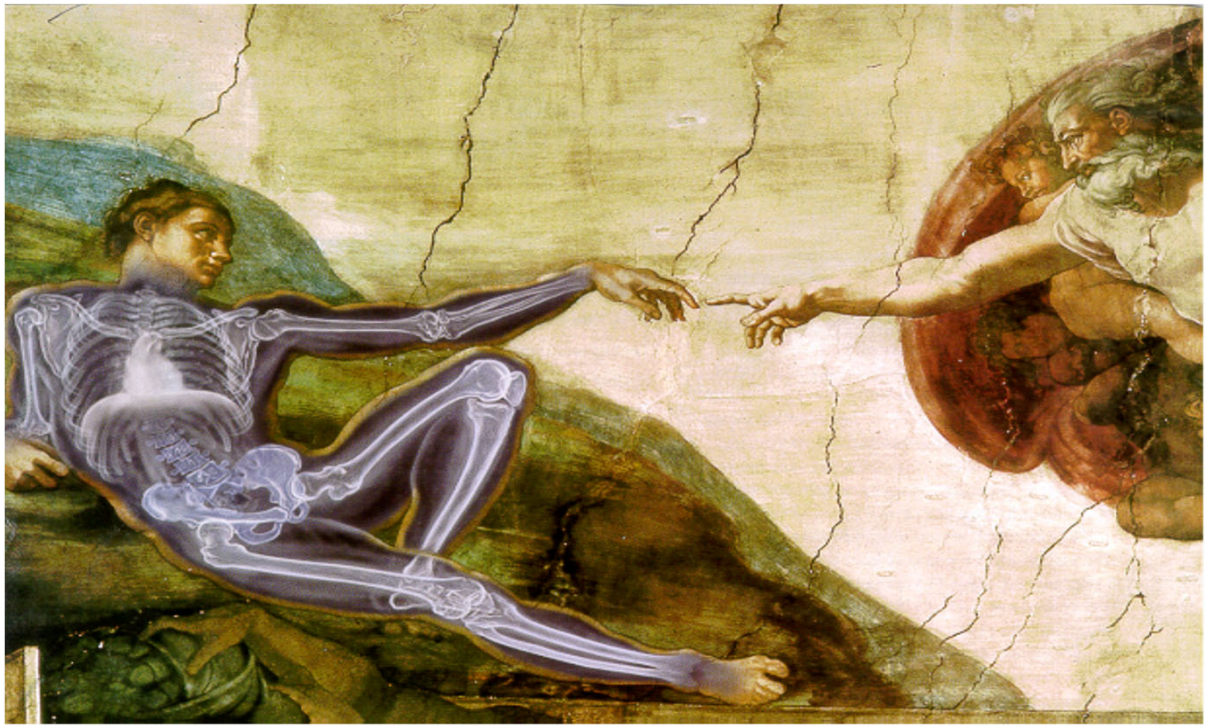
Psoriatic Arthritis

Unmet Needs in the Treatment of PsA



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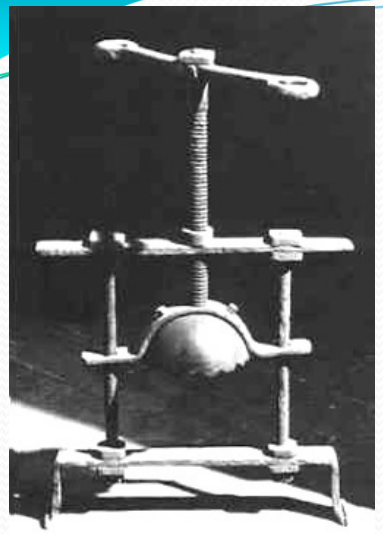
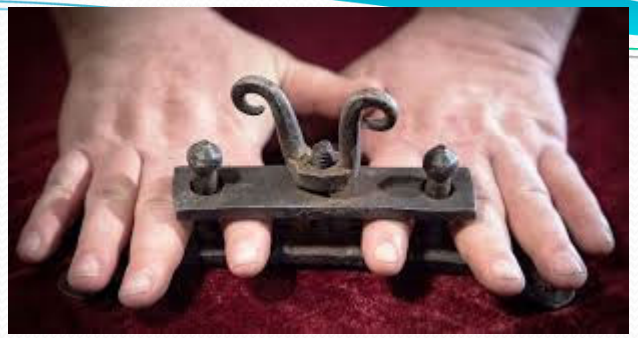
"The human foot is a masterpiece of engineering and a work of art."

