

# Year End Presentation

John Stanfill

# Rheumatoid Arthritis

# Factoids

- From *rheuma* - stream
- First confirmed cases in the early 1800s
- Alcohol may protect against RA
- Famous people with RA
  - Renoir
  - Sandy Koufax
  - Christiaan Barnard
  - Dorothy Hodgkin
  - Lucille Ball, maybe
  - Raoul Dufy

# Rheumatoid Arthritis

- Epidemiology
- Pathophysiology
- Why early diagnosis is important
- How we can help with early diagnosis
- Long term sequelae
- Less commonly involved joints
- Non MSK findings
- Treatment options
- Treatment complications

# Rheumatoid Arthritis - Epidemiology

- 0.5-1% of the population
- 2-3x more common in women
- Any age, but more common 40-60 yrs
- Consistent racially and geographically
- Different forms
  - Common adult
  - Juvenile
  - Systemic
  - Cystic type
- Unknown etiology
  - Autoimmune disease in genetically susceptible people

# Pathophysiology

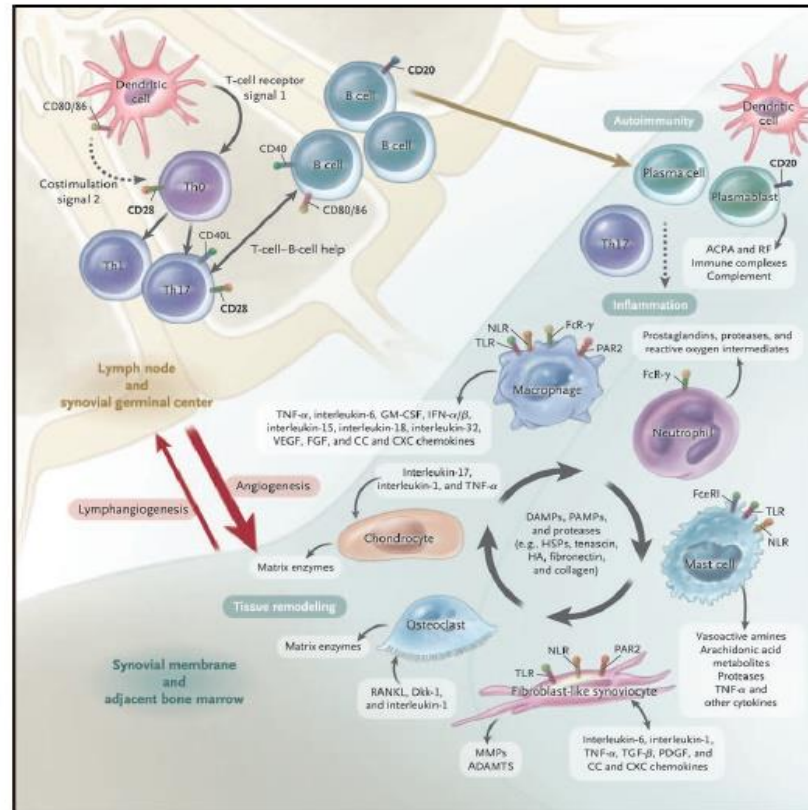
- Cigarette smoking increases risk
- Oral contraceptives decrease risk
- Twin studies show 15-30% concordance between monozygotic twins and 5% between dizygotic twins
- Increased incidence in HLA-DRB1
- Association with several infectious agents

# Pathophysiology

- Citrullination of proteins is a normal physiologic process in dying cells, and these proteins normally do not come into contact with the immune system
- When these proteins and PAD enzymes leak out of the dying cells, the PAD enzymes create citrullinated extracellular proteins=citrullinated antigens
- Leads to immune complex development and production of inflammatory cytokines

# Pathophysiology

■ **Figure. Adaptive and Innate Immune Processes Within the Joint in Rheumatoid Arthritis<sup>1</sup>**



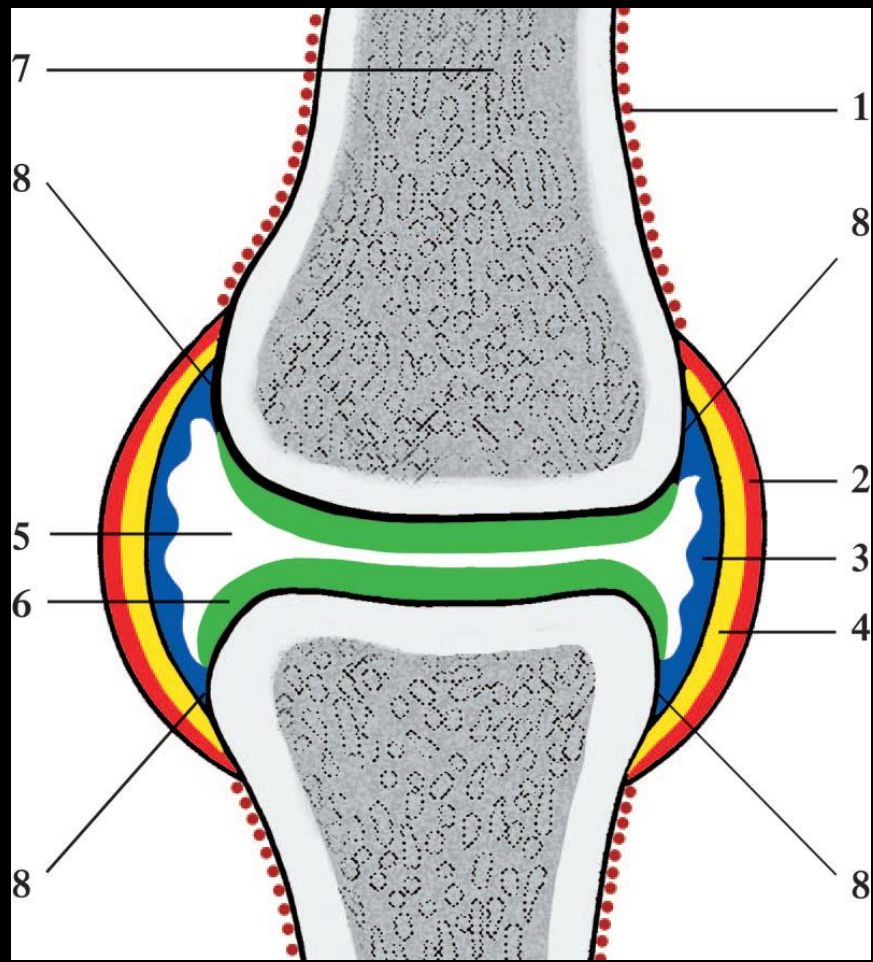
The costimulation-dependent interactions among dendritic cells, T cells, and B cells are shown as occurring primarily in the lymph node; these events generate an autoimmune response to citrulline-containing self-proteins. In the synovial membrane and adjacent bone marrow, adaptive and innate immune pathways integrate to promote tissue remodeling and damage. Positive feedback loops mediated by the interactions shown among leukocytes, synovial fibroblasts, chondrocytes, and osteoclasts, together with the molecular products of damage, drive the chronic phase in the pathogenesis of rheumatoid arthritis. ACPA indicates anti-citrullinated protein antibody; ADAMTS, a disintegrin and metalloprotease with thrombospondin-1-like domains; DAMP, damage-associated molecular pattern; Dkk-1, dickkopf-1; FcR, Fc receptor; FcR1, high-affinity IgG receptor; FGF, fibroblast growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HA, hyaluronan; HSP, heat-shock protein; IFN- $\alpha/\beta$ , interferon- $\alpha/\beta$ ; MMP, matrix metalloproteinase; NLR, nucleotide-binding oligomerization domain-like receptor; PAMP, pathogen-associated molecular pattern; PAR2, protease-activated receptor 2; PDGF, platelet-derived growth factor; RANKL, receptor activator of nuclear factor  $\kappa$ B ligand; RF, rheumatoid factor; TGF- $\beta$ , transforming growth factor  $\beta$ ; Th0, type 0 helper T cell; Th1, type 1 helper T cell; Th17, type 17 helper T cell; TLR, toll-like receptor; TNF- $\alpha$ , tumor necrosis factor  $\alpha$ ; VEGF, vascular endothelial growth factor.

From McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med*. 2011;365(23):2205-2219. Copyright © 2012 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.



# Pathophysiology

- Ultimately, inflammation and exuberant synovial proliferation lead to destruction of various tissues including bone, tendons, ligaments, and blood vessels







**“Your x-ray showed a broken rib,  
but we fixed it with Photoshop.”**

# Why are we so concerned with RA?

- Erosions, cartilage loss and periarticular osteopenia occur within 2 yrs of onset without treatment
- Osseous erosions are permanent
- Osteoporosis
- Carpal tunnel syndrome
- Pericarditis
- Lung disease
- Malignancies

# Rheumatoid Arthritis

- Early Rheumatoid Arthritis is not technically defined but generally used to describe disease duration of less than 1 yr from first episode of clinically detectable joint inflammation
- Goal of treatment = remission which is defined as no apparent disease activity and absence of joint damage and disability progression

# Rheumatoid Arthritis

- This means a diagnosis must be made within a few months to initiate aggressive therapy for the best possible long term outcome
- There is no single clinical manifestation, laboratory test result or imaging finding that allows a diagnosis of RA with certainty



DOJA

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# Presentation

- Patients often present with symmetric peripheral polyarthrititis and early morning stiffness
- Hallmarks such as rheumatoid nodules and erosions on hand/wrist radiographs more typically appear late in the disease process.
- 30% may be RF negative

# Presentation

- Sudden onset with systemic features such as fatigue, fever, weight loss
- PMR
- Oligo- or mono arthritis
- Bilateral carpal tunnel syndrome

# Differential Diagnosis of RA

## Common conditions

- Acute viral polyarthrititis
  - Parvovirus B19
  - Rubella
  - Hepatitis B
- Seronegative spondyloarthropathies
  - Psoriatic
  - Reactive
  - IBD
  - Ankylosing spondylitis
- Connective tissue disorders
  - SLE
  - Sjogren
  - Mixed connective tissue disease
- Crystal diseases
  - Gout
  - CPPD
- Osteoarthritis
- Hypermobility syndrome and fibromyalgia

## Rare conditions

- Sarcoidosis
- Acute relapsing symmetric seronegative synovitis and peripheral edema(RS3PE)
- Rheumatic fever
- Vasculitis
- Infectious arthritis
- Polychondritis
- Sweet syndrome
- Whipple disease
- Paraneoplastic disease
- Fibroplastic rheumatism
- Hemochromatosis
- Arthritis of thyroid disease
- Multicentric castlemans disease or multicentric angiofollicular lymphnode hyperplasia
- Multicentric reticulohistiocytosis

# Organizations and Acronyms

- ACR – American College of Rheumatology
- EULAR – European League Against Rheumatism
- OMERACT - Outcomes Measures in Rheumatoid Arthritis Clinical Trials
- RAMRIS – Rheumatoid Arthritis MRI Score

- One of the major problems with diagnosing the disease in its early stages is the diagnostic criteria were developed from data obtained in patients with established RA

# 1987 ACR Classification Criteria

- 1. Morning stiffness
  - Lasts >1 hour
- 2. Arthritis in 3 or more areas
  - Simultaneous swelling or effusion of one of the 14 joints documented by a physician
- 3. Arthritis of hand joints
  - Swelling of wrist, MCP or PIP
- 4. Symmetric arthritis
  - Simultaneous involvement of the joints of the 2<sup>nd</sup> criterion on both sides of the body
- 5. Rheumatoid nodules
  - Subcutaneous nodules over extensor surfaces and in periarticular areas observed by a physician
- 6. Serum rheumatoid factor
  - Any method that results in a positive test in <5% healthy subjects
- 7. Radiographic changes

# 1987 ACR Classification Criteria

- 7. Radiographic changes
  - Changes typical of rheumatoid arthritis on PA radiographs of the hand and wrist
    - Must include erosions or unequivocal bone decalcification localized to or most marked adjacent to the involved joints
  - Osteoarthritic changes alone do not qualify

# 2010 ACR/EULAR Classification

- Intended to identify patients early in the disease process with a scoring system to predict who would go on to develop progressive or erosive disease

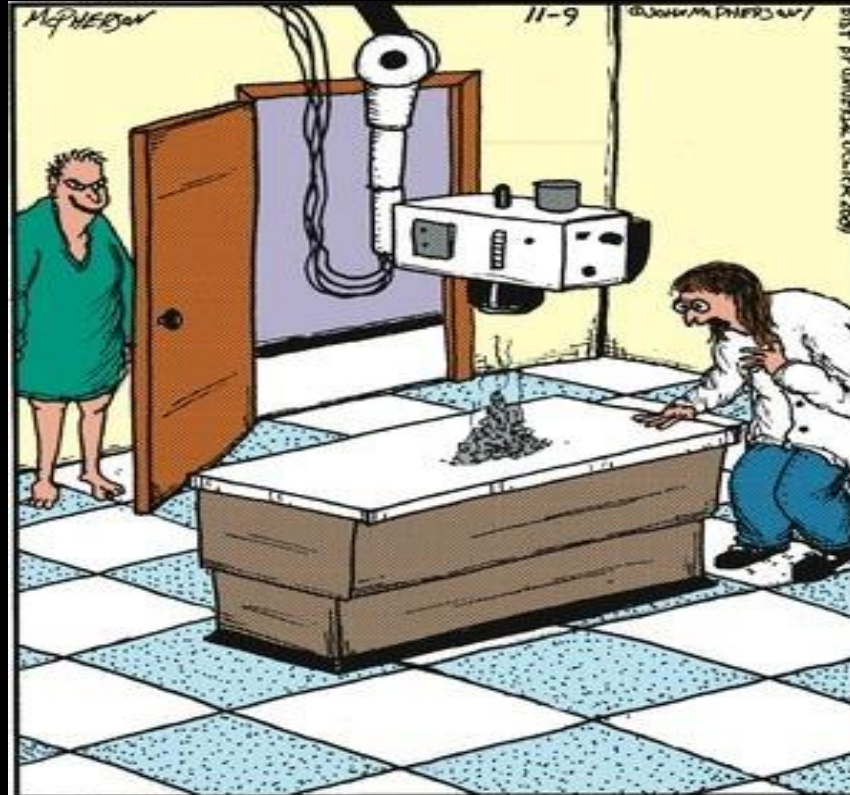


# 2010 ACR/EULAR Classification

- 4 domains
  - Joint involvement
  - Serology
  - Acute phase reactants
  - Duration of symptoms

# 2010 ACR/EULAR Classification

- 4 domains
  - Joint involvement
    - 1 large joint = 0
    - 2-10 large joints = 1
    - 1-3 small joints = 2
    - 4-10 small joints = 3
    - >10 joints including at least 1 small joint = 5
  - Serology
    - Negative RF and ACPA = 0
    - Low positive RF or ACPA = 2
    - High positive RF or ACPA = 3
  - Acute phase reactants
    - Normal CRP and ESRP = 0
    - Abnormal CRP or ESRP = 1
  - Duration of symptoms
    - <6 weeks = 0
    - >6 weeks = 1



Having dumped the bag of ashes on the table, Stew hid behind the door and waited for the X-ray technician's reaction.

