RHEUMATOLOGY PRIMER:

HOW TO START EVALUATING JOINT PAIN LIKE A RHEUMATOLOGIST

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DISCLOSURES

- I have no disclosures

OBJECTIVES

Describe	Describe the appropriate history and physical examination for the patient with a suspected rheumatologic disorder
Distinguish	Distinguish between inflammatory and non-inflammatory musculoskeletal disorders and discuss the clinical features that are common to each
Interpret	Interpret common laboratory testing and clinical evaluation for rheumatologic disorders; particularly rheumatoid arthritis and lupus

WHAT DO RHEUMATOLOGISTS DO?

DIAGNOSE AND TREAT SYSTEMIC AUTOIMMUNE DISEASE AND MUSCULOSKELETAL/ARTHRITIC DISORDERS

LOGISTICS: 2-3 YEAR FELLOWSHIP AFTER INTERNAL MEDICINE OR PEDIATRICS RESIDENCY

DISEASE CATEGORIES IN RHEUMATOLOGY

- Rheumatoid arthritis
- Crystalline arthritis – Gout, pseudogout (CPPD)
- Spondyloarthritis
  - Ankylosing spondylitis, Psoriatic arthritis, Reactive arthritis, Enteropathic arthritis, non-radiographic axial spondyloarthritis
- Connective Tissue Diseases
  - Lupus, Sjogren's syndrome, MCTD, Systemic sclerosis (Scleroderma), Inflammatory myositis, etc
- Vasculitis
  - ANCA associated vasculitides (GPA, MPA, eGPA), Polyarteritis Nodosa, Giant cell (temporal) arteritis, etc
- Other: Behcet's syndrome, autoinflammatory disorders, sarcoidosis

CASE #1

- 50 year old female with history of hypertension, tobacco use and hyperlipidemia who is complaining of joint pain

TAKING A JOINT PAIN HISTORY

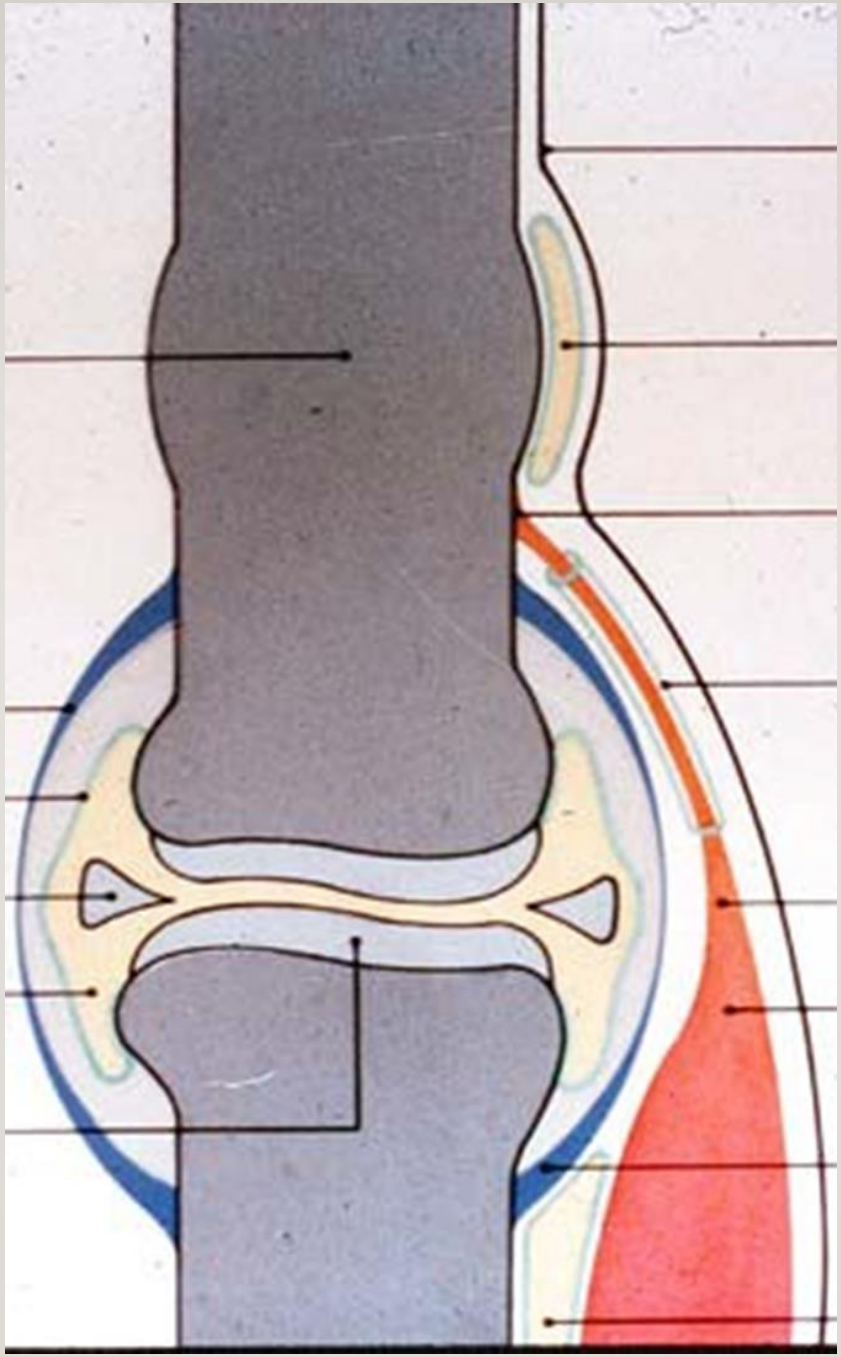
- Is it really the joint?
- Acute vs Chronic
- Age of onset
- Number of joints involved
- Symmetry? Additive or migratory?
- Nature of pain: aching, sharp, burning, stiff, etc
- Joint swelling
- Aggravating: Time of day, activity/rest
- Relieving: Medications, activity/rest
- History of joint injuries or procedures

"Referred"

- Away from the MSK system
- Visceral, neurological

"Arthritis"

- Within the joint
- Subchondral bone
- Cartilage
- Synovial Fluid
- Synovium



"Non-articular"

- Muscle
- Bone

"Peri-articular"

- Around the joint
- Muscle
- Tendon
- Tenosynovium
- Enthesis
- Bursa
- Ligament

INFLAMMATORY OR NOT?

