Athletes and Rheumatic Diseases
Hour 4: systemic autoimmune diseases

Steve S Lee, DO FACR

Core Faculty, Internal Medicine Residency, Kaiser Permanente, Fontana

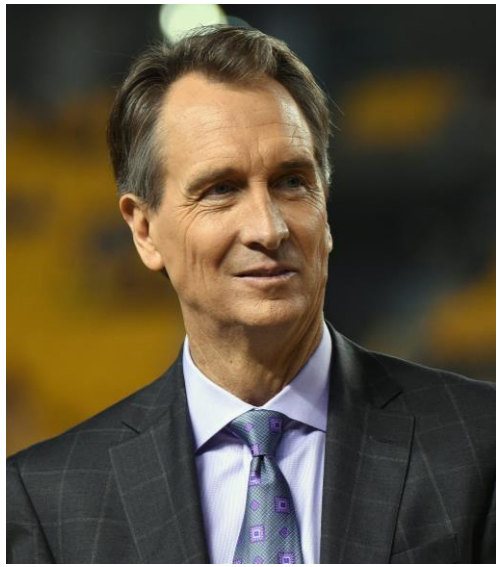
Associate Professor, Western University

Assistant Professor, Loma Linda; UCR

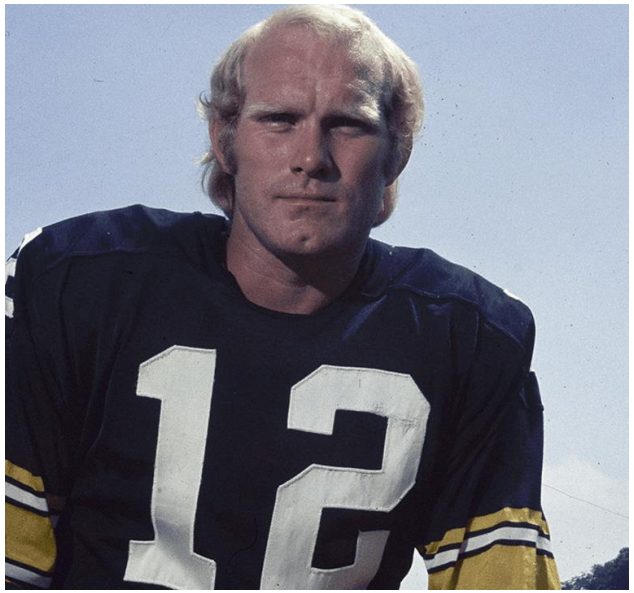
August 1, 2022

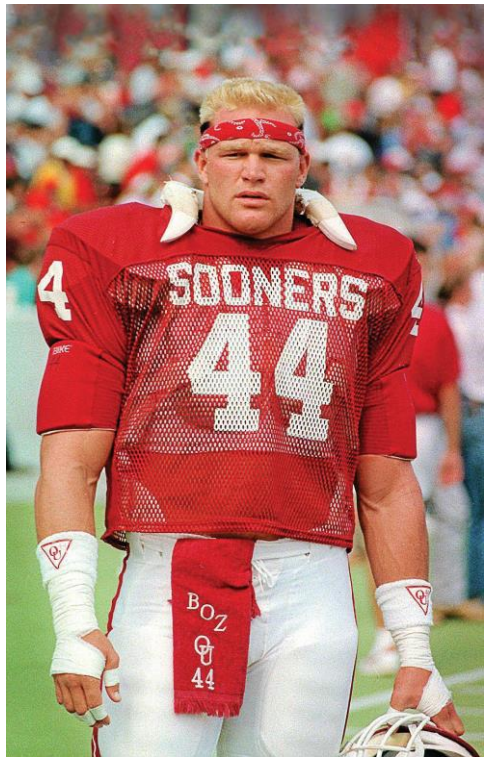
Disclosures

- Clinical Research Funding:
  - Amgen
  - Novartis
  - Roche
- Speaker:
  - Novartis



- This former NFL star entered the broadcaster’s booth soon after his playing days and remains an influential media voice but also serves as a spokeman for the American College of Rheumatology:
- Boomer Esiason
- Terry Bradshaw
- Cris Collinsworth
- Phil Simms
- Brian Bosworth





Former Pittsburgh Steelers quarterback and rheumatoid arthritis patient Terry Bradshaw will serve as the ACR's official spokesperson for Rheumatic Disease Awareness Month in September.

- http://blog.arthritis.org/stories-of-yes/terry-bradshaw-rheumatoid-arthritis/
- https://www.the-rheumatologist.org/article/hundreds-diseases-one-voice/

RA: Key Learning Objectives

- General RA principles and some history
- Recognize clinical features, risk factors
- Recognize classification criteria for RA
- Pathophysiology and treatments

General Points

- Systemic autoimmune disease characterized by chronic inflammation (synovitis):
  - multiple joints
  - small joints in hands and feet
- ~1% of the population; F:M→3:1
- Genetic links similar to SLE

September 6, 2007
N Engl J Med 2007; 357:977-986

ORIGINAL ARTICLE

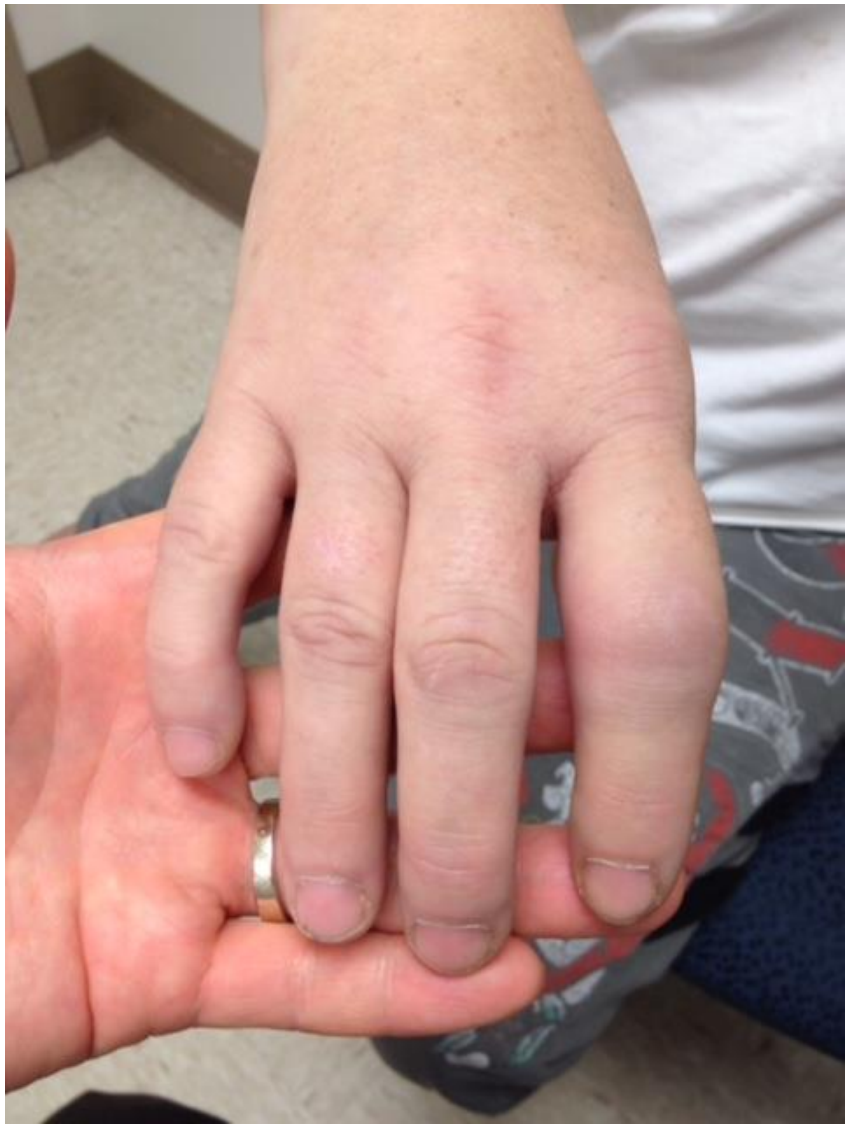
STAT4 and the Risk of Rheumatoid Arthritis and Systemic Lupus Erythematosus

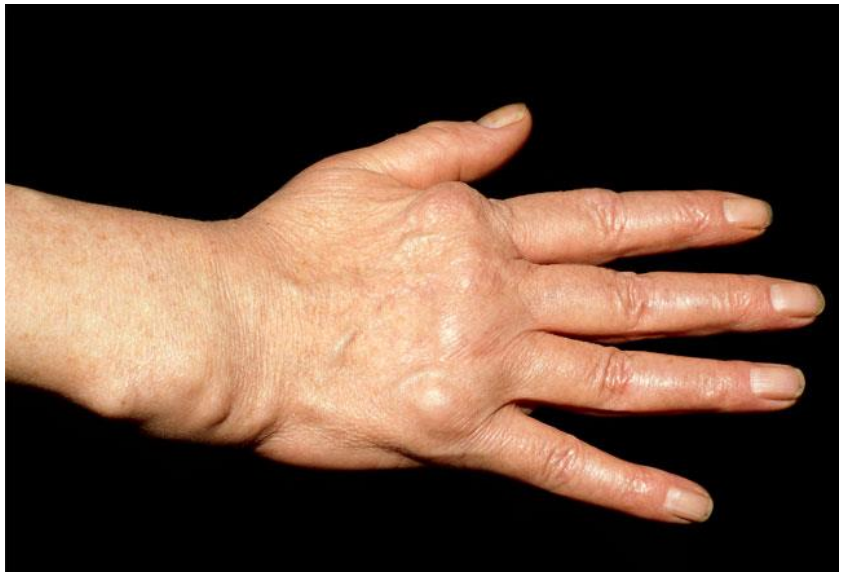
Elaine F. Remmers, Ph.D., Robert M. Plenge, M.D., Ph.D., Annette T. Lee, Ph.D., Robert R. Graham, Ph.D., Geoffrey Hom, Ph.D., Timothy W. Behrens, M.D., Paul I.W. de Bakker, Ph.D., Julie M. Le, B.S., Hye-Soon Lee, M.D., Ph.D., Franak Batliwalla, Ph.D., Wentian Li, Ph.D., Seth L. Masters, Ph.D., et al.

- Loss of joint function, destruction of bone and cartilage
- Shorter life expectancy→ systemic inflammation