# How Can We Help?

- MRI is increasingly being used in the assessment of rheumatoid arthritis due to its capacity to help identify the key pathologic features of this disease entity at presentation.
- Has greater sensitivity for the detection of synovitis and erosions than either clinical examination or conventional radiography
- Allows the detection of bone marrow edema, which is thought to be a precursor for the development of erosions in early rheumatoid arthritis as well as a marker of active inflammation.
- Can help differentiate rheumatoid arthritis from some clinical subsets of peripheral spondyloarthropathies

# MR Protocol

- Typically the more affected wrist is imaged with or without additional imaging of the MPC and PIP joints
- Field strength is not as important
- OMERACT – coronal and axial T1-weighted sequences before and after contrast as well as either T2-weighted fat saturation or STIR
- 3-4 mm slice thickness with a gap of 0.3-0.4 mm

What are the MR findings

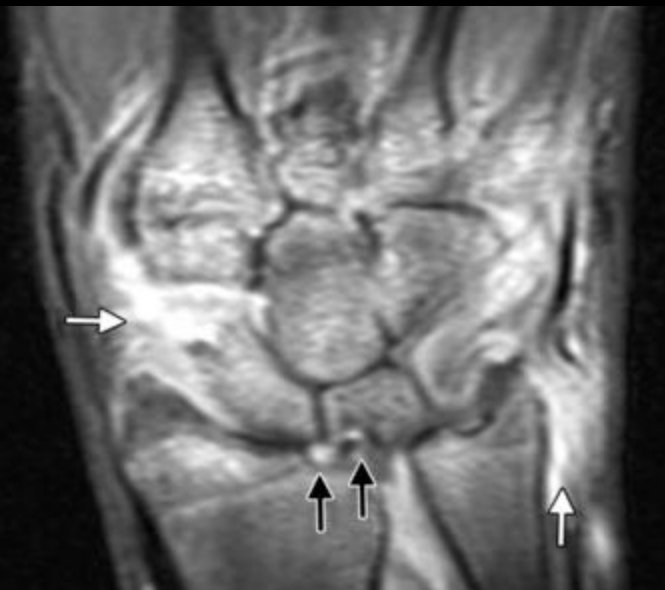
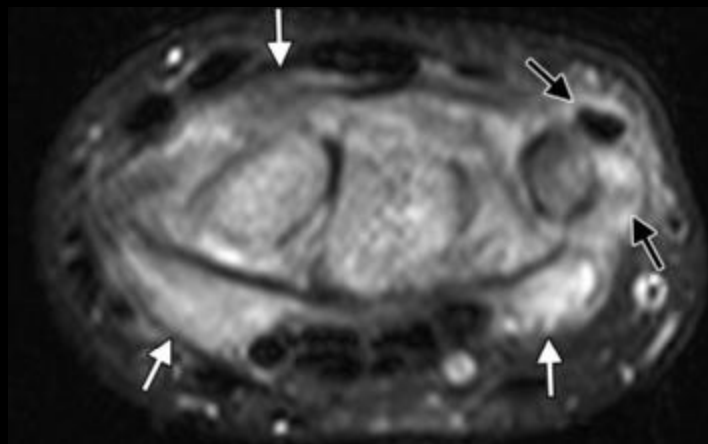
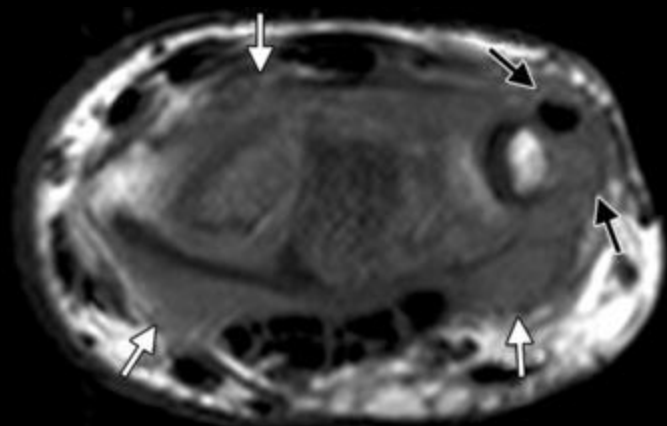
# MR Findings

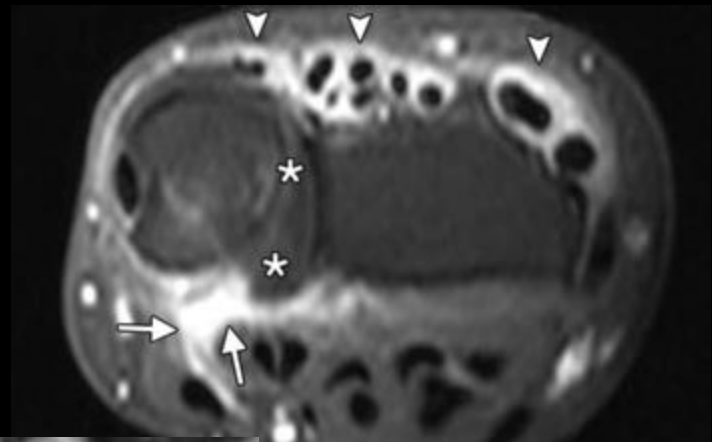
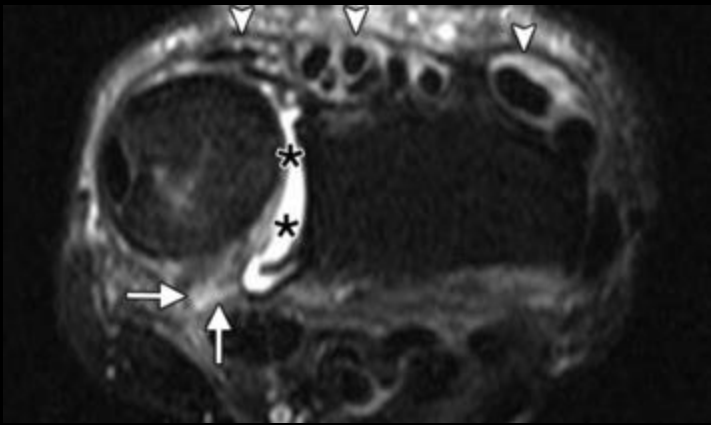
- Joint effusion
- Bone marrow edema
- Erosions
- Synovitis
- Tenosynovitis

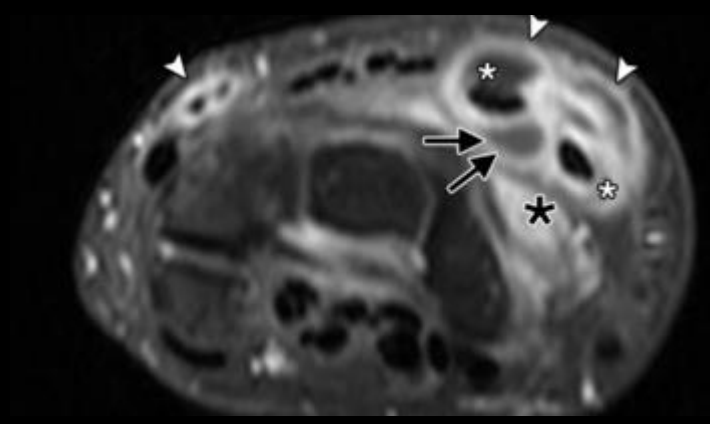
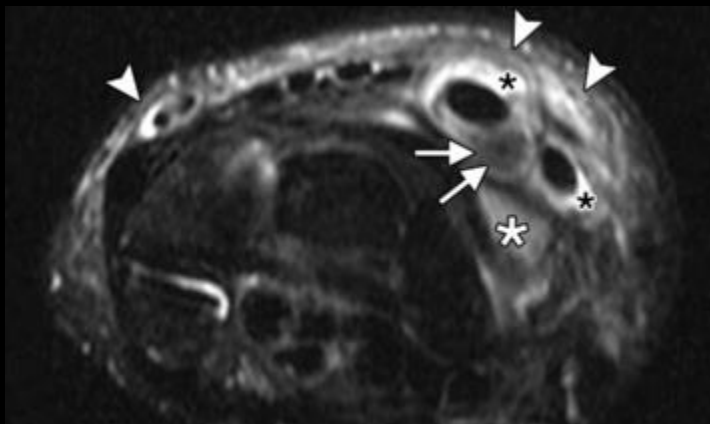
# MR Findings