Feature	Inflammatory	Mechanical
Joint Swelling		
Warmth and redness		
Morning Stiffness		
Fatigue		
Activity		
Rest		
Systemic involvement		
Corticosteroid response		

NUMBER OF JOINTS

Monoarticular (1 Joint)

- Septic arthritis
- Gout
- Pseudogout (CPPD)
- Post-traumatic osteoarthritis

Oligoarticular (2-4 joints)

- Spondyloarthritis
- Polymyalgia Rheumatica
- Osteoarthritis

Polyarticular (5 or more joints)

- RA
- RA
- RA
- SLE/CTD
- Viral (HBV, HCV, Parvo, Covid19, etc)
- Osteoarthritis

Summary statement

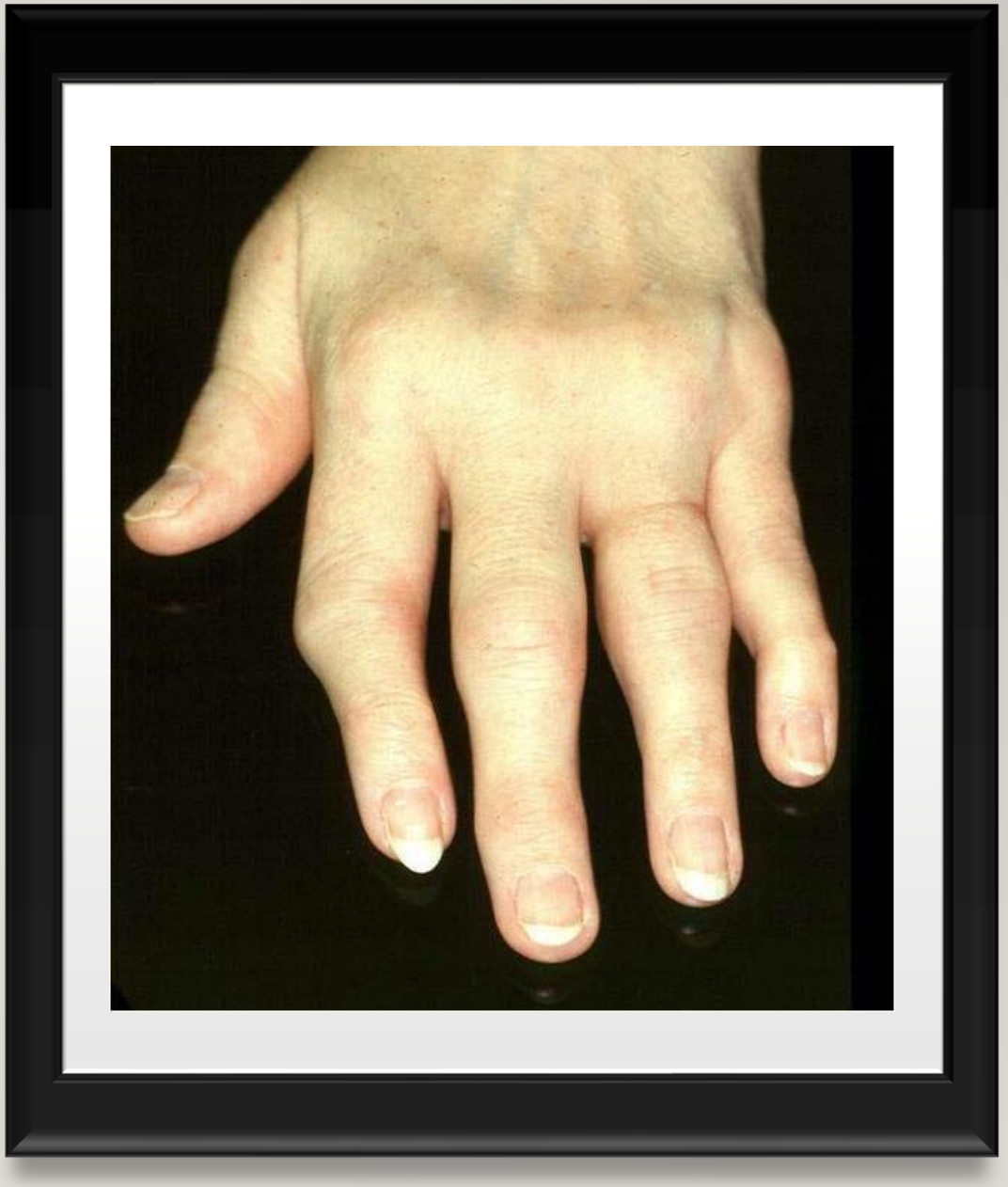
- Number of joints involved
- Symmetric or not
- Small vs large
- Synovitis vs no synovitis
- i.e. "Polyarticular symmetric small joint predominant arthritis with synovitis.

CASE #1 CONTINUED

- Our patient reports the only pain she previously had was lower back pain but starting about 5 months ago she began having pain in her hands and feet. Pain is worse first thing in the morning, joints feel stiff for 90 minutes and gradually improve as the day progresses. She is not sure if she has had any joint swelling. When you ask her to point to the area that hurts the most she points to…

