Spondyloarthropathies (SpAs)

- History, Spectrum of diseases
- Distinguishing characteristics
- Pathogenesis
- Treatment
Proto-typical Spondyloarthropathy

Ankylosing Spondylitis
Clinical Presentation of Classical Ankylosing Spondylitis

- Male, < 45 years old at onset
- Duration greater than 3 months
- Insidious onset of low back pain
- Prolonged AM stiffness
- Nocturnal awakening
- Frequent referral to the buttocks area (“hamstring pain”)
- Not improved with rest
- Dorsal spine pain
- Anterior chest wall pain
Patient History

- 21 yo WF several years of left buttock pain and hip pain, recent worsening
- AM stiffness, pain with ambulation, using a cane, +/- improvement with NSAIDs
- Ortho MRI: erosions of the acetabulae, fluid in hips, inflammatory arthritis
- Total hip replacement being considered. Referred
- Exam: decreased hip rotation, some decreased LS motion
- MRI review also early sacroilitis
Patient History

Continued

• Sed rate 52, HLA-B27 positive.
• Began physical therapy, full dose NSAIDs
• Eventually begun on TNF inhibitor
• Now 25 years old, ambulates with modest limp, no cane, working as a news reporter and recently did 11 mile hike in the Appalachians
• And no hip replacement
History
1800’s

- Gout
- Acute rheumatism / St Vitas dance
- Chronic Rheumatism
- Sciatica
- Rheumatic gout
- Hypertrophic/Atrophic Arthritis
- Osteoarthritis
- Rheumatoid arthritis
- Gout
History
Early 1900’s

- Infectious arthritis
- Rheumatic fever
- Gout
- Chronic arthritis (atrophic, hypertrophic, sciatica, spondylitis (atrophic and hypertrophic)
- Psoriatic arthritis
- Metabolic
- Muscular rheumatism
History
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History

independent entities

• Atrophic Spondylitis/Marie-Strumpell’s/Rheumatoid Spondylitis
• Psoriatic arthritis (?part of the spectrum of RA) (e.g., DIP, nail suggest not)
• Reiter’s Syndrome (Reactive arthritis)
• Enteropathic arthritis (associated with inflammatory bowel disease)
HLA-B27

- 1973 association with ankylosing spondylitis
- Wide spectrum of severity of AS/ inflammatory back disease
- Subsequent association with other previously described conditions (eg AS, reactive arthritis, uveitis, psoriatic arthritis) in the spondyloarthopathies
Undifferentiated Arthritis (Spondyloarthropathies)

Juvenile Pauciarticular Arthritis (Spondylitis)

Arthritis of UC and Crohn’s Disease

Psoriatic Arthritis

Ankylosing Spondylitis

Acute Anterior Uveitis

Reactive Arthritis (Reiter’s)
Spondyloarthropathies

- Undifferentiated Spondyloarthritis (uSPA)
- Psoriatic Arthritis
- Acute Anterior Uveitis
- Reactive Arthritis (Reiter)
- Arthritis Associated with Ulcerative Colitis/Crohn Disease
- Juvenile Spondyloarthritis

Ankylosing Spondylitis

Scientific American Medicine
HLA-B27

- Present in 7-9% of Caucasian population, <1% Japanese population, >10-20% of indigenous populations of the Northern Hemisphere
- 1 to 10% of HLA-B27-positive adults who have a disease-associated B27 (maybe up to 20% esp if + family history)
- Caucasians with AS: 90% positive
- African Americans with AS: 50% positive
- Psoriatic spondylitis/Arthritis of IBD: 50-60% positive
Pathogenesis/HLA-B27

- Encoded by locus on major histocompatibility complex (MHC)
- Multiple subtypes, some more clearly associated with spondylitis
- Present antigens to CD8 T-cells
- Result: production of proinflammatory cytokines (TNF, IL-23, IL-17) and production of effector molecules
- Multiple other non-HLA-B27 mutations occur in HLA-B27 patients
Theories of Pathogenesis

Cross reactive peptides

Generation of cross-reactive peptides derived from bacterial proteins and self-proteins that bind specifically to HLA-B27.
Theories of Pathogenesis

HLA-B27 Misfolding and Dimerization Hypothesis
Key cytokines in Spondyloarthropathies
Effector cytokines

- Synovitis: TNF, IL-17
- Bone destruction: TNF, IL-17
- Osteoproliferation: IL-22
- Enthesitis: IL-17 and IL-23
- Gut inflammation: IL-17, TNF

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Clinical Characteristics

- Inflammatory back disease
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Characteristics of Inflammatory Back Disease

- Lower back pain/buttock pain
- Radiate down the back of the thigh and simulate radicular or hamstring pain.
- AM Stiffness, improved with activity often after several hours.
- Nighttime awakening hours after falling asleep
- Symptoms tend to ease with physical activity, and patients describe stiffening after inactivity.
- Nonsteroidal antiinflammatory agents often partially alleviate symptoms
Characteristics of Inflammatory Back Disease and spondyloarthropathies