- Synovitis – earliest manifestation
  - Characterized by synovial thickening, edema and enhancement
  - Contrast utilized to differentiate from effusion
    - Synovitis will enhance early, within 5 minutes, whereas effusion will typically enhance late, after 10 minutes
    - Fibrotic pannus occurs late in the disease process and does not enhance









# MR Findings

- Bone marrow edema
  - Nonspecific, but a key finding in RA as it is thought to be a precursor to erosions
  - Ill-defined lesion in the trabecular bone with SI of increased water content
  - May be seen alone or with erosion
  - Any time in disease course, but usually confined to subchondral bone in early RA
  - Usually associated with synovitis

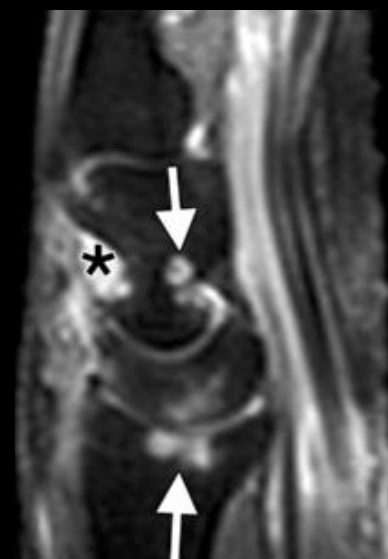
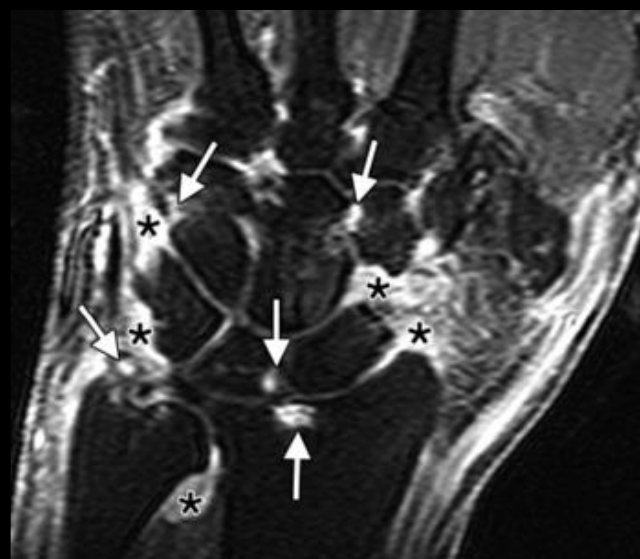


# MR Findings

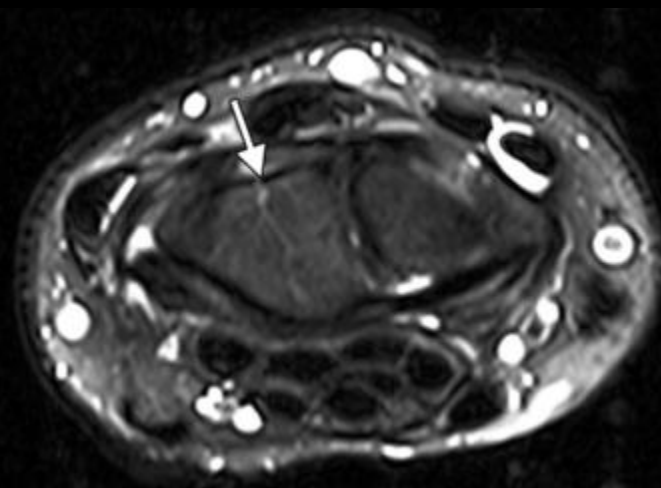
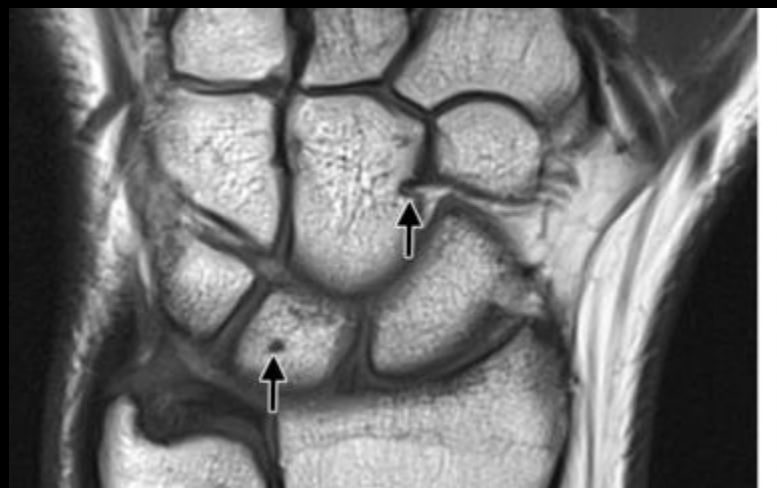
- Erosions
  - More sensitive than radiographs
  - Indicates poor long-term radiographic and functional outcome
  - One of the 1987 ACR diagnostic criteria
  - Enhancement indicates inflamed synovium within the erosion differentiating it from a fluid filled cyst

# MR Findings

- Erosions
  - Begin in the bare area where there is no cartilage
    - Radial aspects of metacarpals at the MCP joints
    - Lateral aspect of 5<sup>th</sup> metatarsal at the MTP joint
  - Pitfalls
    - Nutrient foramina, particularly in the lunate
    - Interosseous ligament attachments





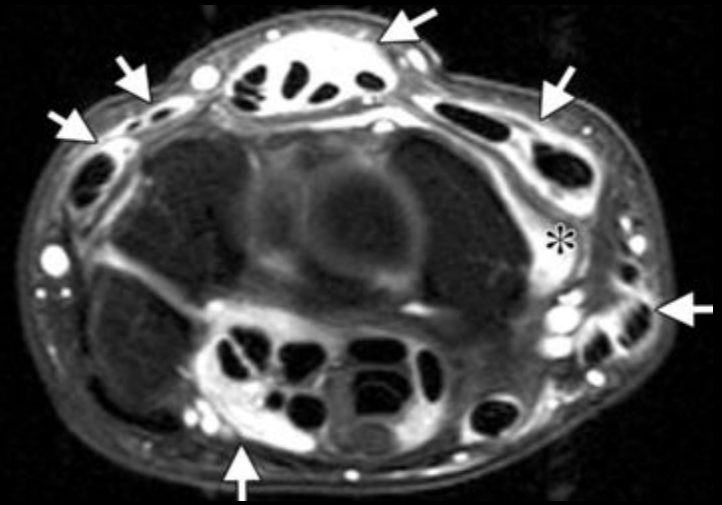
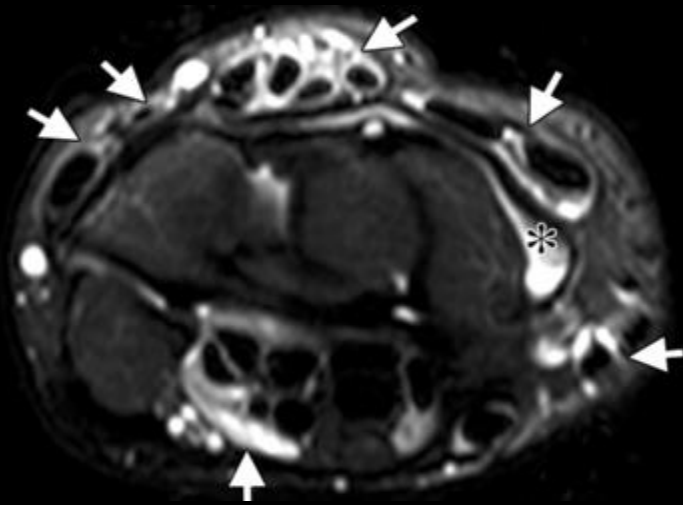
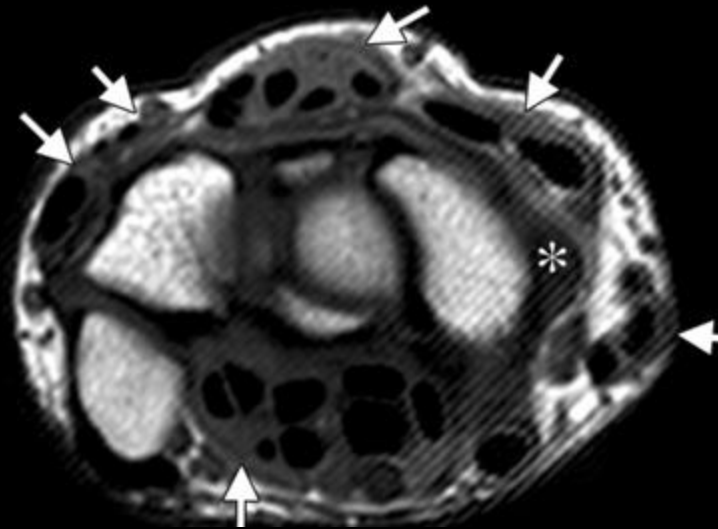