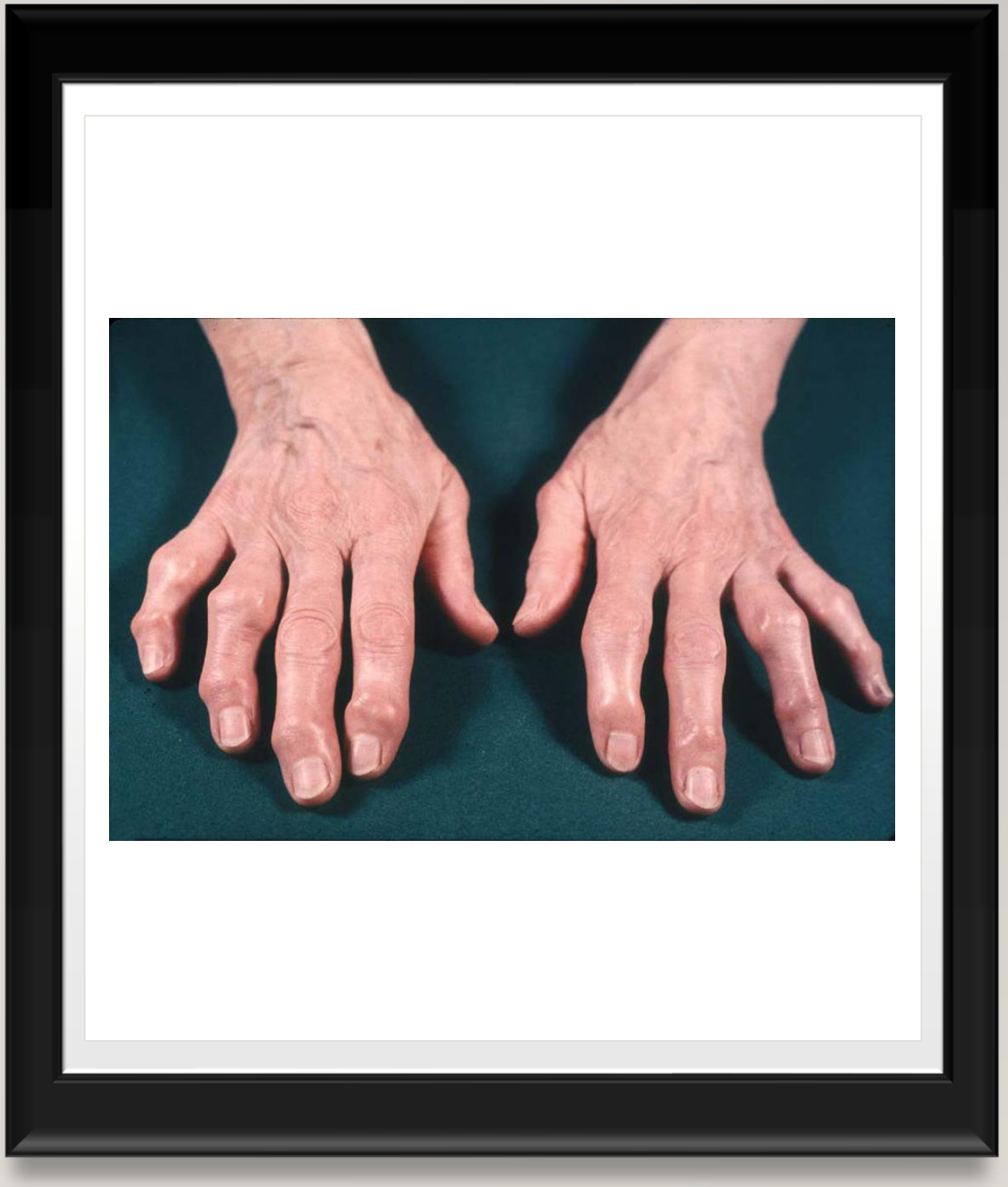
PATIENT'S HAND

- Joints feel boggy, slightly warm and tender. Cannot appreciate distinct joint line.
- Patient cannot make a tight fist or claw.



PATIENT'S MOTHER'S HANDS

- Joints feel bony
- No warmth or bogginess
- DIP joints enlarged (Heberden's nodes)
- PIP joints enlarged (Bouchard's nodes)



EPIDEMIOLOGY OF OA VS RA

RHEUMATOID ARTHRITIS

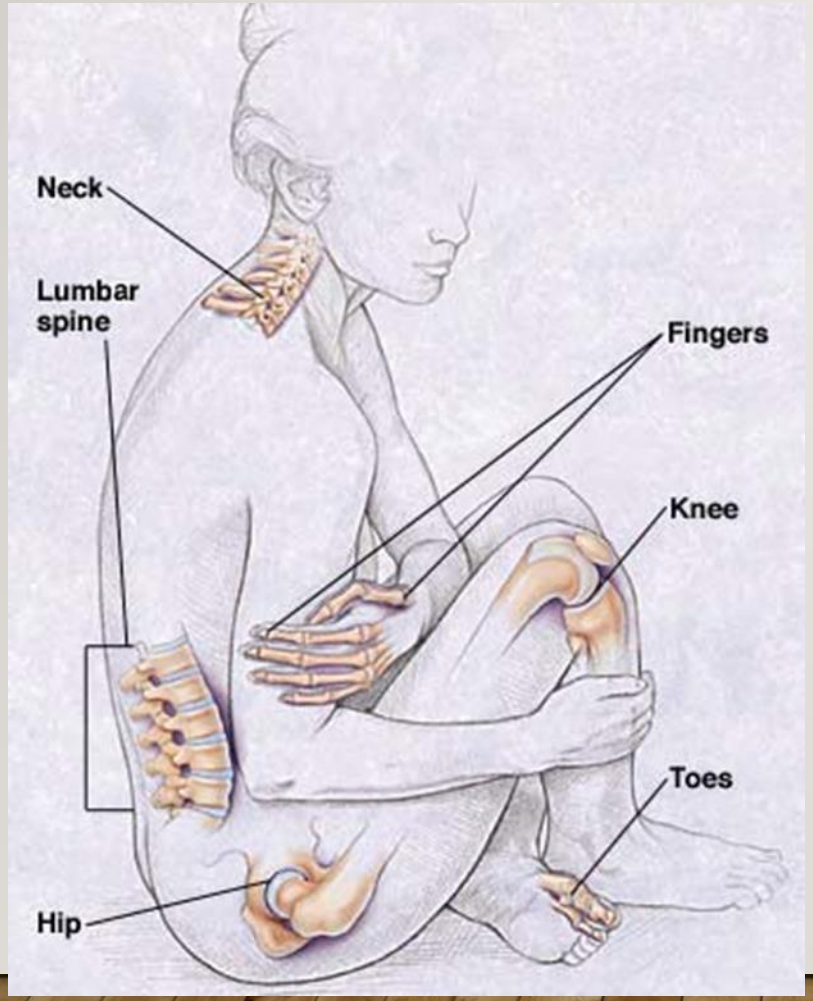
- Prevalence: 0.5-1%
  - Increases with age
  - Typical age of onset 40-60 for females, a bit older for males
- Peak incidence ages 50-60
- Females 2-3 x greater than males

OSTEOARTHRITIS

- Prevalence 34% of adults age 65+
- Peak incidence age 50-80
- Female > male
  - 1.7x for knee OA

RA info adapted from Dr. Michael Davey's presentation dated 9-13-19 entitled "Fellows Overview of RA"
https://www.uptodate.com/contents/epidemiology-and-risk-factors-for-osteoarthritis?search=osteoarthritis&topicRef=105723&source=see_link

JOINTS COMMONLY AFFECTED BY OSTEOARTHRITIS



- Weightbearing joints: Hips, knees, lumbar spine, feet and ankles
- Highly mobile joints: CMCs, PIPs, DIPs, MTPs (particularly 1st MTP), Cervical spine

https://www.mayoclinic.org/diseases-conditions/thumb-arthritis/symptoms-causes/syc-20378339
https://www.fairview.org/sitecore/content/Fairview/Home/PatientEducation/Articles/English/o/s/t/e/o/Osteoarthritis_Common_Sites_86153

CASE #1 CONTINUED

NOW THAT WE HAVE COMPLETED OUR HISTORY AND PHYSICAL EXAM WHAT WORK-UP SHOULD WE DO?

