Rheumatic diseases: Classification and Immunology

Raheem Kherani, B.Sc. (Pharm.), M.D.

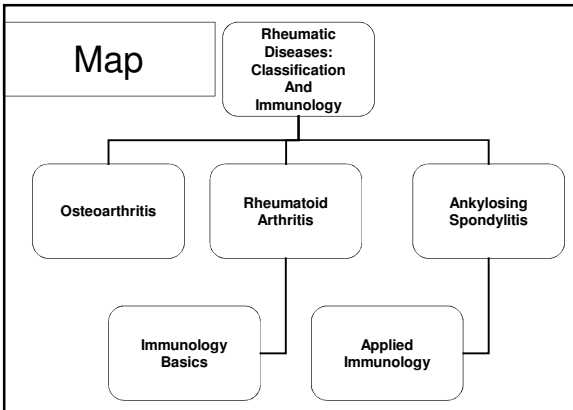
General Objectives

- Approach to pathophysiology and clinical presentation of OA, RA and SpA
- Overview of the immune system
- Introduction to the principles of autoimmune disease

Detailed Objectives

1. Describe the classification system for rheumatic disease
2. In OA, RA and SpA, understand:
   - Where the disease fits into the classification table
   - Epidemiology
   - Etiology and pathogenesis
   - Disease course and clinical manifestations
   - Pertinent laboratory and radiological tests
3. Understand the basic pathogenesis of immune-mediated disease

Map



OA

- Also known as degenerative joint disease
- Most common form of arthritis
- Classified as:
  - Idiopathic (localized or generalized) or
  - Secondary (traumatic, congenital, metabolic/endocrine/neuropathic and other medical causes)
- Characterized by focal and progressive loss of the hyaline cartilage of joints, underlying bony changes

OA

- Usually defined by symptoms, pathology or combination
- Pathology = radiographic changes
  - joint space narrowing
  - osteophytes
  - bony sclerosis
- Symptoms = pain, swelling, stiffness

OA Prevalence

- Overall OA affects
  - 13.9% of adults aged 25 and older
  - 33.6% (12.4 million) of those 65+
  - an estimated 26.9 million US adults in 2005 up from 21 million in 1990
  - Estimated that 59.4 million patients will have OA by the year 2020

OA Unique features

- Disease in weight bearing joints has greater clinical impact.
- About 20-35% of knee OA and ~50% of hip and hand OA may be genetically determined

OA Risk Factors

Modifiable

- Excess body mass (especially knee OA)
- Joint injury (sports, work, trauma)
- Occupation (excessive mechanical stress: hard labor, heavy lifting, knee bending, repetitive motion)
- Men: Often due work that includes construction/ mechanics, agriculture, etc.
- Women: Often due work that includes cleaning, construction, agriculture, etc.
- Structural malalignment, muscle weakness

Non-modifiable

- Gender (women higher risk)
- Age (increases with age and levels around age 75)
- Race (some Asian populations have lower risk)
- Genetic predisposition

Osteoarthritis-Diagnosis

- Clinical
- Supported by X-rays
- Non-inflammatory lab data, if any

OA Clinical

- A.M. stiffness
- Gel phenomenon
- Joint pain and tenderness
- Crepitus
- Bony swelling
- Angulation deformities
- Functional Impairment

OA Features

- Laboratory
  - Noninflammatory synovial fluid
  - Usually < 2000 WBC
- Radiographic
  - Osteophytes
  - Joint space narrowing
  - Subchondral
  - Cysts and sclerosis
  - Malalignment

Natural history of OA

- Progressive cartilage loss, subchondral thickening,marginal osteophytes

Inflammatory Arthritis

- Rheumatoid arthritis
- Spondyloarthropathies
  -Undifferentiated
  -Ankylosing spondylitis
  -Psoriatic arthritis
  -Reactive arthritis (formerly Reiter's syndrome)
  -Enteropathic arthritis / IBD associated
- SLE, Sjogrens, Scleroderma, Polymyalgia rheumatica, Vasculitis, Infectious (bacterial, viral, other), Undifferentiated connective tissue disease

