RHEUMATOID ARTHRITIS

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October 4, 2022

Objectives

- Define rheumatoid arthritis and identify clinical symptoms that would prompt evaluation and referral
- Describe diagnostic criteria for RA according to the American College of Rheumatology (ACR)
- Describe genetic and environmental risk factors for RA
- Describe Disease Modifying Anti-Rheumatic Agent (DMARD) therapies used
- Describe biologic and small-molecule therapies
- Identify extra-articular manifestations of RA

Most Common Chronic Inflammatory Arthritis

- Systemic: Articular and Extra-articular
- Chronic, relapsing/remitting course
- Tissue damage and destruction
  - *Pannus formation and synovial destruction*
- Labs and Imaging are helpful
- History and Exam are key

Who Is At Risk?

- Genetic: HLA DR4 and DR1
  - *60% of the risk, alleles responsible for citrullinated peptide antigens*
- Environment: Smoking
  - *Activates enzymes that promote citrullination in the lungs*
- Infection: bacteria, viruses (EBV, parvovirus B19), gut microbiome
  - *Dental disease: P gingivalis*
- Hormones: Females>Males (2-3:1)
- COVID?

Patient with ”joint pain”

- Location: Polyarticular, small joints > large joints
- Duration: 6 weeks or more
- Timing: AM stiffness > 1 hr
- Quality: Stiffness, change in behavior due to swelling or pain
- Severity: How difficult are things for patient to do
- Modifying factors: AM routine
  - *Is the morning more difficult for you than the evening?*
- Relieving factors: NSAIDs not typically helpful

2010 ACR Criteria

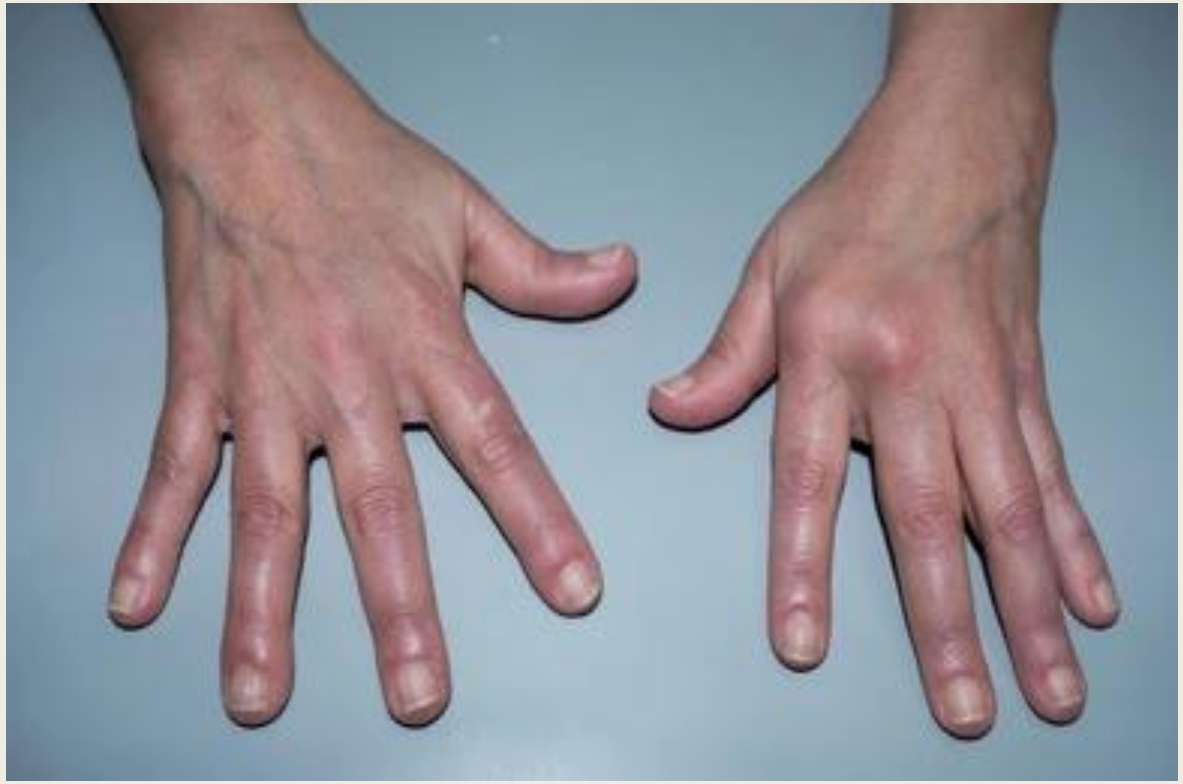
Joint Involvement	Score
1 Large joint (shoulders, elbows, hips, knees, ankles)	0
2-10 Large joints	1
1-3 Small joints (MCPs, PIPs, wrists, 2-5 MTPs)	2
4-10 small joints	3
More than 10 small joints	5