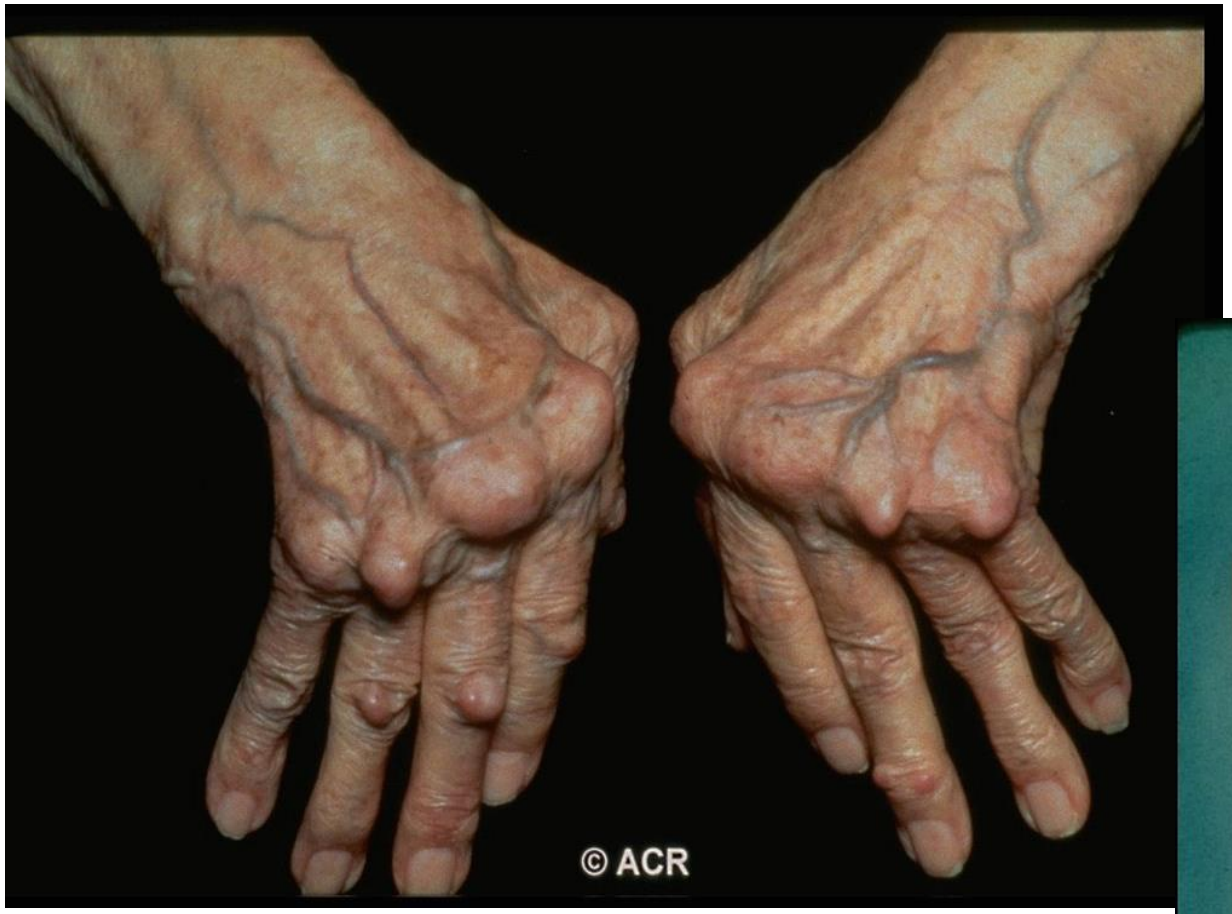

global
BNP PARIBAS
Sport

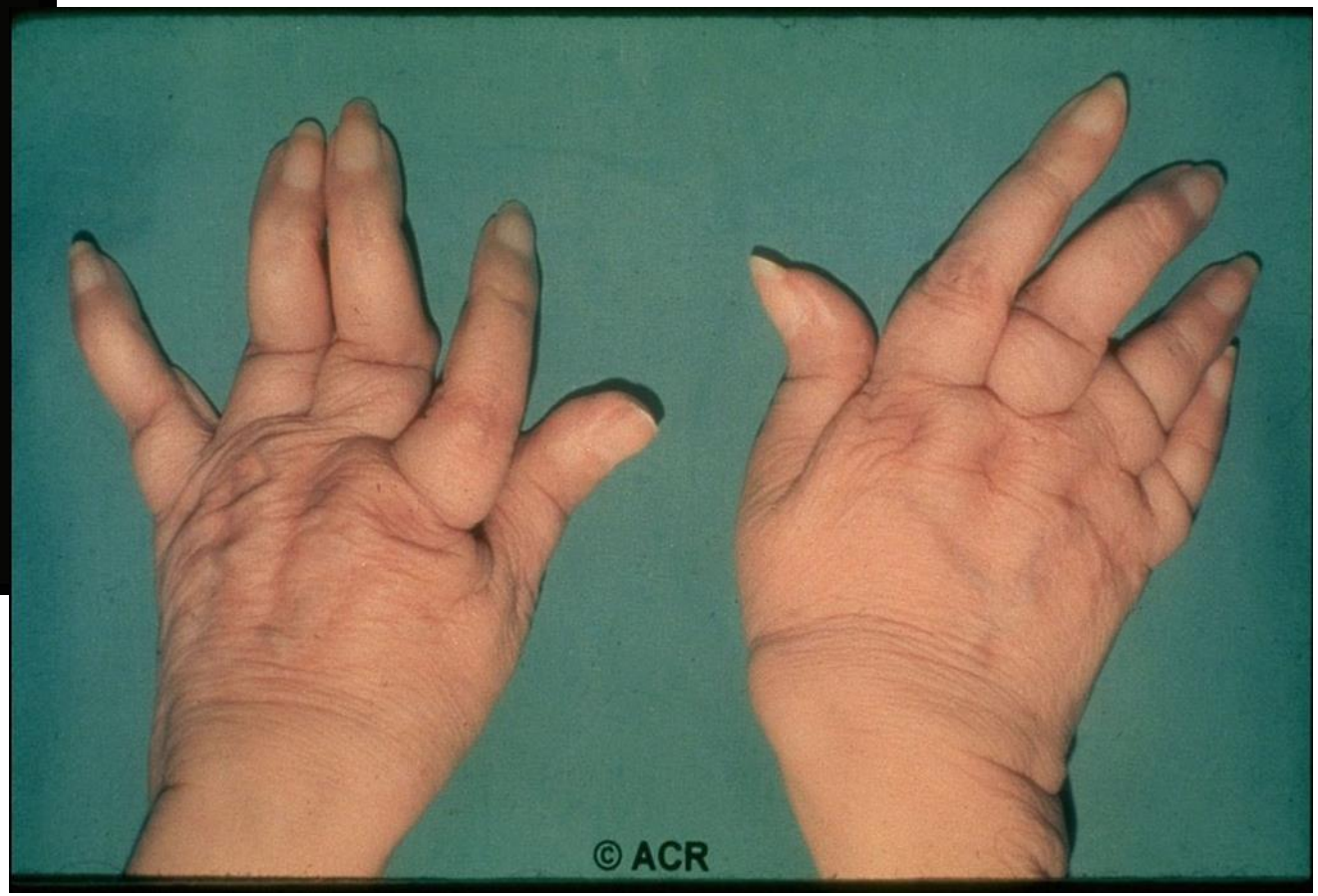
Clinical Features

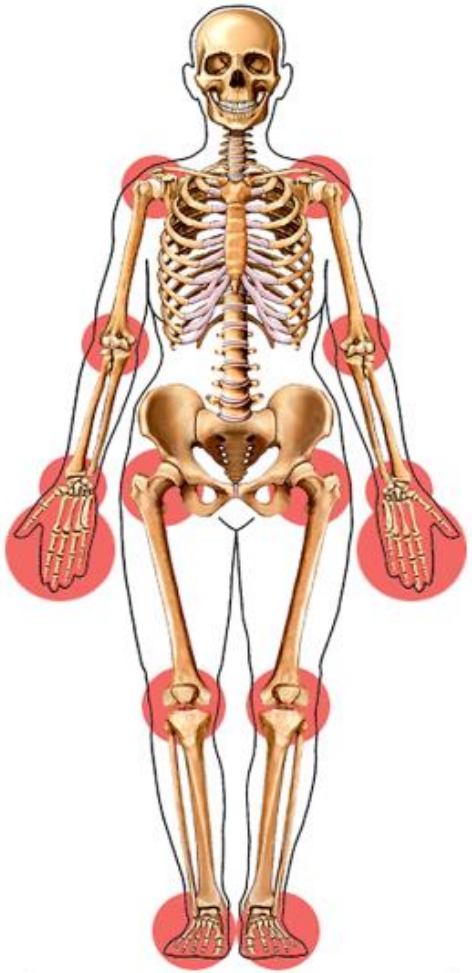




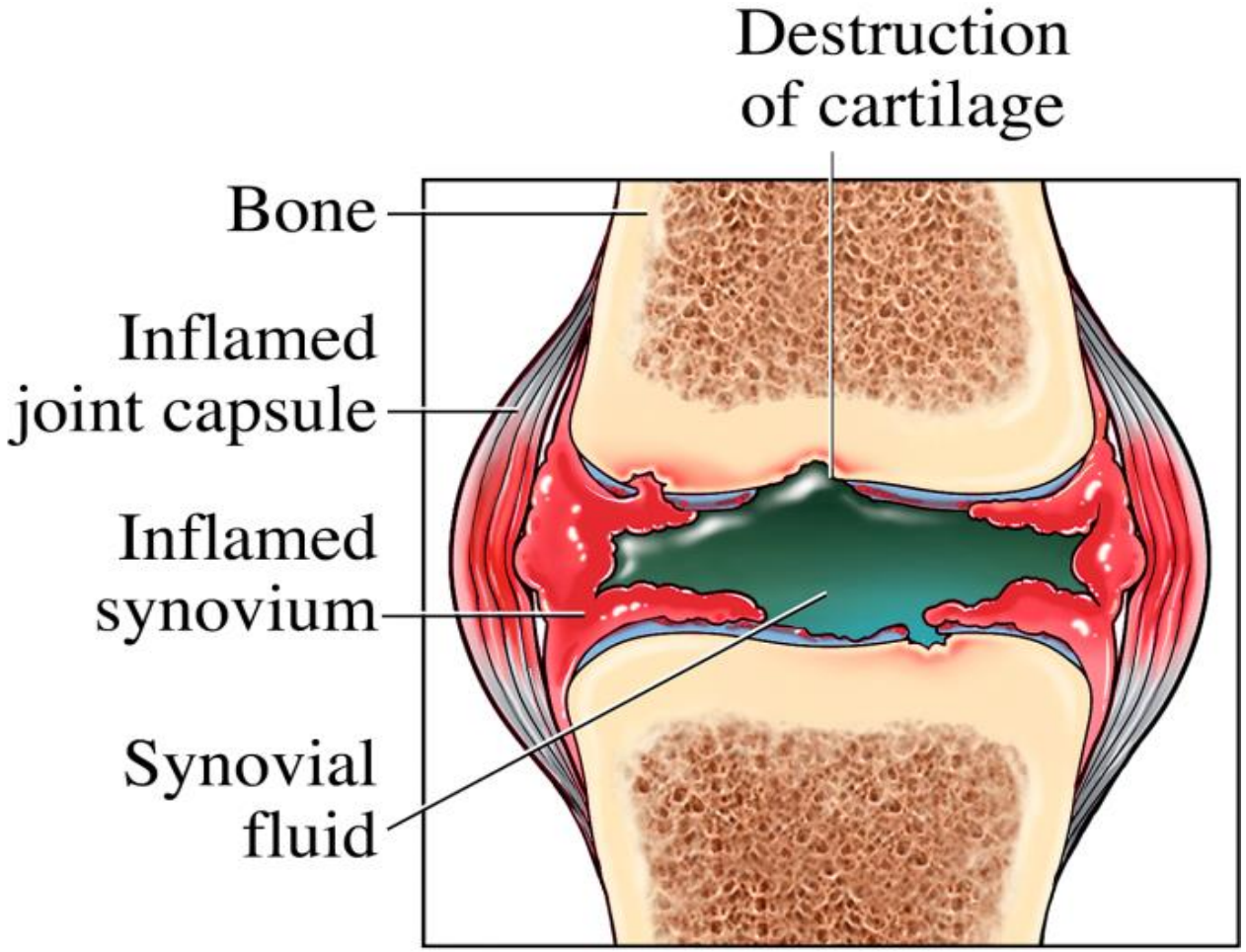
Clinical Features





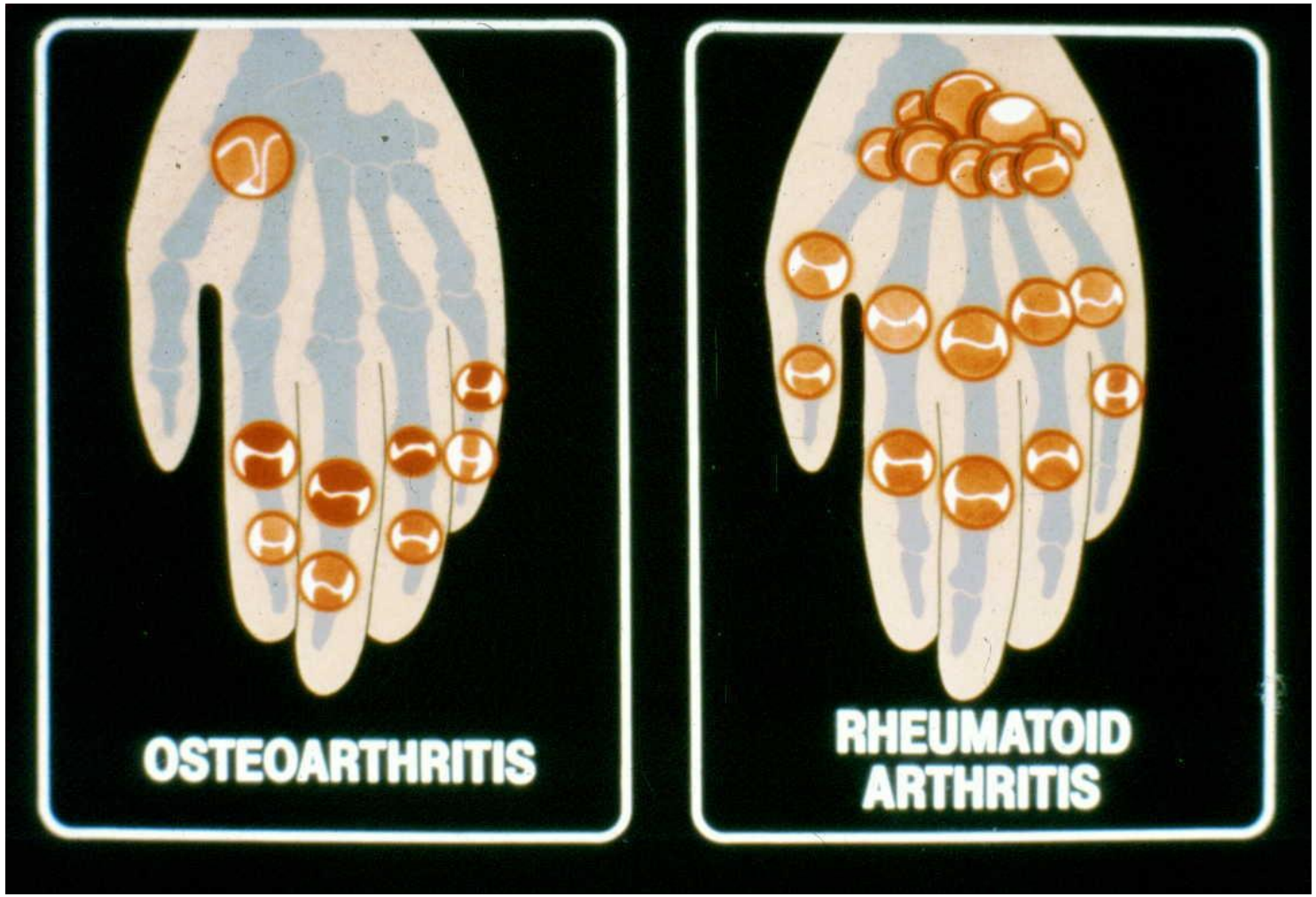


Joint pain occurring
in various joints



Enlarged view of a joint

Osteoarthritis vs. Rheumatoid Arthritis



Extra-articular manifestations

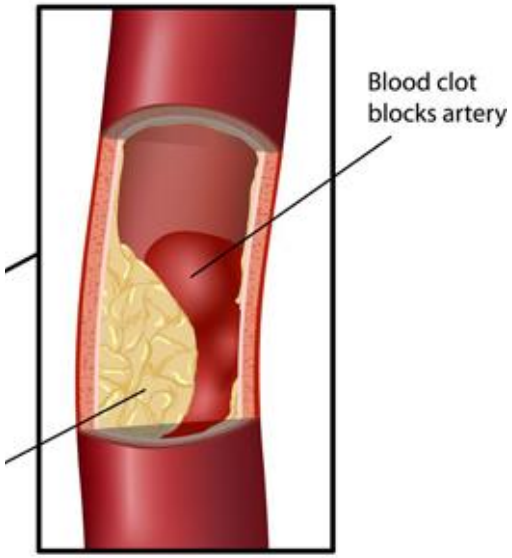
RA: Not Just a Joint Disease

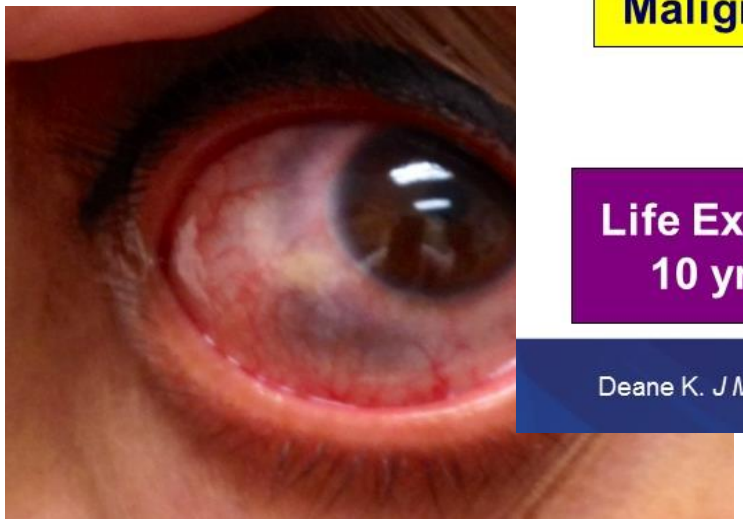
- CVD 10 Years Earlier
- 6-9x ↑ Serious Infections
- 2x ↑ Malignancy
- ↑ Pulmonary Disease
- ↑ GI Bleeding
- Life Expectancy Decreased 10 yr women, 4 yr men

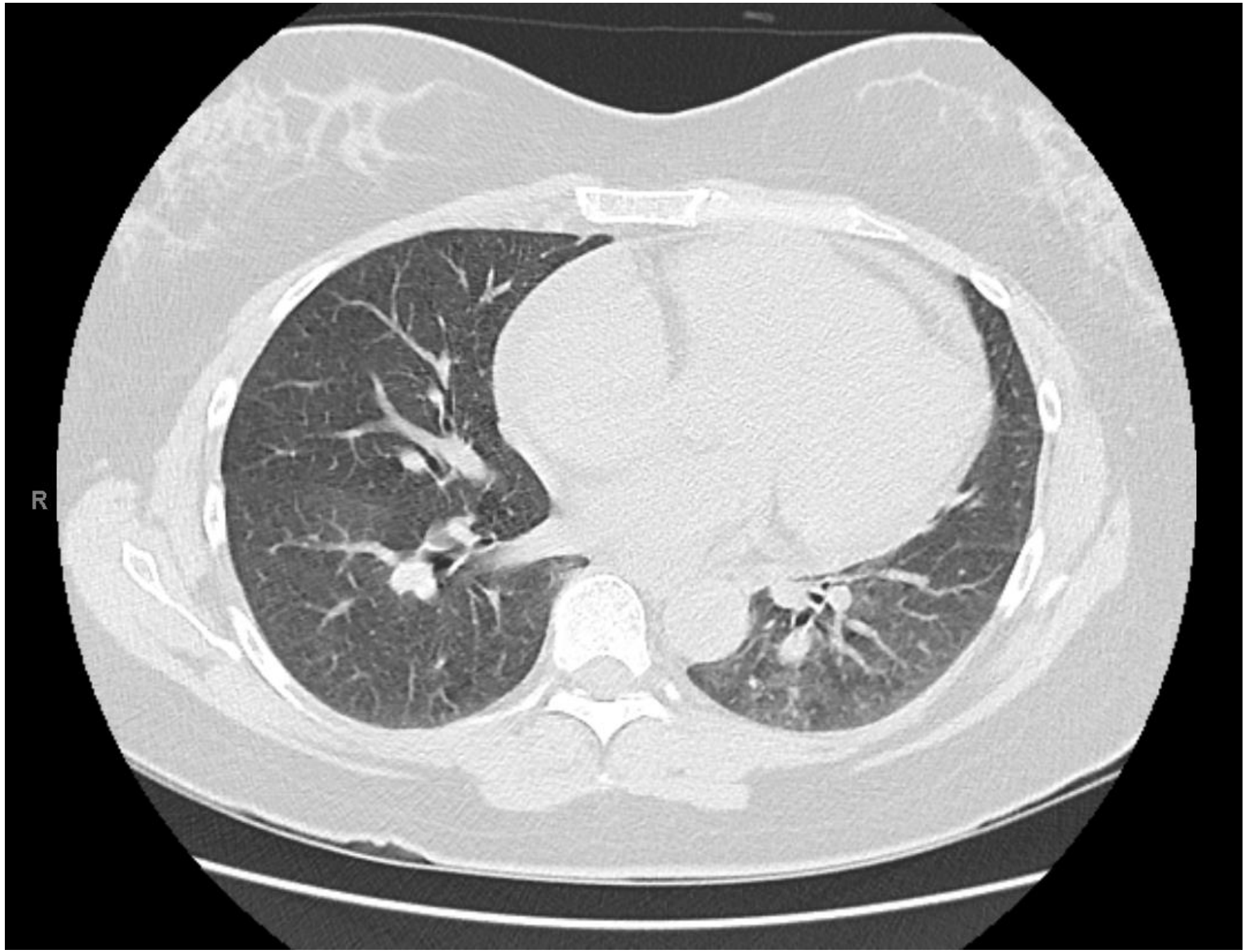
Joint pain
Disability
Destruction

Deane K. *J Musculoskel Med.* 2006;23:S24-S31.