Rheumatoid Arthritis-Background

- Symmetric, inflammatory polyarthritis
- Affects ~1% of our population
- Occurs in women 3x more than men
- Etiology
  -Genetic, class II molecules (HLA-DRB1)
  -Autoimmune
  -?Environmental

Introduction

- RA is a common chronic inflammatory joint condition
- multi-factorial etiology
- variable course with exacerbations and remissions of activity
- inflammation leads to joint damage (erosions)
- can result in severe disability

Historical

- 'Rheumatoid' first used in 1859 by Garrod
- Little evidence for RA prior to 16th Century
- Possibly earlier in New World
- In contrast to OA and Gout

Epidemiology

- Incidence
  1.4/10000 male, 3.6/10000 females
- Prevalence 0.5-2 %
- male:female 1:3
- Worldwide distribution
  higher in Native populations
  absent in some parts of Africa
- Onset any age but maximum
  40 - 70 years in women
  60 - 70 years in men

Genetic factors

- Small increased risk in siblings
- Monozygotic twins
  - 15% concordance
- Dizygotic twins
  - 4% concordance
- HLA DR4

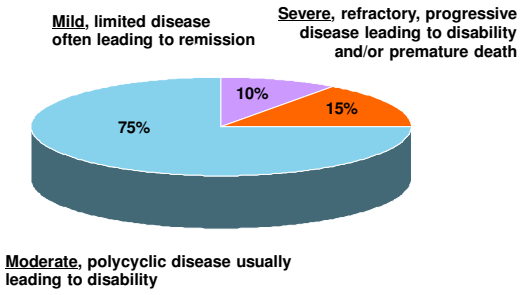
Rheumatoid arthritis is a systemic disease

- Symmetrical polyarthritis
- Prolonged morning stiffness (>45 min)
- Extra-articular manifestations
- Constitutional features (weight loss, fatigue)

History

- Insidious onset
- Slow development of sign & symptoms
- Stiffness
- Polyarticular
- Most common: PIP & MCP of hands
- Morning stiffness > 1hr
- Fatigue, malaise, depression

Clinical course of rheumatoid arthritis



Clinical features

- Symmetrical deforming polyarthritis
  - affects synovial lining of joints, bursae and tendons
  - more then just joint disease
- Presentation
  - Variable
  - Gradual or acute/subacute
  - Palindromic
  - Monoarticular
  - Symmetrical, diffuse small joint involvement

Progression of joint involvement

- Spread occurs within months to years to other joints
  - Almost any joint may be involved
  - Spontaneous remission can occur (after acute onset)
  - Poor prognosis factors exist
- Symptoms
  - Of inflammation
    - stiffness, pain, swelling, warmth, redness

Pattern of joint involvement

- symmetrical
- small joints of hands - DIP spared
- characteristic features
  - Boutonniere
  - Swan neck
  - Z thumb
  - Volar subluxation
  - Ulnar deviation

Functional impairment

- related to underlying disease activity

and

- joint damage due to previous activity

Rheumatoid Arthritis Morbidity and Mortality

RA Patients with Severe Disease (>30 Active Joint Count), 10 year survival is comparable to:

- 3 vessel coronary artery disease
- stage IV Hodgkins Disease

At 2 years, over 50% RA patients would already have suffered irreversible joint damage

Extra-articular manifestations

- Rheumatoid Nodules
- Eye inflammation
  - episcleritis, scleritis
  - corneal melt
- Interstitial lung disease
- Sicca Symptoms
- Felty's

- Rheumatoid Nodules
- Vasculitis
  - small vessel
- Pleuritis
- Pericarditis
- Neuropathy
  - mononeuritis
  - symmetrical peripheral

Investigations

- Hematology
  - CBC, ESR (anemia of chromic disease)
- Biochemistry
  - LFT, CRP
- Immunology
  - RF, ANA, anti-CCP
- Microbiology
  - viral titres
- Radiology
  - XRay, bone scan, MRI

Laboratory Tests

- ESR: elevated
- Serology: Rheumatoid factor
  - Fc of IgG
  - (+) not pathognomonic for RA
    - erosive jt disease, aggressive
  - (-) milder disease course
  - Detectable in non RA pts w/ prolonged infection

