RHEUMATOID ARTHRITIS

Background

1. Definition[1]
    - A chronic, systemic, inflammatory disorder primarily involving joints
    - Arthritis symmetrical; may be remitting; if uncontrolled, erosion of cartilage and bone may occur, leading to destruction of joints and deformity
    - Usually progresses from periphery to more proximal joints
    - In patients who do not fully respond to treatment, significant locomotor disability can occur within 10 to 20 years
    - Unknown etiology
    - Gradual onset

Pathophysiology

1. Pathophysiology
    - T-cell mediated synovial hyperplasia
    - Cytokine activity (tumor necrosis factor-a and interleukin-1)
    - Pannus (locally invasive synovial tissue) causing bone and cartilage erosion
2. Incidence/ prevalence
    - Incidence: 30 / 100,000 adults
        - most common worldwide autoimmune disease
    - Prevalence: 1%
    - Women > Men (3:1)
        - After age 50 years, sex difference less marked
    - Peak age of onset: 35-40
3. Risk factors
    - Genetic[2]
        - Genetic factors contribute from 53-65 percent of risk
    - Environmental
        - Tobacco use
        - Excessive decaffeinated coffee
        - Possible infectious agents (Mycoplasma, EBV, CMV, parvovirus, rubella)
4. Morbidity & mortality
    - Much of joint damage that ultimately results in disability begins early in disease course[3]
    - Disease progression variable; joint failure causes physical disability and resultant economic loss[1]
    - Compared to age- and sex-matched controls:
        - 3x direct medical costs
        - 2x normal rate of hospitalization and 2x mortality
        - 10x normal work disability rate
            - If untreated, 20-30% within three years of diagnosis
        - Increased risk of infections and heart disease
        - Excess mortality from severe RA comparable to that of three vessel CAD or stage IV Hodgkin's

Diagnostics[4]

1. History
    - Patients experience symptoms for average of 9 months prior to diagnosis
        - Pain in affected joints
        - Morning stiffness for at least 1 hr for at least six weeks
        - Swelling of 3 or more joints for at least six weeks
        - Swelling of wrist, MCP, or PIP joints for at least six weeks
            - Single most characteristic clinical feature of early RA is MCP/PCP involvement of both hands
        - Symmetric joint swelling
        - Occasional involvement of cervical spine
        - Constitutional symptoms
            - Fatigue, anorexia, wt loss
            - Low-grade fever
            - Depression
2. Physical exam: (photo 1)
    - Synovial thickening (swollen and "boggy")
    - Palmar erythema
    - Reduced grip strength (sensitive for early disease)
    - Muscle atrophy
    - Ligamentous laxity
    - Hoarseness or stridor (involvement of cricoarytenoid joint)
    - **"Z" deformity**
        - Radial deviation at wrist, ulnar deviation at digits and palmar subluxation of proximal phalanges
    - **Swan neck deformity**
        - PIP hyperextension with DIP flexion
    - **Boutonniere deformity**
        - PIP flexion contracture with DIP extension
    - **Bowstring sign**
        - Prominence of extensor tendons
    - **Rheumatoid nodules**
        - Found in 20% of patients
        - Usually on periarticular structures, extensor surfaces, areas subjected to mechanical pressure
        - Elbow most common
    - Baker's cyst
    - Podiatric
        - Hindfoot eversion
        - **Cock-up deformity**
            - Plantar subluxation of metatarsal heads
        - **Hallux valgus**
            - Abnormal deviation of great toe away from midline of body or toward other toes of foot
        - Lateral deviation and dorsal subluxation of toes
3. Extra-articular manifestations[5]
    - Rheumatoid nodules
    - Interstitial lung disease
    - Pleural/serosal involvement

- Sjögren's syndrome
- **Felty's syndrome**
  - Rheumatoid arthritis, neutropenia, and splenomegaly
  - Often accompanied by weight loss, anemia, lymphadenopathy, and pigment spots on the skin
- Rheumatoid vasculitis
- Osteoporosis
- Carpal tunnel syndrome