# MR Findings

- Tenosynovitis
  - Increased fluid in the tendon sheath
  - Thickening and/or enhancement of the tendon sheath synovium
  - Dorsal compartments more frequently involved, particularly the ECU

# MR Findings

- Tenosynovitis
  - Important for 2 reasons
    - Same process as synovitis and predominates over synovitis in some patients
    - Associated with tendon rupture
      - Usually occurs later



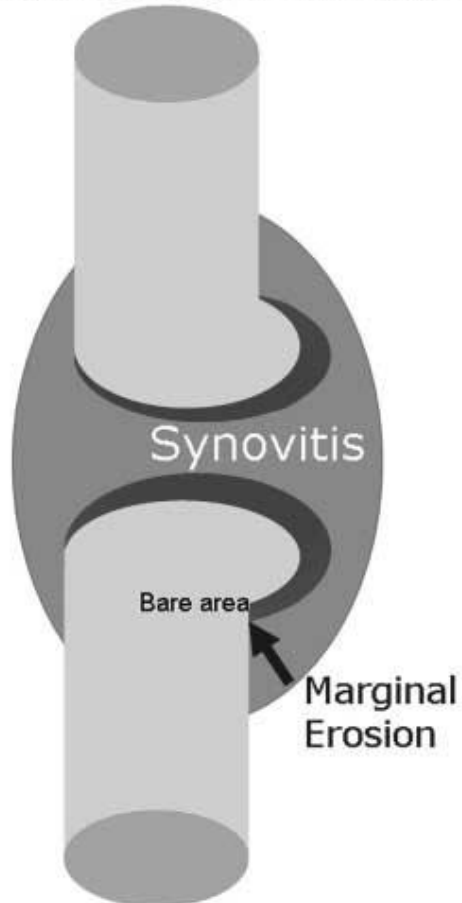
# Other findings

- Joint space narrowing
- Subcortical cysts
- Intra-articular bodies
- Paraarticular osteoporosis
- Hyperemia

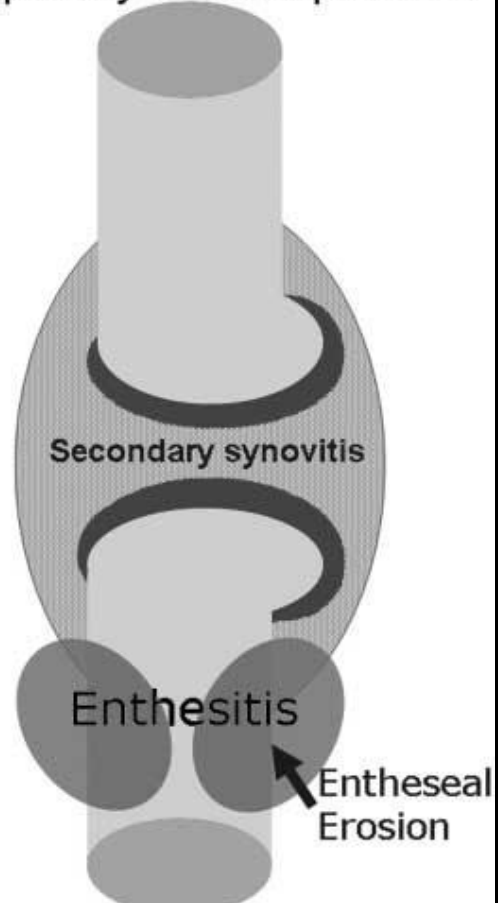
# Differential Diagnosis

- Can be difficult to distinguish early RA from early forms of seronegative spondyloarthropathies
- Distribution, proliferation, osteolysis, ankylosis
- Enthesitis
- Periostitis, marrow edema away from subchondral bone

## Rheumatoid Arthritis



## Spondyloarthropathies





**When radiologists take a selfie**

memes.com



# EULAR Recommendations for the Use of Imaging

- 2013 task force comprised of rheumatologists, radiologists, methodologists, and experienced rheumatology practitioners from 13 countries
- Systematically reviewed 199 studies
- 10 recommendations

# EULAR Recommendations for the Use of Imaging

- 1. When there is diagnostic doubt, CR, ultrasound or MRI can be used to improve the certainty of a diagnosis of RA above clinical criteria alone
- 2. The presence of inflammation seen with ultrasound or MRI can be used to predict the progression to clinical RA from undifferentiated inflammatory arthritis.

# EULAR Recommendations for the Use of Imaging

- 3. Ultrasound and MRI are superior to clinical examination in the detection of joint inflammation; these techniques should be considered for a more accurate assessment of inflammation.
- 4. CR of the hands and feet should be used as the initial imaging technique to detect damage. However, ultrasound and/or MRI should be considered if CR do not show damage and may be used to detect damage at an earlier time point (especially in early RA).

# EULAR Recommendations for the Use of Imaging

- 5. MRI bone edema is a strong independent predictor of subsequent radiographic progression in early RA and should be considered for use as a prognostic indicator. Joint inflammation (synovitis) detected by MRI or ultrasound as well as joint damage detected by CR, MRI or ultrasound can also be considered for the prediction of further joint damage.

# EULAR Recommendations for the Use of Imaging

- 6. Inflammation seen on imaging may be more predictive of a therapeutic response than clinical features of disease activity; imaging may be used to predict response to treatment.
- 7. Given the improved detection of inflammation by ultrasound and MRI than by clinical examination, they may be useful in monitoring disease activity.

# EULAR Recommendations for the Use of Imaging

- 8. The periodic evaluation of joint damage, usually by radiographs of the hands and feet, should be considered. MRI (and possibly ultrasound) is more responsive to change in joint damage and can be used to monitor disease progression.
- 9. Monitoring of functional instability of the cervical spine by lateral radiograph obtained in flexion and neutral should be performed in patients with clinical suspicion of cervical involvement. When the radiograph is positive or specific neurological symptoms and signs are present, MRI should be performed.

# EULAR Recommendations for the Use of Imaging

- 10. Ultrasound and MRI can detect inflammation that predicts subsequent joint damage, even when clinical remission is present and can be used to assess persistent inflammation.



## X-RAYS

How else are they gonna know that it's broken?