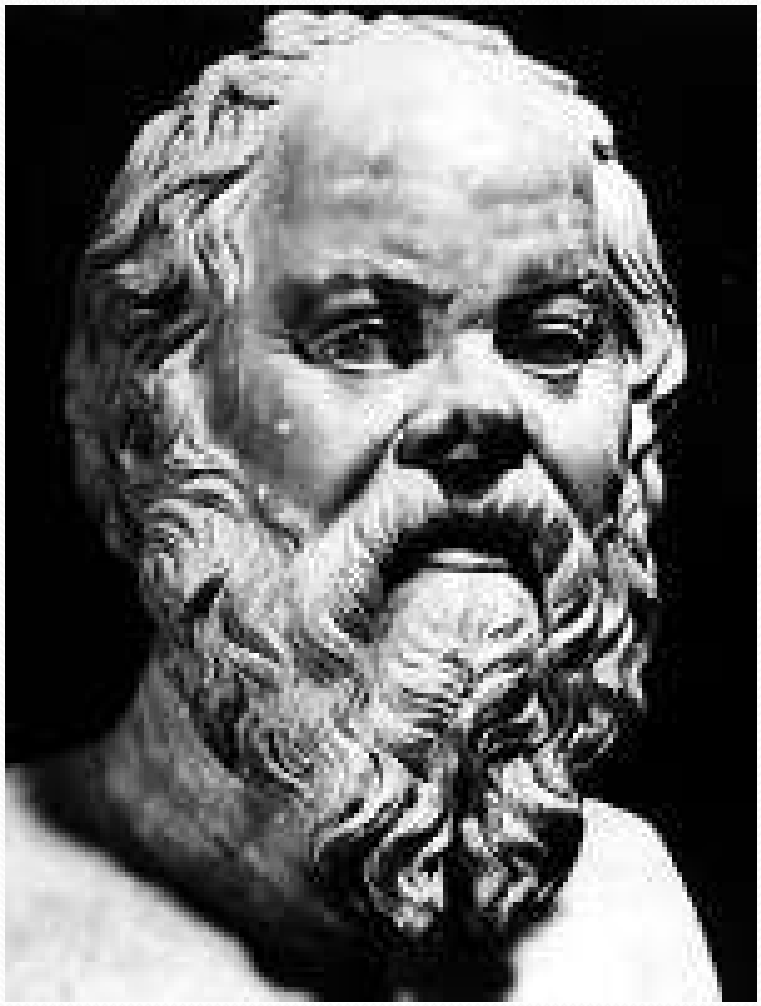
Leonardo da Vinci (1452 – 1519)

GOALS

- Clinically useful
  - Literature based
  - Case based
  - Peri-operative management will apply to other systemic autoimmune diseases
- Short
- Entertaining





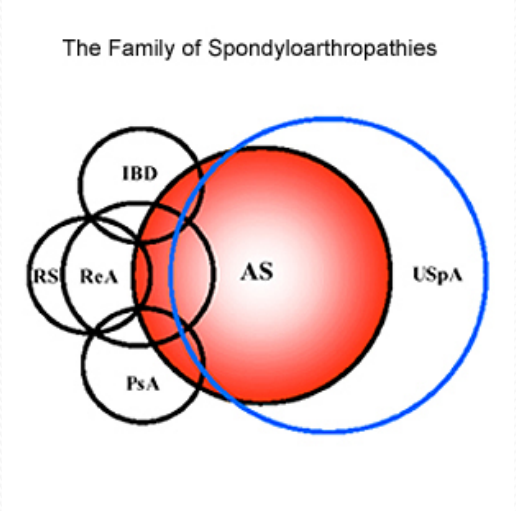


"When our feet hurt, we hurt all over"

Socrates (469 – 399 B.C.)

Spondyloarthropathies

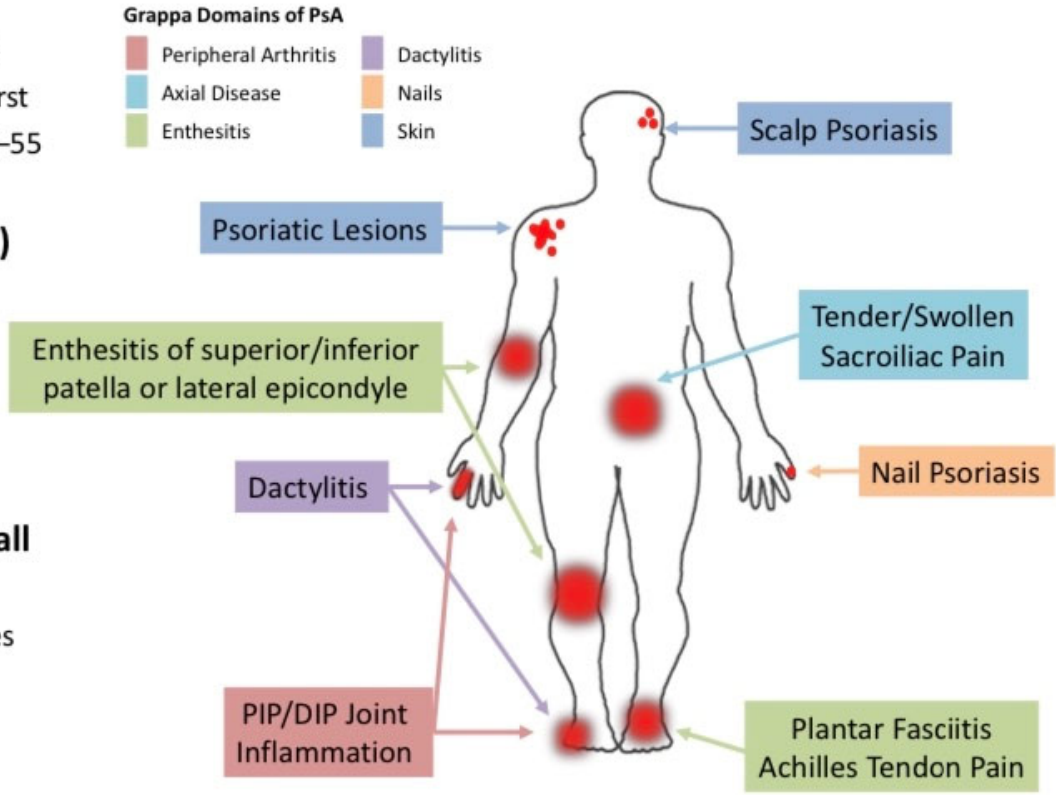
- Ankylosing Spondylitis
- Reactive arthritis (Reiter's syndrome)
- Enteropathic spondylitis / inflammatory arthritis (Crohn's & ulcerative colitis)
- Psoriatic arthritis
- Undifferentiated spondyloarthropathy
- Non-radiographic axial spondyloarthritis