Serology	Points
Negative RF or CCP antibodies	0
Low-positive RF or anti-CCP antibodies (<3X ULN)	2
High-titer RF or anti-CCP antibodies (>3X ULN)	3

Acute Phase Reactants	
Normal CRP or ESR	0
Abnormal CRP or ESR	1

Duration	
Less than 6 weeks	0
More than 6 weeks	1

20 yo F with 4 weeks of hand pain



She tells you:
I have to wake up at 5 am for my 8 am class

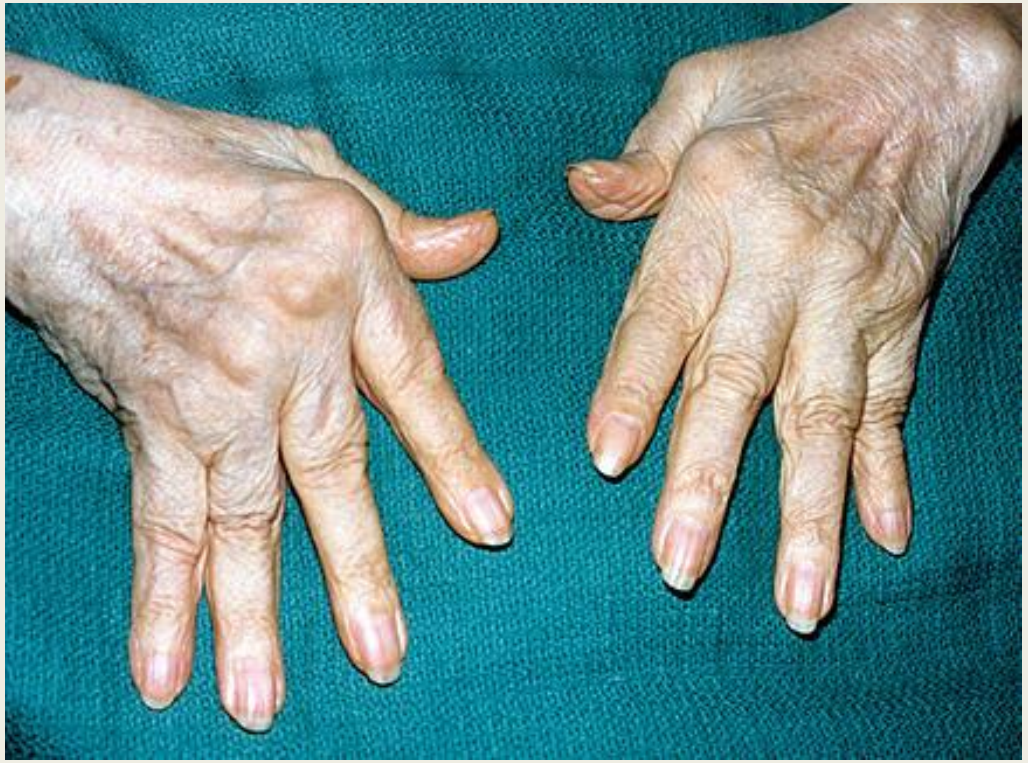
I struggle to type, I've been missing classes in the afternoon due to pain

I had to stop doing yoga/Pilates because my wrists hurt

It's hard for me to wash my hair or pick up clothes off the floor

My maternal grandmother had RA

70 yo F with 2 years of gradual deformities



She tells you:

My kids and husband tell me I need to ask you about my hands

I don’t have pain but my fingers don’t work like they used to

I don’t wear clothes with buttons, shoelaces, or tie my hair up anymore

I’m not taking any medication for my joints, I thought this was just part of getting older

What will you order?

