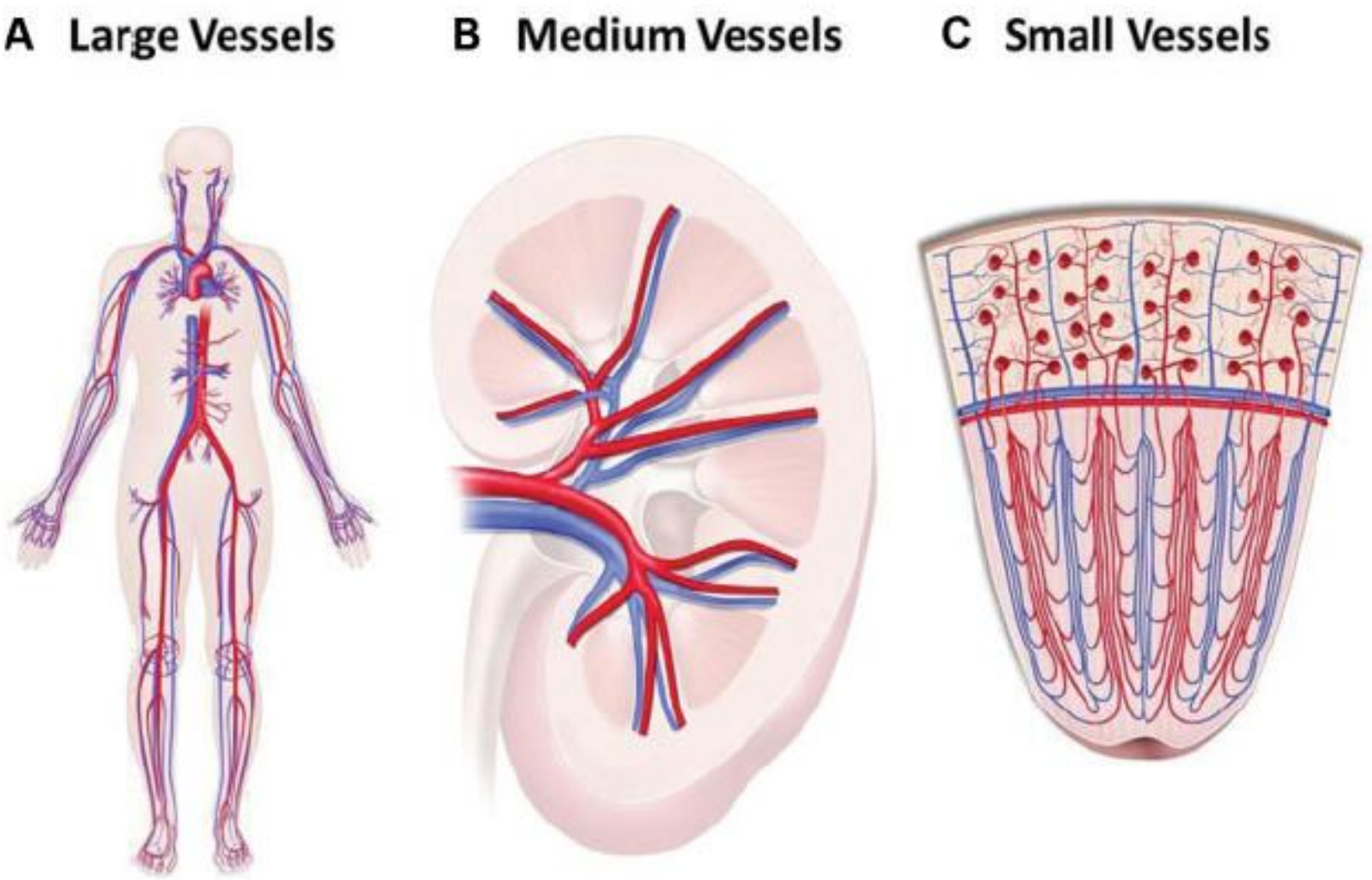


- What’s the next best step in management?
  A. Check ANCA
  B. Check cryos
  C. Check urinalysis
  D. Start prednisone
  E. Refer for skin biopsy