Fundamentals and Framework

Psoriatic Arthritis Is a Heterogeneous Disease With a Wide Spectrum of Clinical Manifestations

- **Affects < 30% of patients with psoriasis**
  - 75% of patients develop skin symptoms first
  - Joint symptoms typically begin at ages 30–55
- **PsA more likely to develop in patients with moderate to severe psoriasis (PsO)**
- **Significant impact on:**
  - Disability
  - Quality of life
  - Comorbidities
  - Economic burden
- **To achieve best outcomes, guidelines call for collaboration between:**
  - Dermatology and rheumatology specialties
  - Specialists and interprofessional team



PIP = Proximal Interphalangeal; DIP = Distal Interphalangeal

Psoriatic Arthritis Subtypes

SUBTYPE	PERCENTAGE	JOINTS
Asymmetric oligoarticular	15-20%	**DIPs, PIPs, MCPs, MTPs, Knees, Hips, Ankles**
Predominant DIP Involvement	2-5%	**DIPs**
Arthritis Mutilans	5%	**DIPs, PIPs**
Polyarthritis (RA like)	50-60%	**MCPs, PIPs, Wrists**
Axial (isolated)	2-5%	**Sacroiliac, Vertebrae**

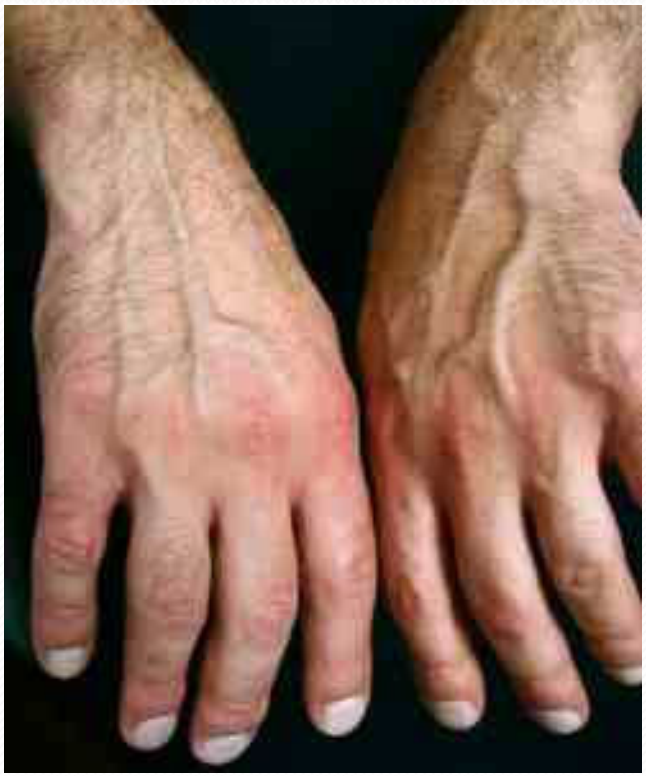
Clinical Features Associated with Subtypes