RheumNow



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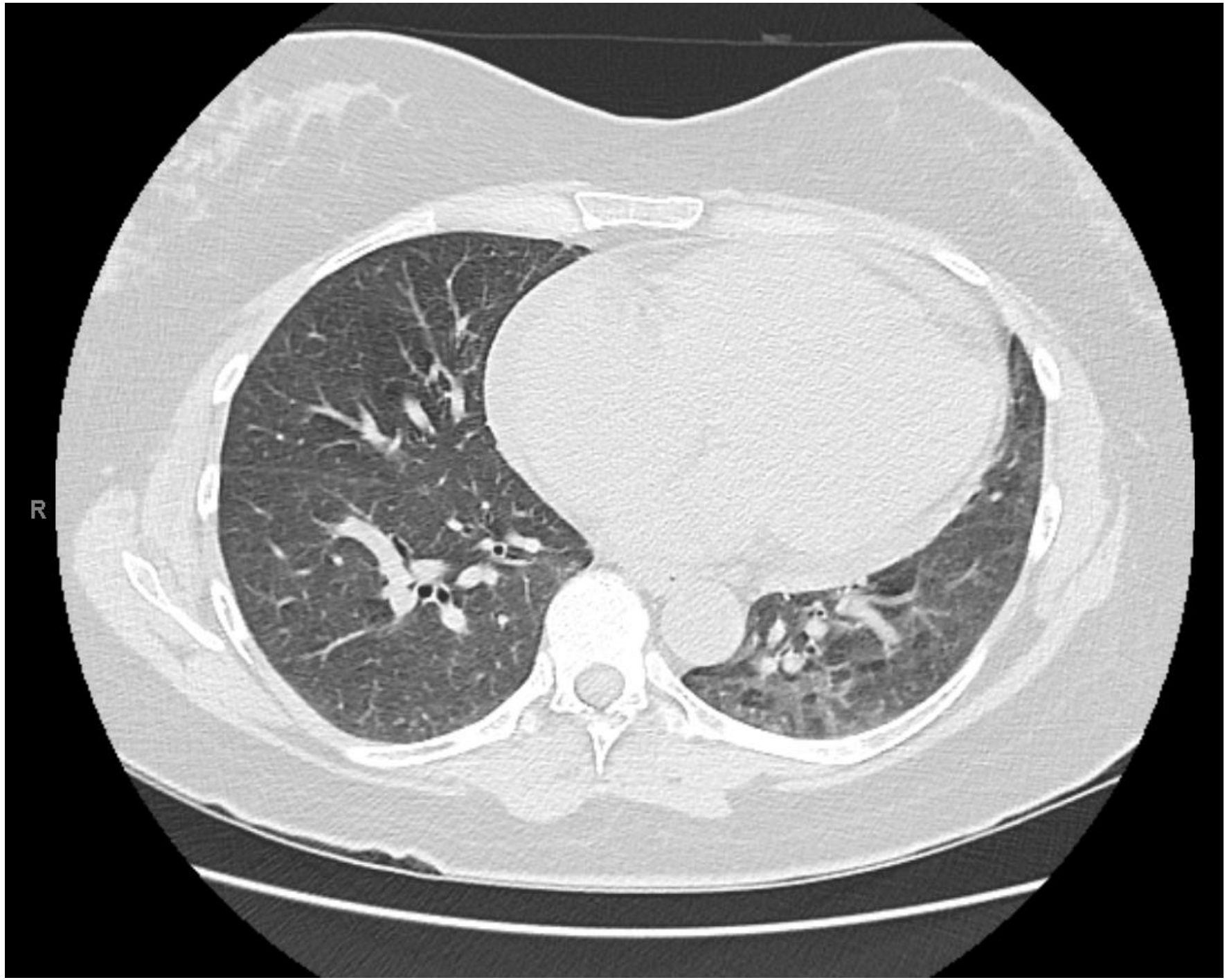
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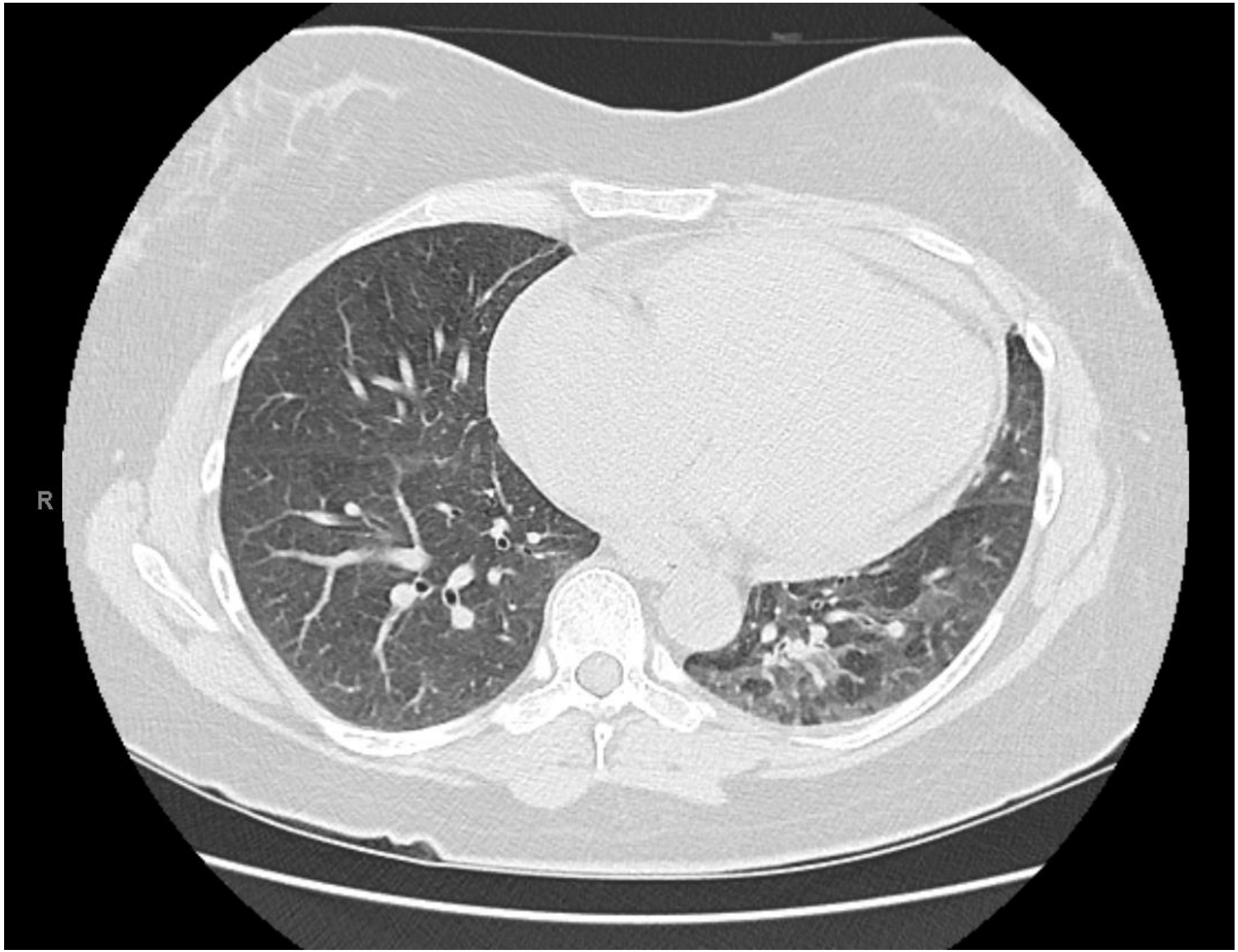
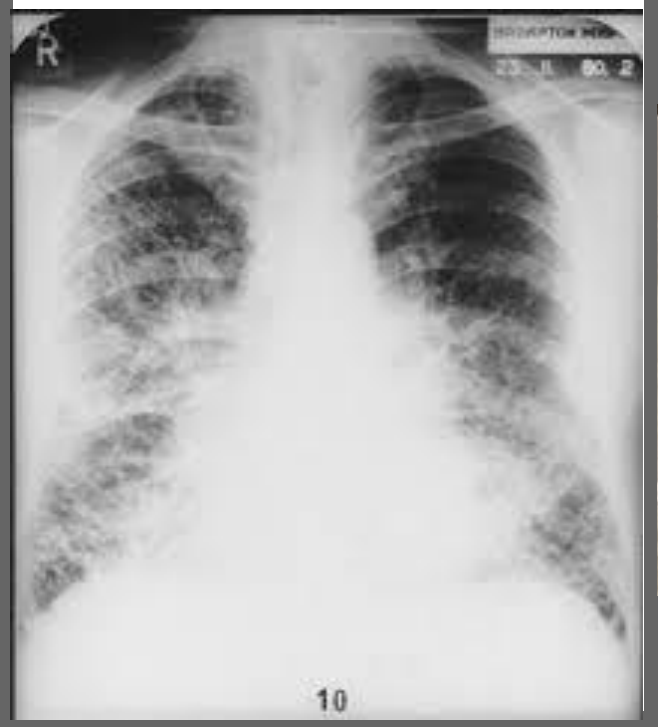
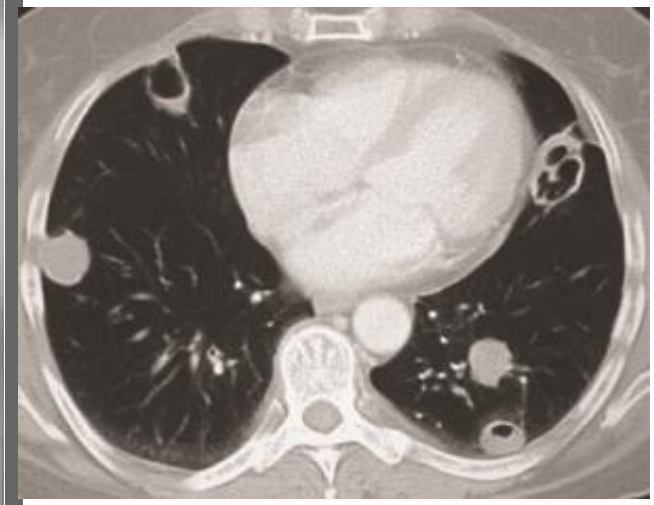

R

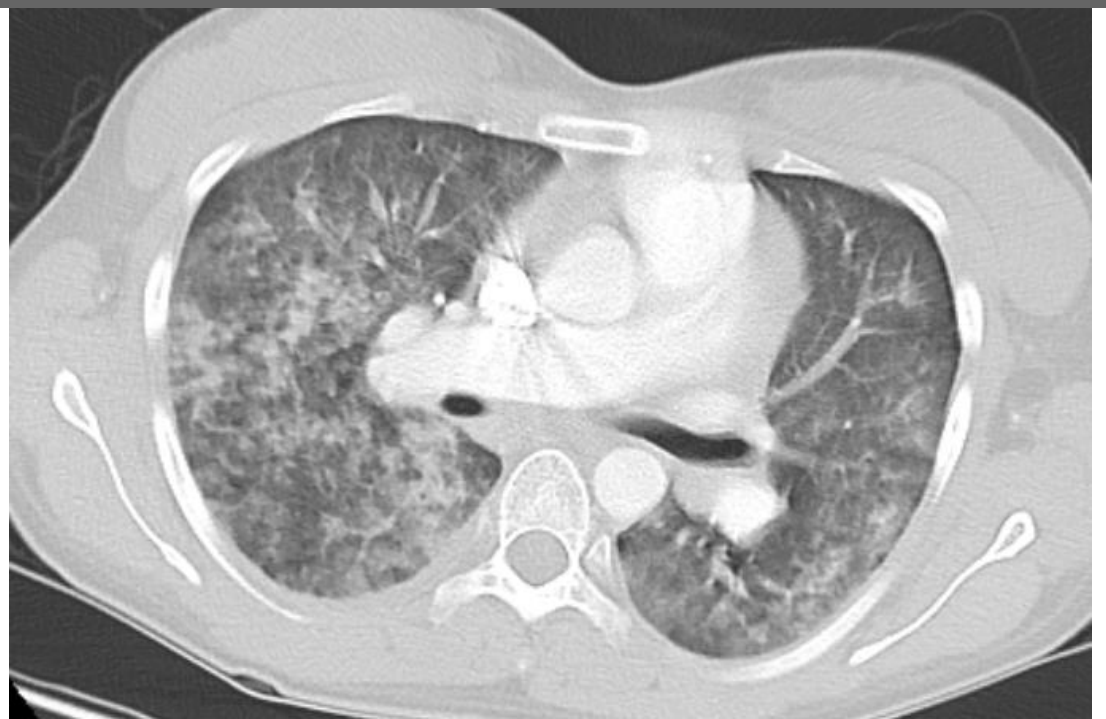
RA:
pulmonary complications

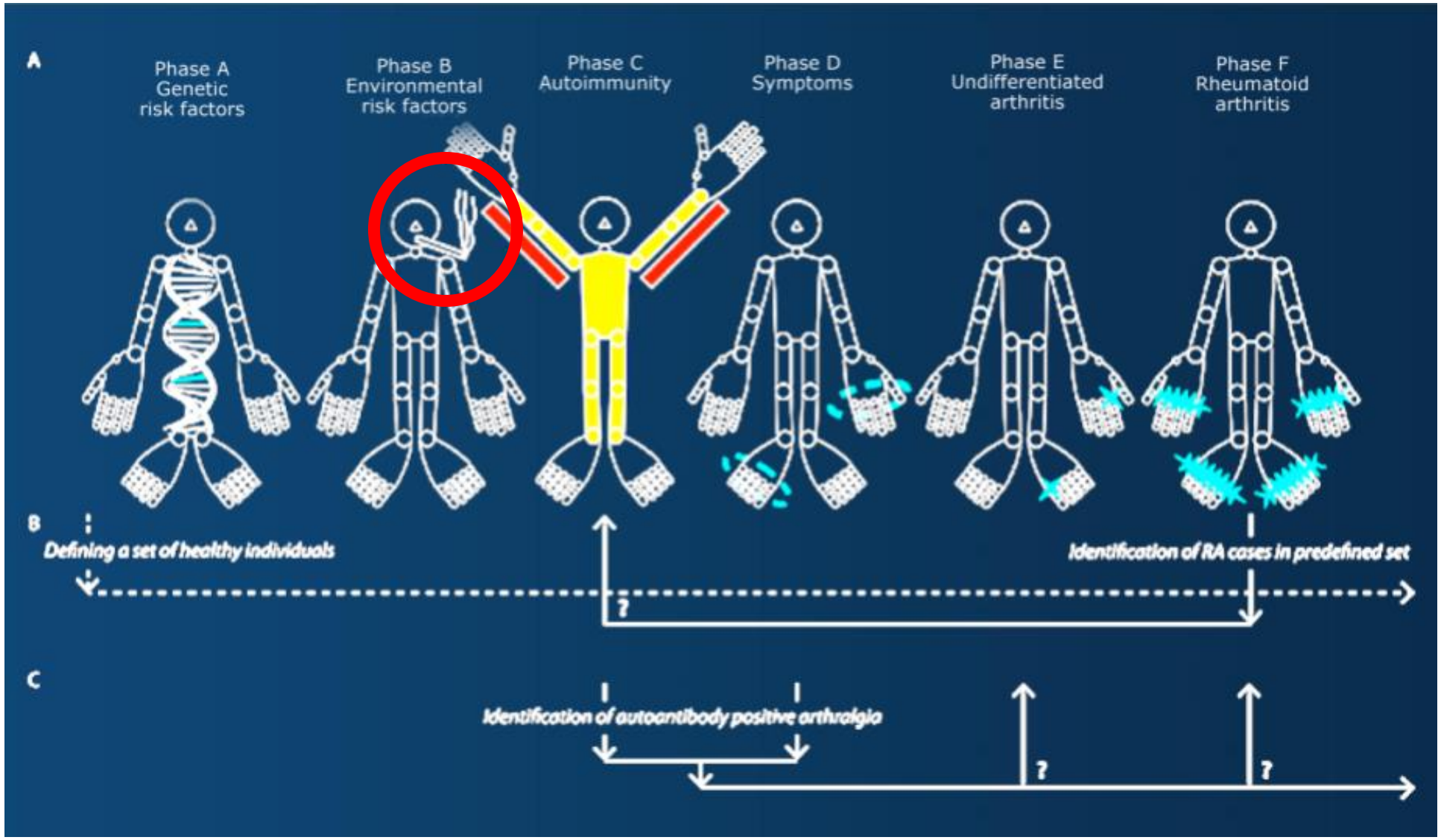
- Pulmonary nodules
- Interstitial lung disease
- PE vs MI

- Medications and complications
  - Methotrexate pneumonitis
  - Opportunistic infection





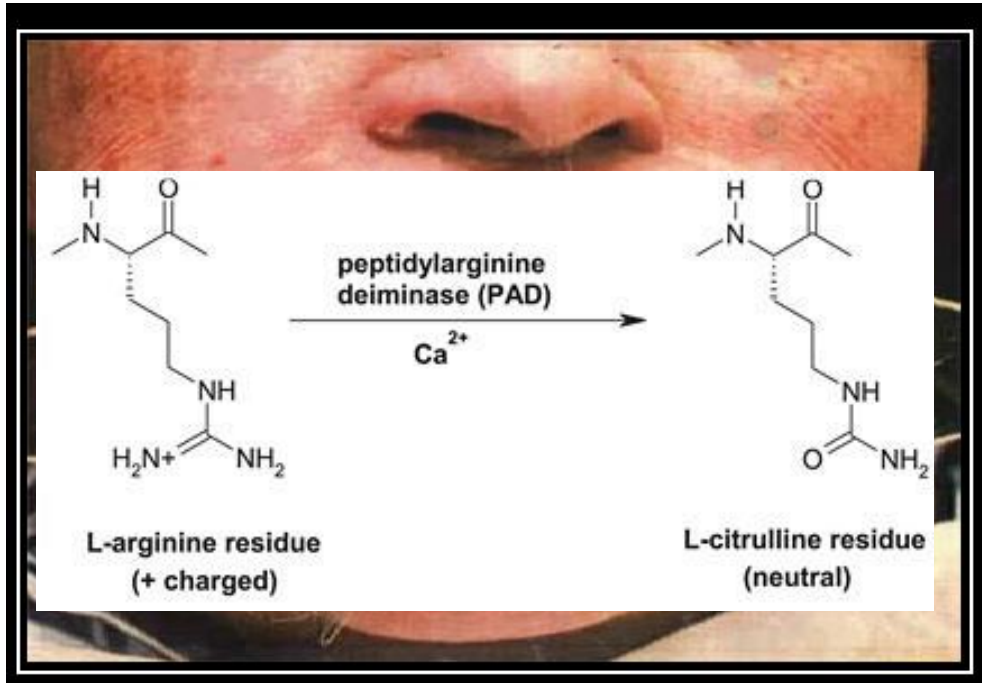


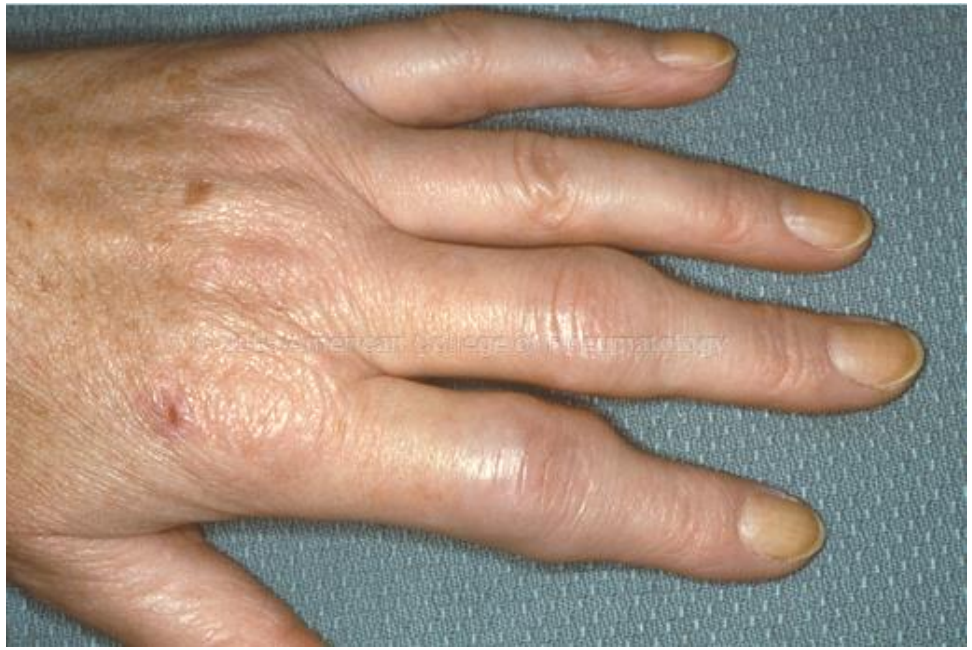

A
Phase A
Genetic
risk factors
Phase B
Environmental
risk factors
Phase C
Autoimmunity
Phase D
Symptoms
Phase E
Undifferentiated
arthritis
Phase F
Rheumatoid
arthritis
B
Defining a set of healthy individuals
Identification of RA cases in predefined set
?
C
Identification of autoantibody positive arthralgia
?
?

