Rheumatoid Arthritis

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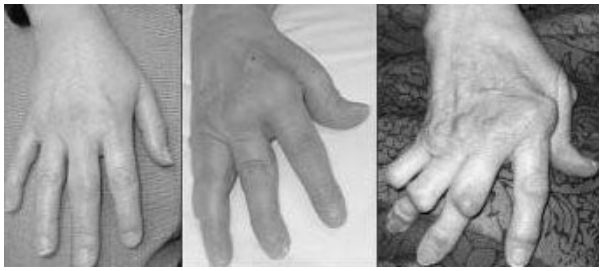


RA Introduction

- **Chronic, systemic, inflammatory**
- **Unknown etiology**
- **Primarily involves joints**
- **Extra-articular manifestations**
- **1% of world's population**
- **Women 3 times more than men**

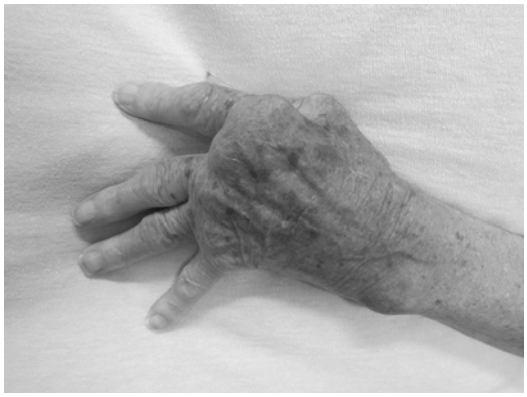


Photo by James Heilman, MD

Onset of RA

- Insidious
- Pain, stiffness, joint swelling
- MCPs, PIPs, thumb IP, wrist, ulnar styloid
- MTPs feet
- Elbow, shoulder, ankle, knee

RA - Differential Diagnosis

- Acute viral polyarthritis
- Connective Tissue Diseases – lupus, early scleroderma
- Sarcoidosis
- Psoriatic arthritis
- Reactive arthritis
- Crystal arthritis

RA Diagnosis

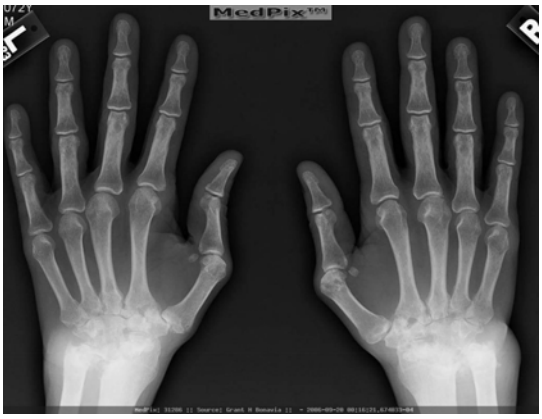
- Symmetrical peripheral polyarthritis
- Morning stiffness
- Rheumatoid nodules
- Laboratory features
- Radiographic bone erosions

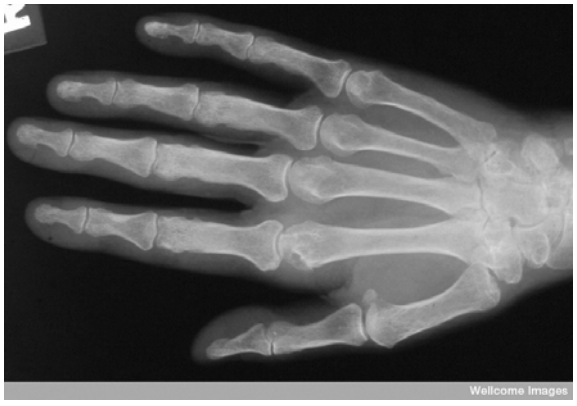
RA - Differential Diagnosis

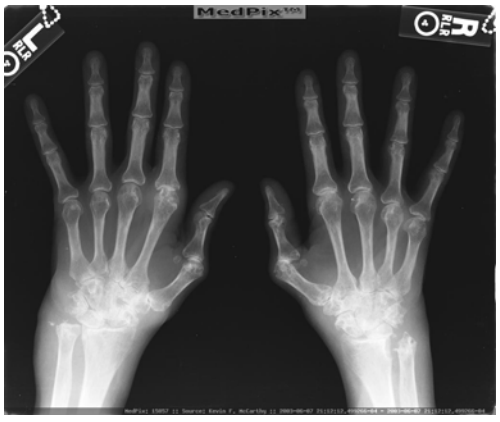
- Infectious arthritis
- Osteoarthritis
- Paraneoplastic disease
- Multinodular reticulohistiocytosis
- Hypermobility syndrome
- Fibromyalgia