4. Diagnostic testing[6]
   - Laboratory evaluation
     - Rheumatoid Factor (RF)[7]
       - Poor positive predictive value (less than 33%)
       - More useful as prognostic indicator than as screening tool
       - Present in 70-80% of patients
       - Found in 5% of healthy persons (increasing with age)
       - Associated with SLE, Sjögren's syndrome, chronic liver disease, interstitial pulmonary fibrosis, sarcoidosis, infectious mononucleosis, TB, syphilis, Subacute Bacterial Endocarditis (SBE), and malaria
     - Anti-CCP (Cyclic Citrullinated Peptide) antibodies[8]
       - Similar sensitivity to RF but higher specificity
     - Anti-mutated citrullinated vimentin[9]
       - Similar results to anti-CCP.
       - Used as an alternative in some laboratories.
     - Positive ANA (Anti-Nuclear Ab) in 30-40% of patients
     - Normochromic, normocytic anemia
     - Leukopenia; thrombocytosis
     - Hypoalbuminemia (due to increased catabolism of albumin)
       - Serum albumin concentrations do not correlate well with other measures of disease activity in this condition[10]
     - Elevated ESR[11]
     - Synovial fluid analysis
       - Elevated protein, normal or decreased glucose
       - WBC 5-50K (PMN predominant)
   - Diagnostic imaging[12]
     - Mostly useful for
       - Assessing relative aggressiveness of disease
       - Monitoring response to treatment
       - Determining need for surgical intervention
     - Plain radiography
       - Erosions identified in 15-30% of patients in first year of disease
       - More than 90% afterfirst two years
     - Ultrasonography
       - May detect inflammatory features in joints without physical signs
     - MRI
       - More sensitive

- Presence of marrow edema predictive of later development of erosive disease

5. 2010 ACR/EULAR classification criteria for RA[4]
    - Identifies factors which best discriminate between those patients who are and are not at high risk for persistent and/or erosive joint disease
        - Number of and site of involved joints:
            - 2 to 10 large joints = 1 point
            - 1 to 3 small joints = 2 points
            - 4 to 10 small joints = 3 points
            - Greater than 10 joints (including at least one small joint) = 5 points
        - Serological abnormality (rheumatoid factor or anti-citrullinated peptide/protein antibody)
            - Low positive (above the upper limit of normal, ULN) = 2 points
            - High positive (Greater than 3 times the ULN) = 3 points
        - Elevated acute phase response (ESR or CRP)
            - Above the ULN = 1 point
        - Symptoms duration.
            - At least 6 weeks = 1 point

Differential Diagnosis[13]

1. Key DDx
    - Psoriatic arthritis
        - Positive family history of psoriasis
    - Reactive arthritis
        - Asymmetrical, large joints, "sausage" digit
    - Crystalline arthritis
        - Gout and pseudogout
        - No morning stiffness
    - Infectious arthritis
        - Usually monoarticular
    - Acute viral polyarthritis
        - Rubella, parvovirus, hepatitis B
        - Rash
    - Osteoarthritis
        - DIP, hard swelling, symptoms worse with activity
    - Seronegative spondyloarthropathies
        - RF rare
    - Other connective tissue diseases
        - SLE
            - Only early symptoms similar
2. Extensive DDx
    - Hypermobility syndrome and fibromyalgia
    - Sarcoidosis
    - Paraneoplastic disease
    - Multicentric reticulohistiocytosis
    - Fibroblastic rheumatism

Therapeutics: Non-Pharmacologic[14]

1. Rest
    - Decreases symptoms
2. Exercise / physical therapy
    - Preserves joint function
3. Counseling
    - Reduces pain, depression and disability
4. Dietary modification
    - Fish oil
5. Physical/occupational therapy
6. Splinting of inflamed joints

Pharmacotherapy

1. Anti-inflammatories (for symptom relief)[15]
    - Aspirin (2.4-5.6 g PO per day div q4-6h)
    - NSAIDs
        - Ibuprofen 300-800 mg PO TID-QID
    - Celecoxib 100-200 mg PO BID (COX-2 inhibitor)
        - Moderate/severe pain; use with DMARDs
        - Generally does not worsen renal function for pts without preexisting renal disease
        - Much lower incidence of tubulointerstitial renal disease versus traditional (COX-1) NSAIDs
        - Lower GI side effects versus conventional NSAIDs
        - Associated with lower risk of renal dysfunction and hypertension when compared with controls
2. Glucocorticoids
    - Intra-articular injections for symptoms relief
    - Oral treatment may be disease-modifying (<10 mg prednisone daily)
3. Disease-modifying Anti-Rheumatic Drugs (DMARDs)[6,16]
    - The decision to add a DMARD depends upon the relative activity of the disease:[17]
        - Functional limitation.
        - Extraarticular disease.
        - Rheumatic factor positivity or presence of anti-cyclic citrullinated peptide (CCP) antibodies.
        - Bony erosions documented radiographically.
    - Non-biologic DMARDS considered primary therapy for RA with any poor prognostic factors – (SOR:A)[16]
    - Dual DMARD tx if single agent tx ineffective
        - MTX+Leflunomide – (SOR:A)[16] – for high disease activity and duration ≥6 months
        - MTX+Sulfasalazine – (SOR:A)[16] – for high disease activity and duration <6 or >24 months
    - Methotrexate (7.5-20 mg PO/IM qweek)[18] – (SOR:A)[16]
        - Follow CBC, creatinine, LFT
    - Leflunomide (10-20 mg PO qD) – (SOR:A)[16]
        - Follow CBC, creatinine, LFT
    - Gold (25-50 mg IM q2-4weeks)