What auto antibody is most highly specific for the detection of RA?

- Anti-ribonucleoprotein (RNP)
- SSA
- Anti-cyclic citrillunated peptide (CCP)
- Rheumatoid factor (RF)
- Anti-tumor necrosis factor (TNF)

Gingival Disease and Autoimmunity





"Antibodies to citrullinated alpha-enolase peptide 1 are specific for Rheumatoid Arthritis and cross-react with porphyromonas gingivalis enolase." Lundberg K., Kinloch A., Fisher, B.A., et al. *Arthritis Rheum*. 58: 3009-19 **2008**.

"Associations of P. gingivalis titers with RF, antiCP suggests that infection with this organism plays a role in disease risk and progression in RA." Mukuls TR, Payne, J.B., Reinhardt, R. A. et al *Int. Immunopharmacol*. 9:38-42 **2009**.

"Antibodies to Porphyromonas gingivalis are Associated with Anticitrullinated Protein Antibodies in patients with Rheumatoid Arthritis and their Relatives." Hitchon et al *J Rheumatol* 37:1105-1112 **2010**.

ACR 1987 Classification Criteria for Rheumatoid Arthritis

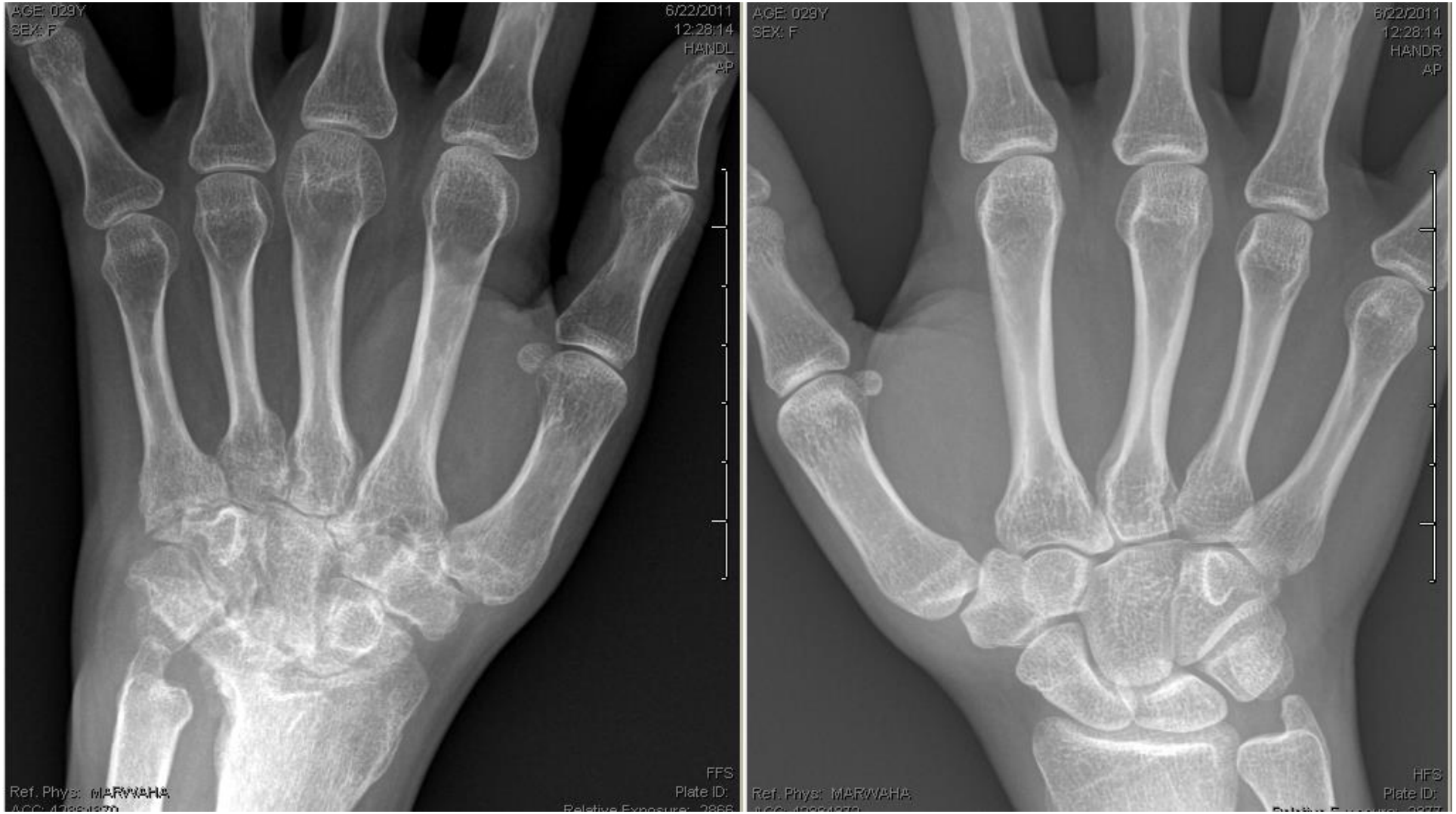
Patients Must Have Four of Seven Criteria:

- Morning Stiffness Lasting at Least 1 Hour*
- Swelling in 3 or More Joints*
- Swelling in Hand Joints*
- Symmetric Joint Swelling*
- Erosions or Decalcification on X-ray of Hand
- Rheumatoid Nodules
- Abnormal Serum Rheumatoid Factor

* Must Be Present at Least 6 Weeks.

Real Case…

- 29 yo WF smoker with left wrist swelling and pain, right MTP swelling and pain x 9 yrs
- No stiffness or nodules or family history
- Previously diagnosed as overuse, tendonitis, ‘degenerative wrist arthritis’; waitress, cross fit
- Does she fulfill 1987 criteria?
- 3/7 classification criteria


AGE: 029Y
SEX: F
6/22/2011
12:28:14
HANDL
AP
Ref. Phys: MARWAHA
FFS
Plate ID:
AGE: 029Y
SEX: F
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12:28:14
HANDR
AP
Ref. Phys: MARWAHA
HFS
Plate ID:

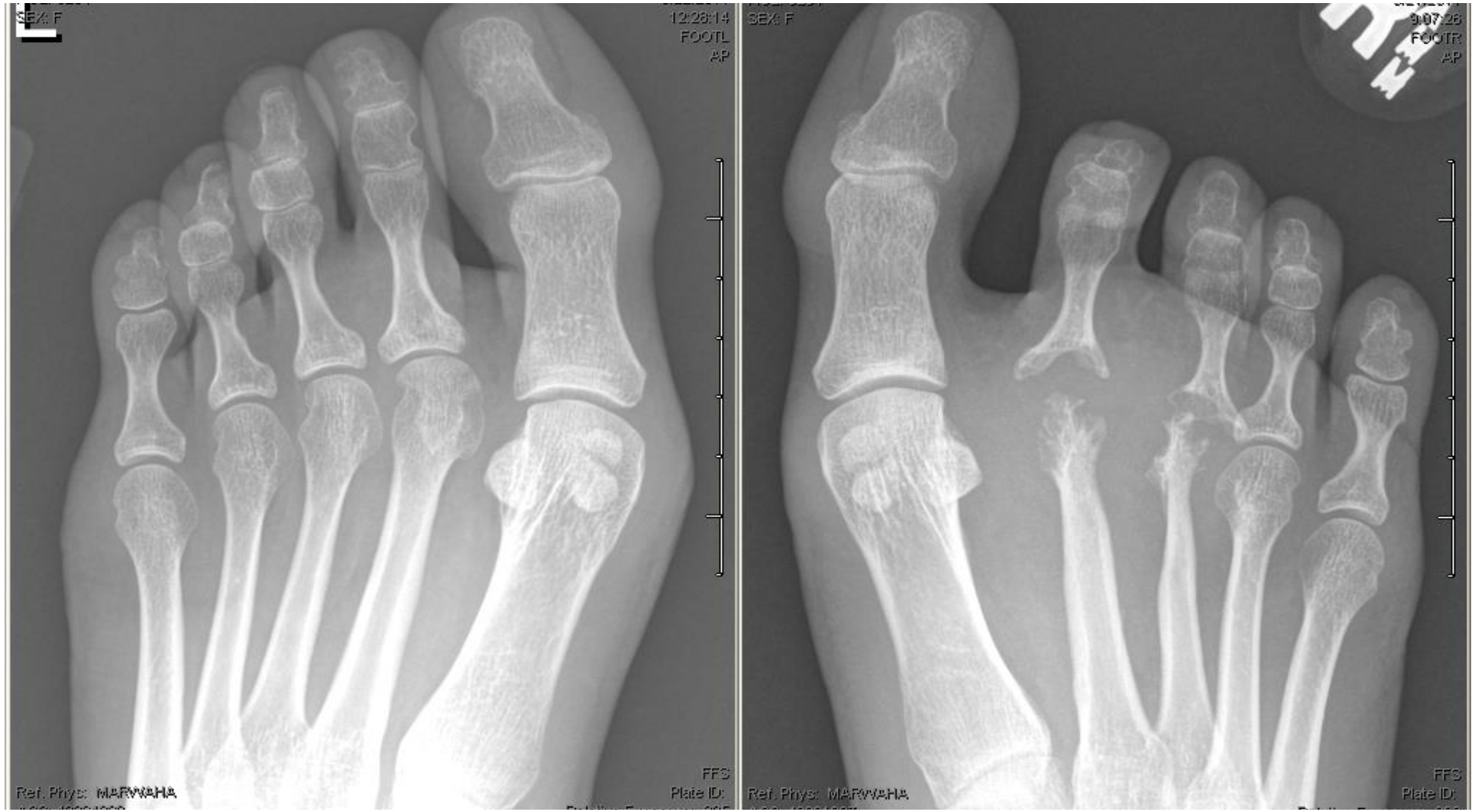
SEX: F
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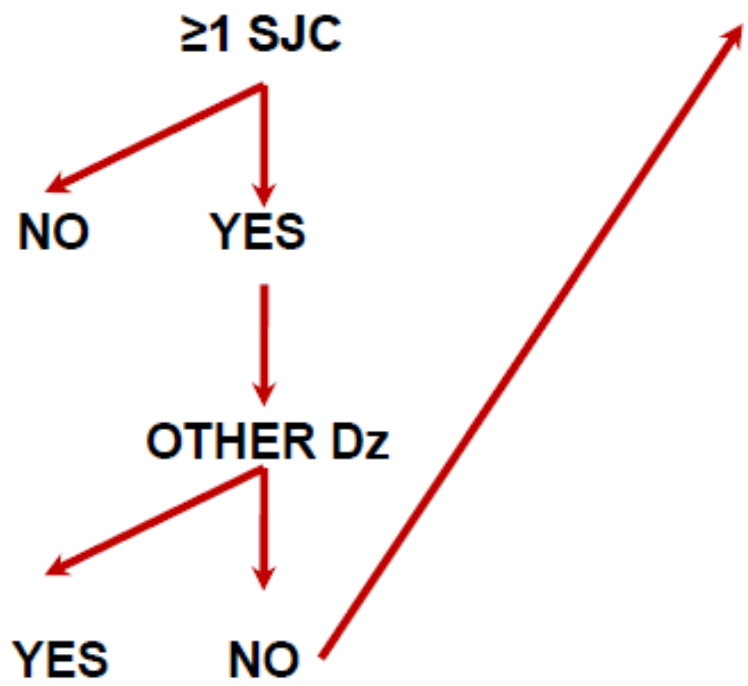
Plate ID:
SEX: F
FOOTR
AP
Ref. Phys: MARWAHA
FFS
Plate ID:

	Ref Rng	6/22/2011
CRP	*<10.0*	20.0 (H)
ESR	*0 - 20 MM/HR*	23 (H)
CCP IGG	*<5.0*	181.8 (H)
RF	*<11*	<5

2010 ACR/EULAR RA classification criteria



RA can be classifiable or diagnosed with a score ≥6

JOINT DISTRIBUTION	
1 large joint	0
2–10 large joints	1
1–3 small joints (large joints excluded)	2
4–10 small joints (large joints excluded)	3
>10 joints (at least 1 small joint)	5
SEROLOGY	
Negative RF and negative ACPA	0
Low positive RF or ACPA (≤3x ULN)	2
High positive RF or ACPA (>3x ULN)	3
SYMPTOM DURATION	
<6 weeks	0
≥6 weeks	1
ACUTE PHASE REACTANTS	
Normal CRP and ESR	0
Abnormal CRP or ESR	1

“undifferentiated arthritis”

Case:

A 56 yo AA female presents with 6 mos of intermittent swelling and stiffness in hands that last 1-2 days and improves spontaneously and with ibuprofen. Bouts every 2 mos. None now

SH: teacher

½ ppd tob; no etoh or drugs

FH: mother with reported RA

Exam: no synovitis appreciable; no chronic changes

Work up?

Component	Latest Ref Rng	6/20/2016
ESR	0 - 30 mm/Hr	20
CRP	<=7.4 mg/L	2.8
RF	<=14 IU/mL	**190 (H)**
CCP IGG	0.0 - 4.9 U/mL	**>1200.0 (H)**

School of Medicine
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

NIH National Institutes of Health

The first prevention trial for RA conducted in the USA.

RA Treatment: Optimizing Outcomes

- Early diagnosis and risk stratification
- DMARDs early (within 3 mos of symptoms)
- “TREAT TO TARGET”
- Steroids
  - bridge to effective DMARD therapy
  - prednisone >10 mg/d rarely needed for joints
  - minimize long term side effects (osteoporosis, DM)
- Co-morbidities
  - atherosclerosis
  - osteoporosis

Traditional DMARD's

- methotrexate/Rheumatrex
- leflunomide/Arava
- sulfasalazine/Azulfidine
- azathioprine/Imuran
- hydroxycholoroquine/Plaquenil
- mycophenolate mofetil/Cellcept
- gold
- minocycline
- doxycyline
- penicillamine
- cyclophosphamide
- cyclosporine

Biologic DMARD's

- TNFα antagonists:
  - etanercept (Enbrel)
  - infliximab (Remicade)
  - adalimumab (Humira)
  - golimumab (Simponi)
  - certolizumab (Cimzia)
  - biosimilars

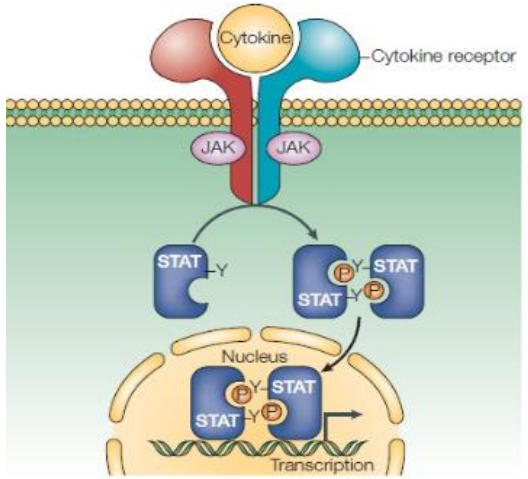
- Interleukin-1 antagonist
  - anakinra (Kineret)

- Suppress T-Cell activation
  - abatacept (Orencia)

- Anti B-Cell monoclonal Ab
  - rituximab (Rituxan)

- Anti-interleukin-6
  - tocilizumab (Actemra)
  - sarilumab (Kevzara)

- Janus kinase (JAK) inhibitors
  - tofacitinib (Xeljanz)
  - baricitnib (Olumiant)
  - upadacitinib (Rinvoq)



From Nature Reviews Immunology

VENUS WILLIAMS DOESN'T LET SJÖGREN'S SYNDROME KEEP HER DOWN.

With help from her rheumatologist, she is back on top of her game. You can be, too! Join the Simple Tasks Community and you'll be entered to win an item signed by Venus.