Anti-Cyclic Citrullinated Peptide Antibodies (anti-CCP)

- sensitivity 47-76%
- specificity 90-96%
- Can occur in active other conditions (TB, SLE, Sjogren's,Polymyositis, Dermatomyositis, Scleroderma)
- (+) CCP Ab
  - more likely to have aggressive disease and progressive radiographic joint damage

	Inflammatory	Non-Inflammatory	Seroneg SpA
Ankylosis	Rare	-	+
Alignment	++	+ (irregular)	
Bone density	++	-	
Sclerosis	-	++	
Osteophytes	-	++	
Periosteal	-	-	+
Cartilage space	++ (symmetric)	+ (symmetric)	
Cysts		Subchondral	
Distribution	PIP/MCP/carpal	DIP/PIP/CMC	
Erosions	+++	- (erosive OA)	
Swelling	+++ (fluid)	++ (H&B nodes)	

Differential diagnosis

- Post viral (parvo, rubella)
- Reactive arthritis
- SLE
- Polyarticular Gout
- Polyarticular OA

Diagnostic criteria

- ARA 1958
- 11 inclusion criteria
  - 7+ classical RA
  - 5-6 definite RA
  - 3-4 probable RA
- 20 exclusion criteria

ACR 1987 (4/7 necessary)

1. Morning stiffness (> 1 hour)
2. Arthritis of at least 3 areas (> 6 weeks)
3. Arthritis of hand joints
4. Symmetrical arthritis
5. Rheumatoid nodules
6. Serum rheumatoid factor
7. Radiographic changes

Prognosis

- Life expectancy reduced by
  - 7 years in men
  - 3 years in women
- Severe morbidity
- sudden onset do better than gradual
- early knee involvement bad
- Bad RA has a worse prognosis than IHD or Hodgkins

Two Types of Immunity

- **Innate**
  - "possessed at birth, possessed as an essential characteristic"
  - Always present
- **Adaptive**
  - "to make suitable to or fit to a specific use or situation"
  - Created and modified

Lymphocytes

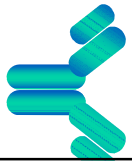
- Two types of lymphocytes
  - ***T-Cells*** (Thymus derived)
    - Natural Killer Cells (Innate Immunity)
    - CD4+ T-Cells (helper cells)
    - CD8+ T-Cells (cytotoxic cells)
  - ***B-Cells*** (Bone Marrow derived)

Adaptive Immunity

- Two Components of Adaptive Immune System
- Humoral (humoral mediated immunity)
  - ***B-Cells*** → Plasma Cells → Antibodies
- Cellular (cellular mediated immunity)
  - ***CD8+ T-Cells*** → Direct Cellular Killing
  - ***CD4+ T-Cells*** → Recruitment of other immune cells (inflammatory response)

Immune Response *Glossary*

- ***Antigen*** – "any substance when introduced into the body stimulates the production of an antibody"
- ***Antibody*** – "a Y-shaped protein, found on the surface of B-Cells or free in the blood, that neutralize antigen by binding specifically to it"
- Also known as an ***Immunoglobulin***



Antigen

Cellular Mediated Immunity

- Via T-Cells
- ***$CD8^+$ T-Cell***
  - Stimulated → Direct Killing
- ***$CD4^+$ T-Cell***
  - Th1 → Stimulated → Macrophage Activation
  - Th2 → Stimulated → B-Cell Activation

Rheumatoid Arthritis (RA)

- RA is thought to be ***T-Cell*** mediated
- Most widely accepted hypothesis:
  - Professional APC encounters some "unknown" antigen
  - It presents this "unknown" antigen to a CD4+ T-helper Cell
  - In a genetically predisposed individual, this starts an immune chain reaction

Damage

- Cytokine cascade results in attraction of PMNs to the joint, penetration through synovial vessels and into joint space
- In active RA up to ONE BILLION cells may gain access to the knee joint EACH DAY and they don't leave!