• Dorsal spine pain
• Anterior chest wall pain (eg sternocostal, manubriosteral, sternoclavicular) 45%
• Juvenile spondyloarthropathy often presents with hip pain and enthesitis (Enthesitis Related Arthritis = ERA)
Clinical Characteristics

Frequency of inflammatory back disease

- Inflammatory back disease
  - Ankylosing spondylitis >80%
  - Reactive arthritis ~10-20%
  - Inflammatory bowel disease ~10%
  - Psoriatic arthritis ~10%
- Chronic low back pain: 20% of the population
  5% of patients with chronic LBP have inflammatory back disease
Physical findings

- Often limited early on
- **Straightening of the normal lumbar lordosis** may be evident on inspection
- **Impaired spinal mobility** may be detected using the Schober which assesses forward flexion of the lumbar spine.
- Decreased chest expansion of < 5 cm (measured at ~nipple line/below breasts.)
- Kyphosis
Schober’s Test

posterior superior iliac spine
Physical findings

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- Kyphosis
Kyphotic appearance
Late Stage Ankylosing Spondylitis
Clinical Characteristics

- Inflammatory back disease
- Peripheral Spondyloarthropathy
Peripheral Spondyloarthritis

General comments

• Present in ~50% of patients with AS
• Predominant symptoms in psoriatic arthritis, reactive arthritis, enteropathic arthritis, often in juvenile spondyloarthritis
• Often asymmetrical, lower extremity predominant
• May be associated with other extra-articular manifestations
  • Enthesitis, dactylitis
  • Uveitis
  • Mucocutaneous and skin lesions, bowel lesions
Peripheral Spondyloarthropathy

General comments: arthritis

Asymmetrical Inflammatory arthritis

Lower extremity predominance
Peripheral Spondyloarthropathy

Enthesesis

• Enthesitis: inflammation at tendinous/ligamentous insertions
  • Achilles tendon
  • Plantar fascia
  • Epicondylitis
  • Atypical sites eg costal muscle insertions, iliac crest
Enthesitis

Inflammatory Enthesitis

- Periosteal new bone formation
- Subchondral bone inflammation and resorption

Enthesitis

Enthesitis
Achilles tendonopathy
Enthesitis
Plantar fasciitis
Sites of enthesitis seen in SpAs

- Nuchal crest
- Manubriosternal
- Costochondral
- Rotator Cuff insertion
- Greater tuberosity of humerus
- Medial/lateral epicondyles
- Iliac crest
- Greater trochanter femur
- Medial/lateral tibial condyles
- Patellar margins
- Achilles insertion
- Spinal processes
- Ischial tuberosity
Peripheral Spondyloarthropathy
Dactylitis

- “Sausage toe or finger”
Peripheral Spondyloarthropathy

Reactive Arthritis

- Reactive arthritis (Reiter’s Syndrome) (post-infectious)
  - Arthritis
  - Conjunctivitis
  - Urethritis
- Follows enteric infections and sexually acquired infections (non-gc) by several weeks. Is NOT an infection/septic arthritis
- Defined triggering event
- Classic triad infrequently seen now
Reactive arthritis

- Mucocutaneous ulcers

  Rash, similar to pustular psoriasis
  (Keratoderma blennorrhagica)
Peripheral Spondyloarthropathy
Enteropathic Spondylitis

- Spondyloarthritis ~5 to 10% of patients with Crohn disease or ulcerative colitis, indistinguishable from ankylosing spondylitis, not parallel the course of the IBD.
- Acute peripheral synovitis ~20% of IBD patients, often associated with flares of the bowel disease, not associated with HLA-B27.
- Microscopic inflammatory lesions are seen on colon biopsies of patients with any axial spondyloarthropathy.
Bowel inflammatory changes and Spondyloarthropathies

• CIBD: 30% have either peripheral arthritis or axial arthritis
• 6% of patients with AS eventually develop CIBD
• 60% of AS patients have subclinical inflammatory bowel findings on pathological evaluation
• Subset of patients with psoriatic arthritis also have inflammatory bowel findings
Peripheral Spondyloarthropathy
Psoriatic arthritis

- ~15-30% of patients with psoriasis have peripheral arthritis
- ~10% of patients with psoriasis have spondylitis (HLA-B27+)
- Similar to other spondyloarthopathies (asymmetrical, may be oligoarthritis)
- Difference: may have more upper extremity involvement
- Widely variable course from episodic to progressive and debilitating
- No correlation of severity or activity of the psoriasis
Psoriatic arthritis
asymmetrical oligoarthritis
Psoriatic arthritis
destructive polyarthritis

Digital resorption
Psoriatic arthritis

Psoriatic nail involvement

Adjacent DIP involvement
Psoriatic arthritis
Nail and DIP involvement

Psoriatic Nail Changes
Uveitis

- 30-40% patients with AS, also seen in other spondyloarthropathies
- Associated with HLA-B27 Abrupt onset of unilateral pain, hyperemia, photophobia, visual blurring
- May recur, may involve contralateral side
- Multiple other causes including sarcoidosis, Lyme disease, syphilis, TB, toxoplasmosis
Diagnosis of Spondyloarthopathy