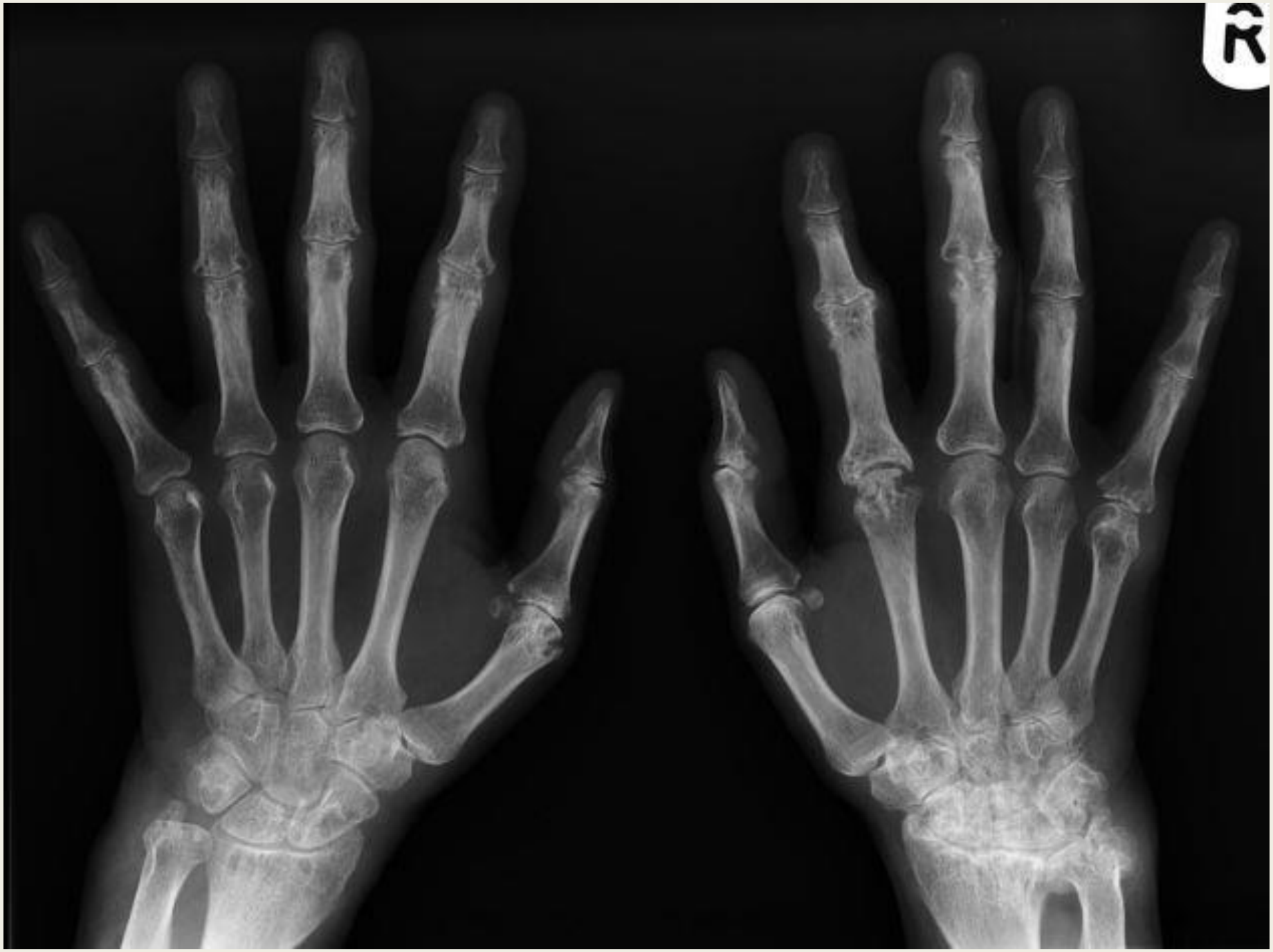
A. RF and CCP
B. TSH
C. UA
D. DsDNA

Workup

- Rheumatoid Factor
  - *Autoantibody directed against Fc fragment of IgG*
  - *False positives or not clinically significant for RA*
- Anti-cyclic citrullinated peptide (CCP)
  - *Directed against citrulline residues, increased specificity (90-95%)*
- ESR
- CRP
- Anemia of chronic disease
- Thrombocytosis

