Non-structural causes of low back pain: Spondyloarthritis (SpA)

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AUTO SHOW


MASTERS

We find what we look for and we look for what we know

Lecture Outline

- Case
- Epidemiology
- Pathophysiology
- Clinical manifestations
- Laboratory findings
- Image characteristics
- Diagnostic Criteria
- Treatment
- Questions/Discussion

Case

- A 42-year-old female presents with a 4-month history of left buttock pain
- Deep and aching with radiation into the posterior thigh and buttock
- Denies numbness, tingling, weakness
- Associated with >1 hour morning stiffness
- Pain improves with physical activity
- Pain was significantly reduced with the use ibuprofen (can no longer take NSAIDs)
- 8-9/10 on NPRS

Case, continued

- Allergies: NKDA
- Medications: Ambien 5 mg PO QHS PRN
- Past Medical History: Ulcerative colitis diagnosed 6-months ago after rupture colon
- Past Surgical History: Partial colectomy on setting of above
- Family History: Non-contributory

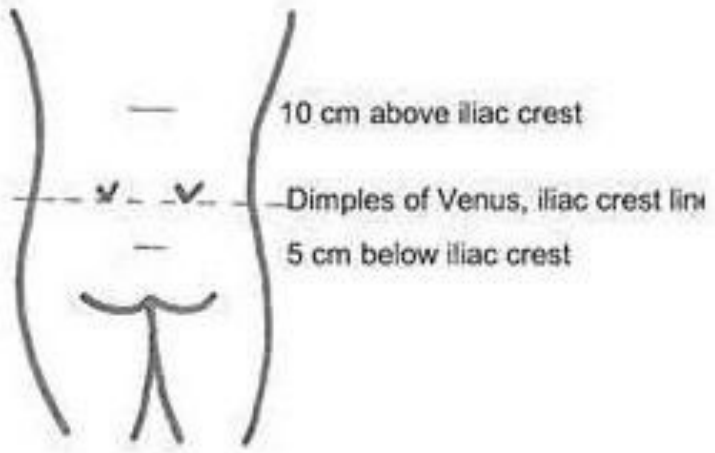
Case, continued

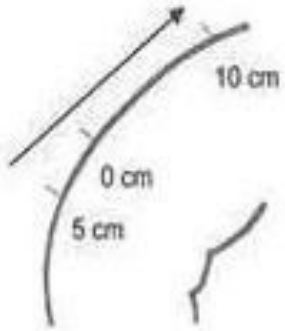
- Other relevant data
  - MRI L-spine
    - Severe left L4-5 facet degeneration with noted synovial cyst
  - Prior procedures
    - Left L4-5 facet cyst aspiration and injection
      - No benefit in anesthetic or corticosteroid phase
    - Epidural Steroid Injection (type a location unknown by patient)
      - Non-diagnostic

Case, continued

PERTINENT FINDINGS: She has a normal, non-antalgic, non-spastic, non-Trendelenburg, non-compensated Trendelenburg gait. She has mild tenderness to palpation through the lumbar paraspinals. She has very minimally positive facet loading maneuvers. She has marked tenderness to palpation at the left PSIS and margins of the sacroiliac joints. She likewise has mild tenderness at the left greater trochanter. She is neurologically intact in the bilateral lower extremities including strength, sensation and reflexes. Her Babinski is downgoing bilaterally, her proprioception is intact at the great toe. She has markedly positive Faber's, as well as sacral spring test on the left.

NOTE:



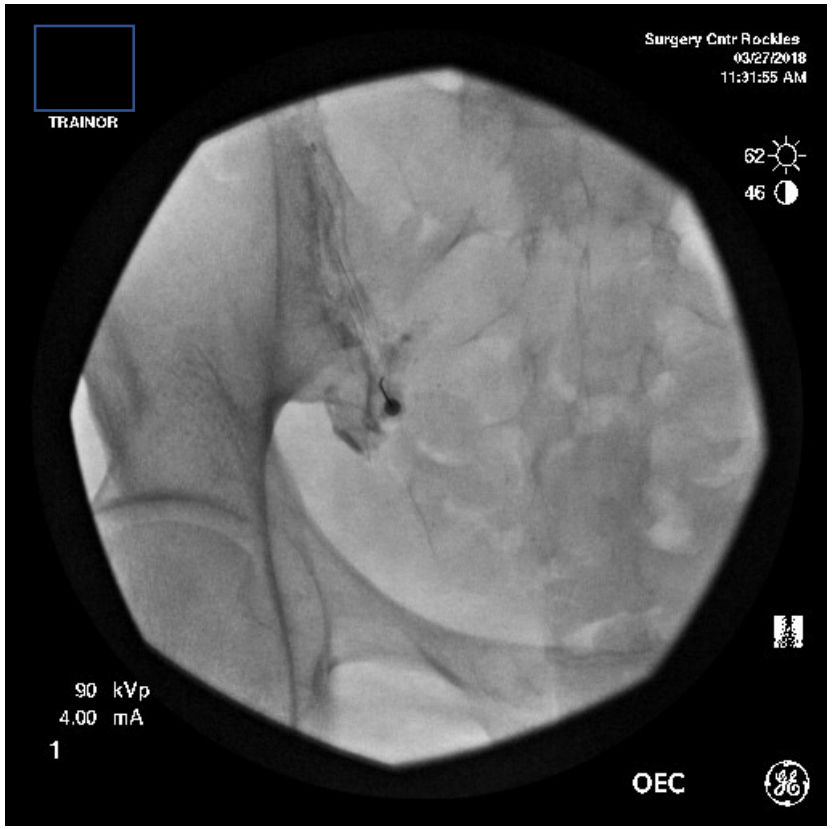


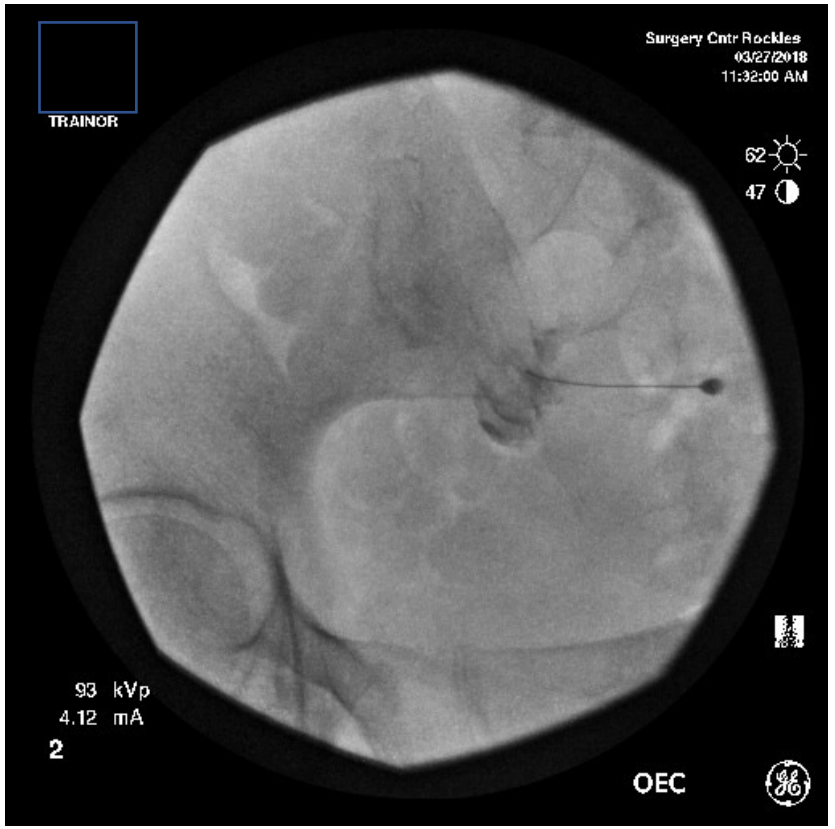
- <5 cm excursion indicates lumbar segmental restriction

Case, continued

- Plan
  - Therapy: patient working 100 + hours/week not logistically possible
  - Medications: Tylenol 1000 mg PO TID, Tramadol 50 mg PO Q6H PRN, in future consider Celebrex after clearance with GI
  - Injections: left SIJ injection under fluoroscopy
  - Surgical considerations: None.
  - Diagnostics: HLA-B27, ESR, CRP

Case, continued





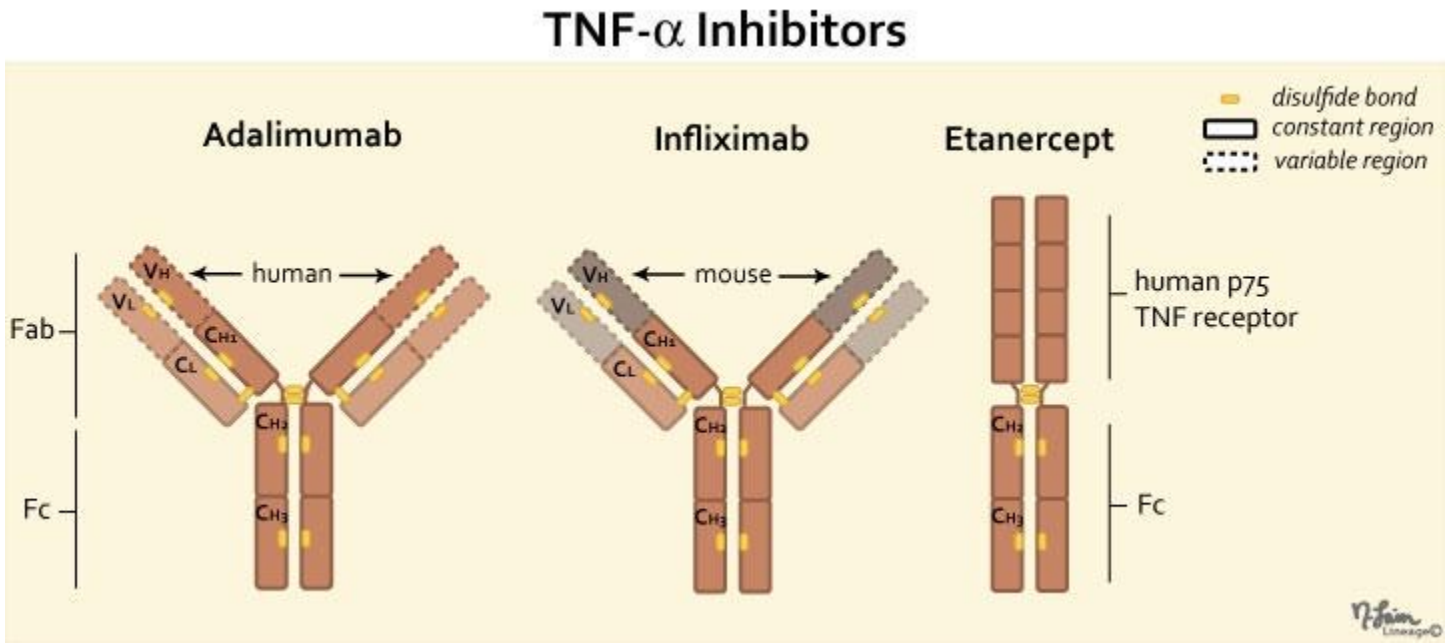
75% IMPROVEMENT IN ANESTHETIC PHASE

Case, continued

- HLA-B27 – Positive
- CRP – Elevated
- ESR – Elevated

Case, continued

- Plan
  - Rheumatology referral for consideration of TNF inhibitor therapy



Spondyloarthritis (SpA)