Rheumatoid Arthritis

- Drugs against TNF-α
  - Infliximab (Remicade®) – Chimeric monoclonal antibody
  - Etanercept (Enbrel®) – Soluble receptor
  - Adalimumab (Humira®) – Humanized monoclonal antibody
  - Certolizumab/golimumab (Cimzia®/Simponi®) - Humanized monoclonal antibody
- Drugs against IL-1
  - Anakinra (Kineret®) - humanized receptor antagonist

Rheumatoid Arthritis

- Drugs against IL-6
  - Tocilizumab (Actemra®) humanized monoclonal antibody
- Drugs against T-cell costimulation
  - Abatacept (Orencia®) - Soluble fusion protein which prevents CD28 from binding to its counter-receptor
- Drugs against B-cells
  - Rituximab (Rituxan®) - Chimeric monoclonal antibody directed against CD20 on B-cells
- Drugs against intracellular targets
  - Tofacitinib (Xeljanz®) – janus kinase 3 (JAK3) inhibitor which influences intracellular signalling

Summary

- Innate and Adaptive Immunity
- B-Cells
  - Act as Professional APCs
  - With Th2 response - turn into plasma cells and synthesize antibodies
- T-Cells
  - Natural Killer Cells – Innate Immunity

Summary

- CD8 T-Cells
  - Interact with MHC Class I (any cell)
  - Direct Cellular Killers
- CD4 T-Cells
  - Interact with MHC Class II (professionals)
  - Th1– Cellular activation - Macrophages
  - Th2– B-Cells - Antibody

Ankylosing Spondylitis Features

- Chronic & progressive form of sero-negative arthritis with axial skeleton predominance
- Affects 0.1-0.2% of the population
- 90-95% of patients are HLA-B27 positive
  - 7% of general population is B27 positive, only 1% of positives will develop ankylosing spondylitis
- Male:female 4-10:1

Features cont.

- Age of onset 15-35 years old
  - juvenile onset associated with more frequent & severe hip & peripheral joint involvement
- Life expectancy generally unaffected
  - most patients able to maintain a normal lifestyle

Features cont.

- Starts with sacroiliac joints
  - begins with sclerosis, eventually get ankylosis
- Progresses to include facet joints, spine, iliac crest, ischial tuberosity, greater trochanter, hips, patella, calcaneus, glenohumeral joints
  - peripheral joint involvement in 30%

Features cont.

- Enthesopathy - calcification & ossification of ligaments, tendons, joint capsules at insertion into bone
- Erosion of subligamentous bone due to inflammatory response
- Fusion of interspinous ligament

Features cont.

- Syndesmophytes - bony bridges between vertebrae & ossification of joint capsule
  - Bamboo spine
- Resorption of vertebral endplates
- Soft tissue findings are new bone formation in outer layers of annulus fibrosis as well as chronic synovitis and capsular fibrosis

Physical Findings

- Patients usually present with low back pain and stiffness, which improves with activity
- Decreased range of motion in lumbar spine
- Thoraco-cervical kyphosis (late)
- One-third of patients will have acute, unilateral uveitis

Other Complications

- Cervical spine fracture, C1-C2 subluxation, cauda equina syndrome
- Peripheral joint ankylosis
- Restrictive lung disease, upper lobe fibrosis
- Aortic root dilation (20%) & murmur (2%)

Genetic Predisposition for Development of Ankylosing Spondylitis (AS)

- AS and HLA-B27 – strong association
- Ethnic and racial variability in presence and expression of HLA-B27

	HLA-B27 positive	**AS and HLA-B27 positive**
Western Europeans	8%	90%
African Americans	2% to 4%	48%

Ankylosing Spondylitis

- Up to 90% of Caucasian patients with AS are positive for HLA-B27
- HLA-B27 is an MHC Class I molecule

Ankylosing Spondylitis

- Remember – MHC is part of the adaptive immune system – so everybody is different
- Those people with HLA-B27 type of MHC Class I are at higher risk for developing AS
- But Why?

Ankylosing Spondylitis

- The HLA-B27 molecule has a specific binding groove
- Only certain peptide fragments will fit into this binding groove
- Big Question: What peptide fragment could be responsible for the initiation of Ankylosing Spondylitis?