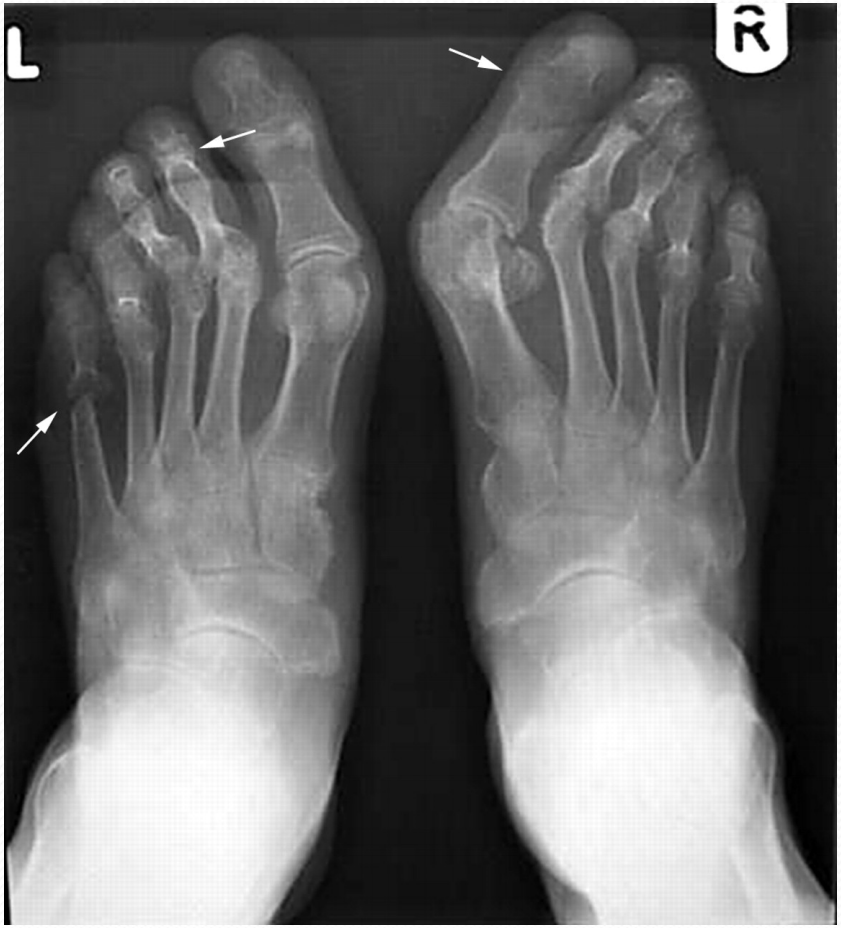
- Asymmetric oligoarthritis: Dactylitis
- Predominant DIP involvement: Nail changes
- Arthritis mutilans: Osteolysis
- Symmetrical polyarticular “RA” like: Fusion of wrists
- Axial involvement: Asymmetric sacroiliitis

Subtypes of Psoriatic Arthritis

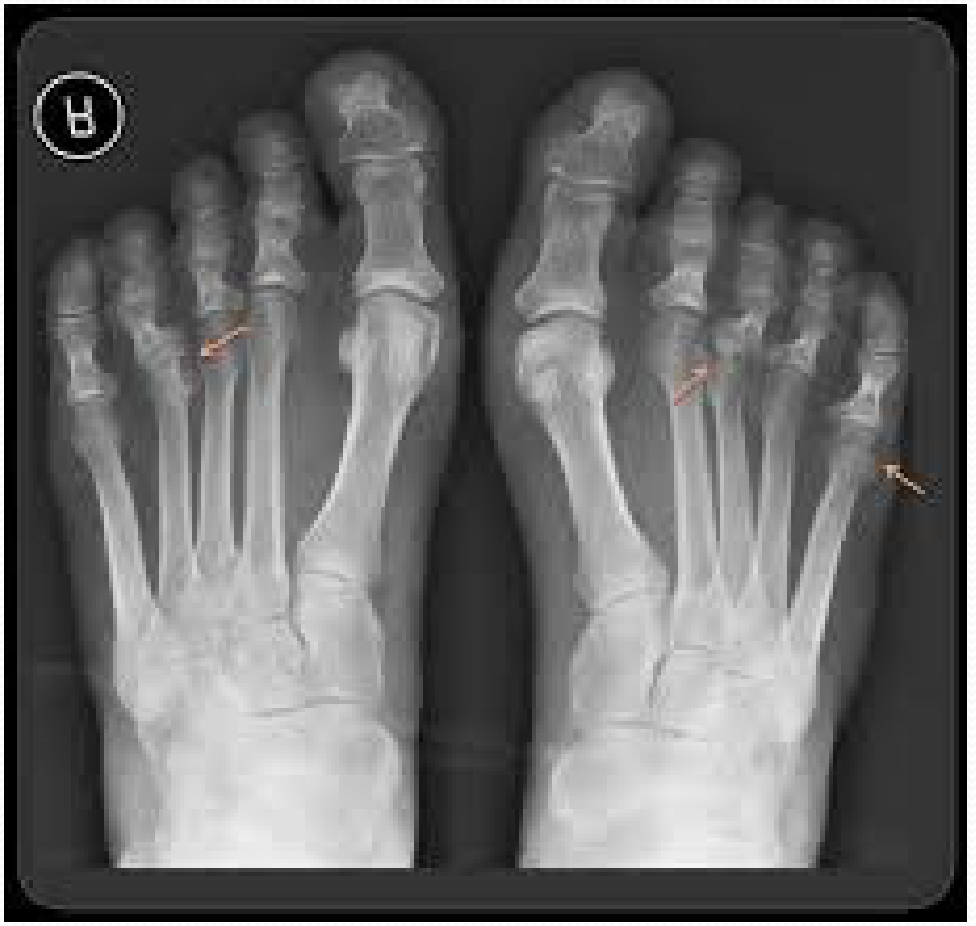
Symmetrical Polyarticular

- Most common presentation (50 – 60%)
- Fusion of the wrists
- Similar **clinical** presentation to RA
- **Radiographic** presentation different