- Ankylosing Spondylitis (AS)
- Non-radiographic axial spondyloarthritis (nr-SpA)
- Psoriatic arthritis
- Arthritis associated with inflammatory bowel disease (IBD-SpA)
  - Ulcerative colitis and Crohn’s disease
- Reactive arthritis (ReA)
  - chlamydia, campylobacter, salmonella, shigella
- Undifferentiated Spondyloarthropathy (uSpA)

Spondyloarthritis (SpA)

- More recent classification
  - Axial
  - Peripheral
- Share many phenotypical characteristics (discussed later)

Why do we care?

- Higher incidence and prevalence than we realize
- Early identification has consequences
  - Early treatment makes a difference
- As surgeons, pain physicians, and physiatrists will likely be the first ones to encounter these patients
  - Back pain is most common presenting complaints

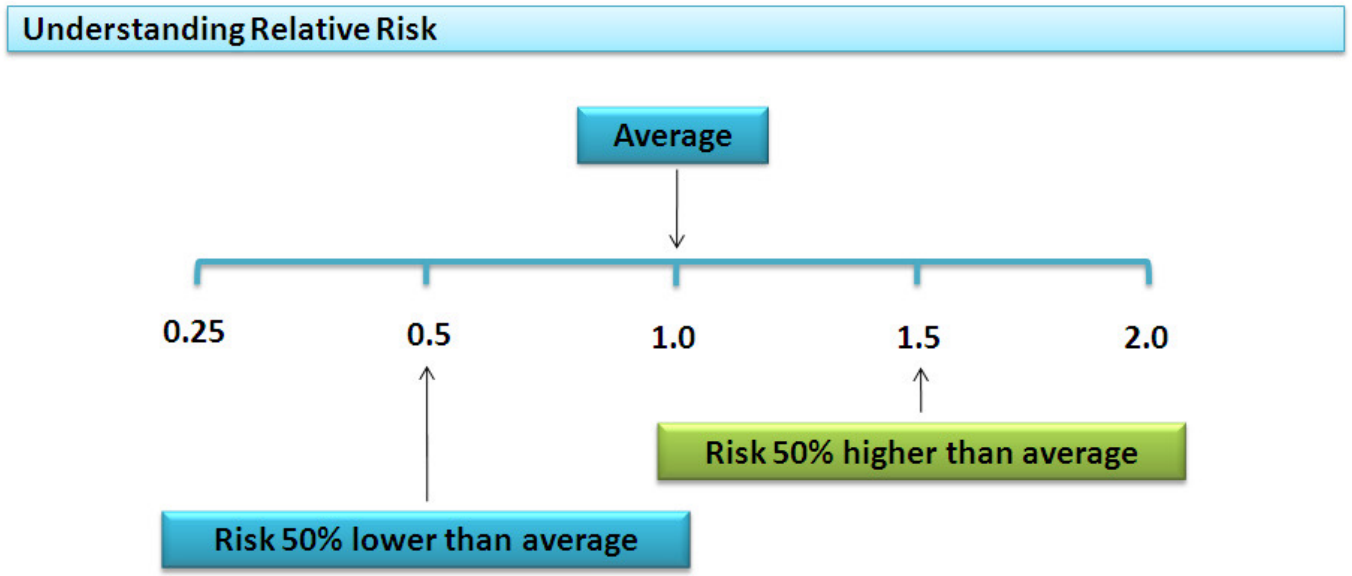
Epidemiology of SpA

- Incidence
  - 0.48 to 63/100,000
- Prevalence
  - 0.1% to 2.5% in general population
    - 4 million people in the U.S. living with SpA
  - Estimated to be 5% in the low back pain population
    - Should see more than one patient per week
  - Higher than rheumatoid arthritis (RA)

Int J Environ Health Res. 2015;25(3):322-9. Curr Rheumatol Rep 2013; 15:351. J Rheumatol 1994; 21:2281-2285

Epidemiology of SpA

- Highly Heritable
  - Relative Risk
    - 1st degree relative: 75.5
    - 2nd degree relative: 20.2
    - 3rd degree relative: 3.5



Pathophysiology of SpA

- Not well understood
  - Likely polygenic

TABLE 1 Keywords extracted from review articles on the pathogenesis of axial spondyloarthritis published in the last 10 y with each keyword counted once per author

Keyword	Count	Rank	Disease phase[a]
HLA-B27	29	1	Initiation
ERAP1	17	2	Not specified
Bone/syndesmophyte formation	14	3	Progression
Microbiome	11	4	Not specified
IL-23/IL-23 gene	8	5	Not specified
TNF-alpha	8	6	Not specified
Genetic risk (unspecified)	7	7	Initiation
Gut inflammation	7	7	Initiation
Enthesitis	6	9	Initiation
T cells	6	9	Not specified
IL-17	5	11	Not specified
B cells	4	12	Not specified
Gut and joint inflammation	4	12	Initiation
HLA-B27 and ERAP1 interaction	4	12	Initiation
IL-1	4	12	Initiation
Mechanical stress	4	12	Not specified
Environmental risk (unspecified)	3	17	Initiation
HLA-B27 and microbiome	3	17	Initiation
Macrophages	3	17	Not specified
PTGER4 gene	3	17	Not specified
Th17 cells	3	17	Not specified
Bone homoeostasis alterations	2	22	Progression
CD8+ T cells	2	22	Initiation
DKK1 signalling	2	22	Progression
HLA-B60	2	22	Initiation
IFN-gamma	2	22	Not specified
IL-23+ Th17-cells	2	22	Not specified
IL-6	2	22	Not specified
NK cells	2	22	Not specified
RUNX3 gene	2	22	Initiation
TLR signalling	2	22	Not specified
Wnt signalling	2	22	Progression

HLA-B27, human leucocyte antigen B27; HLA-B60, human leucocyte antigen B60; ERAP1, endoplasmic reticulum aminopeptidase 1; PTGER4, prostaglandin E receptor 4; RUNX3, runt-related transcription factor 3; IL-1/6/17/23, interleukin-1/6/17/23; IFN-gamma, interferon gamma; TNF-alpha, tumour necrosis factor alpha; NK cell, natural killer cell; DKK1, dickkopf 1; TLR, toll-like receptor.

Keywords that were only used once: "Ankylosis," "ANTXR2,""Autoinflammatory," "Bacteria," "BMP," "CARD15," "CARD9," "Chlamydia," "CYP2D6," "EDIL3," "ERAP2," "Gender," "Gut defences," "HLA-B27 and IL-23/IL-17," "HLA-B27 and inflammation," "HLA-B27 and Th17 cells," "IL-17 IL-23 IL-22 and Th17 cells," "IL-23R," "Immune cells," "Immune system," "Innate immunity," "Joint inflammation," "KIR," "Klebsiella genus," "MICA," "MicroRNA," "MMP," "Myofibroblasts," "PTPN22 and CTLA4," "Smoking," "Stem cells," "Stress," "TIM-3 gene," "TNF-blocker," "TNFRII," "Treg cells," "Type17 cells," "UPR and IFN."

[a]According to the majority of authors.

The most likely mode of inheritance is polygenic with multiplicative interaction among loci.[8] By far, the most important genetic risk factor is human leucocyte antigen (HLA)-B27 and prevalence of HLA-B27 generally mirrors the prevalence of axSpA in a population.[9,10] As HLA-B27 is present in about 70-90% of patients with AS in most ethnic groups, compared, for example 6% of the general population in the United States, it is widely assumed to play a

Pathophysiology of SpA

- HLA-B27 by far most common
  - Present in 70-90% of patients with AS
  - Present in 6% of general population
    - NOT required for diagnosis
- 3 main hypothesis
  1. Arthritogenic peptide hypothesis
  2. Heavy chain homodimer hypothesis
  3. HLAB27 misfolding hypothesis