Imaging

- Bilateral hands
  - *Imaging of ALL the fingers is extremely helpful*
- Baseline and monitor disease progression
- Determine RA vs OA vs gout vs psoriatic arthritis
- Key findings:
  - *Periarticular osteopenia*
  - *Central or marginal erosions*
  - *Joint-space narrowing of MCP and PIP joints*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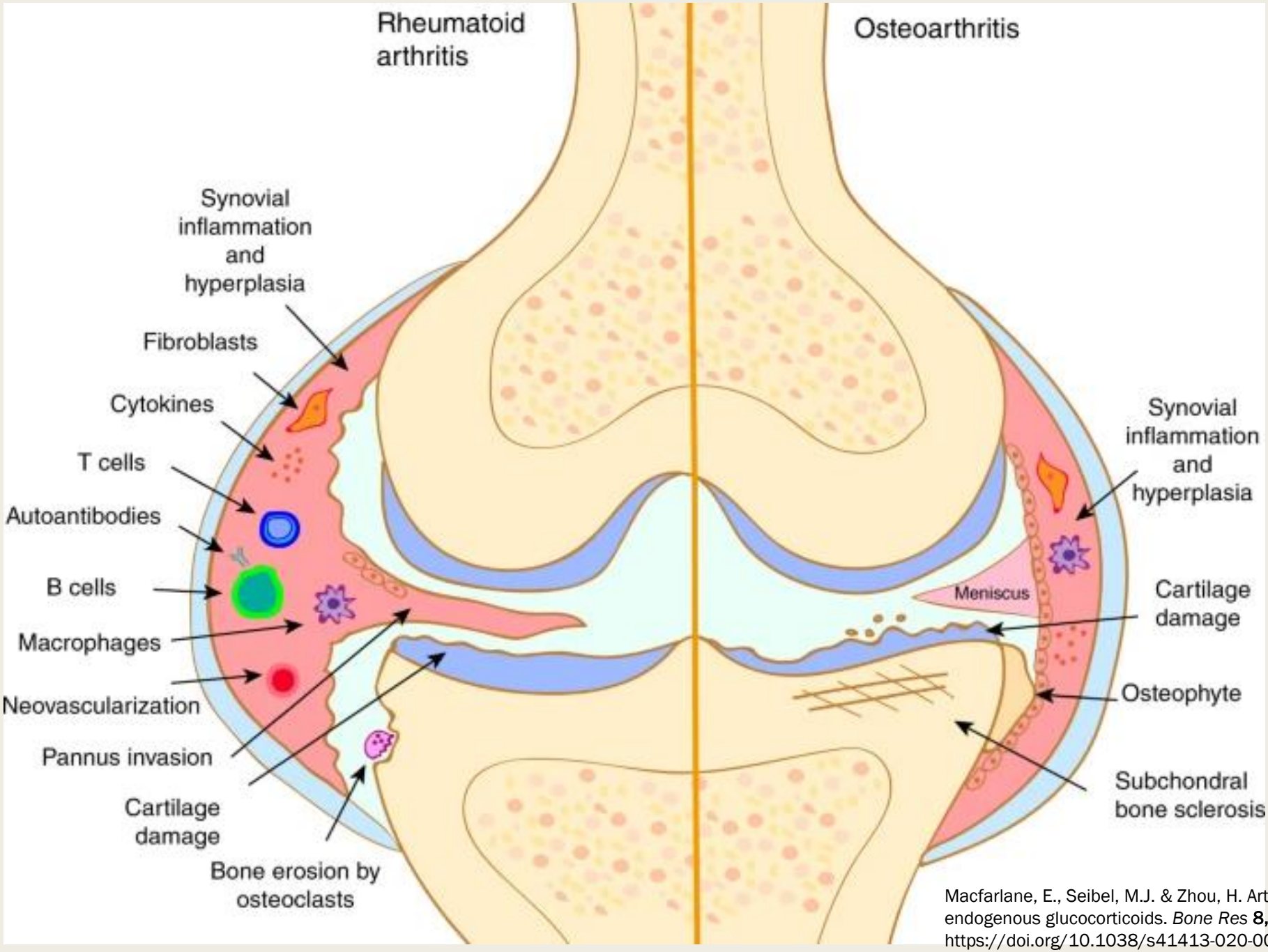
Pathophysiology