Psoriatic Arthritis

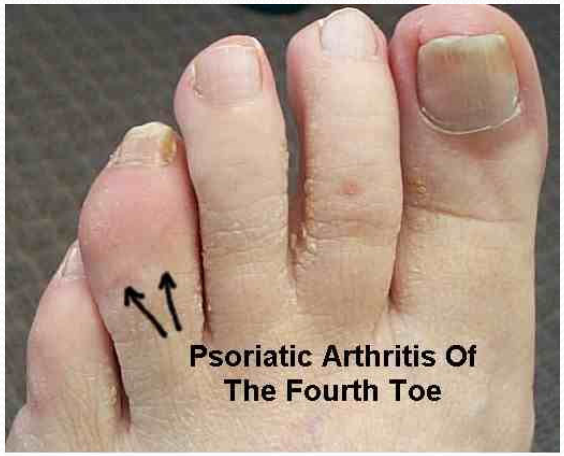


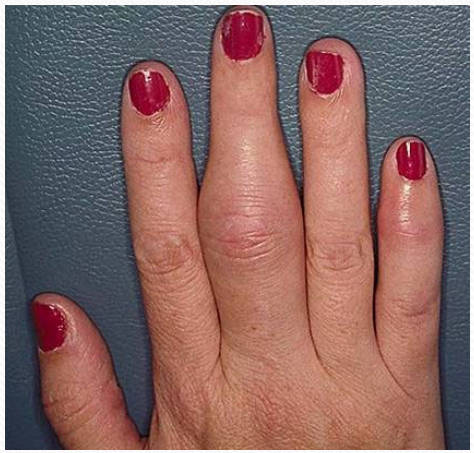
Rheumatoid Arthritis

Subtypes of Psoriatic Arthritis

Asymmetric Oligoarticular

- Second most common presentation (15-20%)
- Dactylitis (sausage digit)
  - Diffuse swelling of the entire digit
  - Synovitis
  - Flexor tenosynovitis