WORK-UP

- X-rays of affected joints
  - Particularly if symptoms for > 1 year
  - Hand and foot x-rays are more helpful in evaluation of inflammatory arthritis as these can show periarticular osteopenia and erosions
  - Lower-extremity joints should be radiographed while weightbearing if possible
- Laboratory evaluation
  - Sedimentation rate, C-reactive protein, Rheumatoid factor, anti-citrullinated peptide antibodies (ACPA or CCP), HCV Ab, HBsAg
  - I would add ANA if there are mucocutaneous manifestations or significant systemic symptoms
  - I would add uric acid for mono or oligoarticular arthritis, particularly of the lower extremities and if the patient is male or has CKD
  - Synovial fluid analysis for crystals, cell count and diff, and culture can be helpful for mono or oligoarticular arthritis

INFLAMMATORY MARKERS

ERYTHROCYTE SEDIMENTATION RATE (ESR)

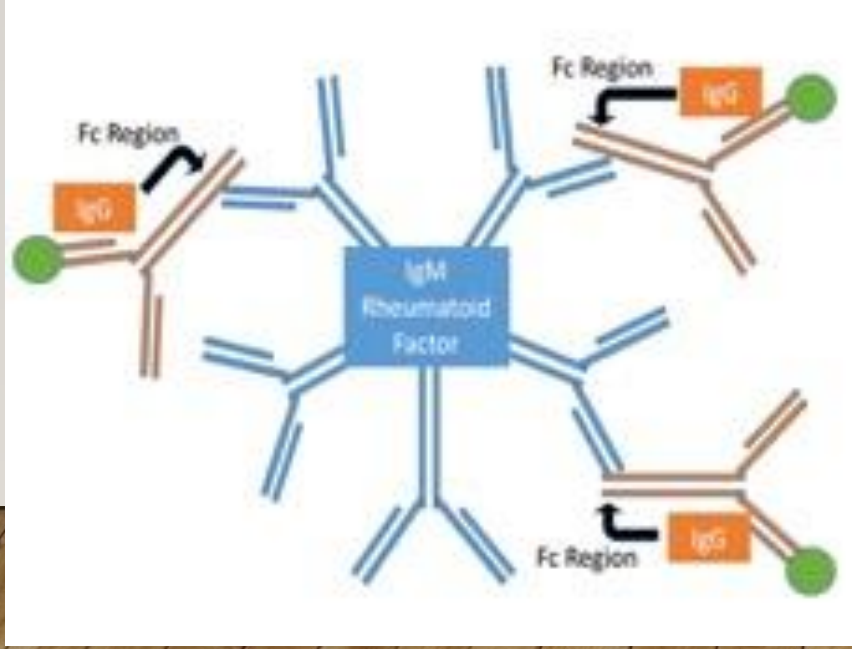
- Surrogate marker for inflammation
- Marks both acute and chronic inflammation
- Changes over days to weeks
- Factors affecting ESR:
  - Specimen handling
  - Anemia (increases ESR)
  - Monoclonal gammopathy
  - Patient's age and sex
- ESR > 100 think infection, malignancy and rheumatologic disease

C-REACTIVE PROTEIN (CRP)

- Acute phase reactant made in the liver
- Changes over course of hours to days
- High-sensitivity CRP (hsCRP) is used as a cardiac risk screening
- Be careful to pay attention to units (mg/dL vs mg/L) when comparing or trending values
- Can be increased in females, obesity and with age

RHEUMATOID FACTOR

- Sensitivity: 69%
- Specificity: 85%
- Positive likelihood ratio: 4.9
- Negative likelihood ratio: 0.38



- IgM autoantibody directed against Fc portion of IgG
- Found in 5% of healthy individuals, increasing to up to 15% with age
- Association with other diseases: Sjogren's (up to 50%), Lupus (15-20%), Chronic HCV (~50%), bacterial endocarditis (40%), sarcoidosis, parvovirus, etc

https://www.ksvdl.org/images/diagnositc_insights/mar2019/Figure-1.jpg

ANTI-CITRULLINATED PEPTIDE ANTIBODIES

- Referred to as ACPA or CCP
- Should be measured when you are sending RF
- Sensitivity: 67% Specificity: 95%
- High titers (>3x ULN) signify worse prognosis but are not useful as markers of disease activity

CASE #1 CONCLUSION

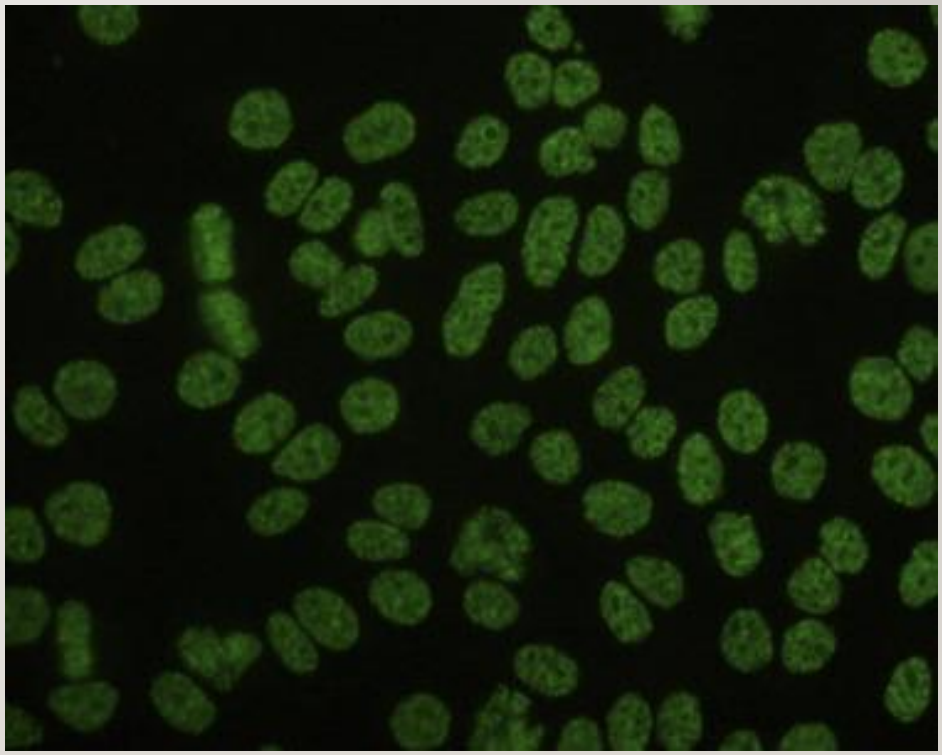
- Labs show RF 60 (positive), ESR 45 (elevated), CRP 1.7 mg/dL (elevated) and CCP negative. Hand and foot x-rays are normal.
- Next steps:
  - Refer to rheumatology
  - Trial of NSAIDs in appropriate patients
  - Consider prednisone
    - Do not use doses of prednisone >20mg daily for RA
    - It is better to avoid it if possible
    - Start at 15-20mg and taper over 2-3 weeks to 5-7.5mg daily or every other day. Can prescribe as 5-10mg daily as needed for joint pain/swelling.
    - A steroid pack or IM injection can be useful to determine steroid responsiveness but not as ongoing treatment (this is a chronic inflammatory arthritis)