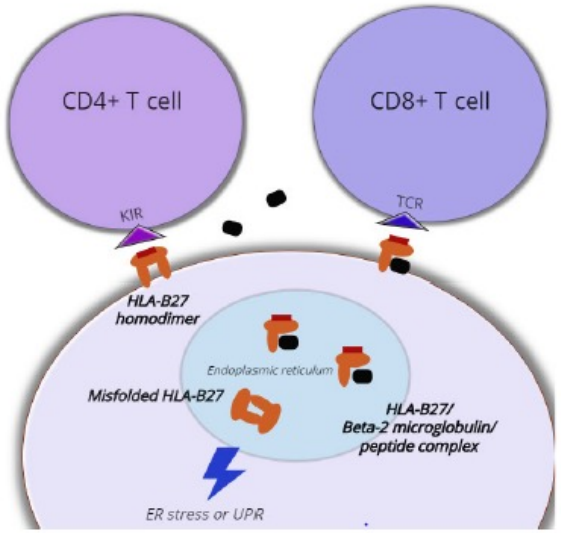


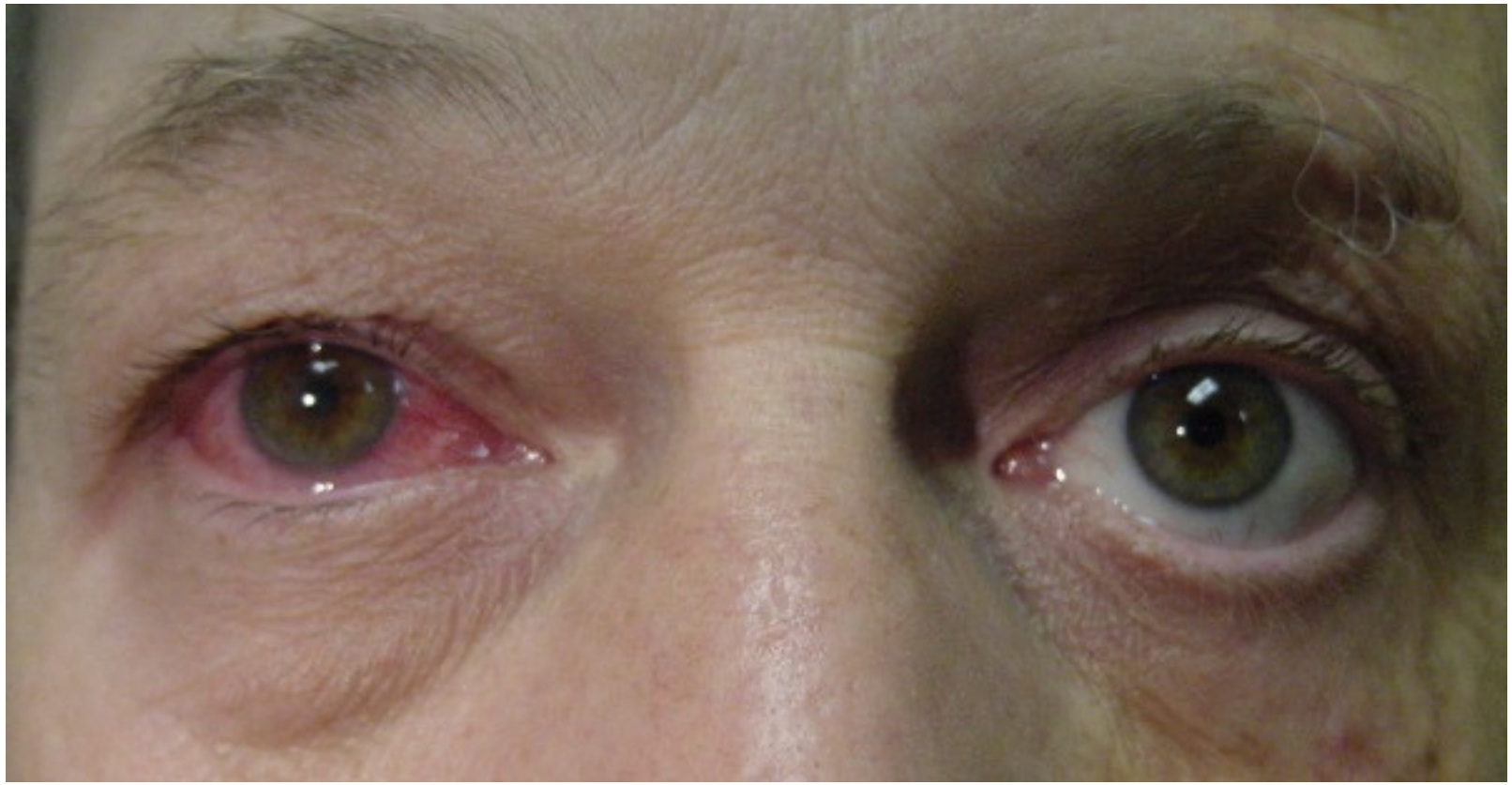
FIGURE 2 Overview of hypotheses explaining role of HLA-B27 in axial spondyloarthritis. A, Arthritogenic peptide hypothesis: Pathogen- or self- derived peptides bound to conventional HLA-B27/ beta-2 microglobulin complexes are recognized by autoreactive CD8+ T cells through the T-cell receptor (TCR). B, Cell surface HLA- B27 free heavy chain homodimer expression hypothesis: HLA-B27 free heavy chains including dysfunctional HLA-B27 homodimers are expressed at the cell surface and activate cells bearing killer immunoglobulin-like receptors (KIR) and/or leucocyte immunoglobulin-like receptors such as CD4+ cells or NK cells. C, Misfolded HLA-B27 hypothesis: Misfolding of HLA-B27 within the endoplasmic reticulum (ER) causes an unfolded protein response (UPR) or other form of cellular stress, or autophagy, which has downstream effects on cellular function (eg, excessive IL-23 release)

Koning, Anoek De, et al. “Pathophysiology of Axial Spondyloarthritis: Consensus and Controversies.” *European Journal of Clinical Investigation*, 2018, doi:10.1111/eci.12913.

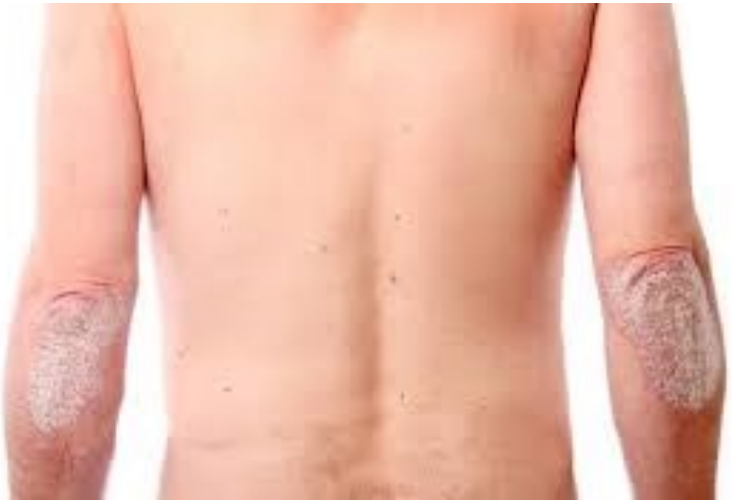
Clinical Manifestations of SpA

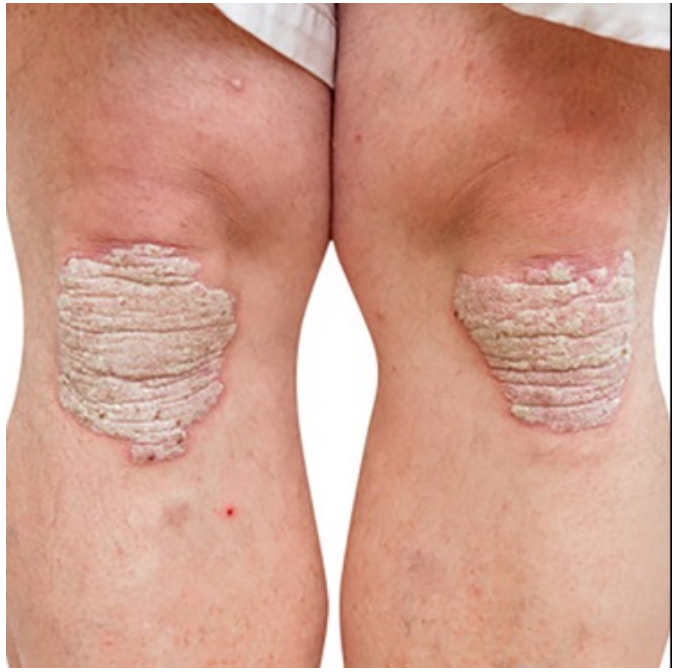
- Non-musculoskeletal
  - Uveitis
  - Psoriasis
  - Features of IBD
  - Genital Lesions
    - In Reactive Arthritis

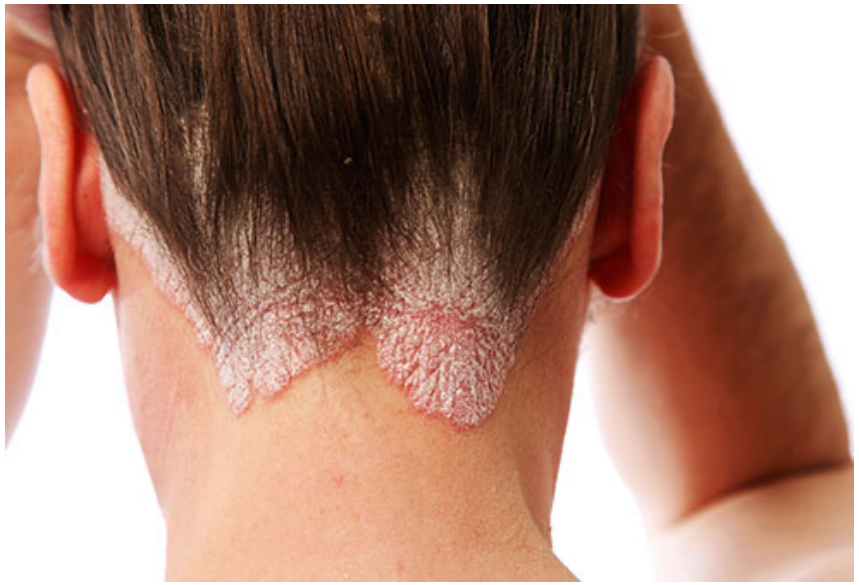
Uveitis



Psoriasis







IBD

- Abdominal pain
- Vomiting
- Diarrhea
- Rectal Bleeding
- Severe internal cramps/muscle spasms in the region of the pelvis
- Weight Loss

Reactive Arthritis

- “Can’t see, pee, or climb a tree”
  - Conjunctivitis
  - Urethritis
  - Arthritis

Clinical Manifestations of SpA

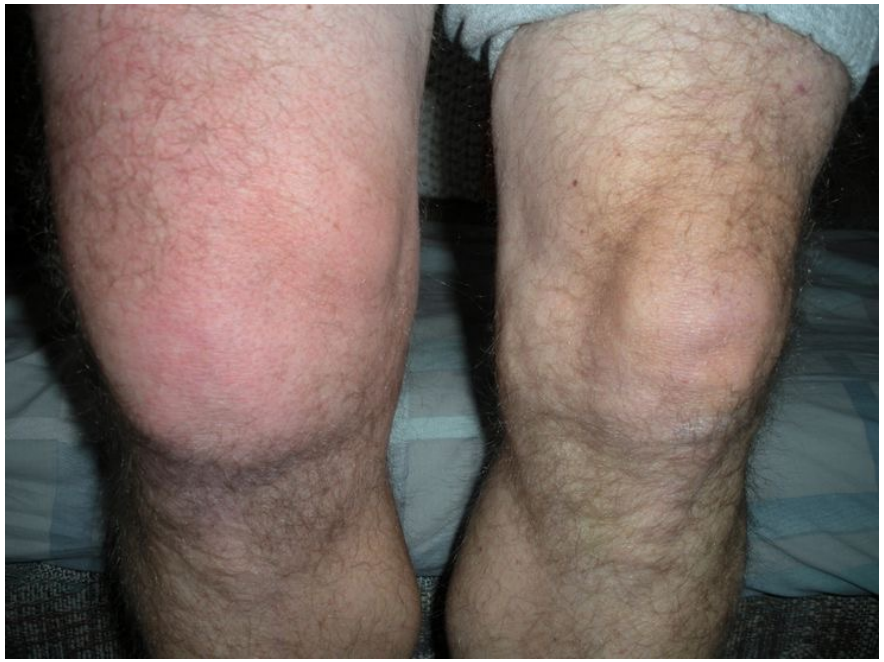
- Musculoskeletal features
  - Inflammatory back pain
  - Peripheral arthritis
  - Enthesitis (enthesopathy)
  - Dactylitis