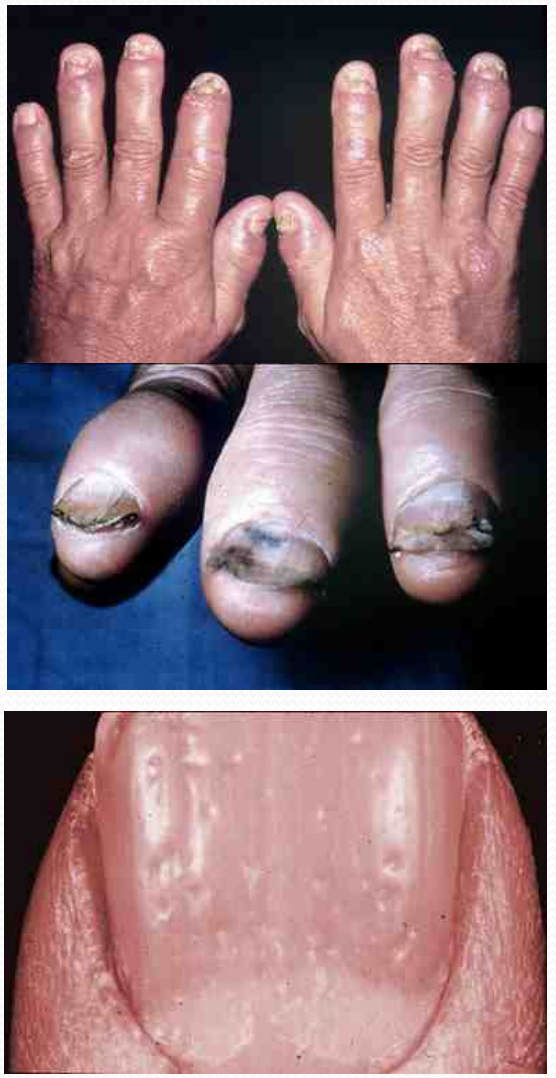




Subtypes of Psoriatic Arthritis

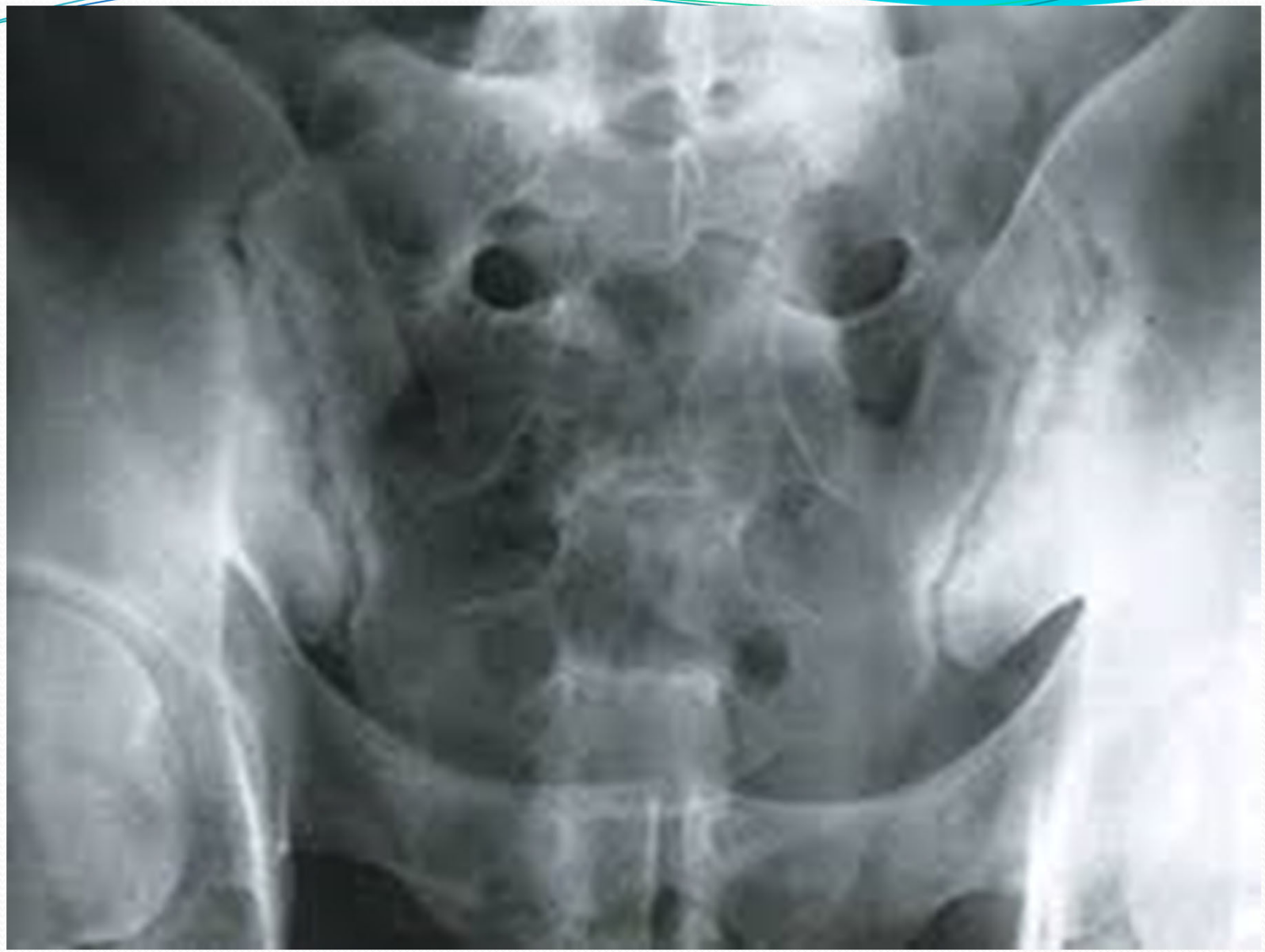
Distal Interphalangeal Joint

- 2-5% of psoriatic arthritis patients
- Nail involvement
  - Pitting
  - Ridging
  - Onycholysis
  - “Oil drop” sign (yellow-orange discoloration)