- HLA-DR B1, Genetic predisposition
- Environmental trigger – typically a virus
- Smoking, triggers citrullination in the lungs
- Activation of CD4 T cells activates macrophages and synovial cells
- Production of IL-4 and TNF
- B lymphocytes activate immune complexes in joints and other tissues
- RANKL activates osteoclasts



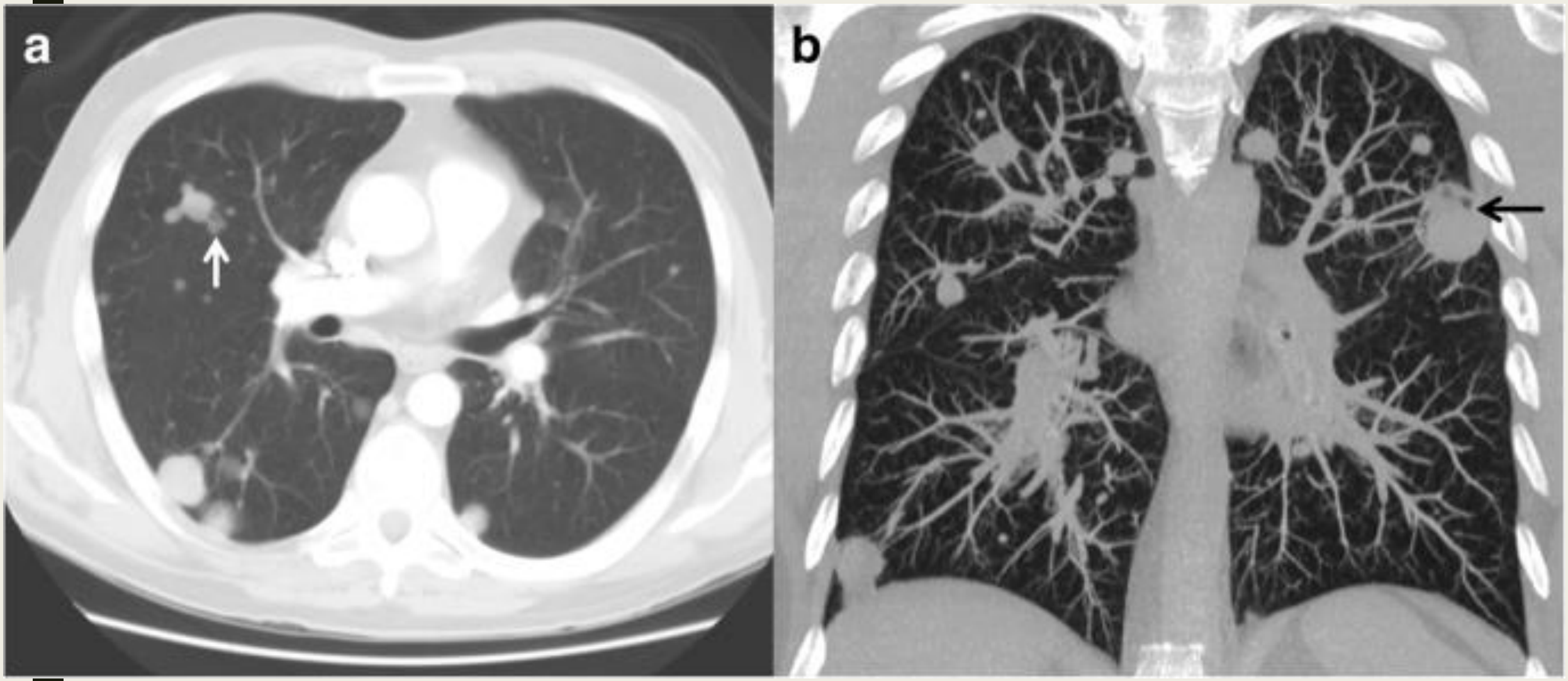
Macfarlane, E., Seibel, M.J. & Zhou, H. Arthritis and the role of endogenous glucocorticoids. *Bone Res* **8,** 33 (2020). https://doi.org/10.1038/s41413-020-00112-2