Inflammatory Back Pain

- Young age at onset, typically seen in those under 40 years old
- Gradual onset of pain
- Symptoms of back pain improve with exercise
- Response to NSAIDs
- Pain does not improve with rest
- Pain at night, often waking a person in the second half of the night
- Morning stiffness that lasts for more than 30 minutes
- Pain lasting for **more than 3 months**
- Alternating buttock pain

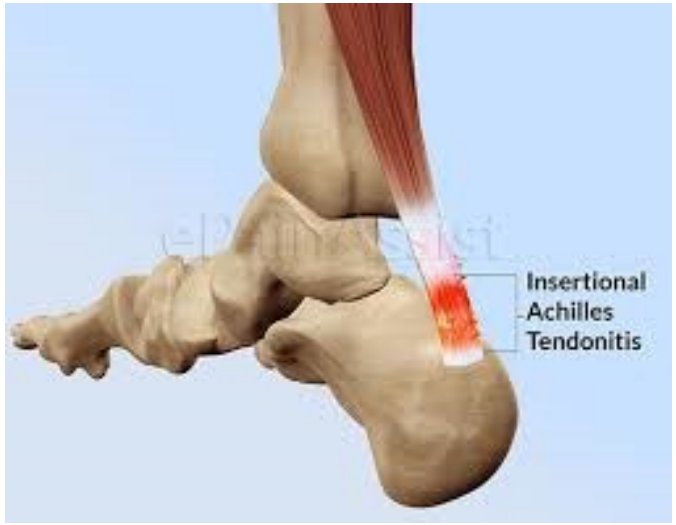
Peripheral Arthritis

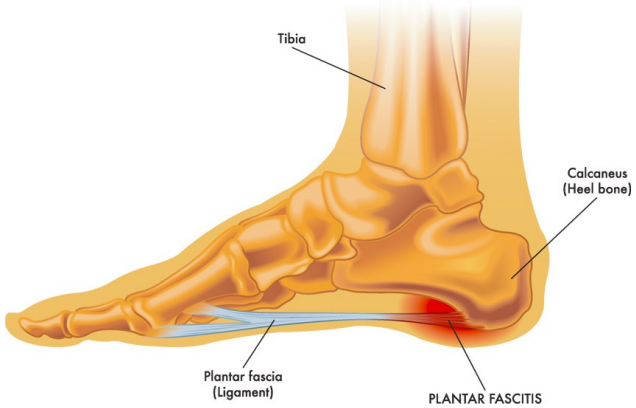
- Acute Onset
- Predominately effects the lower extremities
- Associated with swelling
- Usually asymmetric
- Effects 1 to 3 joints
  - Oligoarthritis



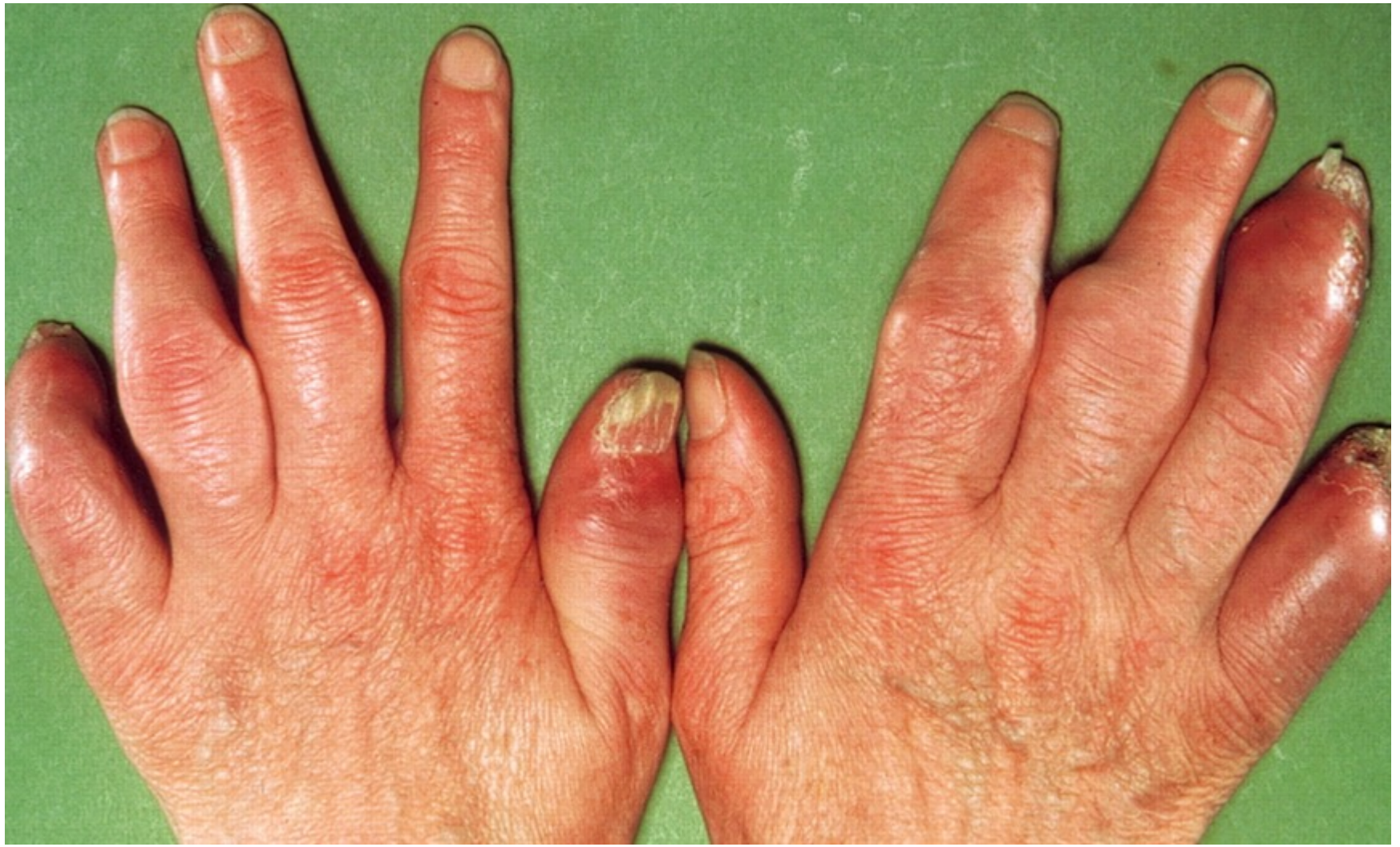
Enthesitis (enthesopathy)

- Inflammation
  - Ligament to bone
  - Tendon to bone
  - Joint capsule
  - Fascia to bone
- Most commonly manifested as:
  - Achilles tendinopathy
  - Plantar fasciitis





Dactylitis



Laboratory Findings

- HLA-B27
  - Positive in 70-90% of patients with AS
  - Positive in 50% to 70% of patients with other forms of SpA
    - Note: HLA-B27 positivity is NOT diagnostic in itself
      - Note even required for the diagnosis
        - Seen in 6% of the general population
- Acute Phase Reactants (ESR and CRP)
  - Elevated in 35% to 50% of patients
    - Elevated CRP is an indication of:
      - Radiographic disease progression
      - Positive response to TNF alpha inhibitors

Imaging Findings

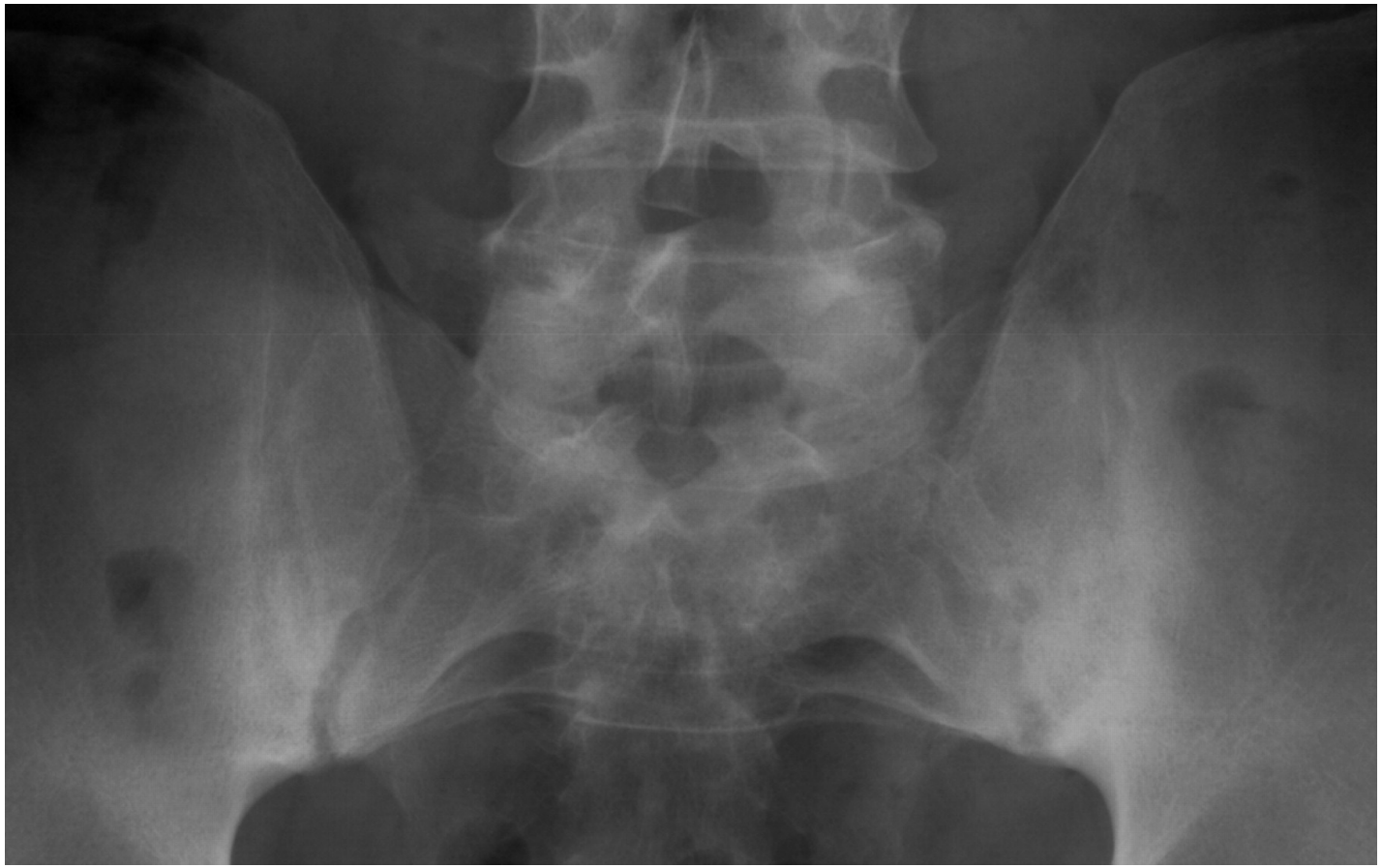
- Plain Radiographs
  - Axial
    - Only specific finding is evidence of **sacroiliitis** (images to follow)
      - May take years to develop
    - Bridging axial **syndesmophytes** seen on <5% of patients in the absence of sacroiliitis
      - 50% of patients develop syndesmophytes during course of disease
  - Peripheral
    - Erosive joint changes
    - Evidence of Enthesitis