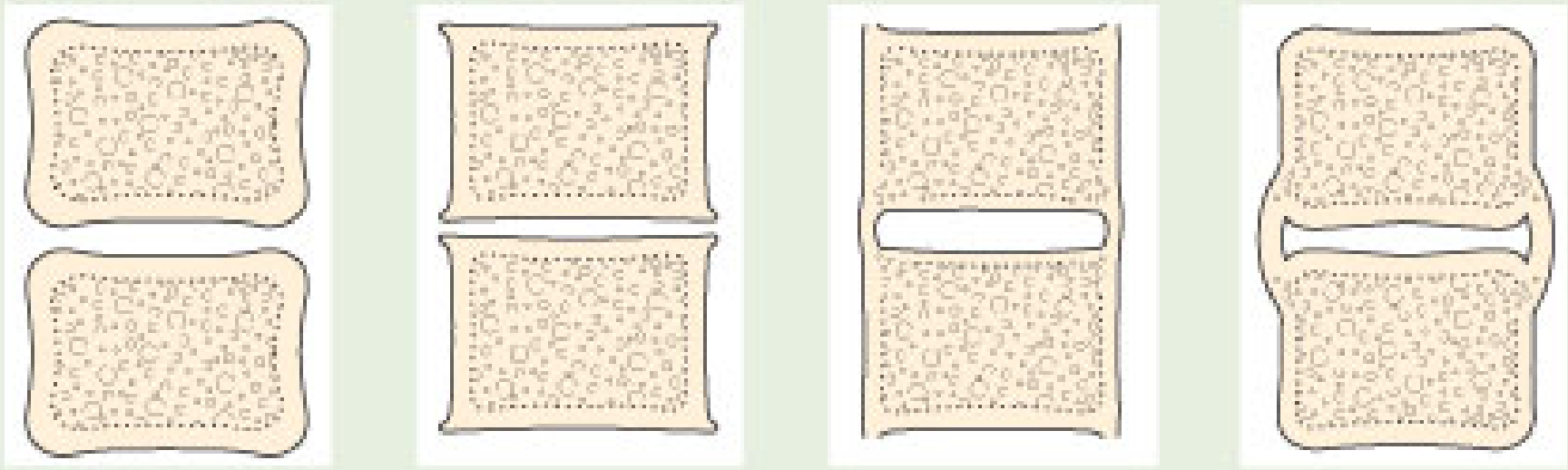


Subtypes of Psoriatic Arthritis
Isolated Axial involvement

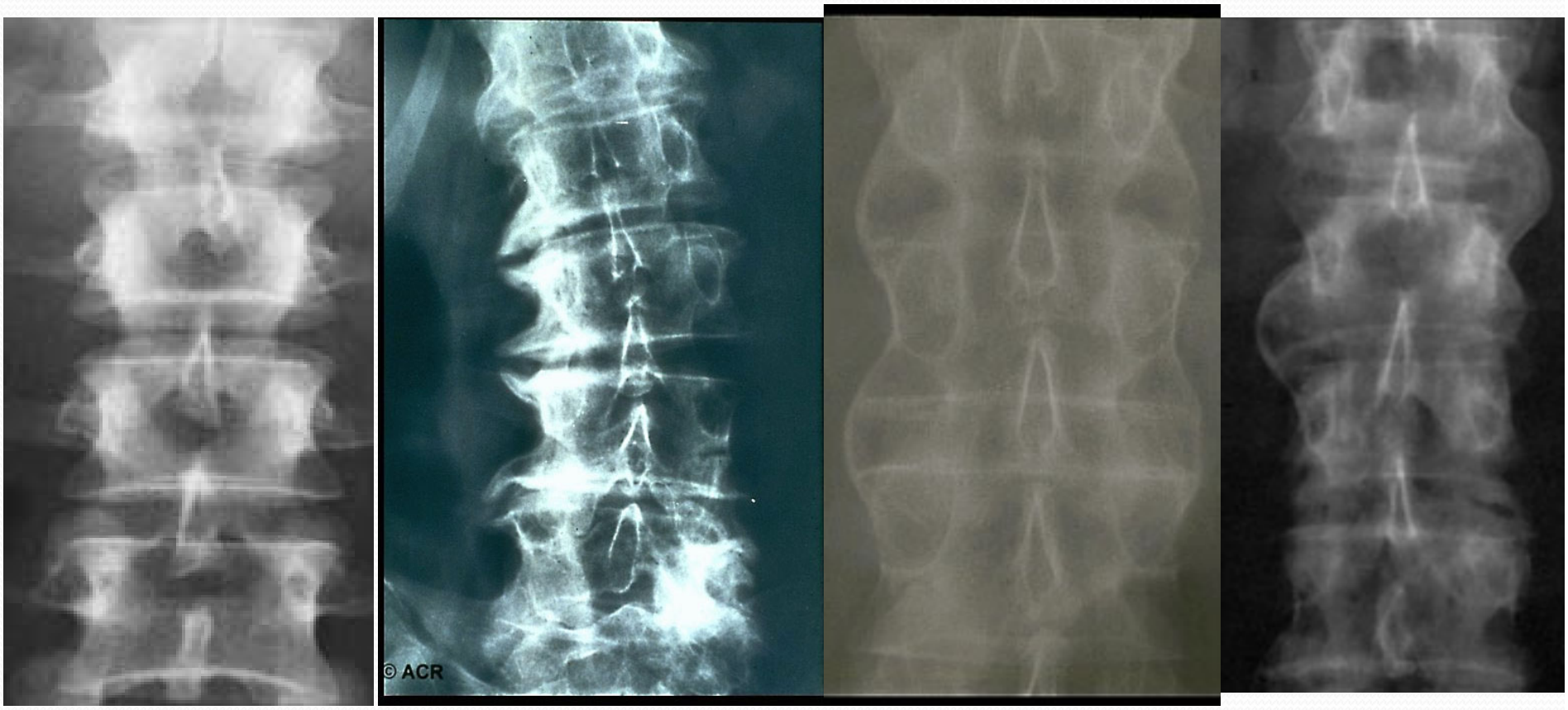
- 2-5% of psoriatic arthritis patients
- Sacroiliitis usually asymmetric
- May affect any level of the spine in "skip" fashion
- Large non-marginal syndesmophytes