- Compatible history and physical exam
  - Including presence of inflammatory back pain, asymmetrical arthritis, heel pain, dactylitis, uveitis, NSAID response
  - FH IBD/psoriasis, NSAID response
- Supportive labs: Elevated inflammatory markers (ESR/CRP) : 50%
  - Inflammatory joint fluid in peripheral arthritis
  - HLA-B27 if compatible history
- Imaging studies: X-ray sacroiliitis : definitive diagnosis
  - If negative x-ray : MRI imaging; if positive: nonradiographic spondylitis
  - If negative MRI : ?alternative diagnosis, ? Non-radiographic spondylitis
Treatment Rationale

- Symptoms
- Progression of peripheral arthritis, recognizing disease variability.
  - Enteropathic peripheral arthritis: often benign course
  - Reactive arthritis: often self-limited but may be persistent in a minority
  - Psoriatic arthritis: widely variable from episodic monoarthritis to severe deformans
- Progression of spondylitis?
Psoriatic arthritis

arthritis deformans
Early Sacroiliitis

Radiographic changes required for a diagnosis of Ankylosing Spondylitis
Sacroiliitis on MRI

Patients with MRI changes without x-ray changes may be considered to have non-radiographic spondylitis.
Fused SI joints
Classic Spondylitis
Inflammation and osteogenesis

• MRI have described an association between the presence of inflammation at vertebral corners and the subsequent development of syndesmophytes at the corresponding vertebral corners on radiography.
• Early treatment of inflammation could potentially alter the course of the spondylitis
Early and later Spondylitis

Scientific American Medicine
Treatment

- NSAIDs (?disease modifying)
- PT
- Non-biological agents (Sulfasalazine, Methotrexate,) for peripheral arthritis
- Biological agents (TNF inhibitors, non-TNF inhibitors) for peripheral and axial disease
- Treat associated manifestations (uveitis, enthesitis)
- Treat associated diseases?
  - IBD (benefit)
  - Enterpathic infection (? May benefit)
  - Psoriasis (non benefit)
Biological Therapies in Spondyloarthropathies

<table>
<thead>
<tr>
<th>TNF inhibitors</th>
<th>TNF inhibitor benefits</th>
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<tbody>
<tr>
<td>Infliximab (Remicade)</td>
<td>• Improvement in signs and symptoms</td>
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<tr>
<td>Entanercept (Enbrel)</td>
<td>• Improve synovitis, enthesitis</td>
</tr>
<tr>
<td>Adalimumab (Humira)</td>
<td>• Improvement in patient function</td>
</tr>
<tr>
<td>Golimumab (Simponi)</td>
<td>• Improvement in MRI dx inflammation</td>
</tr>
<tr>
<td>Certolizumab (Cimzia)</td>
<td>• NOT yet proven beneficial in reducing radiographic progression in the spine</td>
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TNF inhibitor benefits include:
- Improvement in signs and symptoms
- Improve synovitis, enthesitis
- Improvement in patient function
- Improvement in MRI dx inflammation
- NOT yet proven beneficial in reducing radiographic progression in the spine
Risks of Biological Therapy

- Risks of infections
- Reactivation TB, exacerbation of hepatitis B
- Worsening of advanced heart failure
- Uncertainties re: risks of cancer and recurrent cancers
Alternative biological therapies

- Secukinumab (Cosentyx): anti-IL-17: ankylosing spondylitis, psoriatic arthritis
- Ustekinumab (Stelara) IL 12/23: psoriatic arthritis only
Biological Therapies

drug specific issues

- Etanercept not effective in IBD and uveitis
- Adalimumab actually approved to treat anterior uveitis and IBD
- Secukinumab may exacerbate IBD
- Secukinumab is not known to exacerbate multiple sclerosis
- No specific evidence of efficacy for abatacept (Orecia) or tocilizumab (Actemra)
Cardiovascular disease in the Spondyloarthropathies

- The spondyloarthropathies are associated with increased risk for death
- Inflammation and chronic disease play an important role on mortality
- Cardiovascular and cerebrovascular disease are a major cause of death
- Effective treatment could have a beneficial effect also in mortality in AS, since such an effect has been shown in rheumatoid arthritis.
- Treat the disease in order to minimize the inflammation burden and treat comorbidities
?? Questions ??
Sacroilitis on imaging + ≥1 SpA feature

- HLA-B27 plus ≥ 2 other SpA features
  - Inflammatory back pain
  - Arthritis
  - Enthesitis
  - Uveitis

- Dactylitis
- Psoriasis
- Crohn's disease/ulcerative colitis
- Good inflammatory response to NSAIDs
- Family history for SpA
- HLA-B27
- Elevated CRP
Classification criteria for peripheral SpA

Arthritis* or enthesitis or dactylitis, PLUS either

One of these

- Uveitis (anterior)
- Psoriasis
- Crohn's disease or ulcerative colitis
- Preceding infection (within 1 month)
- HLA-B27
- Sacroiliitis on imaging

(Peripheral arthritis; predominantly lower limb and/or asymmetric)

Two of these

- Arthritis
- Enthesitis
- Dactylitis
- Inflammatory back pain (ever)
- Family history of SpA