OSTEOARTHRITIS & CHRONIC INFLAMMATORY ARTHRITIS

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Mechanisms of Host Disease

OUTLINE

PART ONE: THIS LECTURE
• Osteoarthritis
• Rheumatoid arthritis
• Seronegative Spondyloarthropathies

PART TWO
• Crystal induced arthropathies
• Polymyalgia Rheumatica
• Fibromyalgia
• Benign Tumors of the Joints

OBJECTIVES
• Distinguish primary from secondary osteoarthritis.
• Briefly explain the pathogenesis of osteoarthritis.
• Know the cardinal clinical and pathologic differences between inflammatory arthritis and degenerative arthritis.
• Differentiate between the pathogenesis of rheumatoid arthritis, seronegative spondyloarthropathies, and osteoarthritis.
• Describe the subsets of seronegative spondyloarthropathies.
• Compare and contrast the clinical and pathologic findings found in rheumatoid arthritis and seronegative spondyloarthropathies.
IMPACT OF ARTHRITIS

- 1 out of 5 US adults carries diagnosis of arthritis (52 million)
  - Most common is osteoarthritis
  - Other forms include rheumatoid arthritis, lupus, gout
- 22.7 million report limitations due to arthritis
- 2/3 individuals with arthritis are <65 years of age
- More common among women (26%) vs men (19%)
- Estimated to reach 67 million by 2030
- $128 billion in medical expenditures and lost earnings in 2003

http://www.cdc.gov/chronicdisease/resources/publications/aag/arthritis.htm

OSTEOARTHRITIS

Epidemiology
Pathogenesis & Morphology
Clinical Manifestations
Diagnosis
Management
OSTEOARTHRITIS (OA)

- AKA Degenerative Arthritis
- Characterized by degeneration of articular cartilage
  - Distinct from an inflammatory arthritis
  - Chondrocytes of articular cartilage respond to biomechanical and biologic stresses in way that results in breakdown of matrix
- Most common type of arthritis
- Classified as primary or secondary
  - Primary most common

SECONDARY OA

- Trauma
- Inflammatory arthritis
  - Rheumatoid arthritis, infectious arthritis, seronegative spondyloarthropathies
- Dysplastic and hereditary conditions
  - Congenital hip dysplasia, epiphyseal dysplasia, chondrodystrophies, Perthes disease
- Kashiin-Beit disease: Joint hypermobility
- Bone disorders
  - Osteonecrosis, osteochondritis, Paget disease
- Metabolic & endocrine disorders
  - Crystal arthropathies, hemochromatosis, ochronosis, Wilson disease, bleeding disorders, acromegaly

OSTEOARTHRITIS

- Seen most commonly in persons >65 years of age
- Radiographic changes
  - >45 years of age: in knee 37%, hip in 27%, hands in >90%
  - Most with radiographic changes have few symptoms
- Symptomatic OA
  - >45 years of age: 17% in knee, 9% in hip
  - Lifetime risk of symptomatic OA of knee: 66%
  - Higher with obesity and risk factors
MORE FACTS ABOUT OA

• Costs to US per year in healthcare: $185 billion annually
• 27 million people affected in US
• In 2009, OA was 4th most common cause of hospitalization
• In 2009, 905,000 knee & hip replacements performed
  • Cost of $42.3 billion

PATHOGENESIS: RISK FACTORS

• Age strongest risk factor
• Obesity most associated with OA of the knee but may contribute to hip & hand
  • Leptin may have influence on chondrocytes
• Chronic repetitive impact loading
  • Long term weight bearing sports
• Genetic factors
  • Many have family history, especially finger involvement in women
  • Joint dysplasia increases risk for hip OA