CASE #2

- 35-year-old female with a history of hypothyroidism, depression, eczema who is complaining of fatigue and joint pain. You are covering for her primary care doctor who had checked labs and found a positive antinuclear antibody (ANA) titer 1:80. What is your approach?

WHAT IS AN ANA?

- A screening test for connective tissue disease
- Typically done by indirect immunofluorescence (IFA)
- There are many ANA patterns (homogenous, speckled, nucleolar, centromere, etc)
- Titers > 1:160 are generally considered clinically significant



https://www.pathologyjournal.rcpa.edu.au/article/S0031-3025%2816%2900062-3/fulltext

STATISTICAL ANALYSIS OF + ANA TESTING

- Assumptions:
- ANA is positive in 5% of healthy controls
- Prevalence of +ANA in SLE is 99%
- Prevalence of SLE is 1:2000

If 2000 people have ANA testing:

Number of ANA +	
Number of patients with SLE	
Number of ANA + without SLE	
Odds of SLE in ANA +	

ANA titer	N	N with rheumatic disease
1:40	27	0
1:80	28	0
1:160	71	1 (Lupus)
1:320	34	1 (Sjogren's)
1:640	31	4 (2 lupus, 2 Sjogren's)
1:1280	23	8 (2 lupus, 4 Sjogren's, 1 systemic sclerosis, 1 undifferentiated connective tissue disease)
1:2560	6	2 (1 systemic sclerosis, 1 Sjogren's)
1:5120	5	1 (undifferentiated connective tissue disease)
Total	232	17

- Low titer ANA is usually not associated with rheumatologic conditions
- Positive predictive value of + ANA 2.1% for SLE, 9.1% for any rheumatologic condition

(Am J Med 2013; 126:342-358)

ANA PITFALLS

- Many non-rheumatologic conditions are associated with a positive ANA (chronically or transiently)
  - Infections (viral especially), malignancies (solid and hematologic), autoimmune thyroid disease, multiple sclerosis, monoclonal antibody therapies, vaccinations
- Detectable ANA titers are present in up to 25% of the population
- Changes in ANA titers are not a marker of disease activity or severity
- Positive ANA does not confirm any diagnosis
- Titers should generally not be repeated unless there is a change in symptoms or concern for transient ANA elevation
- It is not appropriate to order ANAs as screening for patients with family history of autoimmune disease in the absence of symptoms
- Axial/spinal pain is not an indication for ANA testing

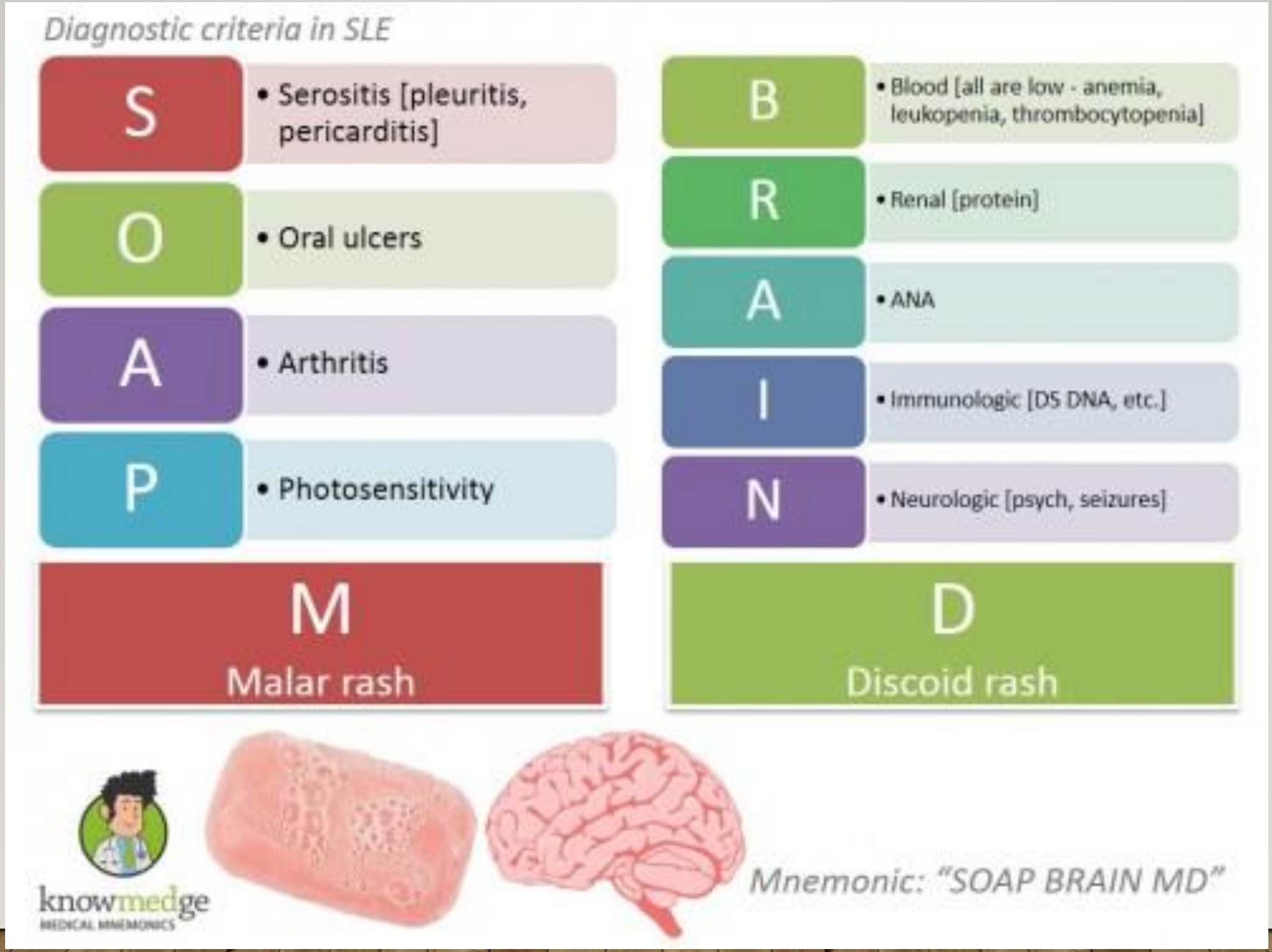
IF YOU HAVE HIGH CLINICAL SUSPICION FOR LUPUS AND + ANA, FURTHER TESTING TO CONSIDER IS:

- CBC with differential
- Creatinine
- UA with microscopy
- Spot Urine Protein to Creatinine Ratio
- C3 and C4 complements
- ENA panel
- dsDNA Ab
- DAT (Coombs)
- RF
- CCP
- HBV and HCV Abs
- HIV

EXTRACTABLE NUCLEAR ANTIGENS

Autoantibody	Primary Disease	Sensitivity	Specificity
DsDNA Ab	SLE	30-80%	High
Smith Ab (Sm)	SLE	15-40%	High
Anti-RNP	SLE	15-40%	Low
	MCTD	100%	Low
Anti-Ro (SSA)	SLE	40%	Low
	SjS	20-75%	Low
Scl-70	SSc	25%	High
Anti-Centromere	Raynaud's	30%	Moderate
	SSc (limited, CREST)	50-90%	
	SSc (Diffuse)	25%	

CLINICAL EVALUATION FOR SLE



https://knowmedge.com/blog/selena-gomez-shares-her-lupus-diagnosis-what-you-need-to-know-for-the-abim-usmle-exams/sle-diagnosis-soap-brain-md-2/

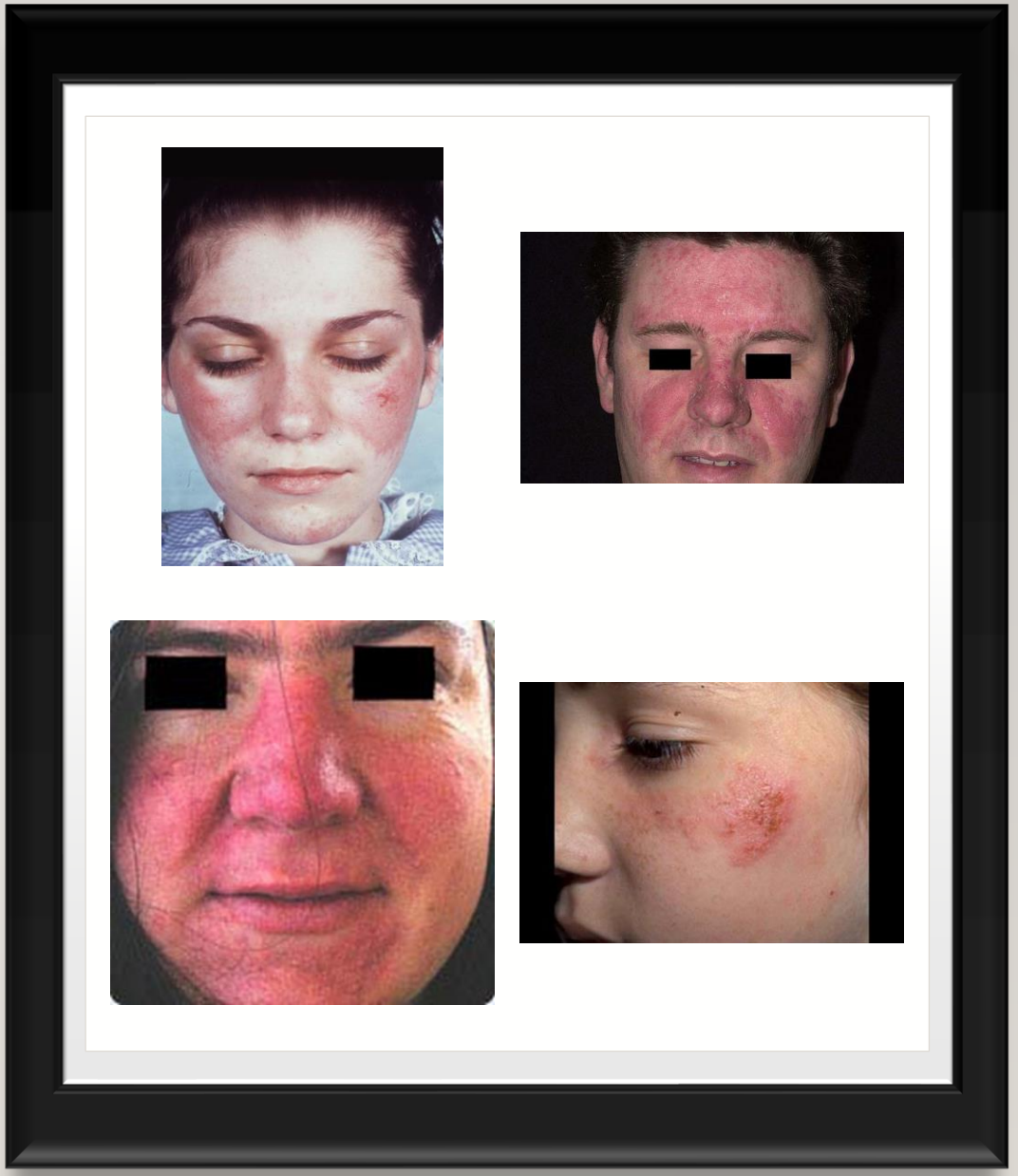
IS THIS A MALAR RASH?

