Rheumatoid Arthritis

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Introduction

• Chronic multi-system disease of unknown cause.
• **Cause is multifactorial**, with genetic and environmental factors playing important roles.
• Actually considered a multitude of many similar diseases, rather than one disease.
• First event is probably antigen-dependent activation of T cells.
• This leads to: activation and proliferation of synovial lining and endothelial cells, recruitment and activation of additional proinflammatory cells from the bone marrow and circulation, secretion of cytokines and proteases by macrophages and fibroblast-like synovial cells, and autoantibody production.
Epidemiology

- Prevalance of RA is approximately 0.8% of population (0.3 to 2.1%)
- Women: Men ratio: 3:1
- Prevalence increases with age
- Sex-differences diminish in the older ages.
- Affects all races.
- Incidence and severity seem to be lower in rural sub-Saharan Africa and in Caribbean blacks.
**Epidemiology**

- Most frequent onset is in 4th and 5th decade of life.
- 80% of all patients develop disease between 30-50 y/o.
- Approximately, 10% of patients with RA will have an affected first-degree relatives.

- **Monozygotic twins** are at least 4 times more likely to be concordant for RA than dizygotic twins.
- About 15-20% of monozygotic twins are concordant for RA—implying that other factors outside of genetics also play a role in pathogenesis.
RA may affect any organ.
Rheumatoid arthritis (late stage)

Boutonniere deformity of thumb

Ulnar deviation of metacarpophalangeal joints

Swan-neck deformity of fingers

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Normal joint

- Cartilage
- Joint capsule
- Joint synovium
- Bone

Joint affected by rheumatoid arthritis

- Bone and cartilage erosion
- Swollen joint capsule
- Inflamed joint synovium
Genes

- The highest risk for concordance of RA is noted in twins who have two HLA-DRB1 alleles.
- Estimated risk of developing RA in person with DRβ1*0401 is about 1/35 and DRβ1*0404 is 1/20.
- The class II major histocompatibility complex allele HLA-DR4 (DRβ1*0401) and related alleles are known to be major genetic risk factors for RA.

- Other associated alleles:
  Israeli Jews, Asian Indians: association with HLA-DR1 (DRβ1*0101),
  Yakima Indians of North America: association with HLA-Dw16 (β1*1402).
More Genes

- It is estimated that HLA genes only contribute a portion of the genetic susceptibility to RA.
- So, other genes outside of the HLA complex are involved.
- **Genes** that control the *expression of the antigen receptor* on T cells and both immunoglobulin heavy and light chains.

- Polymorphisms in the **RNF** and **IL 10 genes** are also associated with RA.
- Region on **chromosome 3 (3q13)**.
- **Environmental factors** also play a role.
- Climate and urbanization have a major impact on the incidence and severity of RA in groups of similar genetic background.
Etiology

• It is postulated that RA is a manifestation of the response to an infectious agent in a genetically susceptible host.

• A number of possible causative agents have been suggested, including: Mycoplasma, Epstein-Barr virus (EBV), cytomegalovirus, parvovirus, rubella.
How infectious agent lead to persistent inflammation

• Persistent infection of articular structures or retention of microbial products in the synovial tissues.

• Molecular mimicry (recent evidence of similarity between products of certain gram negative bacteria and EBV and HLA-DR4 molecule supported this).

• Superantigens might induce disease.

• Cigarette smoking increases risk of developing RA.
Schematic diagram of disease mechanisms

Environment (pathogens, etc)
Genetics (HLA-DR, PTPN22, etc)

- Innate immunity
- Antigen loading into DCs

Migration to central lymphoid organs

Antigen presentation

- Local inflammation
- Local antigen presentation

Synovium

Lymph nodes
Spleen

- Antigen presentation
- Cytokine production
- Autoantibodies

- Osteoclast activation
- Immune complexes
- Complement activation

DC
MΦ
FLS
B
T
МΦ
PMN
OC
T
T
T
B
Autoantibodies

T and B cell migration to joint

T and B cell activation
T Cell Model for Synovitis in RA

Activation
- TNFα
- IL-1
- IL-2
- IFNγ
- IL-6
- TNFβ
- iNOS
- IL-6

Inhibition
- IL-4
- IL-10
- IL-11
- TGF-β
- sIL-IR
- sTNFR

Arthritogenic antigen

T cell activation

Regulation by cytokines

Effector mechanisms for joint destruction

B cells
- Immunoglobulin

Activation of synoviocytes
- Metalloproteinases

Activation of vascular adhesion molecules
- PMNs, lymphocytes, macrophages into joint
Synovium-proliferartin in RA

- In RA, this lining is greatly hypertrophied (8-10 cells thick). Primary cell populations in this layer are fibroblasts and macrophages.
- Hyperplasia of the lining layer and mononuclear infiltrates in the sublining layer.
- Angiogenesis
Synovium in RA
T cell in rheumatoid synovial tissue surrounded by three macrophages

• *Arrows* point to probable intercellular bridging.