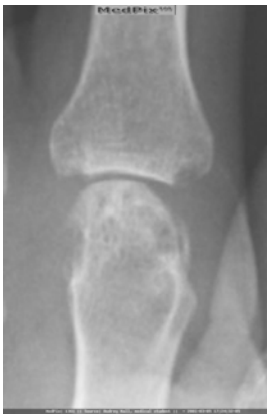
RA - Imaging

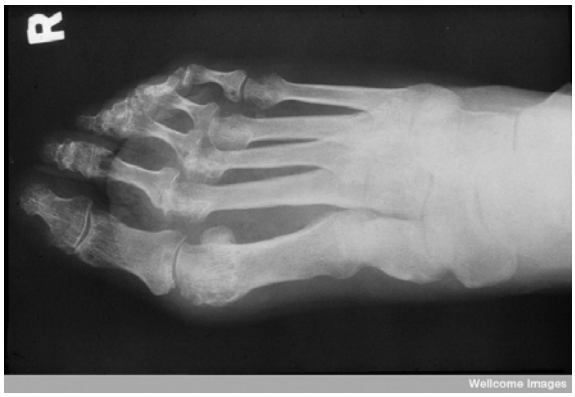
- **Plain films**
- **Ultrasonography**
- **MR imaging**

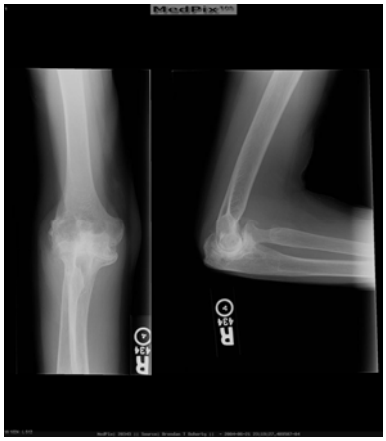












RA – Nonarticular Manifestations

- Osteopenia
- Myositis
- Vasculitis
- Skin involvement
- Eye involvement
- Lung disease

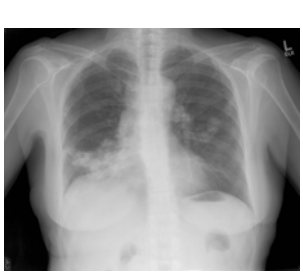
RA – Nonarticular Manifestations

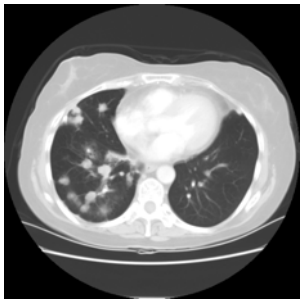
- Cardiac involvement
- Peripheral artery disease
- Sjogren's syndrome
- Nervous system involvement
- Hematologic involvement

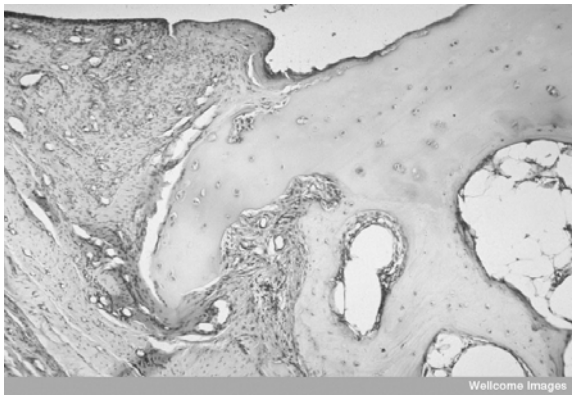
Pathophysiology of RA

- Genetic link with HLA-DR4
- Abnormal B cell – T cell interaction
- Autoantibodies – RF and anti- CCP
- Synovial cell proliferation
- Fibrosis and pannus formation
- Cartilage and bone erosion
- Proinflammatory cytokines – IL-1, TNF-a

Pulmonary Rheumatoid Nodules







1987 ACR Classification Criteria

- Am stiffness – at least one hour
- Arthritis in three or more joint areas
- Arthritis of hand joints (> 1 swollen joints)
- Symmetric arthritis
- Rheumatoid nodules
- Serum RF
- Radiographic changes - erosions

1987 ACR Classification Criteria

- Based on average disease duration of 8 years
- Contains elements associated with disease severity – erosions, nodules, rather than disease development
- Distinguish RA patients from other joint diseases to enter clinical study
- Homogeneous patient group