JOIN US

Venus Williams
U.S. Tennis Pro & Spokesperson, American College of Rheumatology

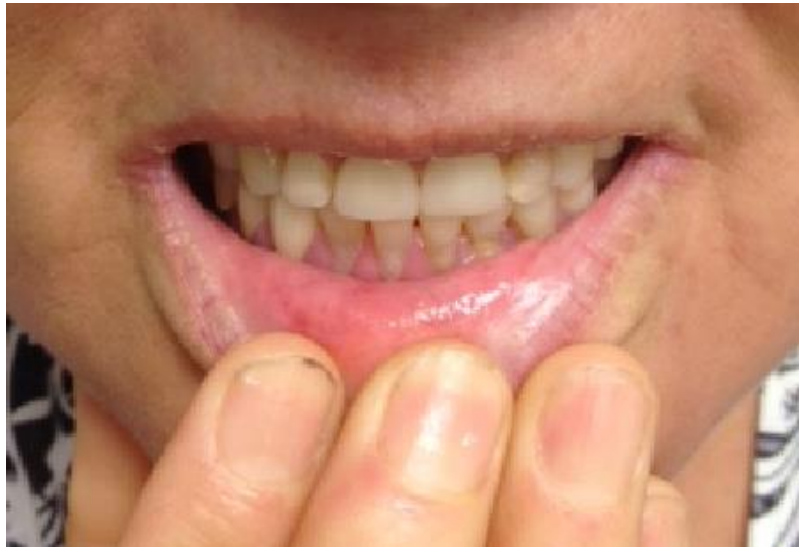
Henrik Samuel Conrad Sjögren
(July 23, 1899 – September 17, 1986)

Sjögren's syndrome – General points

- Idiopathic systemic autoimmune dz affecting exocrine glands
- Lymphocytic infiltration; end organ damage
- 9:1 female: male; primary vs secondary
- Lymphoma, primary biliary cirrhosis, vasculitis

Clinically:

- Keratoconjunctivitis sicca
  - Ocular dryness
- Xerostomia
  - Oral dryness



2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome

Item	Weight/score
Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥1 foci/4 mm^2‡	3
Anti-SSA/Ro positive	3
Ocular Staining Score ≥5 (or van Bijsterveld score ≥4) in at least 1 eye§¶	1
Schirmer's test ≤5 mm/5 minutes in at least 1 eye§	1
Unstimulated whole saliva flow rate ≤0.1 ml/minute§#	1

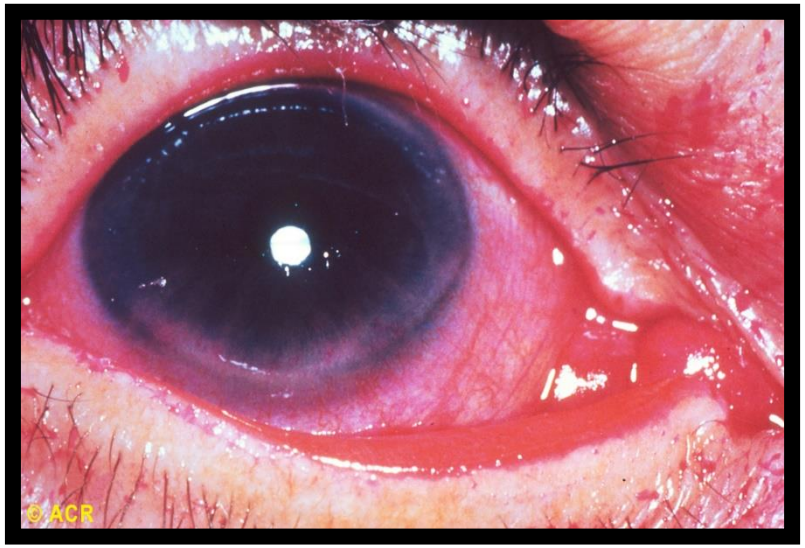
Prior diagnosis of any of the following conditions would exclude participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests:

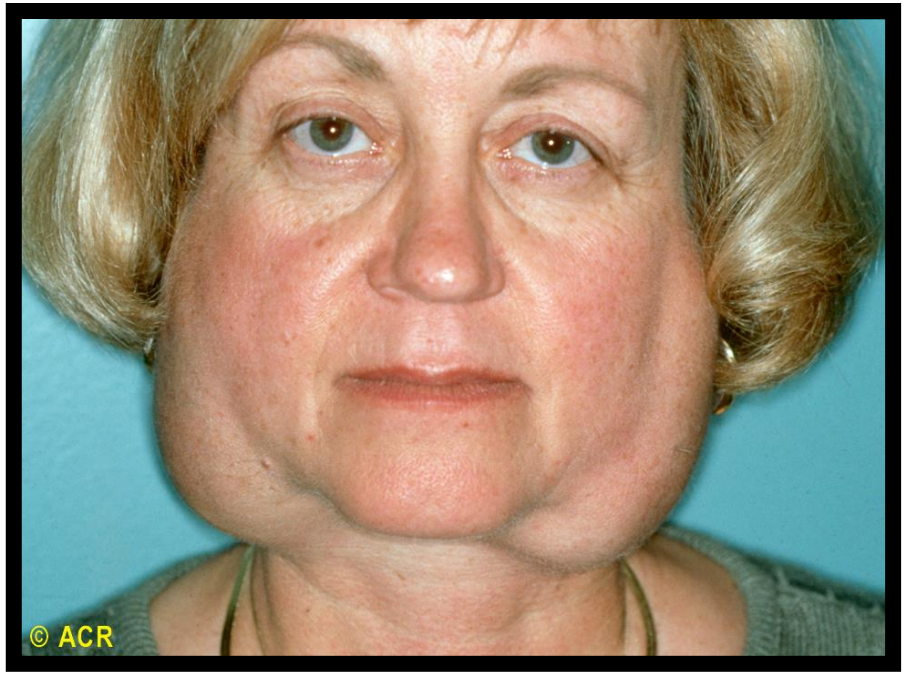
- History of head and neck radiation treatment
- Hepatitis C infection
- Acquired immunodeficiency syndrome
- Sarcoidosis
- Amyloidosis
- Graft versus host disease
- IgG4-related disease

ARTHRITIS & RHEUMATOLOGY
Vol. 69, No. 1, January 2017, pp 35–45

Sjogrens Key Points

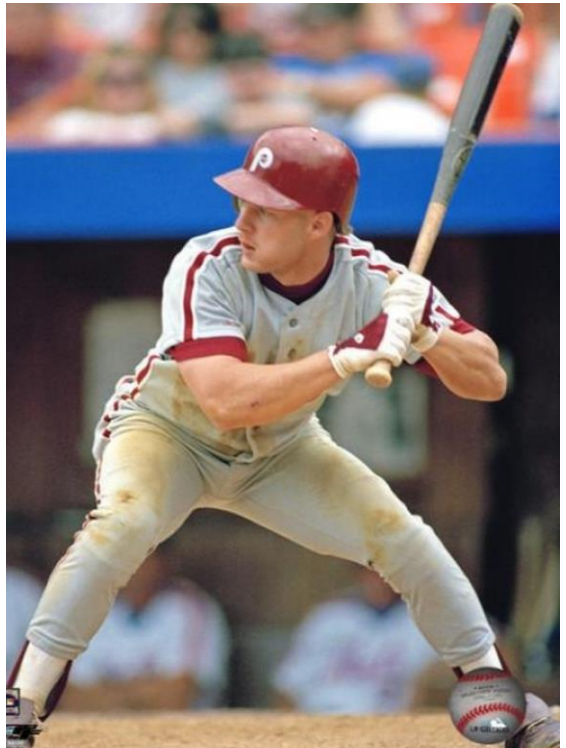
- Symptoms :
  - Mucocutaneous
  - Ophthalmologic
  - Constitutional and musculoskeletal
  - Vasculitis
- Diagnosis
  - Parotid
  - SSA
  - Lymphoma
- Management (all off label)
  - Hydroxychloroquine
  - Mycophenolate
  - Corticosteroids
  - Rituximab?
  - Nipocalimab? Anti-Ig

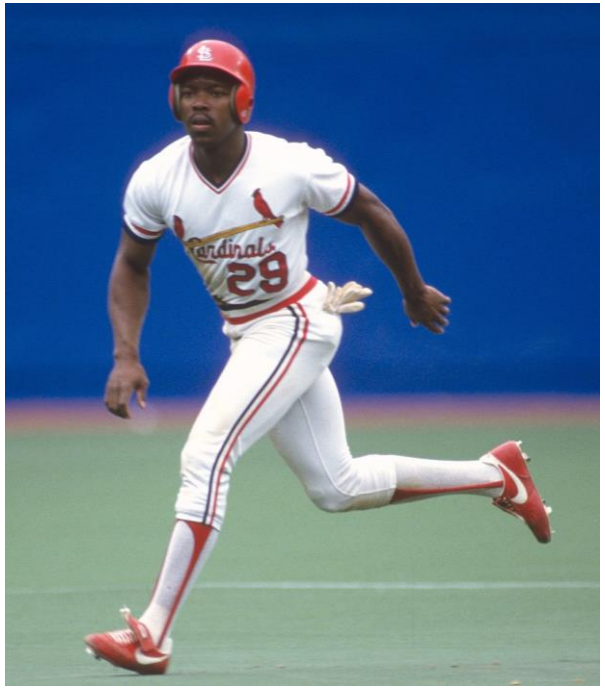


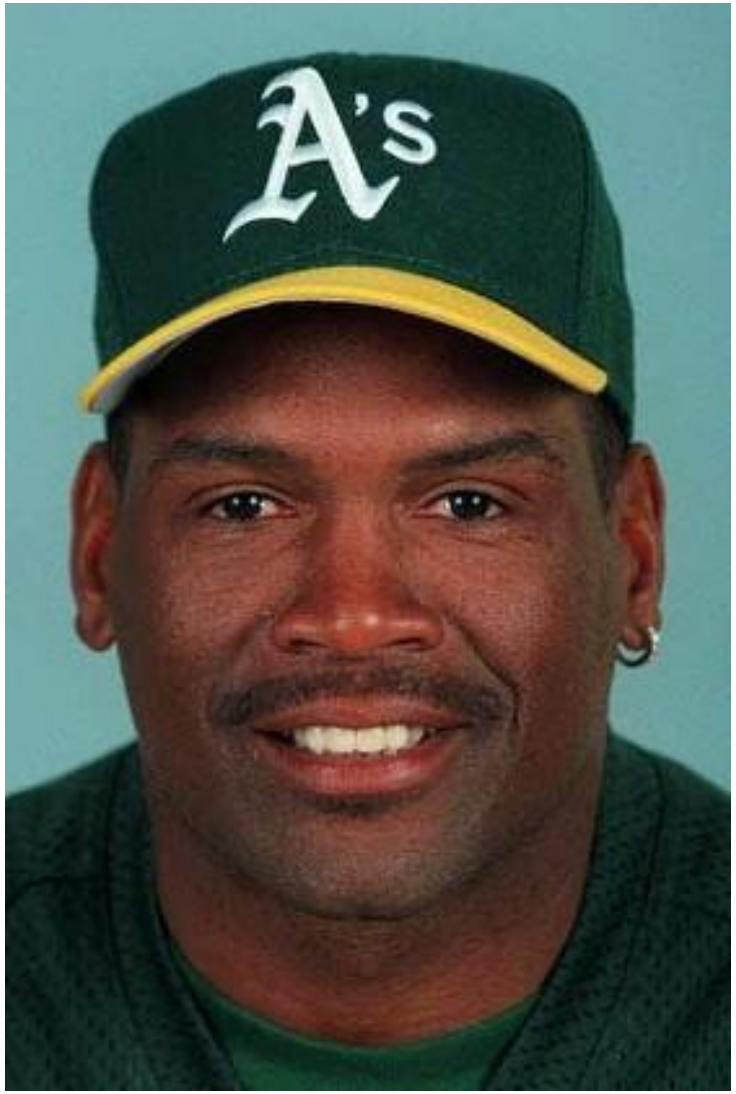


Case 6

- This feared leadoff hitter in MLB holds the distinction of playing in 4 decades and only after developing kidney failure from an autoimmune disease, did he eventually have to retire, only to be inducted into the HOF in 2017:
- Ricky Henderson
- Lenny Dykstra
- Vince Coleman
- Derek Jeter
- Tim Raines







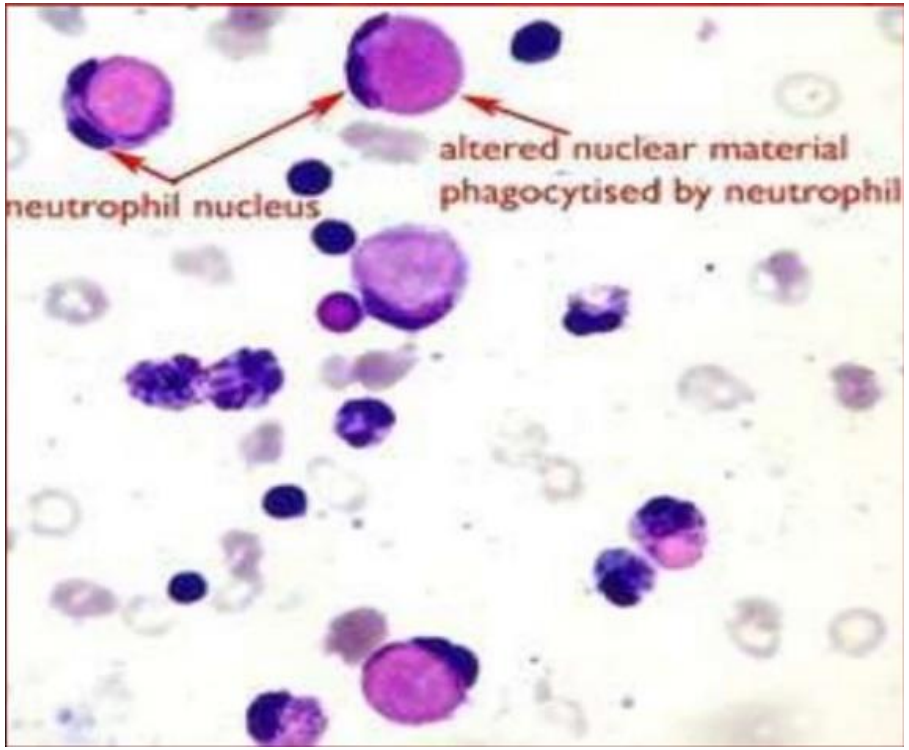
Raines diagnosis: Lupus

Ross McKeon, OF THE EXAMINER STAFF

Aug. 7, 1999

DEFINITION

- “Inflammatory heterogeneous autoimmune disorder affecting multiple organ systems characterized by the production of auto-antibodies directed against cell nuclei”

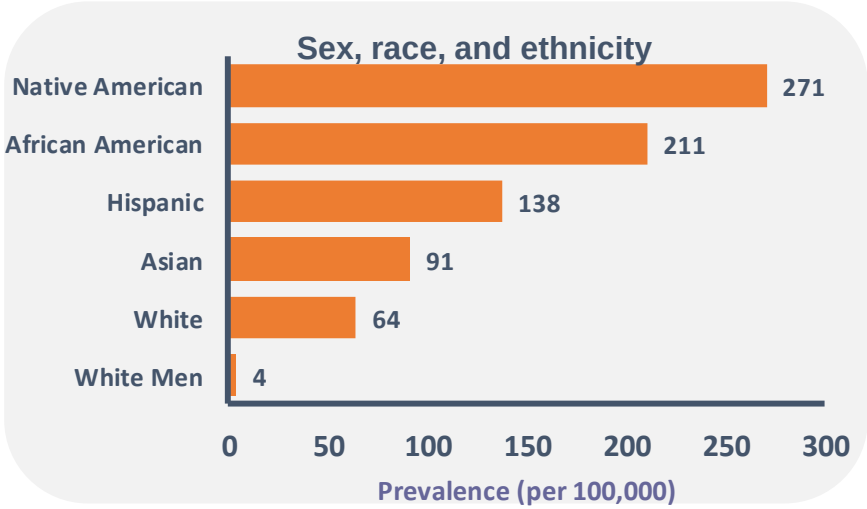


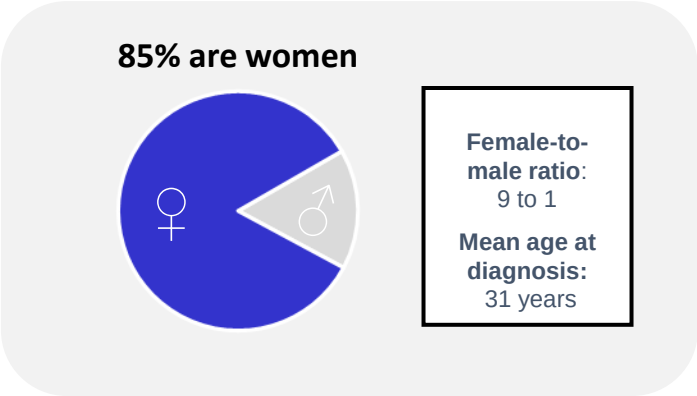
EPIDEMIOLOGY

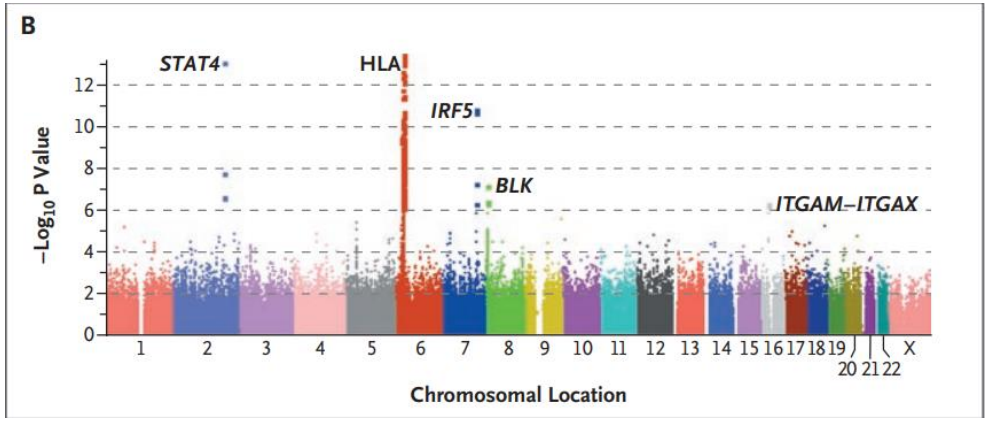
<u>Age, gender, race and genetics</u>

- Peak incidence 14-45 years
- Female predominance
  - severity is =
- Ethnic predisposition
- Genetics:
  - protein tyrosine phosphatase, non-receptor type 22 (PTPN22)
  - HLA DRB1, ITGAM or ITGAX