• Contact between macrophages in T cells can lead to antigen-independent activation of macrophages with production of cytokines and proteases.
T cell in rheumatoid synovial tissue surrounded by three macrophages
Main Initiation of Inflammation

- Initiated by T-lymphocytes recognizing antigens in the synovial tissue.

- Activated T-lymphocytes, macrophages and fibroblasts produce pro-inflammatory cytokines that play a key role in synovitis and tissue destruction.

- TNF alpha and IL-1 are two main pro-inflammatory cytokines that enhance synovial proliferation and stimulate secretion of matrix degrading metalloproteinases, other inflammatory cytokines, adhesion molecules, and prostaglandin E2.
Three stages in RA

• **Initiation phase**: nonspecific inflammation

• **Amplification phase**: amplification

• **Chronic inflammation**: tissue injury
Cytokine Disequilibrium in RA

Proinflammatory

TNFα
IL-1

Antiinflammatory

IL-1ra
sIL-1R
sTNFR
IL-10
IL-4
IL-11
Initially

• The earliest event appears to be nonspecific inflammatory response initiated by an unknown stimulus.

• Macrophages and mononuclear cells accumulate in the sublining layer of the synovium.

• 
  
  increased macrophage-derived cytokines: TNF, IL-1β and IL-6.

• Activation and differentiation of memory CD4+ T cells after antigenic peptides are displayed by a variety of antigen-presenting cells in the synovial tissue.
Macrophage Model for Synovitis in Rheumatoid Arthritis

- RF
- Plasma cell
- Proteases
- ODFR
- PMN
- IL-6
- IL-8
- TNFα
- IL-1
- GM-CSF
- Fibroblast
- PGE₂
- Proteases
Fig. 1

Actions of tumour necrosis factor α

Metalloproteinase induction

- M-, GM-CSF induction
- Interleukin-1, 6 induction

Tumour necrosis factor α

- Acute phase response
- Fever
- Weight loss
- Vascular adhesion molecule induction

Macrophage activation
Activated memory T cells are capable of producing cytokines, especially IFN-γ → amplification of inflammation.

Activated T cells express CD154 (CD40 ligand) can induce polyclonal B cell stimulation and differentiation of memory B cells and plasma cells that promote autoantibodies locally.
CD+4 T cells

• Within rheumatoid synovium: CD4+ T cells differentiate predominantly into TH1-like effector cells → producing proinflammatory cytokine IFN-γ (and appear deficient in differentiation into TH2-like effector cells capable of producing anti-inflammatory cytokine IL-4).

• So, macrophages are activated to produce proinflammatory cytokines: IL-1, TNF and increase expression of HLA molecules.
IL-1 and TNF

- Stimulation cells of pannus to produce collagenase and other neutral proteases.
- *Activation of chondrocytes* → stimulation of proteolytic enzymes that can degrade cartilage.
- Contribute to local demineralization of bone by activating osteoclasts.
- Also, prostaglandin E2 produced by fibroblasts and macrophages may contribute to bone mineralization.
Osteoclasts invading bone in RA

- Tartrate-resistant acid phosphatase–positive osteoclasts are shown invading bone in rheumatoid arthritis (see arrows for examples). This process is regulated by receptor activator of nuclear factor κB ligand (RANKL) in the presence of other cytokines, such as macrophage colony-stimulating factor and tumor necrosis factor-α.
Osteoclasts invading bone in RA
T-Cell Activation

RA is a chronic, autoimmune disease in which the activated T cell is a central player in the immunopathology.

Antigen presenting cell (APC)

CD80/86

Major histocompatibility complex

T-cell receptor

Co-stimulatory pathway

CD28

T Cell

Activated T cells trigger:
- Downstream cells
- Cytokines
- Other mediators of RA immunopathology

Macrophage

TNF-α, IL-6, & IL-1

Inflammation and joint destruction

B Cell
Important co-stimulatory receptors

• **CD 80/86 and CD28**: important communication between antigen presenting cell and T cell (communication).