Sacroiliitis on Plain Radiographs

- Graded 0 to 4
  - Grade 0: Normal
  - Grade 1: Suspicious changes
  - Grade 2: Minimal abnormality – Small localized areas with erosions or sclerosis, without alteration in the joint width
  - Grade 3: Unequivocal abnormality – Moderate or advanced sacroiliitis with erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis
  - Grade 4: Severe abnormality – Total ankylosis

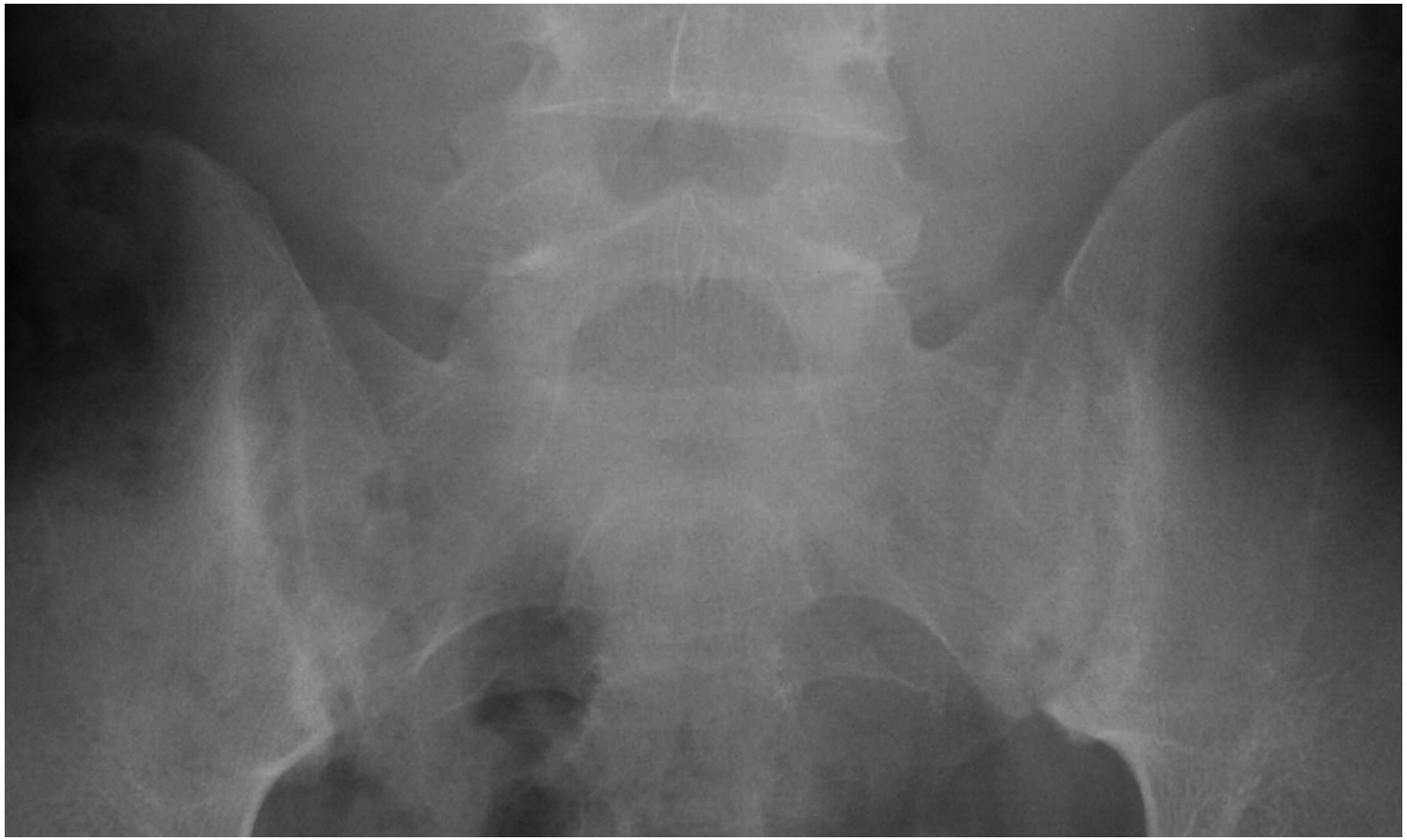
- Considered “Positive for Suggestion of SpA” if:
  - Grade 2 or higher bilateral
  - Grade 3 or higher unilateral

Sacroiliitis on Plain Radiographs (Grade 2)



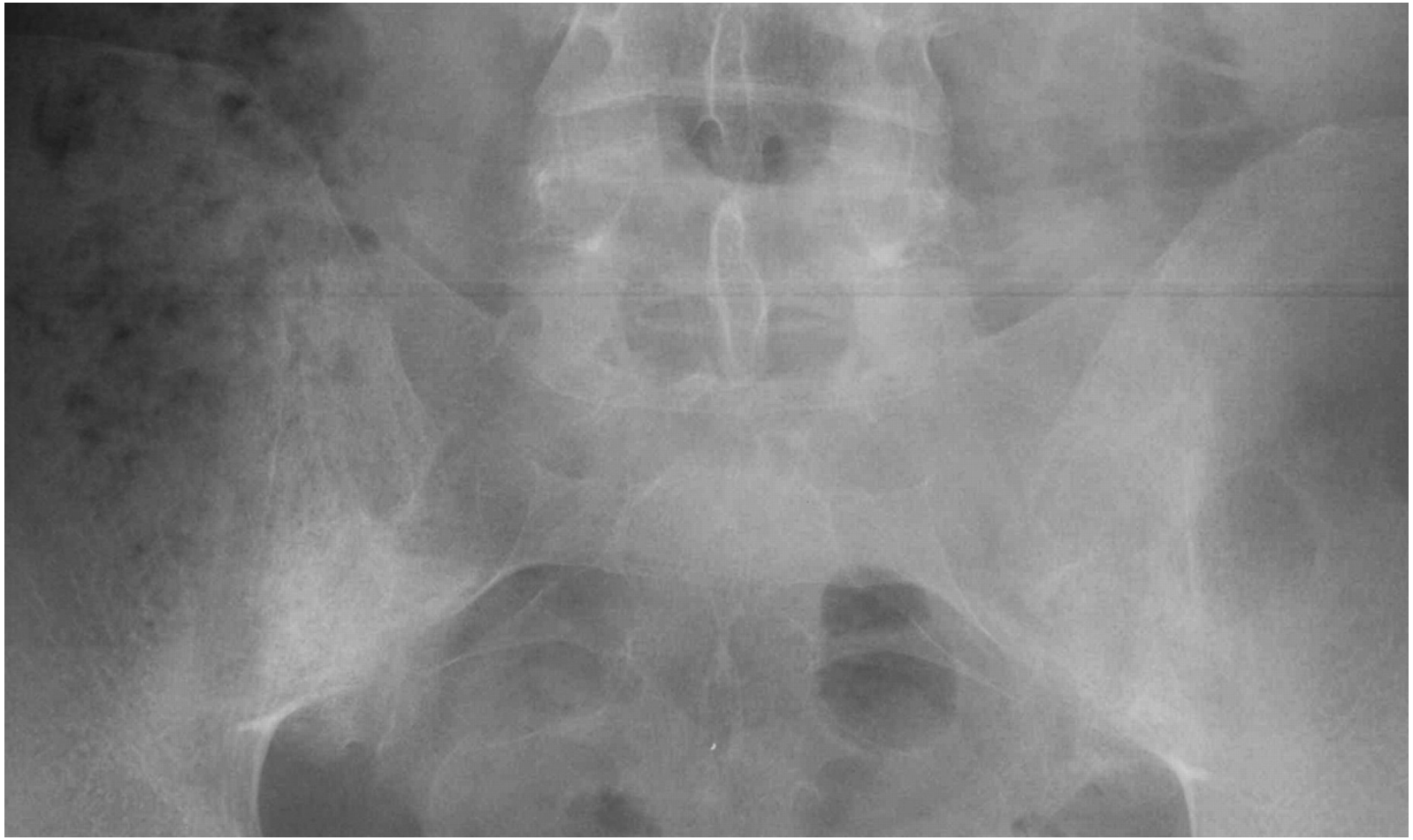
Both sacroiliac (SI) joints show ill-defined margins, sclerosis, and especially at the left SI joint an irregular joint space (grade 2 bilaterally).