Natural History of AS

- Highly variable
- Early stages: spontaneous remissions and exacerbations
- Spectrum of severity
  - Mild with limited sacroiliac or lumbar joint involvement to severe, debilitating disease
- "Pre-spondylitic" phase – unrecognized period of progressive structural damage over a 5-to-10-year period
  - Average delay in diagnosis is 8.9 years

Burden of Illness

- Functional disability
- Potential complications
- Quality-of-life issues
  - Pain, stiffness, fatigue, sleep problems
- Healthcare costs = $6720 annually
  - 75% indirect medical costs
    - Missed workdays
    - Limited-activity days

Obstacles to Desirable Outcomes in AS Until Recently

- Diagnostic and classification limitations
- Lack of universally accepted instruments to assess AS
- Until recently, limited treatment options
  - NSAIDs, COX-2 inhibitors, DMARDs
    - Mostly symptomatic relief only
    - Minimal impact on natural course of disease

Clinical Features of AS

Skeletal	Axial arthritis (eg, sacroiliitis & spondylitis) Arthritis of 'girdle joints' (hips & shoulders) Peripheral arthritis uncommon Others: enthesitis, osteoporosis, vertebral, fractures, spondylodiscitis, pseudoarthrosis
Extra-axial	Acute anterior uveitis Cardiovascular involvement Pulmonary involvement Cauda equina syndrome Enteric mucosal lesions Amyloidosis

Modified New York Criteria for the Diagnosis of AS

- Clinical Criteria
  - Low back pain, > 3 months, improved by exercise, not relieved by rest
  - Limitation of lumbar spine motion, sagittal and frontal planes
  - Limitation of chest expansion relative to normal values for age and sex
- Radiologic Criteria
  - Sacroiliitis grade ≥ 2 bilaterally or grade 3 – 4 unilaterally
- Grading
  - Definite AS if radiologic criterion present plus at least one clinical criteria
  - Probable AS if:
    - Three clinical criterion
    - Radiologic criterion present, but no signs or symptoms satisfy clinical criteria

Disease Activity Assessment

Index	Metric
BASFI	Disability level
BASDAI	Disease activity level
ASAS - IC	Composite sum of disease activity

BASFI = Bath Ankylosing Spondylitis Functional Index
BASDAI = Bath Ankylosing Spondylitis Disease Activity Index
ASAS - IC = ASsessment in Ankylosing Spondylitis Improvement Criteria

Bath Ankylosing Spondylitis Functional Index (BASFI)

- Visual analog scale (VAS) – 10 cm
- Mean score of 10 questions
- Questions level of functional disability, including:
  - Ability to bend at the waist and perform tasks
  - Looking over your shoulder without turning your body
  - Standing unsupported for 10 minutes without discomfort
  - Rising from a seated position without the use of an aid
  - Exercising and performing strenuous activity
  - Performing daily activities of living
  - Climbing 12 to 15 steps without aid

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

- A self-administered instrument (using 10-cm horizontal visual analog scales) that comprises 6 questions:

Over the last one week, how would you describe the overall level of:

- Fatigue/tiredness
- AS spinal (back, neck) or hip pain
- Pain/swelling in joints other than above
- Level of discomfort from tender areas
- Morning stiffness from the time you awake
- How long does morning stiffness last?

Assessment in Ankylosing Spondylitis (ASAS)

- **ASAS 20**: An improvement of ≥ 20% and absolute improvement of ≥ 10 units on a 0–100 scale in ≥ 3 of the following 4 domains:
  - Patient global assessment (by VAS global assessment)
  - Pain assessment (the average of VAS total and nocturnal pain scores)
  - Function (represented by BASFI)
  - Inflammation (the average of the BASDAI's last two VAS concerning morning stiffness intensity and duration)
- Absence of deterioration in the potential remaining domain
  - (deterioration is defined as ≥ 20% worsening)

Patterns of Psoriatic Arthritis

- Distal arthritis
  - involvement of the distal interphalangeal (DIP) joints
- Asymmetric oligoarthritis
  - less than five small and/or large joints are affected in an asymmetric distribution
- Symmetric polyarthritis
  - Similar to rheumatoid arthritis
- Arthritis mutilans
  - A deforming and destructive arthritis
- Spondyloarthropathy
  - both sacroiliitis and spondylitis