Case 15

- 55 yo M with p/w L knee and R ankle pain as well as dyspnea found to have diffuse alveolar hemorrhage.
- ROS – 3 months of sinus congestion, pain, brown/bloody crusting
- CBC w/diff/CMP – normal
- ESR – 94 (< 20mm/hr)
- CRP – 125 (< 8mg/L)
- Urinalysis – normal
- What's the most likely diagnosis?
  A. Microscopic polyangiitis
  B. Granulomatosis with polyangiitis
  C. IgA vasculitis (Henoch-Schonlein purpura)
  D. Polyarteritis nodosa
  E. Cryoglobulinemic vasculitis

What size vessel is involved?

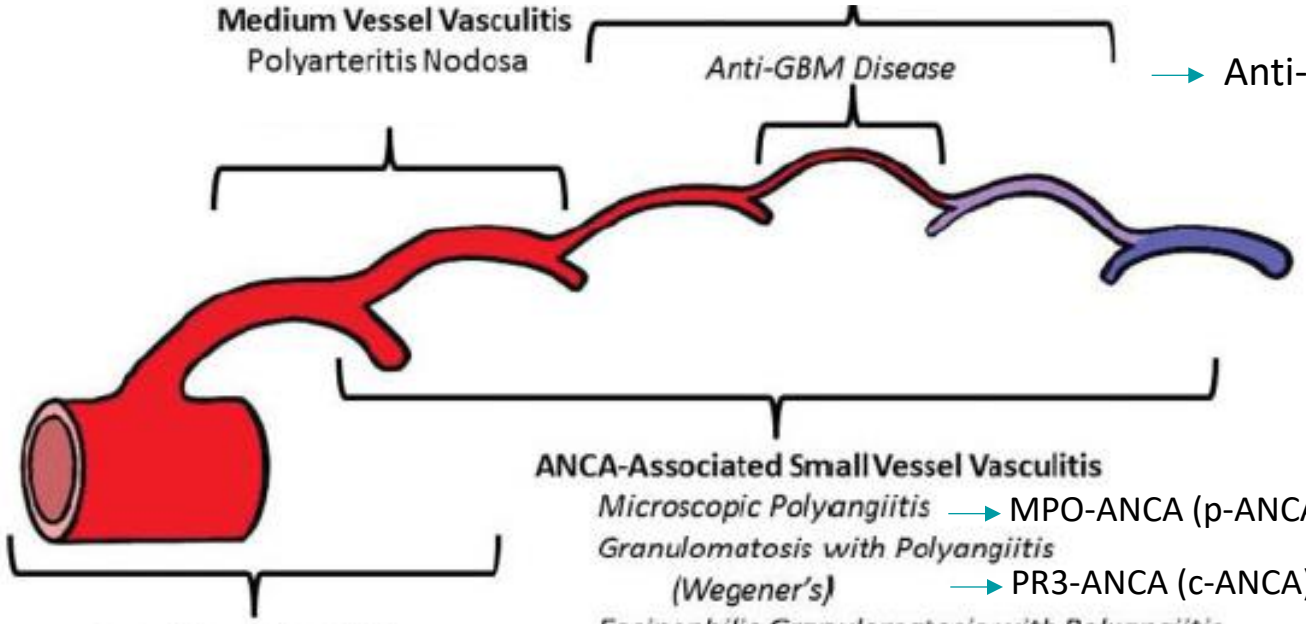


Small vessel “vasculitic” manifestations

Organ	Manifestation
Lung	
Kidney	
GI	
Nervous sys	
Skin	

Approach to vasculitis diagnosis

- ***Clinical symptoms***
- ***Serology***
- ***Pathology***



Immune Complex Small Vessel Vasculitis
Cryoglobulinemic Vasculitis
IgA Vasculitis (Henoch-Schönlein)
Drug induced (hypersensitivity) vasculitis
Secondary vasculitis

Medium Vessel Vasculitis
Polyarteritis Nodosa

Anti-GBM Disease

ANCA-Associated Small Vessel Vasculitis
Microscopic Polyangiitis
Granulomatosis with Polyangiitis (Wegener's)
Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