• **CD154 (CD40 ligand)**: important surface molecules on T cells for stimulation of B cells.
B cells

- Resultant production of immunoglobulin and rheumatoid factor can lead to immune-complex formation with consequent complement activation and exacerbation of the inflammatory process.
- (Production of C3a and C5a and the chemotactic factor C5a).
- Other antibodies to self-antigens might be produced.
What is Rheumatoid Factor

- RF is a series of antibodies that recognize the Fc portion of an IgG molecule as their antigen.
- Could be of any isotype (IgM, IgG, IgA, IgE).
- RF developed in humans as a mechanism in order to remove immune complexes, so conditions associated with chronic inflammation have +RF.
- 70% of pts with RA have +RF and another 10-15% pt develop +RF within 2 years after onset.
- High titers tend to suggest more erosive disease and extraarticular manifestations.
What is Anti-CCP

• Anti-cyclic cytrullinated peptide
• Antibody reacts with the common epitope, which has been identified in the past by anti-filaggrin, anti-perinuclear, and anti-keratin antibodies.
• High specificity of 98% for RA.
• Seen in 70% of seropositive RA pts and 33% of seronegative RA pts.
• Could be present for years before articular manifestations.
• Associated with more erosive RA, also with tobacco exposure.
What is Anti-CCP continued

- Citrullination is catalyzed by peptidyl arginine deiminase (conversion of arginine to citrulline): arginine residues on fibrin and fibrinogen may be favored sites for deimination within rheumatoid joints.
Other important features in pathogenesis

- Autoantigens and T cell proliferation
- Some components of articular cartilage help promote ongoing immune response.
- Cartilage antigen glycoprotein-39
- Circulating immunoglobulin G
- Reactive oxygen and nitric oxide products secreted by inflammatory cells generate covalent crosslinked IgG aggregates with biologic properties of true immune complexes
- Impaired apoptosis, impaired regulation.
- New blood vessel formation (VEGF, MAF, HBGF, PGE1 and E2, IL-8, angiopeietin-1, heparanase, epithelial neutrophil activating peptide 78),
Other factors

- Many cytokines (main TNF).
- Mast cells, myeloperoxidase, elastase, lysozyme, collagenase, acid hydrolases, matrix metalloproteinases, IL-1 beta, prostaglandins, platelet activating factor, leukotrienes,
- Cadherin-11: mediates migration of fibroblast-like synoviocytes over articular cartilage, leading to damage.
- Metalloproteinases
- RANK ligand: receptor activator of NF-kappa B ligand regulates mediated destruction of the joint architecture.
Chronic inflammation

- Cascade of cytokines produced in the synovium activates a variety of cells in the synovium, bone, cartilage.
- Tissue damage (chronic inflammation).
- Time required to progress from one step to the next may vary in different patients.
- The events may persist simultaneously.
- Once established, major pathogenic events operative in an individual patient may vary at different times.
Progressive nature

• The process is chronic and reiterative, with successive events stimulating progressive amplification of inflammation.

• Once memory T cells and B cells have been generated, anti-inflammatory and anticytokine therapy may be capable of suppressing disease manifestations, but typically not preventing recrudescence of disease activity once therapy is discontinued.

• RA is progressive in nature.
References

Treatment
Best Practices in the Treatment of Early RA

- Establish the diagnosis of RA early in the course of the disease
- Differentiate RA from self-limiting forms of arthritis that do not require chronic, aggressive therapy with DMARDs
- Profile the patient to “stratify” the disease and establish a prognosis
  - Mild, moderate, or severe disease
  - Aggressive/progressive vs indolent disease
Best Practices in the Treatment of Early RA

- Define a new target for therapy by using an oncology approach
  - Use the most optimal therapy first to maintain low or no disease activity — “zero tolerance for synovitis”
  - Prevent or postpone development of the hallmarks of established disease, disability, and comorbidities that reduce life span
- Institute tight disease control with the most effective combination of therapeutic agents
The Progression of RA

- Early Intermediate Late
- Disability
- Joint Damage

Severity (arbitrary units)

Duration of Disease (years)

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Traditional DMARDs

- Methotrexate
- Sulfasalazine
- Hydroxychloroquine
- Leflunimide
- Auranofin
- Injectable gold salts (rarely used)
Biologics

- Anti-TNF agents (etanercept, infliximab, adalimumab, golimubmab, cerulizamab)
- Co-stimulatory inhibitor (abatacept)
- Anti-CD20/B-cell depleting RX (rituximab)
- Anti-interleukin 6 (tocalizamab)
Case 1: Staging Early RA and Defining Treatment Outcomes

• Katie M. is the 24-year-old daughter of your colleague, who has asked that you see her in your rheumatology office.