Extra-Articular Manifestations

- Cutaneous: rheumatoid nodules
  - *~30% of patients, olecranon area, induced by methotrexate*
- Kerato-conjunctivitis sicca, episcleritis, scleritis
  - *Most severe form: corneal melt*
- Atherosclerosis
  - *HLD, HTN*
  - *JAK inhibitor therapy*
- Felty syndrome: Neutropenia, splenomegaly
- Large granular lymphocyte leukemia

Lung Disease

- Most often presents after joint manifestations
- Increased incidence of interstitial lung disease as first presentation
- Nodules
- Pleural effusions
- Cricoarytenoid arthritis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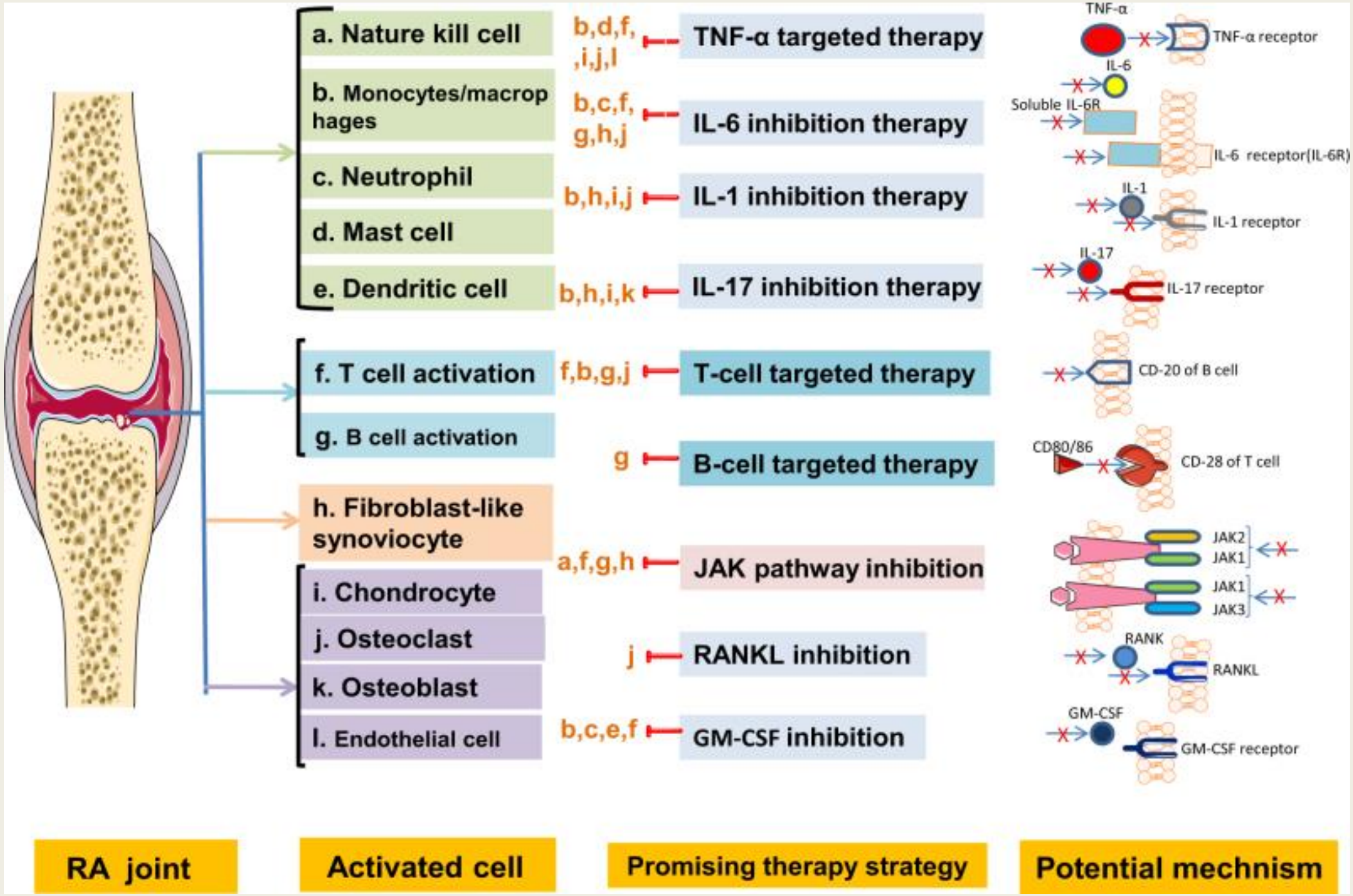
b