1987 ACR Classification Criteria

- Four of seven criteria must be present
- Criteria one through four must have been present for at least six weeks
- Sensitivity of 79% - 80% and specificity of 90% - 93% for established RA
- Sensitivity of 77% - 80% and specificity of 33% - 77% for early RA

2010 Classification Criteria

- Task force of Rheumatologists from USA and Europe
- American College of Rheumatology – ACR
- European League Against Rheumatism – EULAR
- Increased sensitivity and specificity to diagnose RA in an early phase of disease

2010 ACR/EULAR Criteria

- Target population – who should be tested
- 1 joint with synovitis or swelling
- Not better explained by another disease
- Score of > 6/10 for definite RA

Serology

• Negative RF and negative anti-CCP	0
• Low positive RF or low positive anti-CCP	2
• High positive RF or high pos anti-CCP	3

Joint Involvement

• 1 large joint	0
• 2-10 large joints	1
• 1-3 small joints	2
• 4-10 small joints	3
• > 10 joints (at least one small joint)	5

Acute Phase Reactants

• Normal CRP and normal ESR	0
• Abnormal CRP or abnormal ESR	1

Duration of Symptoms

- < 6 weeks 0
- > 6 weeks 1
- A score of > or = 6/10 is needed for classification of a patient with definite RA

References

- Henkel G, Debut New RA Classification Criteria in August, The Rheumatologist, Vol 4, No. 8, Aug 2010.
- Van der Helm-van Mil AH and Huizinga TWJ, The Key to Early Rheumatoloid Arthritis, The Rheumatologist, Vol 4, No. 9, Sept 2010.

References

- Diagnosis and differential diagnosis of rheumatoid arthritis, UpToDate, 2010
- Clinical features of rheumatoid arthritis, UpToDate, 2010
- Overview of the systemic and nonarticular manifestations of rheumatoid arthritis, UpToDate, 2010

Management Of Rheumatoid Arthritis

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General Principles

- Early accurate diagnosis- first 3-6 months critical
- Early Referral to Rheumatologist
- Risk stratification & Prognostication
- Emphasis on both non pharmacological vs pharmacological treatment
- Assessment of comorbidities

Non Pharmacological

- Patient Education
- Rest
- Exercise
- Physical Therapy
- Occupational Therapy
- Dietary Modification
- Vaccinations/Bone Health/Cardiovascular health

Poor Prognostic Factors

- Presence of anti-cyclic citrullinated peptide antibody
- Presence of markedly elevated rheumatoid factor
- High disease activity with marked elevations in ESR and or C-reactive protein, poor functional status
- Extra articular disease with rheumatoid nodules, lung disease etc.
- Presence of erosions and or joint space narrowing by x-ray ultrasound or MRI
- Delayed diagnoses and treatment

Pharmacological

- NSAIDS
- Analgesics
- Glucocorticoids
- Non Biologic /Synthetic DMARDS
- Biologic DMARDS

*Goal is Remission/Low disease activity without toxicity

NSAIDS

- Analgesics & Anti-inflammatory
- Do not alter disease outcome
- Use in RA is not evidence based & is not part of management algorithm

Glucocorticoids

- Prednisone or Prednisolone
- Oral, Intraarticular, Parenteral routes
- Doses less than 7.5 mgm qd recommended for short periods of time, higher doses recommended only for early aggressive disease
- Reduce pain & inflammation and also prevent disease progression
- Poor Toxicity profile especially infections
- Attention to Osteoporosis prophylaxis

Analgesics

- Darvocet, Tramadol, Percocet, Vicodin etc.
- No effect on disease outcome, but frequently used for pain management

Non biologic DMARDS

- Methotrexate
- Leflunomide/Arava
- Sulphasalazine
- Injectable Gold
- Hydroxychloroquine/Plaquenil
- Azathioprine/ Imuran
- Cyclosporin

Methotrexate

- Oral, SQ, I/V, I/M routes, dose from 7.5- 30 mgm weekly
- Adverse effects of Hepatotoxicity, Renal toxicity, Myelosupppression, Lymhoma, Pulmonary fibrosis
- Monitor for CBC, Cr, LFT-every one month initially, every 3 months on stable dose
- Screen for Hepatitis B& C

* Drug of choice unless C/I

Sulphasalazine

- Works by inhibiting Prostagalndin synthesis systemically
- Average dose of 1 gm - 2gm BID
- Folic acid supplementation
- Monitor for GI upset, CBC, LFT & Renal function
- Can cause reversible azoospermia in males