- Environmental triggers
  - UV light
  - Viruses
  - Hormones (Estrogen)
  - TOBACCO







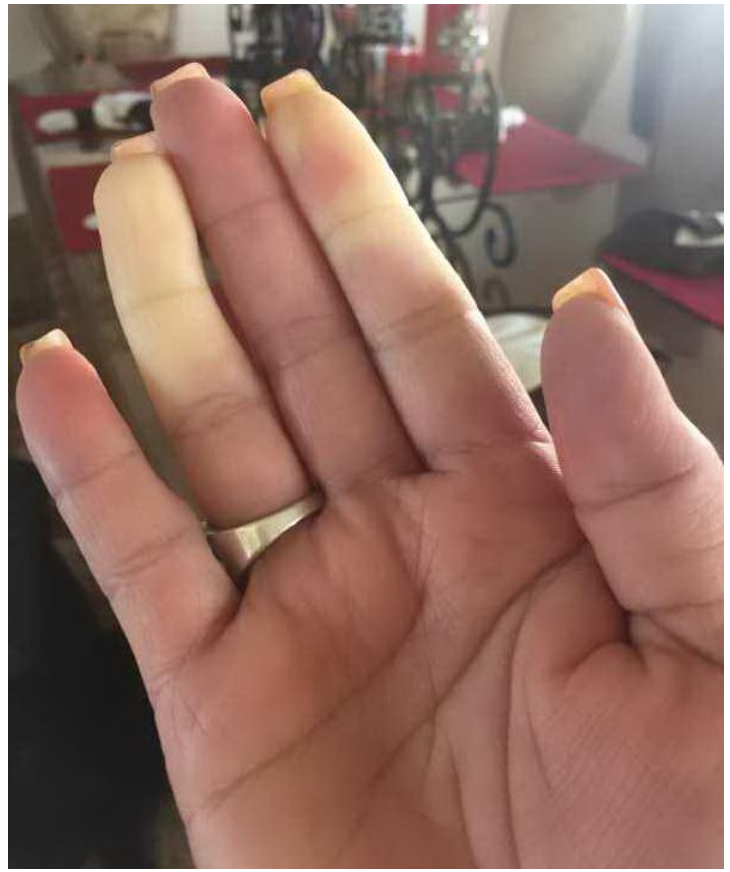
Hom G, Graham RR, Modrek B, Taylor KE, Ortmann W, Garnier S, Lee AT, Chung SA, Ferreira RC, Pant PK, Ballinger DG. Association of systemic lupus erythematosus with C8orf13–BLK and ITGAM–ITGAX. New England Journal of Medicine. 2008 Feb 28;358(9):900-9.

CLINICAL FEATURES: General Clinical

- Fatigue
- Fevers
- Malaise

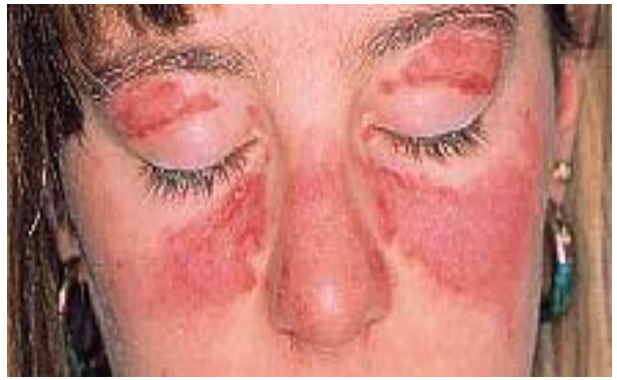
- Weight loss
- Anorexia
- Alopecia

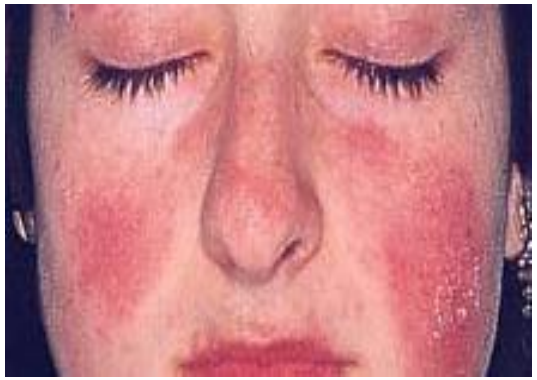
- Raynaud’s
- Lymphadenopathy

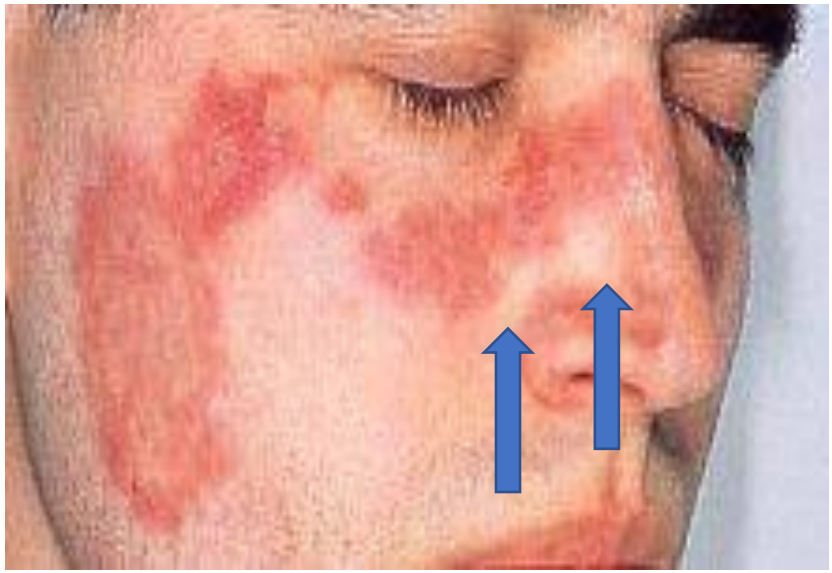


Dermatologic domain

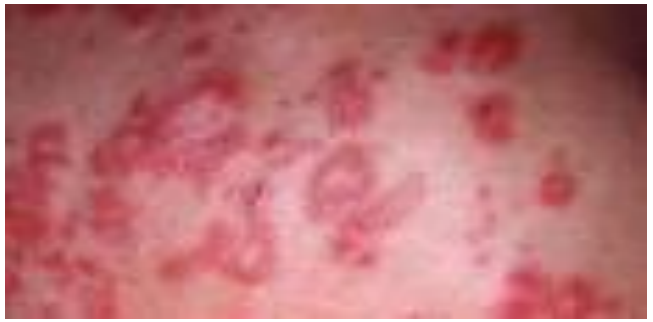
- Malar Rash
  - Fixed erythema; malar eminences
  - Spares the nasolabial folds

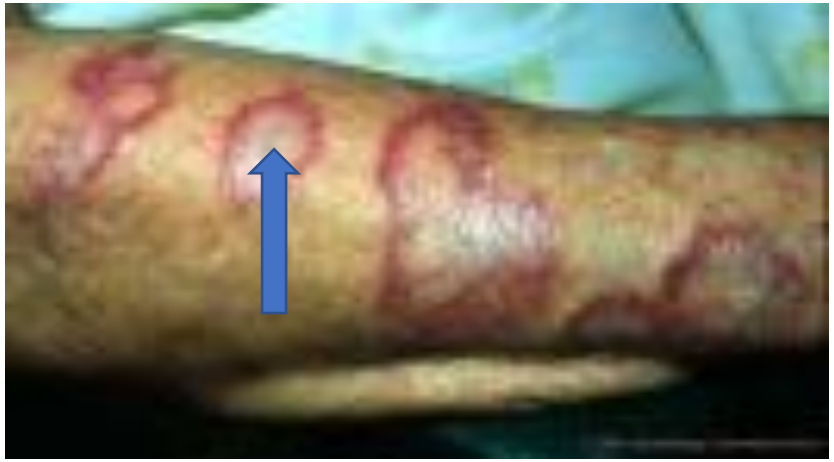






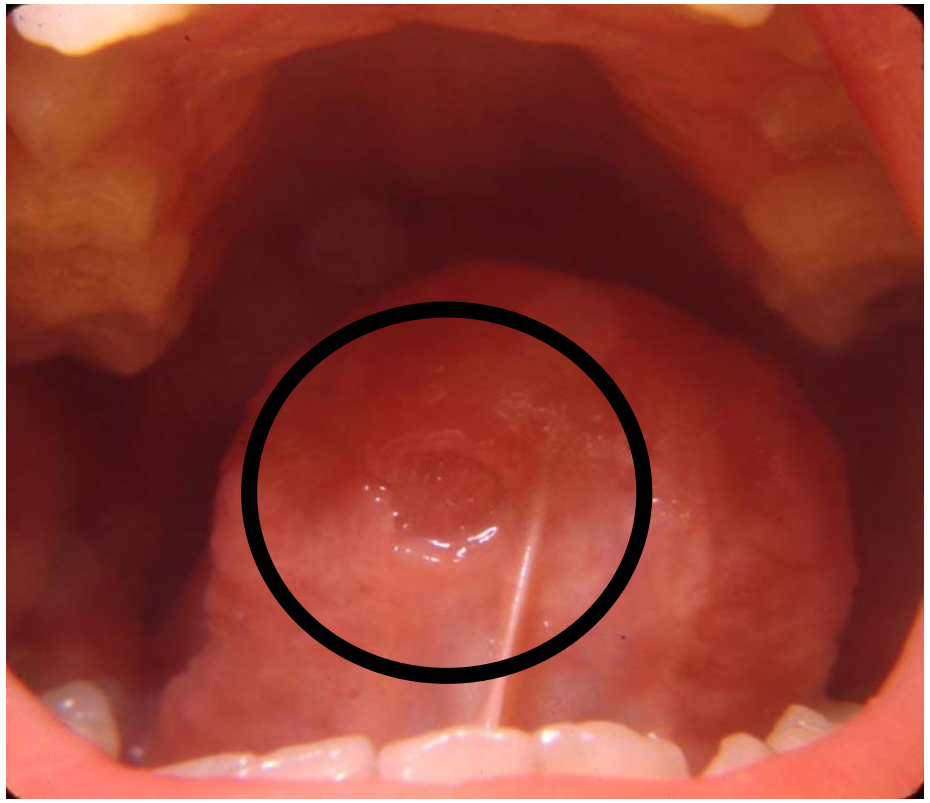
- Discoid Lupus Erythematosus (DLE)
  - Erythematous patches with central clearing
    - keratotic scaling
    - follicular plugging

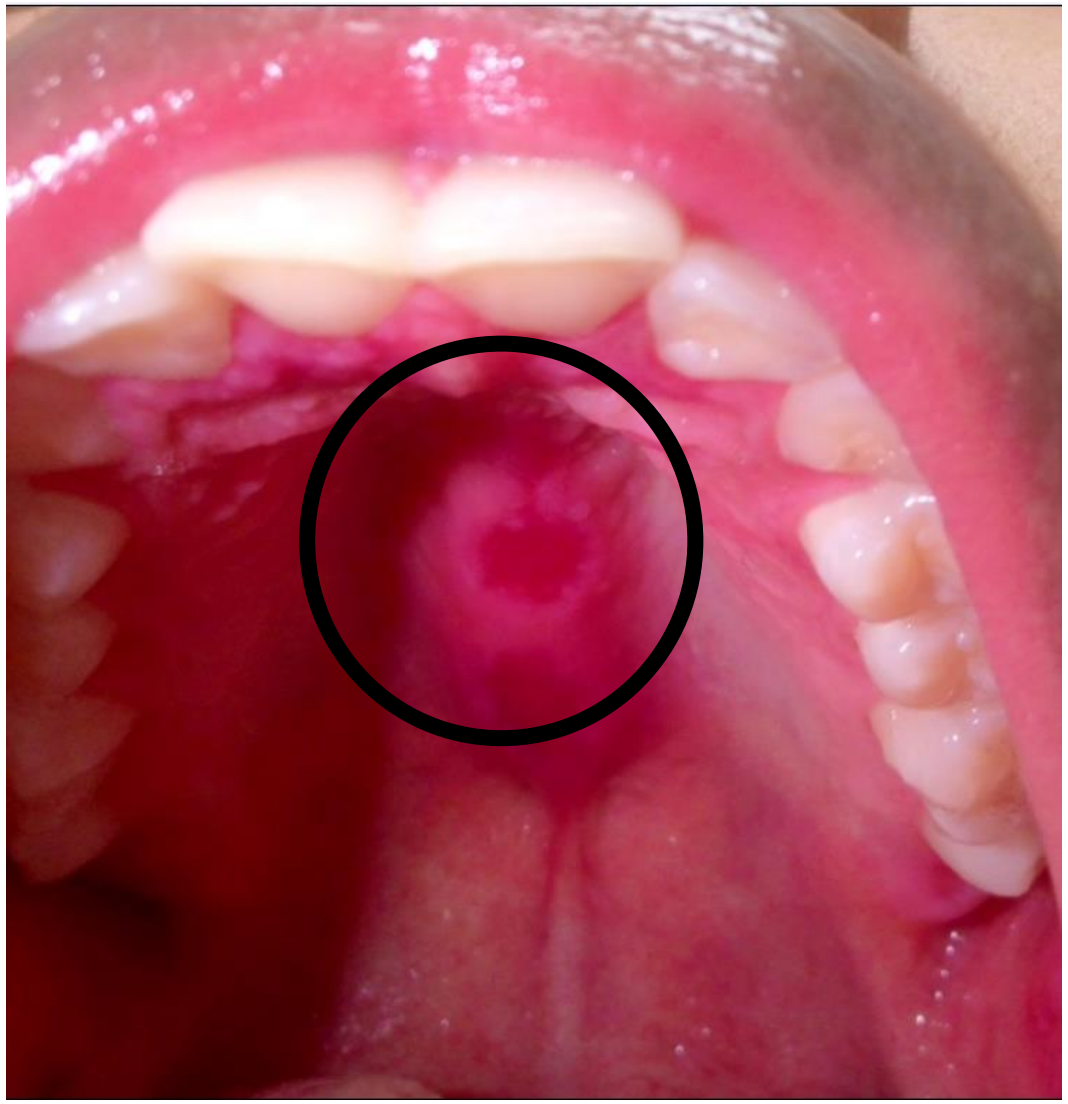




ORAL ULCERS

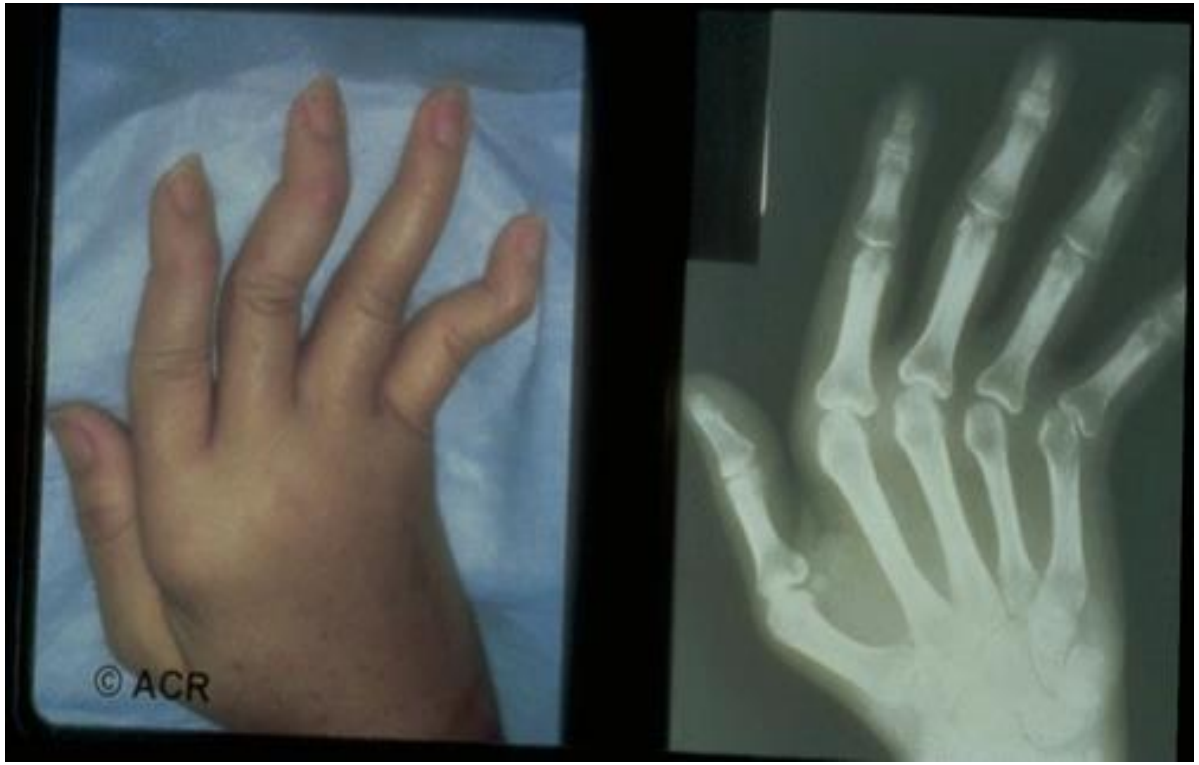
- Oral/nasopharyngeal ulceration
- Usually painless