Treatment

- Early diagnosis and aggressive early therapy
  - *Low dose prednisone if waiting for referral (prednisone 5-10 mg daily)*
- Disease-Modifying Antirheumatic Drugs (DMARDs)
- Non biologic:
  - *Methotrexate, leflunomide, sulfasalazine, hydroxychloroquine*
  - *JAK inhibitors (targeted synthetic): baracitinib, tofacitinib, upadacitinib*
- Biologic: Tumor Necrosis Factor (TNF- α) Inhibitors
  - *Etanercept, adalimumab, infliximab*
  - *Mimic human proteins*


a. Nature kill cell
b. Monocytes/macrophages
c. Neutrophil
d. Mast cell
e. Dendritic cell
f. T cell activation
g. B cell activation
h. Fibroblast-like synoviocyte
i. Chondrocyte
j. Osteoclast
k. Osteoblast
l. Endothelial cell
b,d,f,,i,j,l
TNF-α targeted therapy
b,c,f,g,h,j
IL-6 inhibition therapy
b,h,i,j
IL-1 inhibition therapy
b,h,i,k
IL-17 inhibition therapy
f,b,g,j
T-cell targeted therapy
g
B-cell targeted therapy
a,f,g,h
JAK pathway inhibition
j
RANKL inhibition
b,c,e,f
GM-CSF inhibition
TNF-α
TNF-α receptor
IL-6
Soluble IL-6R
IL-6 receptor(IL-6R)
IL-1
IL-1 receptor
IL-17
IL-17 receptor
CD-20 of B cell
CD80/86
CD-28 of T cell
JAK2
JAK1
JAK1
JAK3
RANK
RANKL
GM-CSF
GM-CSF receptor
RA joint
Activated cell
Promising therapy strategy
Potential mechnism

- 67 yo F is evaluated for 3-year history of severe RA. She had an inadequate response to methotrexate and low-dose prednisone. She responded well to infliximab, but eventually lost efficacy. She was then placed on tocilizumab with methotrexate.
- She notes several months of prominent fatigue. She also has DM2, HTN, HLD.
- She is on methotrexate, folic acid, tocilizumab, basal insulin, lisinopril, metoprolol, atorvastatin, ibuprofen, omeprazole

Exam: Normal VS, no swollen or tender joints, RRR and lungs are clear.

Labs show WBC 5.6, Hgb 9.3, MCV 111, Platelet 330

Which of the following is the most likely cause of her anemia?

(A) Inflammation

(B) Iron deficiency

(C) Methotrexate

(D) Tocilizumab

- Methotrexate can cause megaloblastic anemia from folic acid deficiency
- Expect some increase in MCV but if >105 then patient may need more folic acid
- Can also cause increased LFTs, more toxic with CKD
- Requires Q3 month lab monitoring
- Treat like a controlled substance

A 28 yo F presents with positive home pregnancy test. She has a 2-year history of seropositive RA. Her only medication is hydroxychloroquine. She was stable on methotrexate but this was stopped 4 months ago in anticipation of conception.

Exam shows normal vital signs and swelling of the 2nd and 3rd MCP joints bilaterally.

Which of the following is the most appropriate treatment at this time?

(A) Add adalimumab

(B) Add leflunomide

(C) Discontinue hydroxychloroquine

(D) No change in therapy

- Adalimumab is safe while pregnant
- Uncontrolled disease can lead to pregnancy complications
- Typically co-management with MFM if biologics are involved
- Teratogenic meds for boards (leflunomide, methotrexate, JAK inhibitors)

References

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