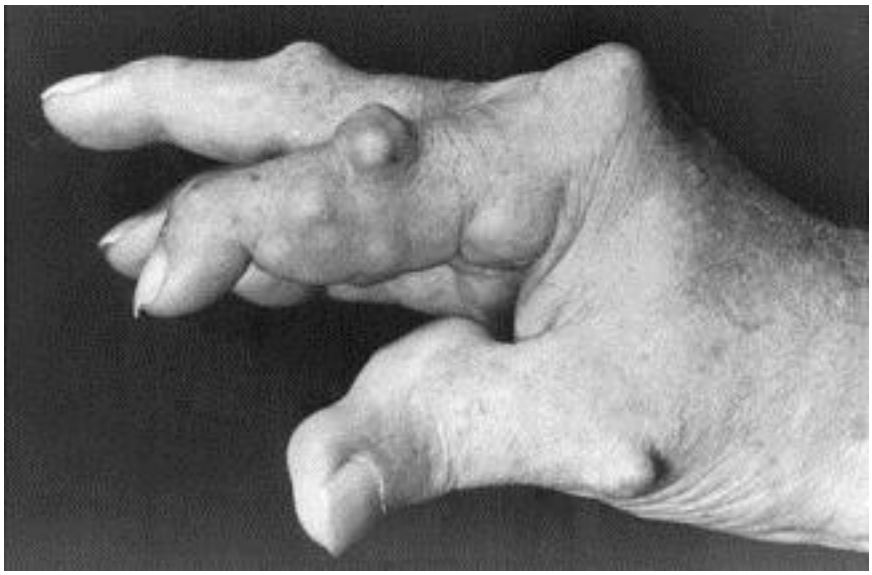
- Anti-malarials (hydroxychloroquine 200 mg PO qD) – (SOR:C)[16]
  - Need periodic retinal exams by eye-care specialist
- D-penicillamine (250 mg PO BID-TID)
- Sulfasalazine (1g PO BID) – (SOR:B)[16]

4. Anti-TNFα agents- biologic DMARDs (PPD prior to treatment) – (SOR:C) for early disease/(SOR:A) for inadequate non-biologic DMARD response[16]
   - Etanercept (50 mg SC qweek)
   - Infliximab (3 mg/kg IV q8weeks)
   - Adalimumab (40 mg SC q2weeks)
   - Anakinra (100 mg SC q24h)
5. Immunosuppressive therapy[18]
   - Azathioprine (1-2.5 mg/kg/d PO divided qD-BID)
   - Cyclosporine (2.5-4 mg/kg/d PO divided BID)
   - Cyclophosphamide (1.5-3 mg/kg PO qD)
   - Surgery
     - Joint replacement
     - Hand reconstruction
     - Synovectomy
6. Intra-articular hyaluronic acid[19]
   - Some evidence of possible small, short-term benefit
     - Diminishes after 15 weeks

Follow-Up[6,16]

1. Validated clinical outcome measurement[16]
   - Tender joint count
   - Swollen joint count
   - Patient's assessment of pain (visual analog scale, VAS)
   - Patient's global assessment of disease activity (VAS)
   - Physician's global assessment of disease activity (VAS)
   - Patient's assessment of physical function/disability
   - Acute phase-reactant value (ESR, CRP)
2. Complete remission defined by the absence of the following
   - Symptoms of active inflammatory joint pain
   - Morning stiffness
   - Fatigue
   - Synovitis on joint examinations
   - Progression of radiographic damage on sequential radiographs
   - Elevation of ESR or CRP

Photo 1: From Canoso JJ: Rheumatology in primary care, Philadelphia, 1997, WB Saunders



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