# Rheumatoid Arthritis

- Now that we have discussed the early findings of RA on MRI, we will look at other sites and long term sequelae that we want to avoid

# Classic Findings



# Classic Findings



# Cervical spine

- Cervical spine involved much more frequently than thoracic or lumbar
- Occipito-atlanto-axial joints
  - Subluxation and pannus may lead to cord compression
- Follows a pattern of progression
  - Reducible anterior atlantoaxial subluxation
  - Vertical subluxation of the axis
  - Subaxial subluxation
  - Subluxations more prominent and more common in patients with mutilating/more erosive disease
- 60% have cervical spine involvement











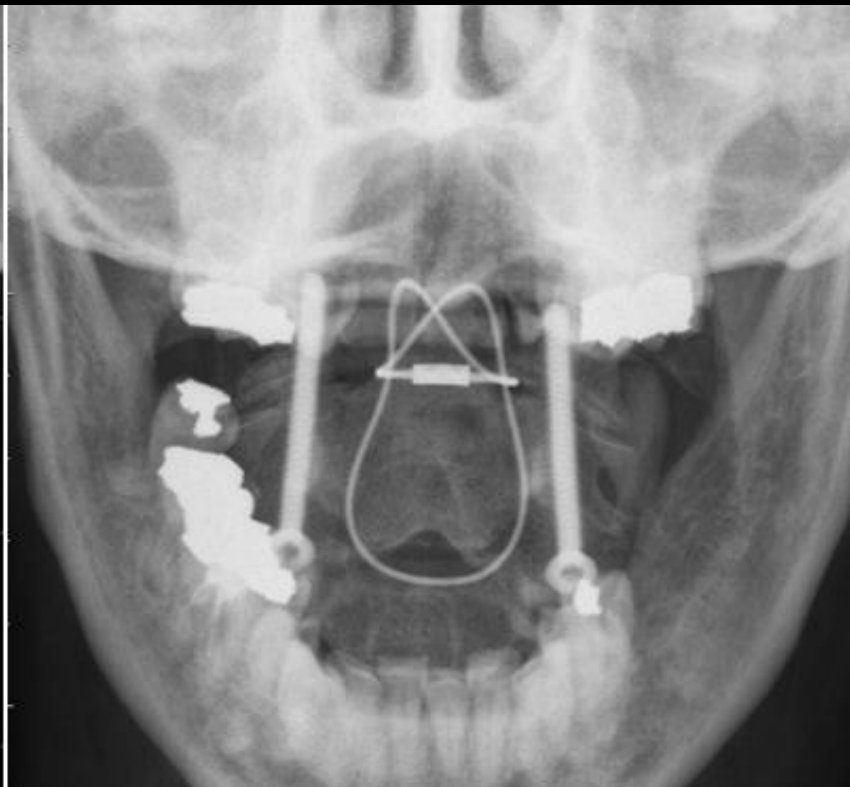
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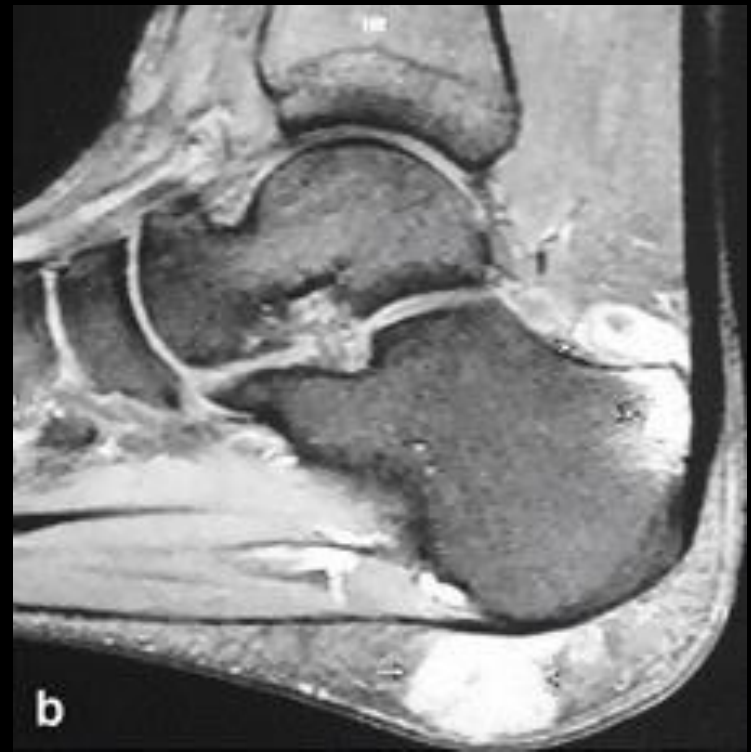


# Cervical Spine

- Treatment
  - involves posterior fixation of the involved levels
  - Transoral resection of pannus if cord compression
- Pitfalls on imaging
  - Flexion and extension radiographs may be inadequate secondary to inadequate patient motion
  - Calcifying epidural mass with odontoid erosions indicates crystal deposition