Leflunomide

- Anti-inflammatory & Anti-proliferative action due to inhibition of Pyrimidine synthesis
- Dose of 10 to 20 mgm qd
- Monitor for CBC, LFT, Renal function and infections-monthly initially, every 3 months later
- Efficacy comparable to Methotrexate
- Screen for Hepatitis B & C

Plaquenil

- Works by inhibiting chemotaxis & impairing complement mediated antigen antibody reactions
- Dose - 200 mgm bid or 6 mgm /kbw
- Check G6PD levels
- Monitor for CBC, Retinal toxicity & Myopathy. Baseline and yearly eye exams recommended
- Efficacy in early disease as mono therapy is limited

Biologic DMARDS

- TNF Antagonists
  - Etanercept or Enbrel, soluble receptor antagonist
  - Adalimumab or Humira, fully humanized monoclonal antibody
  - Infliximab or Remicade, partially humanized monoclonal antibody
  - Cetrolizumab or Cimzia, pegylated soluble receptor antagonist
  - Golimumab or Simponi, fully humanized monoclonal antibody

Precautions with Biologic DMARDS

- Infections - Bacterial, opportunistic, Viral
- Screen for Hepatitis B & C, T.B., Attention to vaccinations
- Precipitation of other autoimmune diseases like lupus
- Demyelinating diseases like multiple sclerosis
- Malignancies especially lymphomas
- Multifocal Leucoencephalopathy especially with Rituxan

Biologic DMARDS

- IL-1 Receptor antagonists - Anakinra
- IL-6 Receptor antagonists - Tocilizumab or Actemra
- Inhibitors of Tcell-B cell costimulatory molecules - Abatacept / Orencia
- Monoclonal antibodies against B cells- Rituximab/Rituxan

* Combination of biologics from 2 different groups is not recommended as it does not increase efficacy but increases toxicity

Optimal Treatment of Rheumatoid Arthritis

EULAR/ACR Recommendations

Three overarching principles

15 recommendations

EULAR -

European League Against Rheumatism

ACR -

American College of Rheumatology

Overarching Principles

- Rheumatologists to be the primary caretakers
- Treatment should aim at best care and should be a shared decision between patient and the rheumatologist
- Medical and productivity costs should be considered by the treating rheumatologist

Recommendations

- In DMARD naïve patients, synthetic mono therapy rather than synthetic combination therapy should be considered
- Glucocorticoids in short courses recommended in combination with synthetic DMARDs in early disease
- If treatment target not achieved with first DMARD strategy, switch to biologic if poor prognostic factors, and switch to another synthetic DMARD in the absence of these factors

Recommendations from EULAR and ACR

- Initiate treatment with nonbiological DMARDs as early as possible
- Treatment should be to a target of remission or low disease activity as early as possible and should be adjusted frequently, every one to 3 months till achieved
- Methotrexate should be part of the first treatment strategy in active RA
- If methotrexate contraindicated or poorly tolerated, Arava, sulfasalazine or injectable Gold should be the next choice

Recommendations

- If target not achieved with combination of methotrexate and another synthetic DMARD, with or without glucocorticoids, add a TNF inhibitor
- If first TNF inhibitor fails, change to another TNF inhibitor, Abatacept, rituximab or Tocilizumab
- In refractory severe rheumatoid arthritis or if biologics contraindicated, consider treatment with Azathioprine, Cyclosporin as monotherapy or as combination therapy

Recommendations

- Intensive medication strategies with frequent monitoring should be considered in every patient, especially those with poor prognostic factors
- If patient in persistent remission, first taper glucocorticoids, then taper biological DMARDs especially if patient on combination therapy with synthetic DMARDs
- In cases of sustained long-term remission, very cautious titration of synthetic DMARD could be considered, flares are common!

Conclusions

- Interesting and promising times for treatment of rheumatoid arthritis
- Financial constraints brought by progress to be considered
- Anchor drugs like methotrexate and glucocorticoids beneficial for many patients so risk stratification and prognostication important
- Move towards early aggressive induction regimens followed by tapering (synonymous to treatment for cancers) - as best chance of remission appears to be with this approach

Recommendations

- DMARD naïve patients with poor prognostic factors might be considered for combination of methotrexate plus a biological agent at the outset
- Adjusting treatment should take into account not only disease activity but factors such as progression of structural damage, comorbidities and toxicities

References

- Treatment of Rheumatoid Arthritis, Up-to-Date.com
- Smolen JS et al. Annals of Rheumatic Diseases. 2010; 69: 964-975