NORMAL MORPHOLOGY

• Specialized connective tissue
  • Collagen, proteoglycans, water, chondrocytes
• Collagen: Mostly type II collagen
  • Distributed compressive forces
  • Tethers cartilage to subchondral bone
  • Dissipates weight bearing force, protecting soft tissue & subchondral bone
• Proteoglycans
  • Aggrecan: high fixed negative charge allows for retention of water
  • Chondrocytes mediate turnover of matrix components
  • Sparsely scattered
  • Chondrocytes influenced by factors (e.g) growth factors, cytokines, physical stimuli
**MORPHOLOGY: OA**

- Articular cartilage
- Loss of homogeneity, disruption & fragmentation of surface
- Deeper layers of cartilage invaded by capillaries from calcified cartilage
- Chondrocytes which are normally isolated cells now proliferate & cluster
- Osteophytes form
- Early OA: water content of diseased cartilage increases & cartilage swells
- Increase in both anabolic & catabolic activity
  - Eventually, anabolic cannot keep up with catabolic activity
  - Degradative enzymes released by chondrocytes
  - Matrix less structurally sound & less organized; cannot withstand forces
  - Causes for biochemical & metabolic changes not fully understood

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**OSTEOARTHRITIS**

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**OA: CLINICAL CHARACTERISTICS**

- Localized joint pain
- Stiffness
- Worse with weight bearing
- Better with rest
- Very little morning stiffness
- Distal & Proximal interphalangeal joints
  - Heberdens & Bouchards nodes
- Knees, Hips, Cervical & lumbar spine
- Joint crepitus
- Swelling not common
- Bony enlargement
OA: XRAYS & LABS

- Xrays
- Decreased joint space
- Subchondral sclerosis & cysts
- Osteophytes (spurs)
- Remember, xray findings may not always be proportionate to pain

LABS
- No useful tests
- Not inflammatory

OSTEOARTHRITIS

American College of Rheumatology Image Library
Image: 06-04-0084

American College of Rheumatology Image Library
Image: G036

American College of Rheumatology Image Library
Image: G036

American College of Rheumatology Image Library
Image: G036
OSTEOARTHRITIS

OA: MANAGEMENT

- No cure
- Manage risk factors: physical therapy, exercise, weight loss, dietary measures
  - Quadriceps strengthening in knee OA
- Pharmacologic
  - Acetaminophen, Nonsteroidal anti-inflammatory drugs & other analgesics
  - Intra-articular steroid injections in selected cases
- Surgery
  - Joint replacement
**RHEUMATOID ARTHRITIS**

- Systemic
- Chronic
- Inflammatory
- Autoimmune

- Primarily involves joints but can affect extra-articular organs
  - Lungs (interstitial lung disease, pleural effusion)
  - Anemia of chronic disease
  - Eyes (episcleritis, scleritis)
  - Skin (vasculitis), soft tissue (rheumatoid nodules)
  - Heart (pericarditis)
  - Central nervous system rarely (pachymeningitis), peripheral neuropathy

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**EPIDEMIOLOGY & RISK FACTORS**

- Prevalence of 1%
- 5 times more common in women vs men
- Peak incidence 2nd-5th decade of life

- Genetic risk factors: HLA-DRB1 locus
- Genetic susceptibility

- Environmental risk factors
  - Potential triggers: infectious (P. gingivalis and others)
  - Prevalence of periodontal disease 2 fold amongst RA
  - Smoking and anti-CCP antibodies (cyclic citrullinated peptide)
  - Relative risk 1.4 for developing RA compared to nonsmokers

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**RHEUMATOID ARTHRITIS VS OSTEARTHRITIS**

- Inflammatory (swelling)
- Degenerative (no swelling)
- Prolonged morning stiffness
- Limited morning stiffness
- Systemic manifestations
  - Localized symptoms
  - Joints involved:
    - DIPs, PIPs, CMCs
    - Lumbar spine commonly involved
  - PIPs, MCPs, wrists
  - Lumbar spine not involved
PATHOGENESIS