Sacroiliitis on Plain Radiographs (Grade 3)



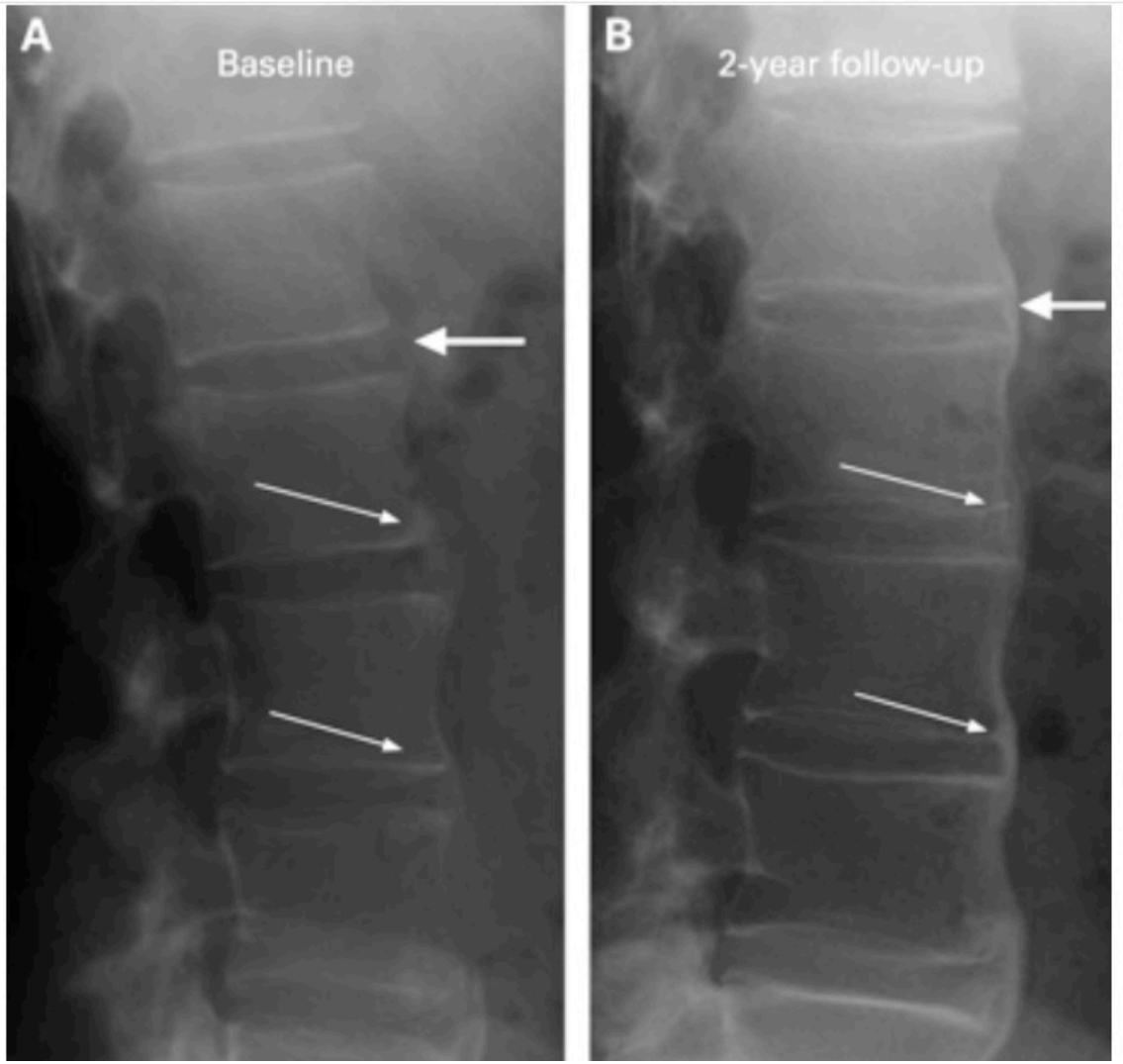
Sclerosis at the iliac side, widespread erosions, pseudo widening of the joint space, blurring of the joint margins in both sacroiliac (SI) joints (bilateral grade 3).

Sacroiliitis on Plain Radiographs (Grade 4)



Both sacroiliac (SI) joints show complete ankylosis (grade 4).

Syndesmophytes on Plain Radiographs



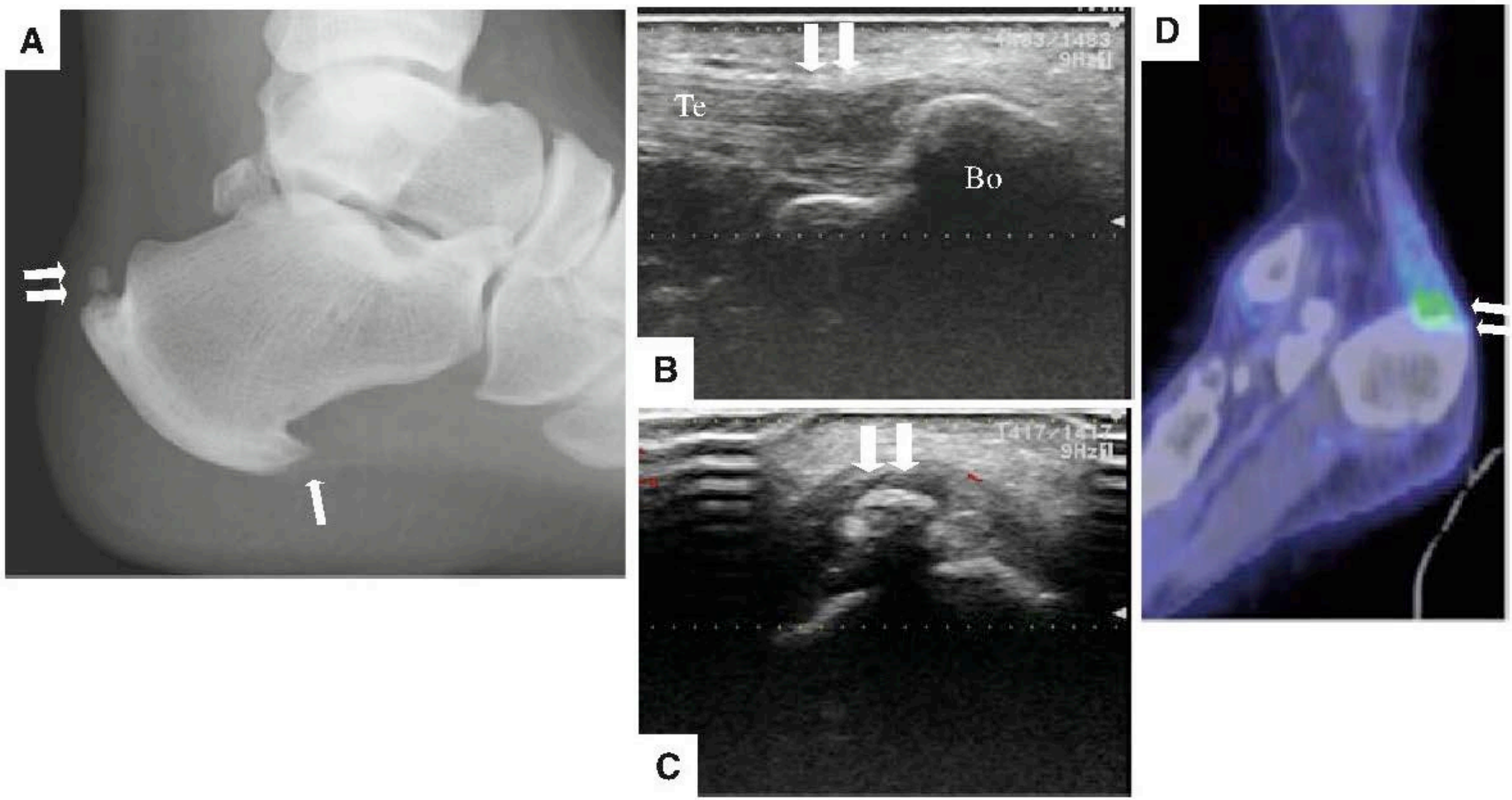
Differentiation from DISH

Table 1. Distinguishing features of DISH and AS

	DISH	AS
Usual age of onset	> 50 y	< 40 y
Dorsal kyphosis	Frequent	Very frequent
Limitation of spinal mobility	Frequent	Very frequent
Pain	Unusual	Very frequent
Limitation of chest expansion	Frequent	Very frequent
Roentgenography		
Hyperostosis	Very frequent	Frequent
SI joint erosion	Absent	Very frequent
SI joint (synovial) obliteration	Unusual	Very frequent
SI joint (ligamentous) obliteration	Frequent	Very frequent
Apophyseal joint obliteration	Absent	Very frequent
ALL ossification	Very frequent	Unusual
PLL ossification	Very frequent	Frequent
Syndesmophytes	Absent	Unusual
Enthesopathies (whiskering) with erosions	Absent	Very frequent
Enthesopathies (whiskering) without erosions	Very frequent	Frequent
HLA-B27 (European "whites") [63,64]	About 8%	About 90%
HLA-B27 (African Americans) [63,64]	About 2%	About 50%

ALL—anterior longitudinal ligament; AS—ankylosing spondylitis; DISH—diffuse idiopathic skeletal hyperostosis; PLL—posterior longitudinal ligament; SI—sacroiliac.

Imaging Findings of Enthesitis



Evolution in the concepts of SpA

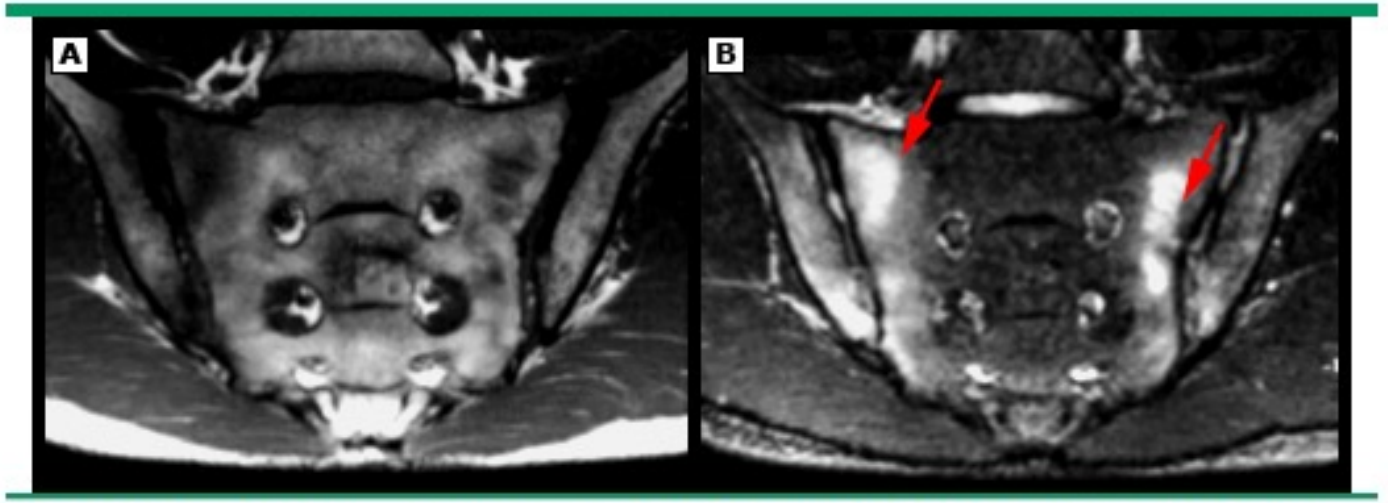
- Problems with Radiographic Evidence and AS
  - Decision on radiographs challenging
  - Late Dx
    - Miss opportunity for early treatment TNF-alpha antagonists effective
    - Particularly if start in early stage
- Solution: New concepts
  - Non-radiographic stage of axial SpA identified with MRI
  - Inflammatory Back Pain