Acute cutaneous lupus (Malar rash)

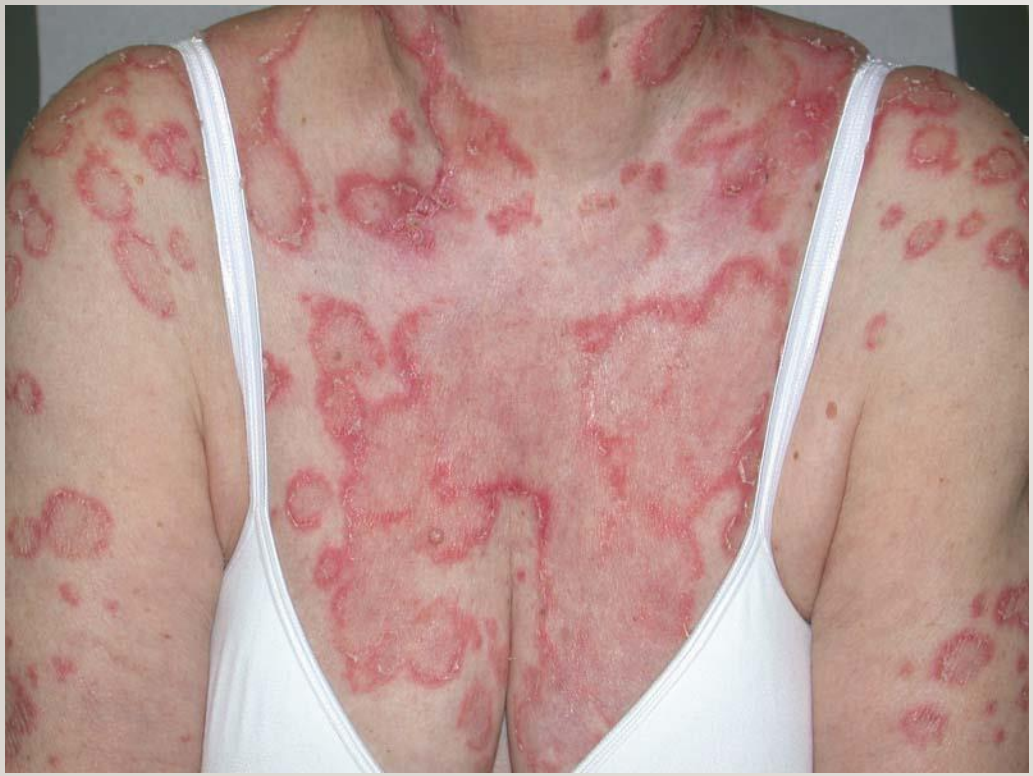
Seborrheic dermatitis

Rosacea

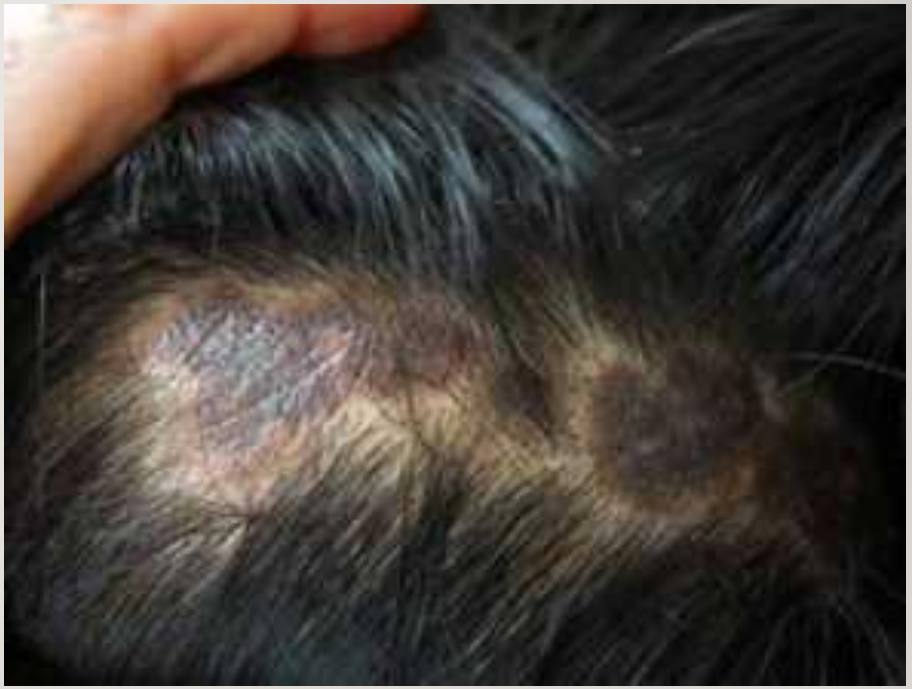
Polymorphous light eruption



CUTANEOUS LUPUS

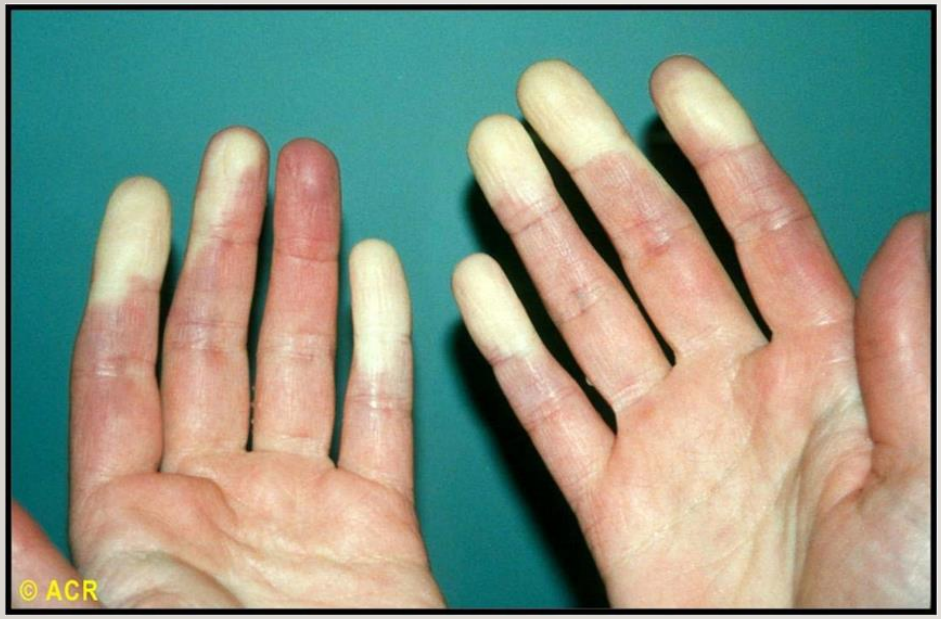


https://www.dermatologyadvisor.com/wp-content/uploads/sites/20/2019/03/ch1174.fig1_.jpg



https://dermnetnz.org/assets/collection/Discoid-lupus-erythematosus/discoid-lupus-erythematosus-0017__ProtectWyJQcm90ZWN0II0_FocusFillWzI5NCwyMjIsInqiLDFd.jpg