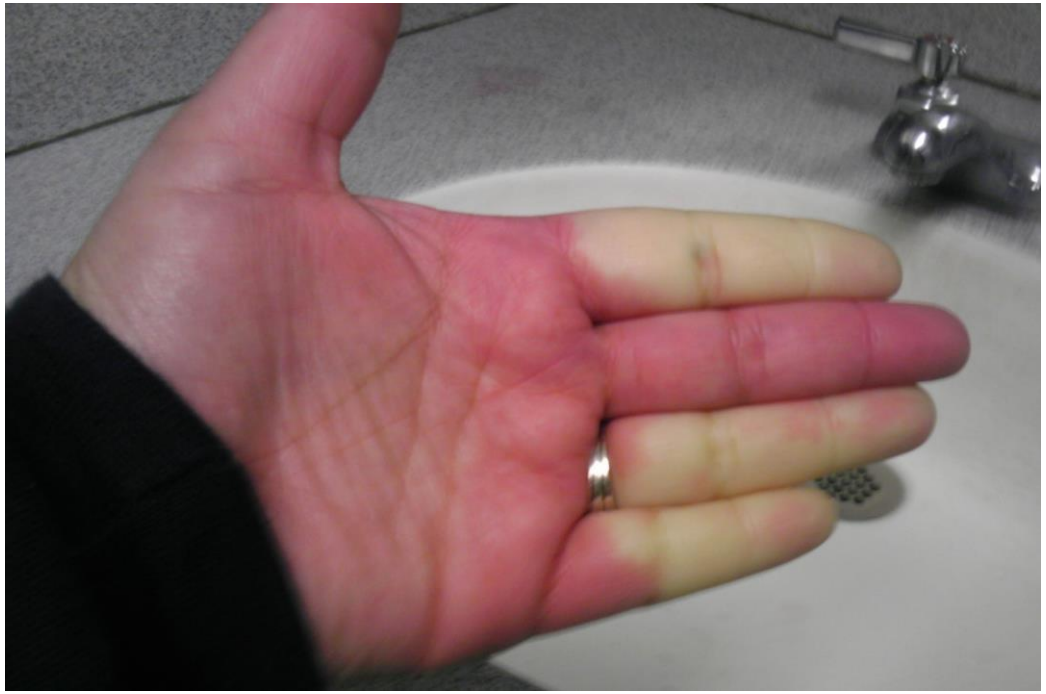
CLINICAL FEATURES: Musculoskeletal

- transient, small joints, symmetrical
- “Jaccoud’s” arthritis
- Most common presenting feature of SLE (90%)

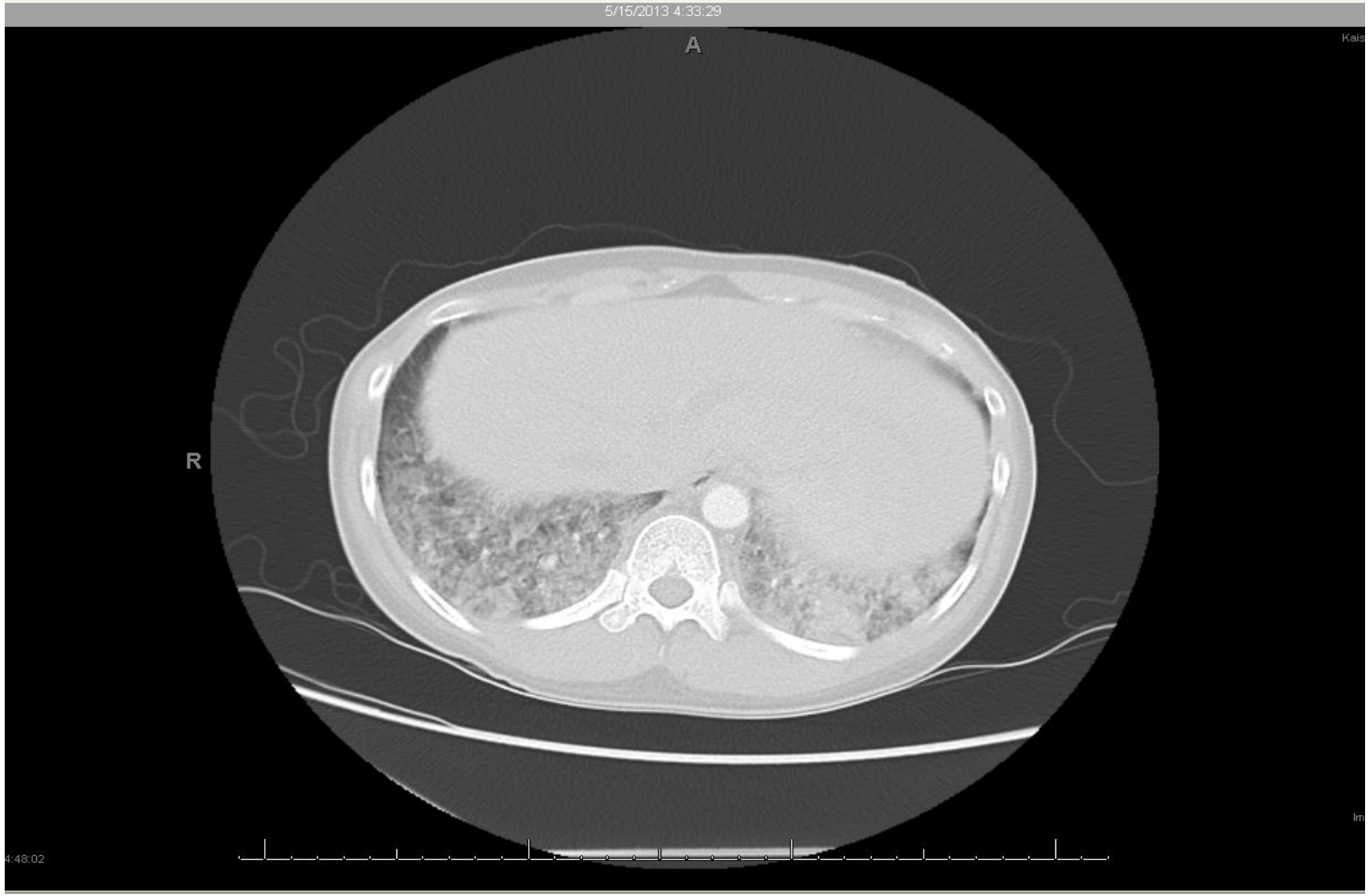


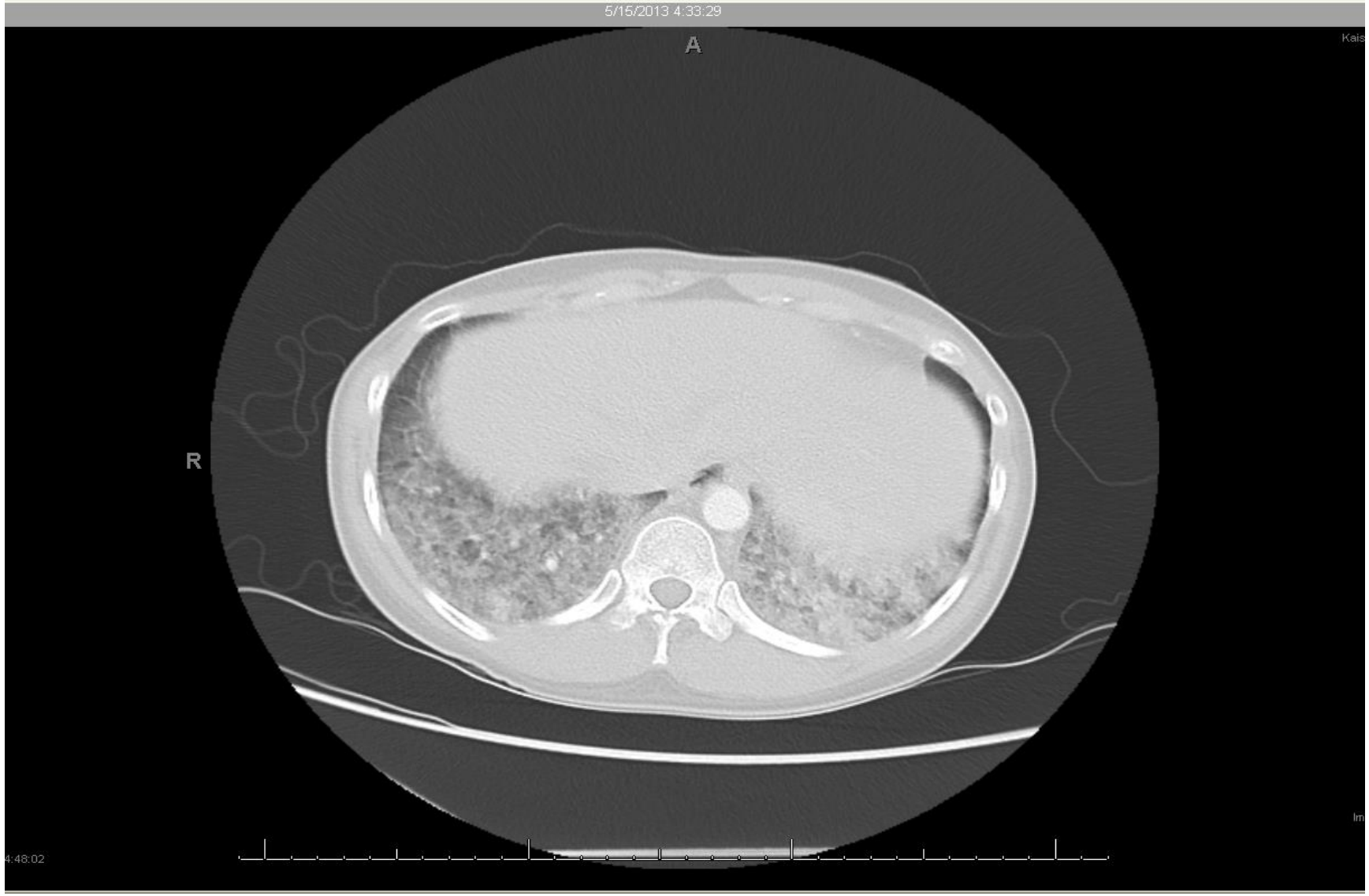
Case 2

23 Cambodian female with several weeks of worsening white, painful fingers that can turn blue and red. She tried natural options including CBD, plant-based diet and mindfulness as well as echinacea for “immune health”



She now presents to ED with dyspnea and hemoptysis. She is intubated. CT chest reveals….


5/15/2013 4:33:29
A
R
4:48:02


5/15/2013 4:33:29
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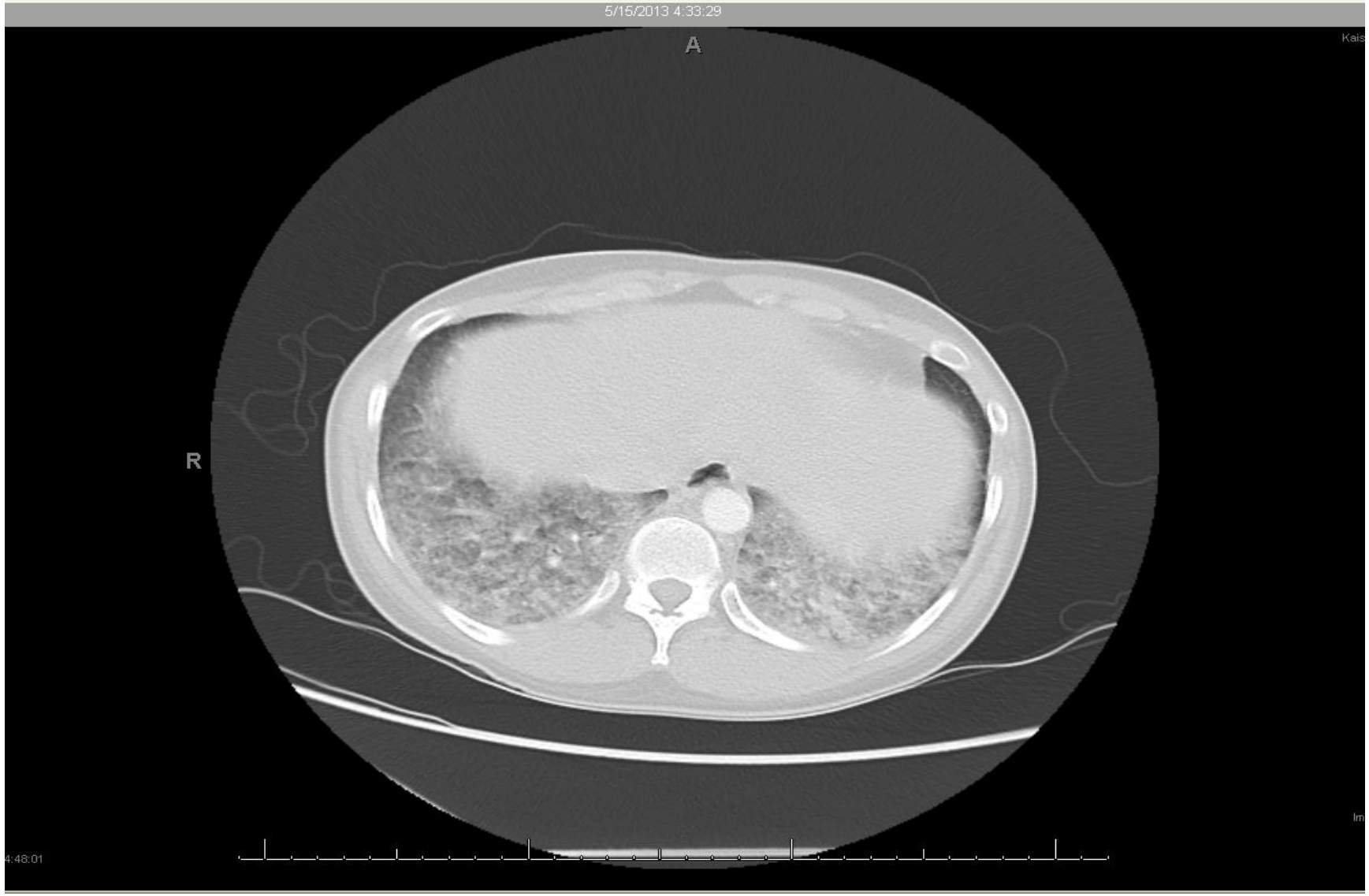
5/15/2013 4:33:29
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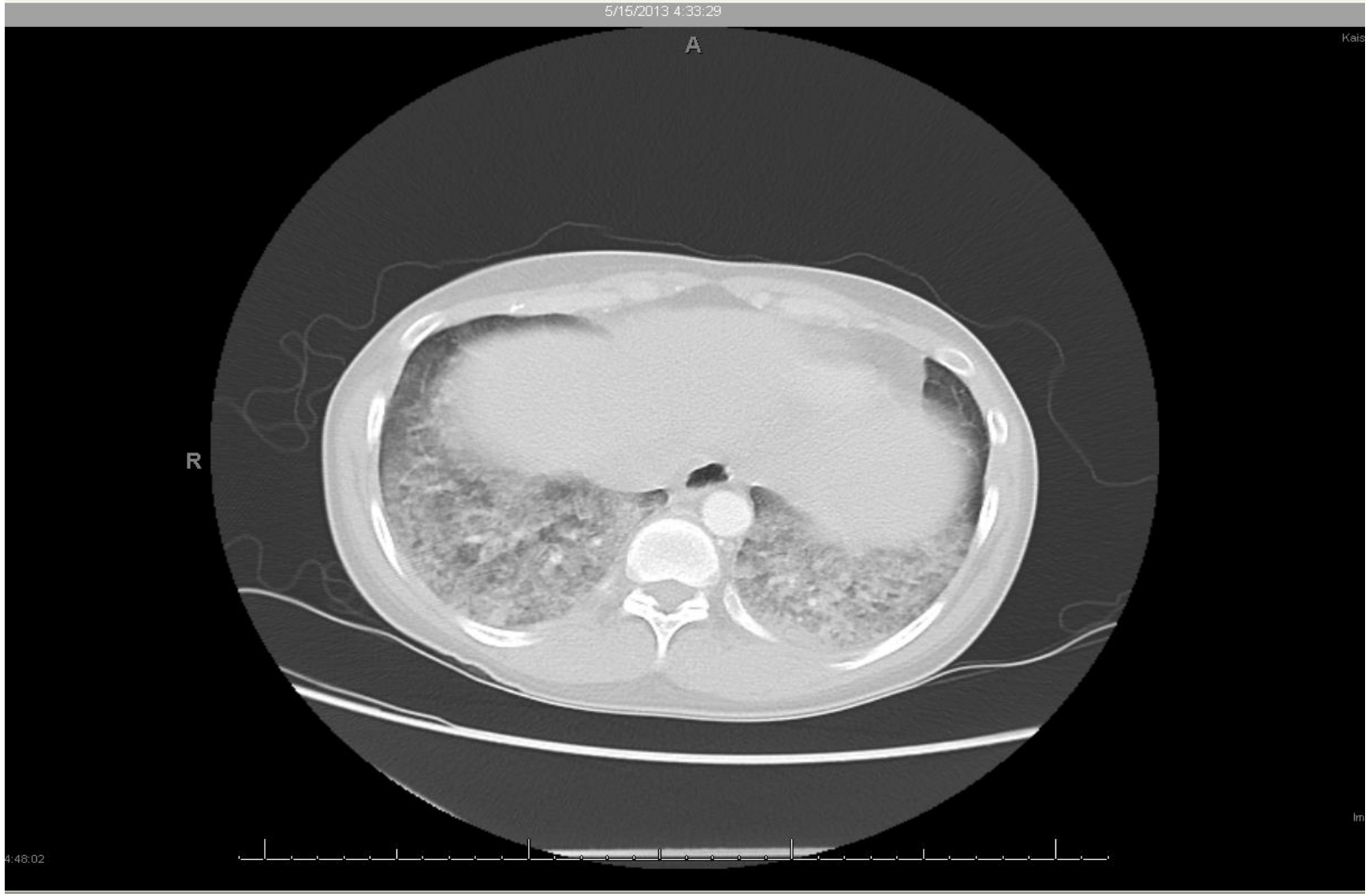

5/15/2013 4:33:29
A
R
4:48:02

CLINICAL FEATURES: SEROSITIS

- Pleural
  - Pulmonary hemorrhage (EMERGENCY)
- Peritoneal
  - Mesenteric vasculitis
- Cardiac
  - Pericardial effusion

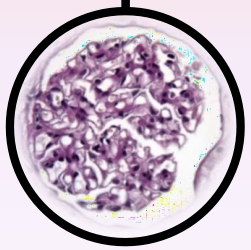
(Steroid and mycophenolate worked for my patient!)