MRI and SpA

- Definition of Sacroiliitis according to the Assessment of SpondyloArthritis International Society (ASAS)
  - Bone marrow edema (BME)
    - short tau inversion recovery (STIR)
    - T2-weighted images with fat suppression
      - Bright
      - Dark on T1

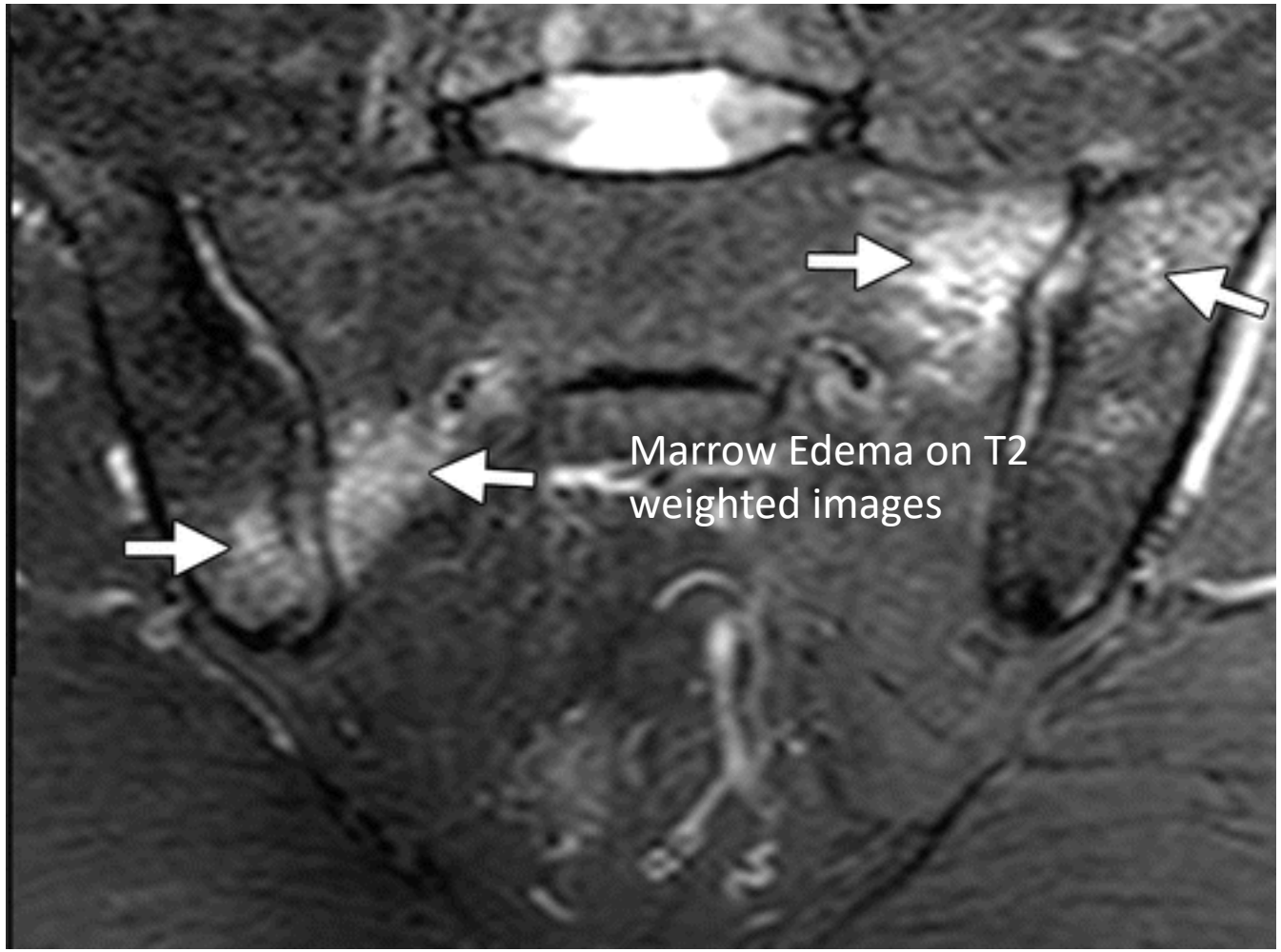
MRI and SpA

Magnetic resonance imaging of a patient with active sacroiliitis

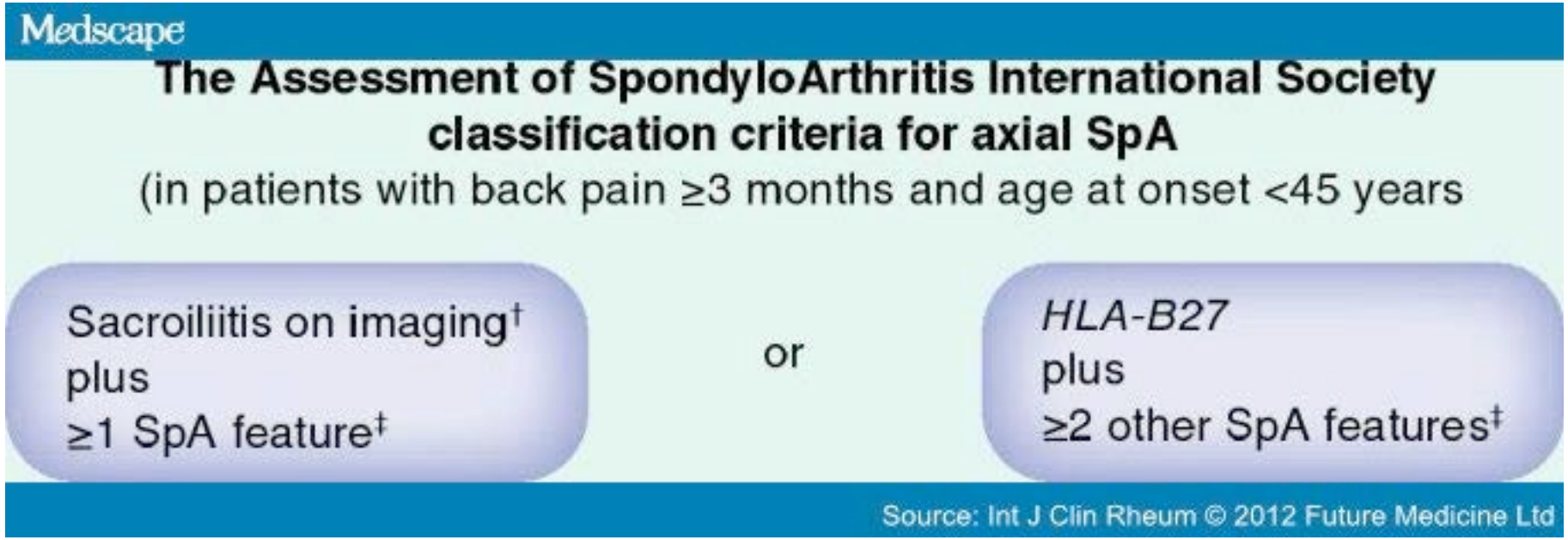


Panel A shows the T1 sequence. Panel B shows the STIR sequence. The bright white areas in STIR, which are not seen in the T1, are the areas of bone edema (arrows).

MRI and SpA



Diagnostic Criteria- Axial SpA



Diagnostic Criteria- Axial SpA

Sacroiliitis on imaging*

plus

≥ 1 SpA feature**

or

HLA-B27

plus

≥ 2 other SpA features**

****SpA features:**

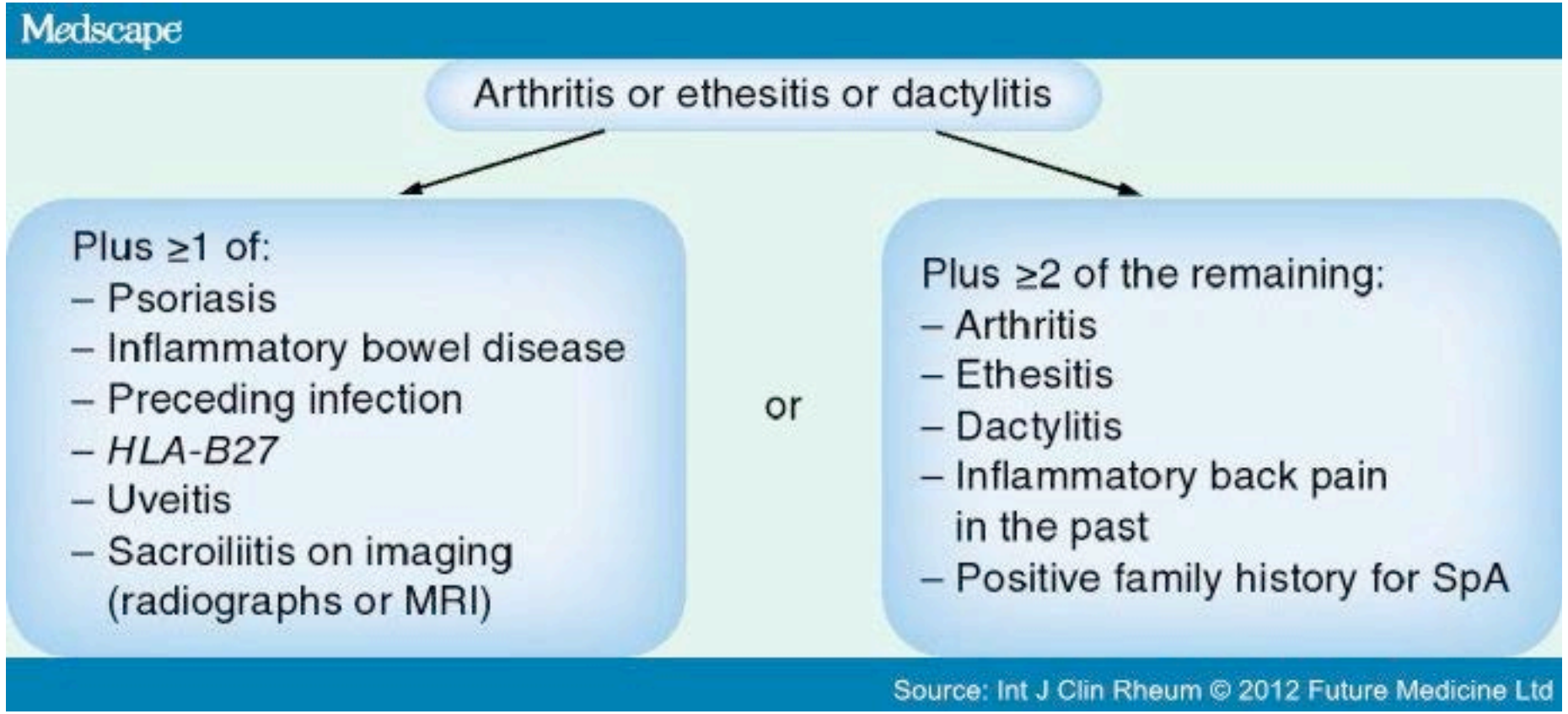
- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn's disease/ulcerative colitis
- Good response to NSAIDs
- Family history for SpA
- HLA-B27
- Elevated CRP