RAYNAUD'S

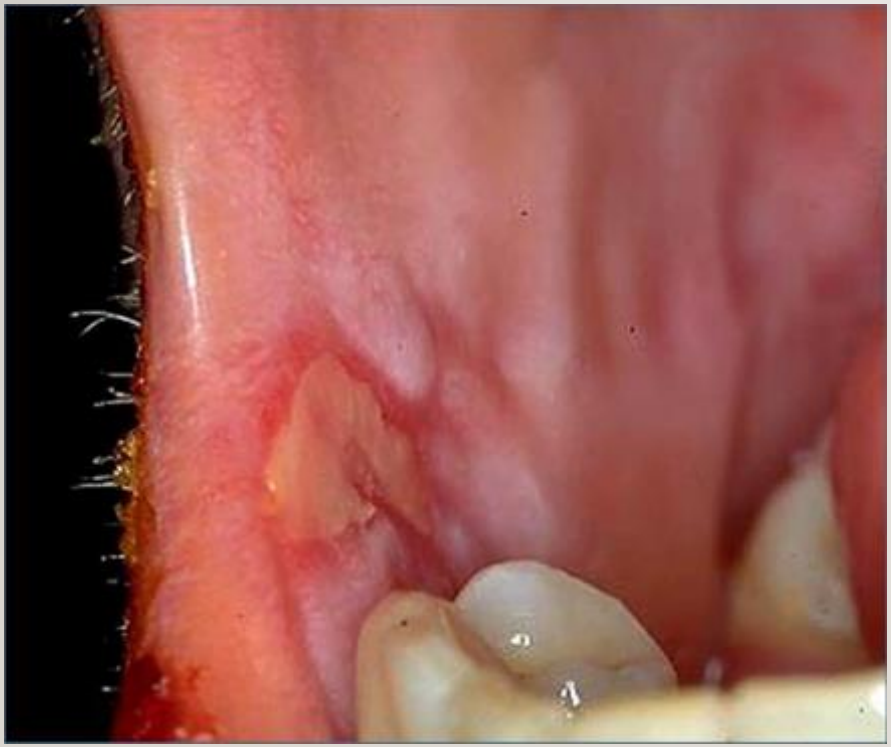


- Three phases: white (pallor), blue (cyanosis), red (rubor)
- Very common in healthy patients, up to 20%
- May be primary or secondary
- Digital ulceration is always pathologic
- Thumb involvement is suggestive of pathologic Raynaud's
- Triggers: Cold exposure, caffeine, nicotine, stress/anxiety, stimulants

LUPUS EVALUATION CONTINUED…

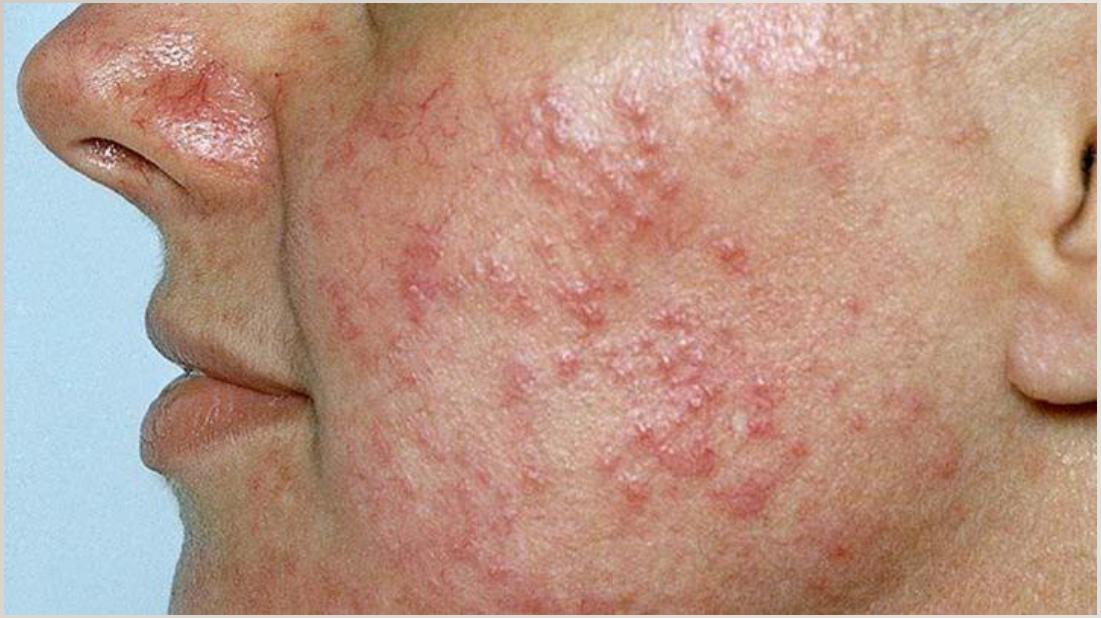
- Serositis
  - Pleural or pericardial effusions, chest pain worst with deep breathing or lying flat, positional abdominal pain
- Neuropsychiatric
  - Seizures, psychosis, delirium
- Arthritis
  - Stiffness +, Pain and tenderness +, Joint swelling +/-, typically polyarticular small joint predominant arthritis
- Clotting
  - History of clots (arterial or venous), History of miscarriages, pre-eclampsia or eclampsia, Livedo reticularis
- Renal
  - History of kidney disease, foamy urine or decreased urine output, tea colored urine, edema

ORAL ULCERS (MUCOSITIS) IN SLE



- Nasal and oral ulcerations
- Typically painless, asymmetric
- May flare with sun exposure
- Hard palate, buccal mucosa, vermillion border
- DDx: aphthous stomatitis, GPA, celiac disease, Crohn's disease, HSV, Syphilis, viral infections

CASE #2 CONTINUED…



- The patient reports a facial rash that worsens within 5 minutes of sun exposure, she says her pain is all over. She has had Raynaud's since childhood. She also reports poor sleep, chronic migraines, and alternating constipation and diarrhea with bloating. Other lupus ROS is negative.
- Exam: This facial rash, no synovitis but diffuse tenderness, rest of exam is normal.
- Other laboratory testing is normal.

https://www.everydayhealth.com/rosacea/is-it-something-else/

2019 ACR/EULAR Classification Criteria for Systemic Lupus Erythematosus

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

https://www.rheumatology.org/Portals/0/Files/Classification-Criteria-Systemic-Lupus-Erythematosus.pdf

TAKE HOME POINTS

- Try and differentiate between joint centered and non-joint pain
- Try and differentiate between inflammatory and non-inflammatory joint pain
- Try and develop a summary statement when evaluating a new patient with joint pain
- Have a high clinical suspicion (pre-test probability) before sending rheumatologic testing
- A negative ANA virtually excludes lupus
- Lab testing alone is not sufficient to diagnose systemic rheumatologic disease

ACKNOWLEDGEMENTS

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QUESTIONS?

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