

RHEUMATOID ARTHRITIS

Background

1. Definition¹

- 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- α 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

- Genetic²
 - 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 course³
- Disease progression variable; joint failure causes physical disability and resultant economic loss¹
- 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

Diagnostics⁴

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 manifestations⁵

- 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 testing⁶
 - 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) antibodies⁸
 - Similar sensitivity to RF but higher specificity
 - Anti-mutated citrullinated vimentin⁹
 - 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 condition¹⁰
 - Elevated ESR¹¹
 - Synovial fluid analysis
 - Elevated protein, normal or decreased glucose
 - WBC 5-50K (PMN predominant)
 - Diagnostic imaging¹²
 - 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% after first 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 RA⁴
- 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 Diagnosis¹³

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-Pharmacologic¹⁴

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-TNF α agents- biologic DMARDs (PPD prior to treatment) – (SOR:C) for early disease/(SOR:A) for inadequate non-biologic DMARD response¹⁶
 - Etanercept (50 mg SC qweek)
 - Infliximab (3 mg/kg IV q8weeks)
 - Adalimumab (40 mg SC q2weeks)
 - Anakinra (100 mg SC q24h)
- 5. Immunosuppressive therapy¹⁸
 - 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 acid¹⁹
 - Some evidence of possible small, short-term benefit
 - Diminishes after 15 weeks

Follow-Up^{6,16}

1. Validated clinical outcome measurement¹⁶
 - 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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