- Activation of CD4+ helper T cells
  - Environmental trigger in genetically predisposed individual
- T and B cell responses to self antigens
  - Activated CD4+ helper T cells, TH17 cells, B lymphocytes & plasma cells, macrophages
- Inflamed synovium
  - Increase in inflammatory cytokines (IL1, IL6, TNF, IL8, IL17, IFN gamma)
- Fibroblasts, chondrocytes, synovial cells respond to pro-inflammatory milieu
  - Destructive enzymes: collagenase, stromelysin, elastase, PGE2
- Osteoclast response
  - Increased expression of RANKL (receptor activator of nuclear factor kappa B ligand)
  - Osteoclast activation leading to bone erosions

MORPHOLOGY: PANNUS FORMATION

- Chronic papillary synovitis
- Synovial cell hyperplasia & proliferation: THICKENED
- Pervascular inflammatory cell infiltrates: DENSE
  - CD4+ T cells, plasma cells, macrophages
- Angiogenesis: VASCULAR
  - Neutrophils & organizing fibrin on synovial surface: LAYENED
- Increased osteoclast activity: ERODED
**RA: Diagnosis**

- Clinical Diagnosis
  - Chronic, symmetrical, inflammatory polyarthritis
  - Extra-articular manifestations may occur
    - Rheumatoid nodules, interstitial lung disease
- Blood tests
  - Rheumatoid factor
  - Anti-CCP antibody
  - Elevated inflammatory markers (sedimentation rate, C-reactive protein)
- X-rays
  - Erosions and peri-articular osteoporosis
- Synovial fluid
  - Inflammatory, low glucose, nonspecific

**Rheumatoid Nodule**

Rheumatoid nodule: area of fibrinoid necrosis (center) surrounded by palisading histiocytes (arrows).

**Treatment**

- Non-steroidal anti-inflammatory drugs
  - Often not enough as monotherapy
- Corticosteroids (prednisone)
  - As a bridge
  - Too many side effects to use as monotherapy
- DMARDS (disease modifying anti-rheumatic drugs)
  - Mainstay long-term treatment
  - Mostly immunosuppressive
- Non-biologic DMARDs
  - Methotrexate
  - Leflunomide
RA TREATMENT: BIOLOGICS

- Anakinra
- Anti-IL1
- Etanercept, Adalimumab, Infliximab
- Anti-TNF alpha
- Tocilizumab
- Anti-IL 6
- Abatacept
- CTLA4 agonist
- Blocks CD28 co-stimulation of T cells
- Rituximab
- Anti-CD20
- Causes destruction of B cells
- Tofacitinib (oral)
- JAK1 and 3 inhibitor
- Janus associated kinase
- Blocks signaling for inflammatory cytokines

SERONEGATIVE SPONDYLOARTHRITIS

- Ankylos = Greek for “bent,” fusion
- Spondylos = Greek for “vertebral disk”
- Group of inflammatory arthritides which primarily involve ankylosing of the spine
  - Inflammatory back pain
  - Improves with exercise, not relieved by rest
- Different pattern of joint involvement compared to RA
  - Cyclic, symmetric, more large joints involved
  - Axial involvement: sacroiliitis (upper buttck pain, worse in the morning, associated with stiffness), “bamboo spine” (not seen in RA)
- Enthesitis = inflammation of tendon insertions (not seen in RA)
- Extra-articular manifestations
  - Scleritis (not seen in RA), genitourinary tract (in reactive), skin (in psoriatic), GI tract (in IBD associated)

SPONDYLOARTHRITIDES

- Psoriatic arthritis
- Ankylosing spondylitis
- Inflammatory Bowel Disease (IBD) related
- Reactive Arthritis
  - Formerly known as Reiter Syndrome
  - Undifferentiated spondyloarthritis

EPIDEMIOLOGY

- 348 - 1,310 per 100,000 among persons 25 years and older in US
- 639,000 – 2,417,000 adults in US
- HLA B27
  - Allele of MHC I (or HLA Class I)
  - 90% of Caucasian patients with AS, 50% of African Americans with AS
  - 80-70% in psoriatic or IBD related spondyloarthritis
  - 7-9% of healthy population
- Typically age 16-30 years