Large Vessel Vasculitis
Takayasu Arteritis
Giant Cell Arteritis

	Labs	Clinical findings
Immune Complex Small Vessel Vasculitis		
Cryoglobulinemic Vasculitis	→ Cryos	
IgA Vasculitis (Henoch-Schönlein)		→ Purpura
Drug induced (hypersensitivity) vasculitis		
Secondary vasculitis	→ ANA	
Medium Vessel Vasculitis Polyarteritis Nodosa		
Anti-GBM Disease	→ Anti-GBM	
ANCA-Associated Small Vessel Vasculitis		
Microscopic Polyangiitis	→ MPO-ANCA (p-ANCA) 80%	
Granulomatosis with Polyangiitis (Wegener's)	→ PR3-ANCA (c-ANCA) 60-90%	→ Sinusitis, Mass lesions
Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)	→ MPO-ANCA (p-ANCA) 50%	→ Eosinophilia, Asthma/allergic rhinitis
Large Vessel Vasculitis Takayasu Arteritis Giant Cell Arteritis		

MOC REFLECTIVE STATEMENT

- Considering categories of disease can help simplify diagnostic workup
  - Inflammatory arthritis – RF, CCP, ANA
  - Connective tissue disease – ANA first
  - Vasculitis – ANCA, cryo, ANA, GBM if DAH or GN

- Focus on:
  - Differentiating inflammatory vs non-inflammatory arthritis based on LID
  - Features that raise suspicion for rheumatic disease
    - Inflammatory arthritis
    - Inflammatory back pain
    - Non-differentiating CTD manifestations
    - Non-differentiating vasculitic manifestations
  - Identify differentiating features

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Extra case 1

- 35 year old female presents with unprovoked DVT
- Testing reveals ACL IgM 30 (ULN 20), ACL IgG 22, B2GP1 IgM/IgG negative, lupus anticoagulant negative

What is the next best step in management?

a. Start apixiban
b. Start enoxaparin to coumadin bridge
c. Start enoxaparin to coumadin bridge and recheck labs in 3 mos

The 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria

Laboratory

7. Antiphospholipid antibody (aPL) testing by coagulation-based functional assays: lupus anticoagulant test	A. Negative or not tested	0
	B. Positive (single—one time)	1
	C. Positive (persistent)	5
8. aPL testing by solid-phase assays: IgG/IgM anticardiolipin (aCL) and IgG/IgM anti–β_2-glycoprotein I (anti-β_2GPI) antibody enzyme-linked immunosorbent assay (persistent¶)	A. Negative or not tested	0
	B. Moderate or high positive (IgM alone) (aCL and/or anti-β_2GPI)§	1
	C. Moderate positive (IgG) (aCL and/or anti-ß$_2$GPI)	4
	D. High positive (IgG) (aCL or anti-β_2GPI)	5
	E. High positive (IgG) (aCL and anti-β_2GPI)	7

Clinical domains and criteria	Weight		Weight
D1. Macrovascular (Venous Thromboembolism [VTE])		**D2. Macrovascular (Arterial Thrombosis [AT])**	
VTE with a high-risk VTE profile[(c)]	1	AT with a high-risk CVD profile[(c)]	2
VTE without a high-risk VTE profile[(c)]	3	AT without a high-risk CVD profile[(c)]	4

- Microvascular manifestations (nephropathy, cardiomyopathy, alveolar hemorrhage)
- Cardiac valve thickening or vegetation
- Thrombocytopenia (< 130 x 10^9)

TOTAL SCORE

Classify as Antiphospholipid Syndrome for research purposes if there are at least 3 points from clinical domains AND at least 3 points from laboratory domains

Barbhaiya et al Arthritis Rheumatol. 2023 Oct;75(10):1687-1702

Extra case 2

- 62 yo M with h/o HLD p/w weakness x 3 months. Stopped statin 6 months ago due to personal preference.
  - Exam – no rash, 4/5 proximal muscle strength
  - Labs – CK 10,500
  - CT C/A/P - normal

- Which of the following antibodies is most likely to return positive?
  - MDA5
  - Jo-1
  - HMGCoA reductase
  - CN1A
  - PM-Scl