***Sacroiliitis on imaging:**

- Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
  or
- Definite radiographic sacroiliitis according to mod. New York criteria

Sensitivity 82.9%, specificity 84.4%; *n* = 649 patients with chronic back pain and age at onset <45 yrs.
Imaging arm (sacroiliitis) alone has a sensitivity of 66.2% and a specificity of 97.3%. ** Note: Elevated CRP is considered a SpA feature in the context of chronic back pain

Diagnostic Criteria- Peripheral SpA



Treatment

SPECIAL ARTICLE

American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis

Michael M. Ward,[1] Atul Deodhar,[2] Elie A. Akl,[3] Andrew Lui,[4] Joerg Ermann,[5] Lianne S. Gensler,[4] Judith A. Smith,[6] David Borenstein,[7] Jayme Hiratzka,[2] Pamela F. Weiss,[8] Robert D. Inman,[9] Vikas Majithia,[10] Nigil Haroon,[9] Walter P. Maksymowych,[11] Janet Joyce,[12] Bruce M. Clark,[13] Robert A. Colbert,[1] Mark P. Figgie,[14] David S. Hallegua,[15] Pamela E. Prete,[16] James T. Rosenbaum,[17] Judith A. Stebulis,[18] Filip van den Bosch,[19] David T. Y. Yu,[20] Amy S. Miller,[12] John D. Reveille,[21] and Liron Caplan[22]

Treatment

Table 2. Strength of recommendations in GRADE*

Strength	Interpretation	Implications for clinicians	Implications for policymakers
Strongly in favor	Almost all informed patients would choose to receive the intervention	Should be accepted by most patients to whom it is offered	Should be adopted as policy
Conditionally in favor	Most informed patients would choose the intervention, but a sizable minority would not	Large role for education and shared decision-making	Requires stakeholder engagement and discussion
Conditionally against	Most informed patients would not choose the intervention, but a small minority would	Large role for education and shared decision-making	Requires stakeholder engagement and discussion
Strongly against	Most patients should not receive the intervention	Should not be offered to patients	Should be adopted as policy

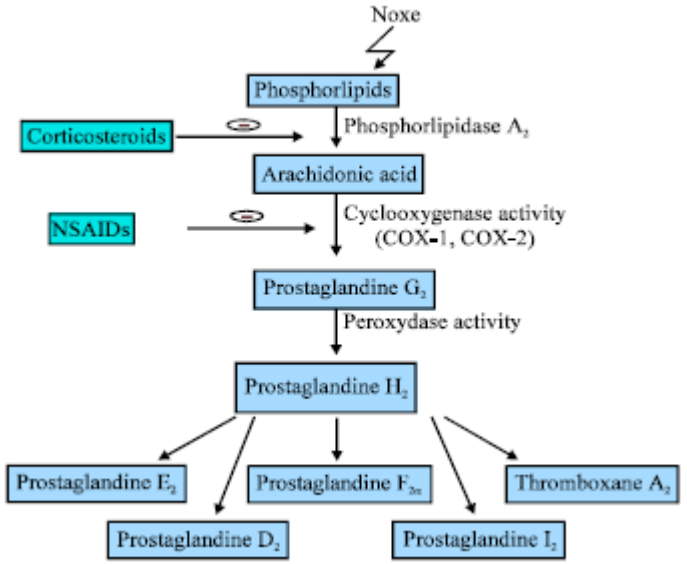
* GRADE = Grading of Recommendations, Assessment, Development and Evaluation.

Treatment- Medication Management

- Non-steroidal Anti-inflammatories (NSAIDs)
  - Strongly Recommend
    - Treatment with NSAIDs
  - Conditionally Recommend
    - Continuous treatment with NSAIDs vs. on-demand NSAIDS
  - No recommendations on any particular NSAID over another

Treatment- Medication Management

- NSAIDS
  - Maximum dose is usually required
  - 70% to 80% of patients with AS report significant improvement
  - Trials should last at least 4-weeks
  - Consider more COX-2 selective in addition to GI PPx
  - If cardiac risk factors consider naproxen



Treatment- Medication Management

- Tumor Necrosis Factor Inhibitors (TNFi) (adalimumab, etanercept, and infliximab)
  - Strongly recommend
    - TNFi in patients with active AS despite treatment with NSAIDs
  - Do not recommend one TNFi over another, except:
    - Monoclonal Ab over etanercept in patients with IBD or iritis/uveitis

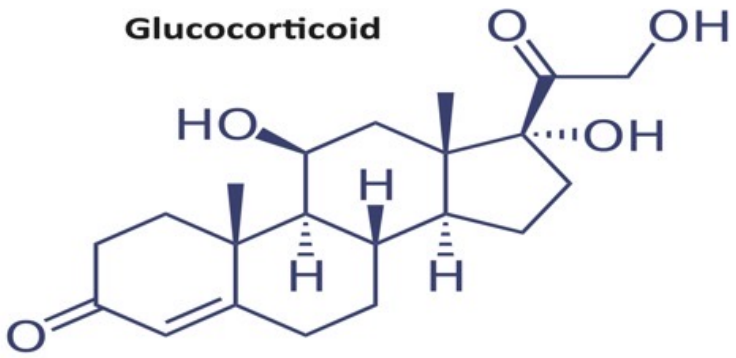
Treatment- Medication Management

- TNFi
  - Callhof, et al. 2014
    - Systematic Review
      - 2400 patients
        - Statistically significant improvement in
          - Disease activity
          - Function
- Does timing of treatment matter?
  - Studies show that patients are more likely to experience remission, if:
    - Shorter disease duration, which is the best predictor
    - Elevated CRP
    - Young age

Callhoff, Johanna, et al. “Efficacy of TNFÎ± Blockers in Patients with Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis: a Meta-Analysis.” *Annals of the Rheumatic Diseases*, vol. 74, no. 6, 2014, pp. 1241–1248., doi:10.1136/annrheumdis-2014-205322.

Treatment- Medication Management

- Glucocorticoids
  - Strongly recommend
    - AGAINST the use of systemic steroids
      - Note: did not address procedural interventions on guidelines
- Literature Review on Sacroiliac Joint Injections in AS
  - Limited to case reports



Treatment- DMARDs

- DMARDs
  - Little evidence to support their use in AS
  - Some evidence that Sulfasalazine may be beneficial
    - More effective in peripheral disease than axial disease

Treatment- Physical Therapy

- Strong recommend
  - Physical Therapy vs. no Physical Therapy
- Conditionally recommend
  - Active physical therapy (supervised exercise) vs. passive therapy interventions (massage, ultrasound, and other thermal modalities)
  - Land based vs. aquatic based exercises

Treatment- Physical Therapy

- Goals
  - alleviate pain
  - increase spinal mobility
  - Improve functional capacity
  - Reduce morning stiffness
  - Correct postural deformities
  - Increase mobility
  - Improve the psychosocial status of the patients

https://www.physio-pedia.com/Ankylosing_Spondylitis

Treatment- Physical Therapy

- Common deformities
  - Excessive Thoracic Kyphosis
  - Compensatory Cervical Lordosis
  - Resulting hip flexion contracture
- Deformity prevention
  - Proper sleeping posture on a solid, flat bed without pillow. Frequent sleeping or lying in prone position.
  - Posture exercises with upper back hyperextension (performed with avoidance of lumbar hyperextension).
  - **Breathing exercises to increase or maintain rib cage excursion**, as well as instruction in abdominothoracic breathing.
  - Range of motion exercises for hips and knees to prevent flexion limitation and contractures.
  - Periodic rest periods with avoidance of fatigue.
  - Bracing or corseting (combined with exercises).

https://www.physio-pedia.com/Ankylosing_Spondylitis

Treatment- Prevention

- Conditionally recommend
  - Screening for osteoporosis/osteopenia with DXA scan
- Strongly recommend against
  - Screening for cardiac conduction defects with ECG
  - Screening for valvular heart disease with Echo

Common Laboratory Tests for other Rheumatologic Diseases

- **Rheumatoid Factor (RF)-** only positive in 60% of patients at time of diagnosis
- **Anti-cyclic citrullinated peptide (CCP) antibodies-** highly sensitive (76%) and specific (96%) for RA
- **Antinuclear antibody (ANA)-** sensitive but not necessarily specific
  - 98% of patients with SLE
  - 40%-to 70% of those with other connective tissue
  - 20% with autoimmune thyroid and liver disease
  - 5% of general population
- **Anti double-stranded DNA (anti dsDNA)-** specific (95%) but not sensitive (60%) for SLE

Schur, Peter H. "Laboratory Tests in Rheumatic Disorders." *Oxford Medicine Online*, 2014, doi:10.1093/med/9780199358274.003.0028

Conclusions

- Spondyloarthritis is more common than we realize
  - If we don’t look for it we won’t find it
- Early diagnosis is important and associated with higher rate of response to treatment
- HLA-B27 is common (70-90%) but is NOT required for the diagnosis
- Spondyloarthritis is associated with non-musculoskeletal conditions
  - ASK as part of HPI in patients with no obvious structural cause of back pain (especially if <45 years)
- NSAIDs, TNFi, and PT are mainstays of treatment

Questions?

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