CLINICAL FEATURES: Renal (Lupus Nephritis)

- Hallmark: proteinuria (>0.5 gms daily) and casts
  - “Foamy” urine
  - Nephrotic syndrome
    - Hypoalbuminemia
    - Hyperlipidemia
    - Thrombophilia

ISN/RPS Lupus Nephritis Classification System and Prevalence (In Those Biopsied)

Class I

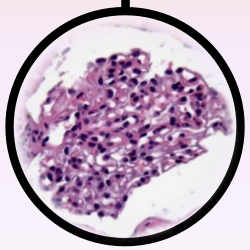


Minimal mesangial LN[1,2]

- Normal glomeruli[1]
- Mesangial immune deposits[1]

Prevalence:
0.4%[3,*]

Class II

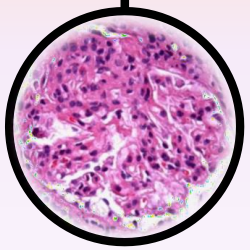


Mesangial proliferative LN[1,2]

- Mesangial hypercellularity and/or matrix expansion[1]
- Mesangial immune deposits[1]

Prevalence:
11.1%[3,*]

Class III

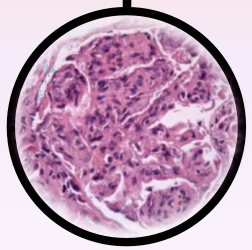


Focal **proliferative** LN[1,2]

- <50% glomeruli involved, endocapillary hypercellularity[1,4]
- Active, chronic, and/or active/chronic lesions[5]

Prevalence:
25.1%[3,*]

Class IV

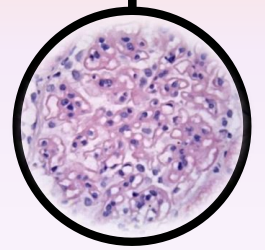


Diffuse **proliferative** LN[1,2]

- IV-S – diffuse segmental LN; IV-G – diffuse global LN[1,2]
- ≥50% glomeruli involved, subendothelial deposits[1]; endocapillary hypercellularity[4]
- Active, chronic, and/or active/chronic lesions[5]

Prevalence:
53.1%[3,*]

Class V



Membranous LN[1,2] with global or segmental, continuous, granular, subepithelial immune deposits

- Subepithelial deposits[1]
- Active or chronic glomerular lesions (Class III + V/IV + V)[1]

Prevalence:
10.3%[3,*,†]

---

1. Kiremitci S, Ensari A. *ScientificWorldJournal.* 2014;2014:580620. doi: 10.1155/2014/580620. **2**. Hahn BH, et al. *Arthritis Care Res (Hoboken).* 2012;64(6):797-808.
3. Faezi S, et al. *Rheum Res.* 2017;2(2):51-59. **4**. Bajema IM, et al. *Kidney Int*. 2018;93(4):789-796. **5**. Markowitz GS, D'Agati VD. *Kidney Int.* 2007;71(6):491-495.

Immunological findings

- **ANA** - 95-100%-sensitive but highly nonspecific for SLE
- **Anti-dsDNA**-specific(60%)-specific for SLE
- 4 RNA associated antibodies
  - **Anti-Sm (Smith)**
  - Anti Ro/SSA-antibody
  - Anti La/SSB-antibody
  - Anti-RNP
- **Antiphospholipid antibodies**
  - Lupus anticoagulant-antibodies to coagulation factors. Prolonged aPTT
  - Anti-cardiolipin
  - Anti-beta 2 glycoprotein
- **Depressed serum complement (c3, c4)**
- Anti histone antibodies
- **Coombs**

2012 SLICC Classification Criteria

RheumTutor.com

SLICC† Classification Criteria for Systemic Lupus Erythematosus

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)
OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

Clinical Criteria

1. Acute Cutaneous Lupus*
2. Chronic Cutaneous Lupus*
3. Oral or nasal ulcers *
4. Non-scarring alopecia
5. Arthritis *
6. Serositis *
7. Renal *
8. Neurologic *
9. Hemolytic anemia
10. Leukopenia *
11. Thrombocytopenia (<100,000/mm^3)

Immunologic Criteria

1. ANA
2. Anti-DNA
3. Anti-Sm
4. Antiphospholipid Ab *
5. Low complement (C3, C4, CH50)
6. Direct Coombs' test (do not count in the presence of hemolytic anemia)

†SLICC: Systemic Lupus International Collaborating Clinics
* See notes for criteria details

Petri M, et al. Arthritis and Rheumatism. Aug 2012

2019 European League Against Rheumatism/ ACR Classification Criteria for Lupus

Arthritis & Rheumatology, First published: 06 August 2019, DOI: (10.1002/art.40930)

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	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
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		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

CLASSIFICATION CRITERIA

- Useful for trials, but diagnosis is ultimately **clinical**
- Not all “Lupus” is SLE
  - Drug induced lupus (anti-histone antibody)
    - Anti-hypertensives (hydralazine)
    - Anti-infectives (Isoniazid, terbinafine)
    - Procainamide
    - Anti-epiletics
  - Discoid Lupus
  - Subacute Cutaneous Lupus Erythematosus (SCLE)
  - Lupus pernio (recall sarcoid)
- Non-rheumatic:
  - HIV, HBV, HCV, endocarditis, viral infections
  - hematologic malignancies, lymphoma
  - rosacea, OA and TPO antibodies

SLE – Treatment I

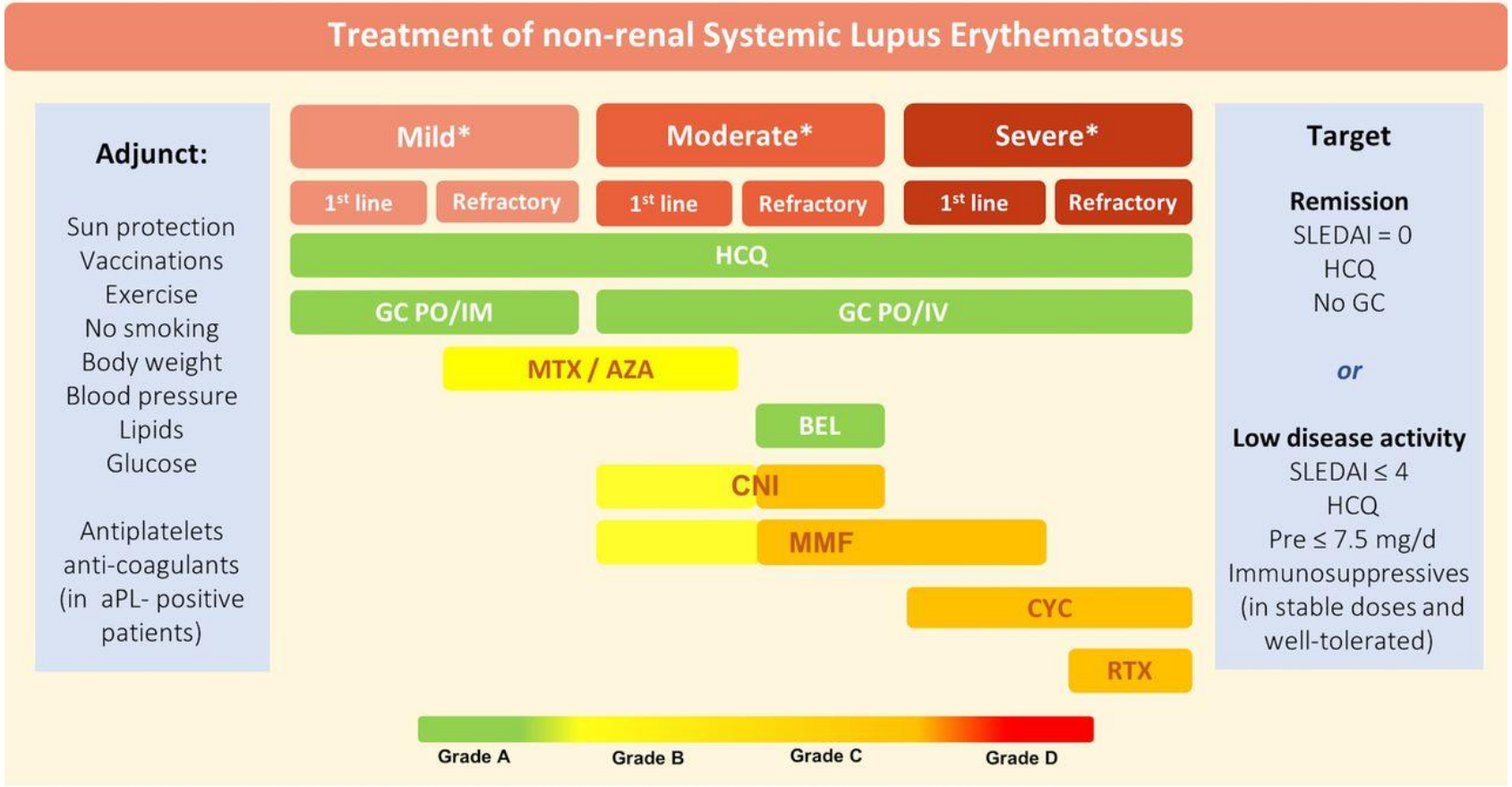
- **Mild severity** (mild skin or joint involvement)
  - NSAID
  - low dose glucocorticoids
  - hydroxychloroquine

- **Intermediate severity** (serositis, cytopenia, marked skin or joint involvement):
  - glucocorticoids (1 mg/kg/day)
  - azathioprine
  - methotrexate, leflunomide
  - mycophenolate mofetil

SLE – Treatment II

- **Severe life-threatening organ involvements** (pulmonary hemorrhage, pericarditis, nephritis, systemic vasculitis, hematologic, neuropsychiatric manifestations)
  - glucocorticoids (methylprednisolone up to 1000 mg/day x 3 days)
  - cyclophosphamide
  - plasmapheresis
  - IV immunoglobulin
  - mycophenolate mofetil
  - rituximab
  - belimumab, 2011 (FDA→ lupus nephritis: dec 17, 2020)
  - voclosporin (FDA→ lupus nephritis: jan 22, 2021)
  - anifrolumab (FDA → lupus aug 2, 2021)

Treatment of non-renal SLE—recommended drugs with respective grading of recommendation. aPL, antiphospholipid antibodies; AZA, azathioprine; BEL, belimumab; BILAG: British Isles Lupus Assessment Group disease activity index; CNIs, calcineurin inhibitors; CYC, cyclophosphamide; GC, glucocorticoids; HCQ, hydroxychloroquine; IM, intramuscular; MMF, mycophenolate mofetil; MTX, methotrexate; Pre, prednisone; PO, per os; RTX, rituximab; PLTs: Platelets; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.



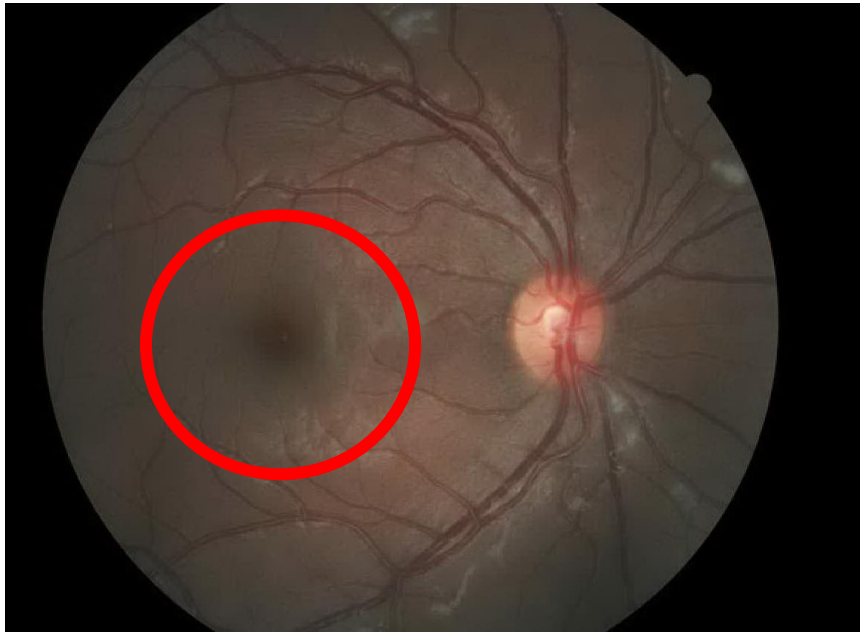
Mild: constitutional symptoms/ mild arthritis/ rash ≤9% BSA/PLTs 50-100 x 10^3/mm^3; SLEDAI≤6; BILAG C or ≤1 BILAG B manifestation
Moderate: RA-like arthritis/ rash 9-18% BSA/cutaneous vasculitis ≤18% BSA; PLTs 20-50x103/mm3/serositis; SLEDAI 7-12; ≥2 BILAG B manifestations
Severe: major organ threatening disease (nephritis, cerebritis, myelitis, pneumonitis, mesenteric vasculitis; thrombocytopenia with platelets <20x103/mm3; TTP-like disease or acute hemophagocytic syndrome; SLEDAI>12; ≥1 BILAG A manifestations

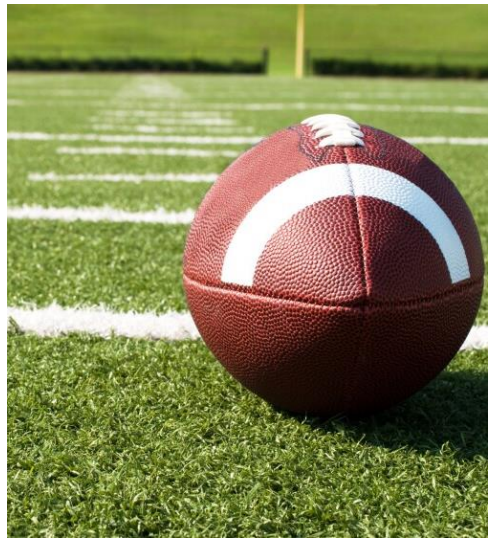
Antonis Fanouriakis et al. Ann Rheum Dis 2019;78:736-745

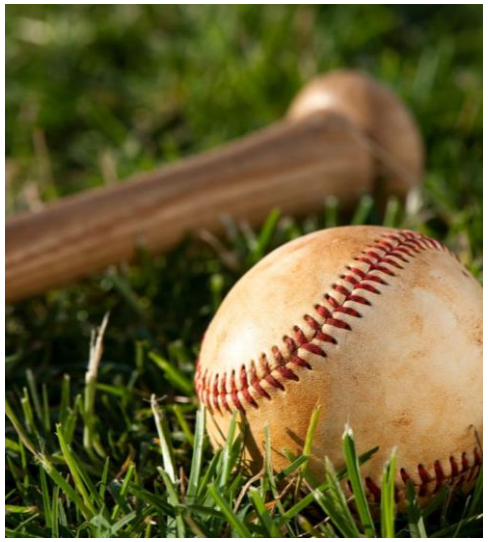
ARD

SLE – TREATMENT PRINCIPLES

- Only 6 FDA approved treatments, many off label
- Recognize side effects, toxicity, infection risk and other complications
- Cholesterol, aspirin, sunscreen, ACE inhibitors, tobacco cessation, calcium, 25 OH vit D
- Teratogenicity
- Adherence
- Rare hydroxychloroquine AE:







LOMALINDASTEVE@GMAIL.COM

Summary: Rheumatic diseases in the active patient:

Many early symptoms may be similar to those of young training athletes

- Mechanical LBP, sciatica and spondylolysis vs IBP
- Sprain, tendonitis, meniscal tear vs synovitis vs enthesitis
- Fatigue, exercise tolerance

Keys:

- Mechanism of injury (or lack thereof)
- Family pedigree
- Demographics (lupus, RA, sjogrens, SpA)
- ROS (constitutional, MSK, skin, pulm, renal)
- Extensive exam and lab work up
- Recognition of rheumatic syndromes