PATHOGENESIS:

- Arthrogenic theory
- AKA “Molecular Mimicry”
- Yersinia, Shigella, Salmonella, Campylobacter, Chlamydia
PATHOGENESIS: THEORY II

- Misfolding & dimerization hypothesis
- Unrelated to antigen presentation
- Tendency to misfold & form dimers
  - Leads to inappropriate stimuli & inflammation
- Homodimers
  - TNF α induction
  - Direct activation of NK cells, dendritic cells & CD4 T cells
  - CD4 T cells then produce IL-17


SPONDYLOARTHRITIS: PATHOGENESIS

- TNF α plays a role
  - Similar to RA
- IL-17, IL-23, TH 17 cells also play a substantial role
  - Different from RA
- IL-17
  - Important role in defense against extracellular bacteria
  - Dysregulated expression leads to joint destruction
    - Increase in proinflammatory cytokines
    - Increase in metalloproteinases
    - Increase in RANKL activity
- IL-23
  - Strongly overexpressed in gut of AS patients
  - Promotes highly specific enthesal inflammation


PATHOGENESIS: IL-17

- Increase in proinflammatory cytokines
- Increase in metalloproteinases
- Increase in RANKL activity

SPONDYLOARTHROPATHY: SACROILIITIS

- Granulation tissue erodes through bone & cartilage into joint cavity
- Synovial hypertrophy
- Infiltration of sub synovium: macrophages, lymphocytes, plasma cells
- Advanced disease:
  - Erosion of bone
  - Cartilage fusion (loss of joint space)
  - Sclerosis in pararticular bone
- Osteoblast activation eventually leads to replacement of cartilage by new bone -> AKA ankylosis


SPINAL ANKYLOSIS

- Two important processes:
  - Spinal inflammation
  - Spinal subluxation
  - Inflammation at vertebral corners & subsequent development of syndesmophytes
- Evidence for link between both
  - But also evidence that osteoporosis may not be completely dependent on inflammation


SYNDESMOPHYES

- Sclerosis & squaring of vertebral corners
- Syndesmophytes leading to complete bridging ossification
Spondyloarthropathy: Diagnosis

- Inflammatory back and/or buttock pain
- Chest wall pain
- Enthesitis (ie Achilles tendon, plantar fascia)
- Dactylitis: sausage shaped swelling of digit caused by flexor tenosynovitis
- Extra-articular: uveitis (25-30% of patients)
- Sacroiliitis on imaging (MRI or xray)

Subsets of Spondyloarthropathy

- Ankylosing spondylitis: “Bamboo spine”
- Reactive arthritis: TRIAD of nongonococcal urethritis, conjunctivitis, arthritis
  - Many however have only the arthritis
  - Follows certain ocular infections & sexually acquired infections
- Keratoderma blennorrhagica
  - Self limiting over 4-12 months (10-20% develop chronic spondyloarthropathy)
- IBD associated spondyloarthropathy
  - 5-10% of patients with Crohn disease or Ulcerative colitis
- Psoriatic arthritis
  - Peripheral psoriatic arthritis in 15-30% of patients with psoriasis
  - Over spondyloarthropathy in 10% of patients with psoriatic arthritis

Keratoderma Blennorrhagicum
DACTYLTIS

SYPNDYLOARTHROPATHY: TREATMENT

- Education & Physical Therapy
- Non-steroidal anti-inflammatory drugs
  - Limitations, especially with underlying IBD
- Oral DMARDs (disease modifying anti-rheumatic drugs)
  - Sulfasalazine, methotrexate
- Biologic Therapies
  - Anti-TNF α
    - Adalimumab, Etanercept, Infliximab
  - Anti-IL-23/IL-12
    - Ustekinumab
  - Anti-IL-17 in development
    - Ixekizumab, Secukinumab (clinical trials in psoriasis)