# Heel

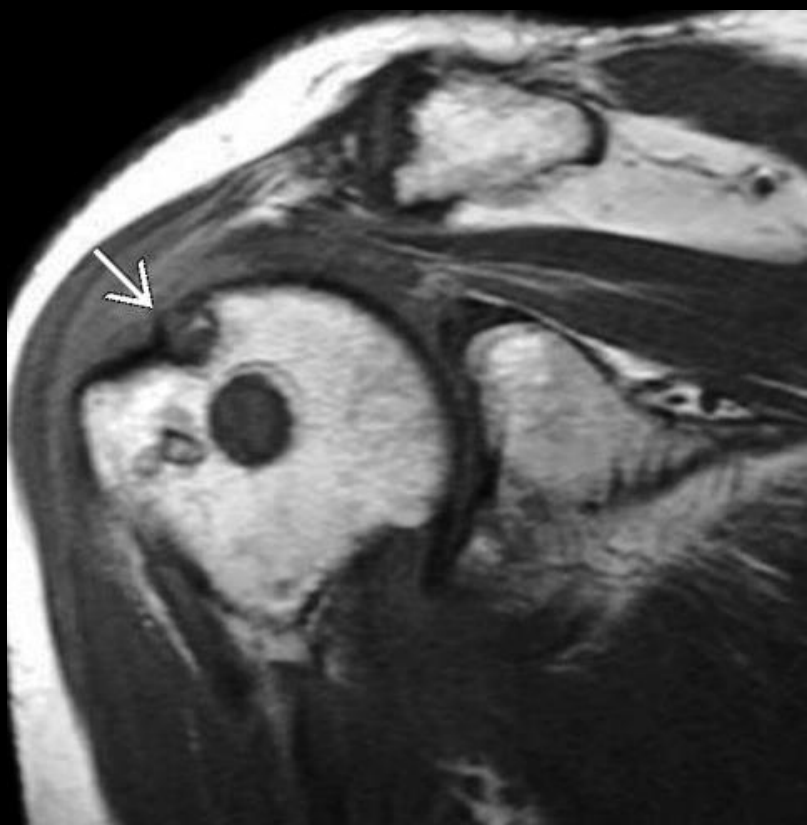


# Sesamoid involvement



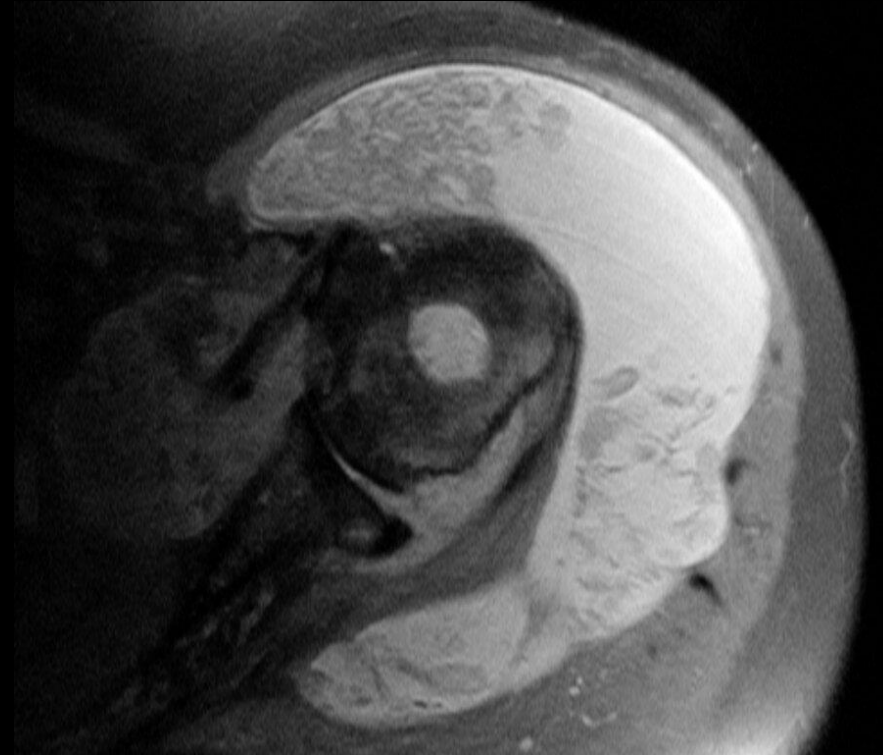
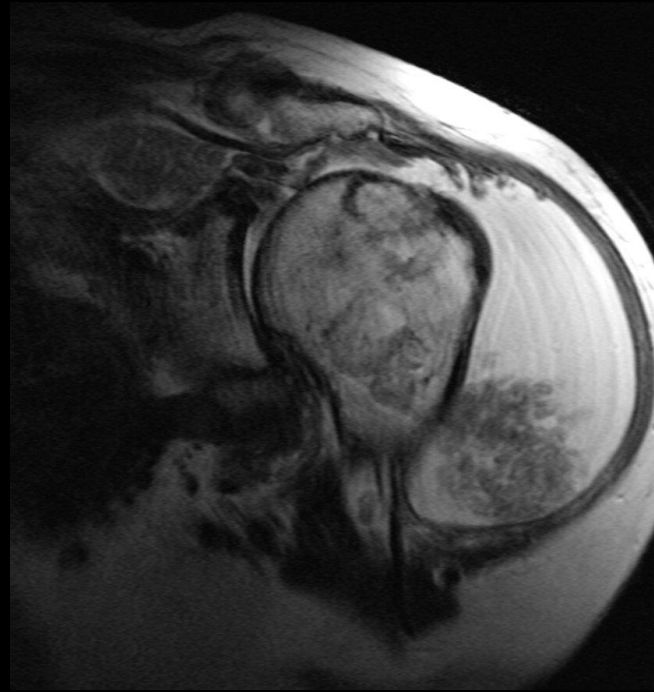
# Other joints

- Shoulder
  - Erosions of HH and glenoid
  - Elevated HH related to RCT
  - Hatchet like mechanical erosion at medial aspect of surgical neck of the humerus
  - Erosion of the distal clavicle
- Elbow
  - Effusion, erosions and olecranon bursitis
- TMJ
  - Erosion and flattening of the anterior and posterior condylar surfaces giving a sharpened pencil
  - Limited opening ROM

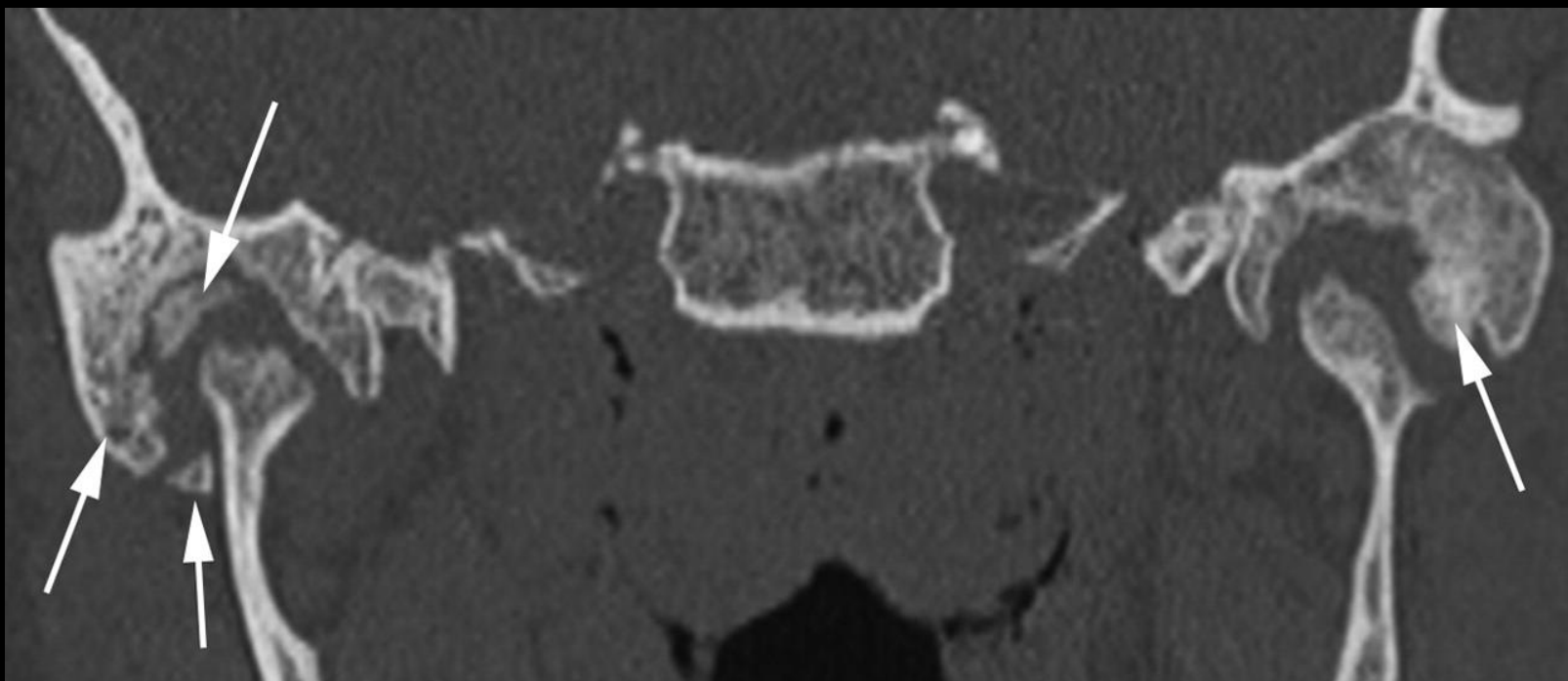












# Other Joints

- Hip
- Knee
  - Large effusion with synovitis
  - Uniform involvement of all three compartments
  - Joint space narrowing
  - Ligamentous laxity leading to deformity
  - Insufficiency fractures
- SIJ
  - MRI sensitive for inflammatory changes
  - CT sensitive for erosions









# RA and DISH

- RADISH
- Combination produces atypical findings



# Non MSK findings of RA

- Lungs
  - Involvement more common in men
  - Pleural thickening and/or effusion
  - Interstitial fibrosis
  - Bronchiectasis, bronchial wall thickening
  - Rheumatoid nodules
  - Caplan syndrome
    - Multiple lung nodules in coal miners with RA
- Heart
  - Pericardial effusion
  - pericarditis



# Nonradiological findings

- Skin nodules
  - Up to 20% of RA patients
  - Gradual or rapid
  - Elbows, forearms, heels and fingers
  - Skin ulcers related to vasculitis
- Eye manifestations
  - Scleritis
  - Sjogren's
- Cardiovascular
  - MI
  - Myocarditis
  - Nodules within the myocardium
  - Anemia
  - Felty syndrome

# How are those bagels?





# Nonradiological findings

- Susceptibility to infection
  - Related to the disease process and medications
- Emotional effects
  - 10% with severe depression
- Scott et al. Long-term outcome of treating rheumatoid arthritis: results after 20 years. The Lancet.