• Three months ago, Katie had spontaneous onset of symmetrical small-joint synovitis in her hands and feet for which she has been taking naproxen 500 mg BID. She has done fairly well with this, but adds acetaminophen PRN. The naproxen upsets her stomach so she also takes omeprazole OTC.
Case 1 (continued)

• History: symmetrical arthritis and AM stiffness
• Patient has no history of prior triggers (e.g., infection, psoriasis, inflammatory bowel disease, or photosensitivity)
• Grandmother had severe, deforming RA
• Exam:
  – Modest bilateral swelling and some pain in the wrists, MCPs, PIPs, ankles, subtalar joints, and MTPs
  – Mild, decreased finger curl and wrist extension and flexion
  – No rashes suggestive of systemic lupus erythematosus or psoriasis
  – Small, movable, olecranon nodules are apparent
Case 1 (continued)

- Labs: drawn and pending
- In-office ESR: 68 mm/h
- In-office imaging: X-rays show juxta-articular osteopenia but no erosions
- Assessment: early RA
Case 1 (continued)

• How would you stage the severity of Katie’s early RA?
  – TJC, SJC, physician’s global assessment, HAQ, DAS-28, DAS-44, X-ray, MRI, ultrasound, biomarkers (eg, RF, ESR, CRP)?
  – A combination of these tests and measures?
• How do you distinguish early from established disease in this patient?
• How do you distinguish mild from severe disease?
• Is Katie a “high risk” patient?
• Would you wait for more information before making a treatment decision?
• If so, what additional information do you need?
  – CBC
  – Chemistry profile
  – Serology
  – Parvovirus
  – Anti-CCP antibodies
  – HLA B27
  – Additional imaging data (X-ray, MRI)
Case 1 (continued)

- NSAID
- Prednisone
- Methotrexate
- Hydroxychloroquine
- Leflunomide
- Combination of 2 DMARDs
  - MTX + another conventional DMARD
  - MTX + TNF antagonist (which one?)
- TNF antagonist alone (if so, which one?)
Case 1 (continued)

• What treatment would you start today in each of the following situations:
  – The patient is negative for RF and anti-CCP antibodies?
  – X-rays are normal, but MRI shows erosions?
  – The patient is positive for hepatitis C?
  – The patient is PPD+ but has no history of active TB?

• How will you monitor the patient’s clinical course?
  – Physician’s global assessment?
  – Patient’s global assessment?
  – Health Assessment Questionnaire, Disease Activity Score?
  – Tender Joint Count/Swollen Joint Count?
  – Imaging studies?
  – Labs (eg, ESR, C-reactive protein)?

• How will you define complete remission?
Case 1: Clinical Lessons

• “Staging” patients with early RA—defining the severity of disease
• Defining the “high risk” patient who needs aggressive therapy and distinguishing him/her from one who has self-limiting disease requiring only symptomatic treatment
  – What are the prognostic factors?
• Aligning therapy with clinical status
• Defining remission
• Long-term monitoring of a patient’s clinical status
Case 2: “Killing Me Softly”

- Sue U. is a 53-year-old woman who has seropositive RA and has been seeing you for 10 years. She has been “doing fine” on a regimen of MTX 15 mg/wk and low-dose prednisone (3 mg/d).
- Today, she tells you that she is having some difficulty using her computer keyboard.
Case 2 (continued)

• On exam, Sue U. has no pain and little swelling, but ulnar deviation is becoming more evident

• Labs: CBC, ESR, CRP, and chemistries are within normal limits

• Imaging: X-rays of hands and feet, which showed juxta-articular osteopenia 5 years ago, have not been repeated because the patient had been “doing fine.” Today’s X-rays of the hands show erosions of carpal bones and MCPs in both hands, with moderate joint space narrowing

• Assessment: long-standing seropositive RA
Case 2 (continued)

- Is what you have been doing adequate for monitoring joint damage in this patient?
- Are your clinical assessments good enough since there seems to be a disconnect between Sue U.’s signs and symptoms and the progression of her joint damage?
- What labs should be drawn?
- Would you perform X-rays more frequently?
- What joints would you X-ray?
- How would you score the X-ray damage?
- Would you perform MRI or ultrasound on this patient?
- How would you modify her treatment?
  - Increase the dose of prednisone?
  - Use a combination of traditional DMARDs?
  - Add a TNF inhibitor to MTX? (If so, which one?)
  - Will aggressive combination therapy protect this patient from further damage or is it “too late”?
Case 2: Clinical Lessons

• Potential disconnect between an RA patient’s clinical signs and symptoms and radiographic progression of disease
  – Synovitis and erosive disease may be mediated by 2 distinct processes

• Appropriate clinical assessments in patients with erosive disease who think they are “doing fine”

• Is it ever “too late” for aggressive therapy in patients with RA?