Rheumatoid arthritis: an overview

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RA prevalence

• Chronic inflammatory disease affecting approximately 0.5-1% of the general population
  – Prevalence is higher in North America (approaching 7% in some American Indian tribes or Eskimos) and Northern Europe
  – Lower in countries around the Mediterranean, Central Europe, Asia and South America

• Slightly higher prevalence in women
  – F:M ratio 4-5:1 in < 50 yo, 2:1 in > 60 yo
RA manifestations

- Chronic symmetric polyarticular arthritis typically affecting the small joints of hands and feet
- Characterized by inflammation of the synovium, hyperplasia of the intimal lining as a result of increase in macrophage- and fibroblast-like synoviocytes (pannus)
- Destruction of articuler structures (cartilage and bone): bone erosions
Joint histology

Normal

Collagen-induced arthritis
RA: extra-articular manifestations

- Pulmonary: interstitial lung disease
- Cardiac: pericarditis, myocarditis
- Vasculitis (scleritis, episcleritis, corneal melt, neuritis)
- Secondary Sjögren’s (keratoconjunctivitis sicca)
- Felty’s (splenomegaly, leukopenia, neutropenia)
5: Rheumatoid Arthritis

5-C-2  Rheumatoid arthritis: hand, fusiform swelling
5: Rheumatoid Arthritis

5-C-3  Rheumatoid arthritis: hands, ulnar deviation and muscle atrophy
5: Rheumatoid Arthritis

5-C-4 Rheumatoid arthritis: hands, chronic changes
5: Rheumatoid Arthritis

5-C-8 Rheumatoid arthritis: hand, arthritis mutilans (clinical appearance and roentgenogram)
5: Rheumatoid Arthritis

5-C-19 Rheumatoid arthritis: subcutaneous nodule, olecranon
5: Rheumatoid Arthritis  5-C-20  Rheumatoid arthritis: subcutaneous nodules, fingers
Rheumatoid arthritis: foot deformities
5: Rheumatoid Arthritis

5-C-14 Rheumatoid arthritis: episcleritis
5: Rheumatoid Arthritis

5-C-15  Rheumatoid arthritis: scleromalacia
5: Rheumatoid Arthritis

5-C-16 Rheumatoid arthritis: scleromalacia perforans
5: Rheumatoid Arthritis

5-C-17 Rheumatoid arthritis: scleromalacia perforans, herniation
RA: morbidity & mortality

• Morbidity:
  – Related to extra-articular manifestations: ocular disease, Sjögren’s syndrome, interstitial lung disease, vasculitis
  – Not related to inflammation: infections, cancer and cardiovascular events*

• Mortality: increased mortality due to CV events (40%), cancer (17%), infection (14%), respiratory disease (9%), renal disease (6%)
ACR Classification Criteria for RA

- **Joint involvement**
  - 2-10 large joints (1)
  - 1-3 small joints (2)
  - 4-10 small joints (3)
  - > 10 joints (5)

- **Serology**
  - Low RF+ & low ACPA+ (2)
  - High RF+ & high ACPA+ (3)

- **Acute-phase reactants**
  - Abnormal CRP or ESR (1)

- **Duration of symptoms**
  - ≥ 6 weeks (1)

- **Definite RA:** Score ≥ 6/10
RA pathogenesis

Genetic Susceptibilities  \(\rightarrow\) Environmental Factors
MHC (HLA-DR4, PAD-4, PTNP22, etc.)  (infections, cig smoking)

Autoantibody production

2\textsuperscript{nd} trigger?

Disease manifestation
RA: the Rheumatoid Factor Era

• “Rheumatoid factor” initially identified by its ability to agglutinate sheep red blood cells that has been coated with rabbit serum

• Kunkel showed that this factor is an antibody that recognizes the Fc portion of human IgG (Franklin et al., J. Exp. Med 1957)

• 60s and 70s: RA is an immune-complex disease formed by RF and perhaps other Abs that fix complement

• Caveat: RF is present in only 2/3 of RA patients and in individuals with no RA (i.e. not specific and not sensitive)
RA: The T Cell Centric Era

• Although IC theory could explain the acute inflammatory features of RA, the synovium is rich in T cells

• Genetic studies point to a susceptibility epitope on MHC molecule: HLA-DR (DR4, DR14, DR1)
  – Binds and presents arthogenic peptides to T cells
  – Shape T cell repertoire and permits escape from tolerance or survival of autoreactive clones
  – Serves as target for autoreactive T cells owing to molecular mimicry (bacteria, viruses).

• Animal models strengthened the T-cell-dependency theory. Autoantibody fell out of favor
RA: Cytokine Network

- By the late 1980s new molecular techniques were available to measure cytokines in RA synovium

RA: The ACPA Era

• van Venrooij & colleagues described citrulline as the epitope recognized by anti-citrullinated peptide antibodies (ACPA) in RA (Schellekens et al. JCI, 1998)

• Citrullination is a normal physiological process that occurs inside many dying cells

• Generation of ACPA is MHC dependent

van Venrooij et al. *Nat Rev Rheumatol* 2011
ACPA$^+$ vs ACPA$^-$ disease

- ACPA$^+$ occurs before clinical manifestation
- ACPA$^+$ predicts more aggressive disease
  - More strongly associated with cig smoking
  - More erosive as disease progresses
  - Increased risks of cardiovascular disease
- ACPA$^+$ may predict treatment response
  - MTX, B-cell depletion
Treatment of RA

• Cornerstone: MTX

• Biologics:
  – Anti-cytokine mAbs (TNF-\(\alpha\), IL-1, IL-6)
  – Anti-T cell: CTLA4-Ig (co-stimulation modulator)
  – B cell depletion: anti-CD20

• Others:
  – Kinase inhibitors: Syk and JAK kinases
  – PAD4 inhibition?