# Treatment

- Medical
  - Combination therapy.
  - Methotrexate
  - Corticosteroids
    - Rapid control of inflammation
  - NSAIDs
    - Symptomatic pain relief
    - Does not alter disease progress
  - DMARDs (AKA csDMARDs or sDMARDs)
    - Suppress joint destruction
    - Sulfasalazine, antimalarials, gold
  - Biologics (AKA bDMARDs)
    - Anti TNF- $\alpha$ , anti-interleukin-1
- Surgical
  - Synovectomy
  - Arthroscopy
  - Arthrodesis
  - arthroplasty



# Rauol Dufy

- Prolific Fauvist painter
- Diagnosed in 1935
- Article in *Life* magazine portrayed his illness
- Invited to participate in a trial of corticosteroids by some guys in Boston
- His next painting was called “La Cortisone” which he gifted to the drug company developing the medication

# 2013 EULAR recommendations

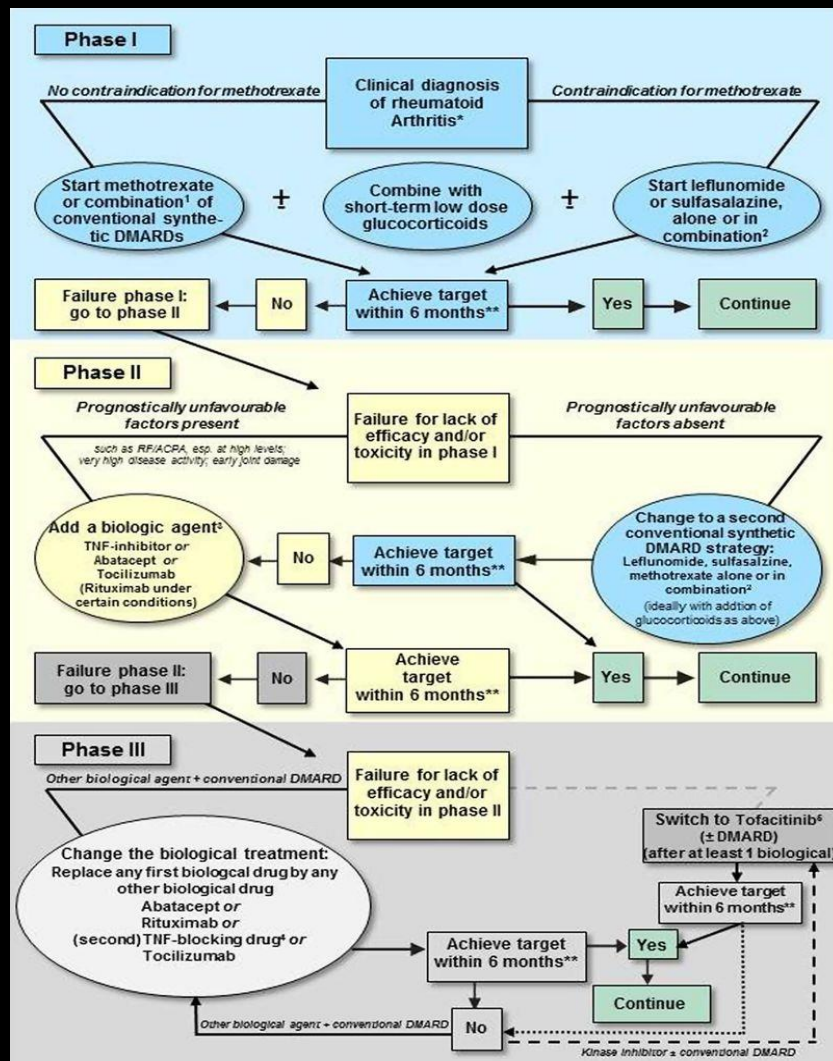
- Begin therapy with DMARDs as soon as a diagnosis of RA is made
- Goal of treatment is remission
- Follow up active disease every 1-3 months and inactive/stable disease every 6-12 months
- Methotrexate should be part of the first treatment strategy in patients with active RA

# 2013 EULAR recommendations

- If MTX is contraindicated or there is early intolerance, leflunomide or sulfasalazine should be considered as part of the first treatment strategy
- In DMARD-naïve patients, monotherapy or combination therapy should be used
- Low dose corticosteroids should be considered as part of the initial therapy for up to 6 months, but should be tapered as soon as clinically feasible
- If treatment target is not achieved with sDMARD therapy, then a different sDMARD therapy should be chosen if there are no poor prognostic factors. If there are, then bDMARD should be started

# 2013 EULAR recommendations

- If MTX with or without glucocorticoids and other scDMARDs is insufficient, bDMARD should be added
- If a first bDMARD has failed, try another bDMARD
- Tofacitinib may be considered after bDMARD has failed – (\$25,000/yr)
- If patient is in remission after tapering glucocorticoids, bDMARD can be tapered, especially if in combination with csDMARD
- If patient remains in long term remission, scDMARD can be tapered



\*2010 ACR-EULAR classification criteria can support early diagnosis. \*\*The treatment target is clinical remission, according to ACR-EULAR definition or, if remission is unlikely to be achieved, low disease activity. The target should be reassessed if no improvement is seen after 3 months. <sup>1</sup>Combinations of hydroxychloroquine, <sup>2</sup>Combinations of sulfasalazine or leflunomide (except with methotrexate, have not been well studied, but may include combinations with low-dose hydroxychloroquine), <sup>3</sup>Combinations of TNF-inhibitors with conventional synthetic DMARDs, <sup>4</sup>Combinations of TNF-inhibitors with conventional synthetic DMARDs, <sup>5</sup>DAEMA approved biologics, where licensed. Lines: Full black line, recommended; as shown; grey interrupted line, recommended for use after biologics failure (ideally two failed biologics); interrupted black line, recommended after two biologics failed, but efficacy and safety after failure of abatacept, rituximab and tocilizumab not sufficiently studied; black dotted line, possibly recommended, but efficacy and safety of biological use after tofacitinib failure unknown at the time of developing the 2013 update of the recommendations.

Smolen JS et al. Ann Rheum Dis. doi:10.1136/annrheumdis-2013-204573

# Treatment Related Complications

- Methotrexate
  - oral ulcers, transient elevation of liver enzymes, nausea, vomiting
  - Pneumonitis
    - SOB, cough and fever
  - Severe infection, cytopenia, respiratory failure, seizures, gastrointestinal
- Other DMARDs and Biologics
  - Have similar efficacy and side effect profile but are more expensive and less well studied



- Glucocorticoids
  - Immunodeficiency
  - Hyperglycemia
  - Osteoporosis
  - Weight gain
  - Cushing's
  - Glaucoma
  - Cataracts
  - Withdrawal

# Summary

- Who gets RA
- Pathophysiology
- Why early diagnosis is important
- How we, as radiologists, can contribute
- Late manifestations of the disease
- Treatment options
- Their complications

# When is MRI Useful in Inflammatory Arthropathy

- Cases of suspected but unconfirmed inflammatory joint disease
- Early unclassified arthritis to assist in developing the differential diagnosis
- Early rheumatoid arthritis
- Long-term evaluation of treatment

# Thanks

- To Dr. Resnick
  - for curtailing my entirely too broad of a topic
  - And everything else this year
- Dr. Pathria
  - for many of the images
  - and the many words of encouragement throughout the year
- Erica
  - for the sesamoid slide
- Mike, Chris and August
  - for helping me this week
- Everyone else
  - For your attention

Have a seat Kermit. What I'm about to tell you might come as big shock...



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