BONY CHANGES IN VERTEBRAL COLUMN



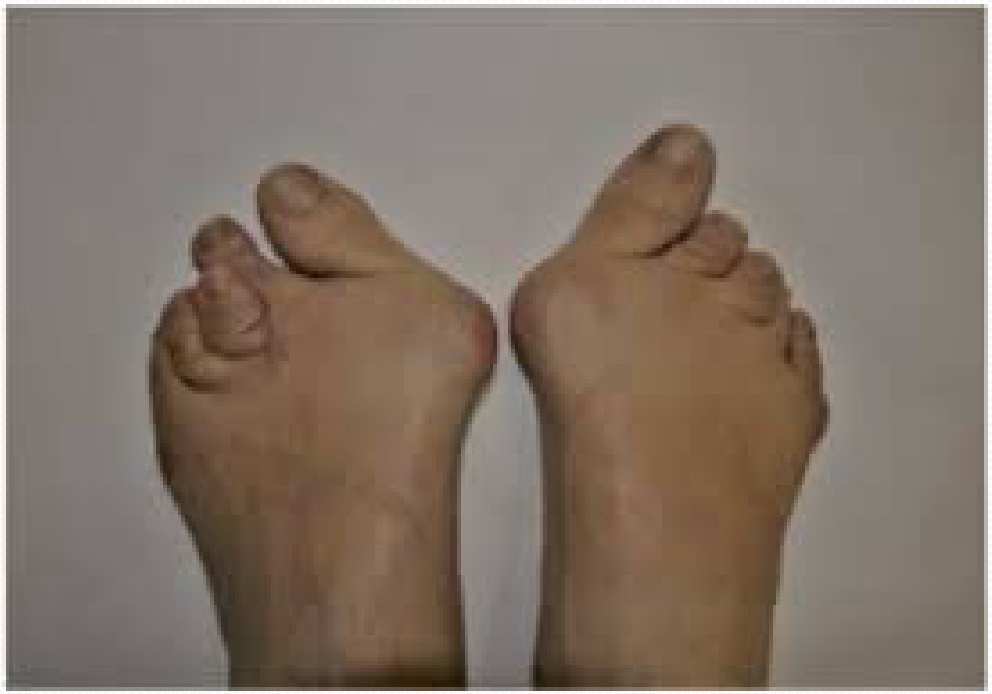
Radiographic Data

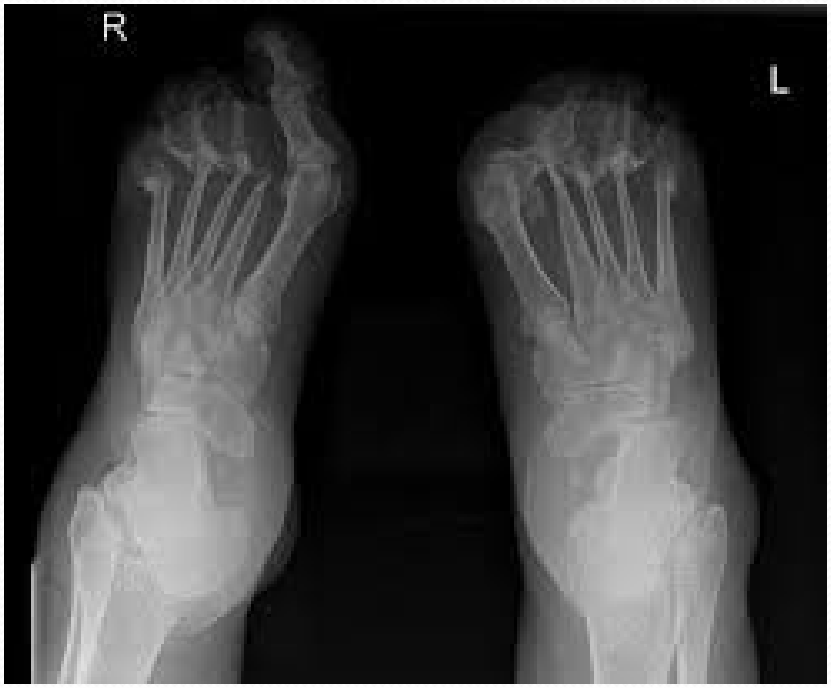


Subtypes of Psoriatic Arthritis

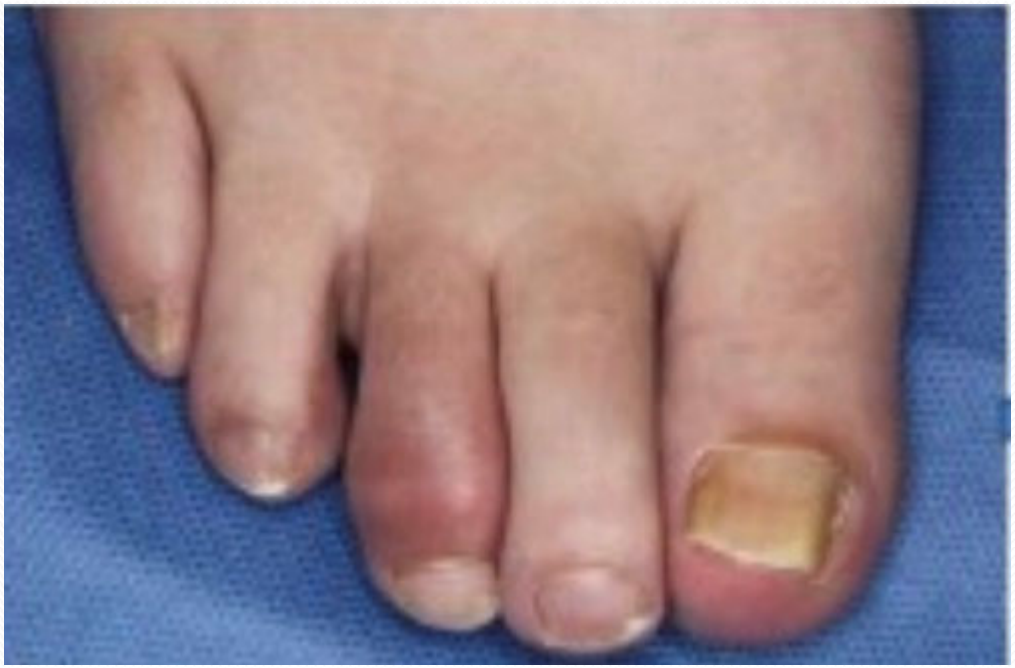
Arthritis Mutilans

- 5% of psoriatic arthritis patients
- Osteolysis





Case 1: Dactylitis



Differential Diagnoses

- Infection
- Seronegative Spondyloarthropathies
  - Psoriatic Arthritis
  - Ankylosing spondylitis
  - Enteropathic arthritis
  - Reactive arthritis
- Crystalline arthropathy (Gout or CPPD)
- Sickle cell
- Sarcoid

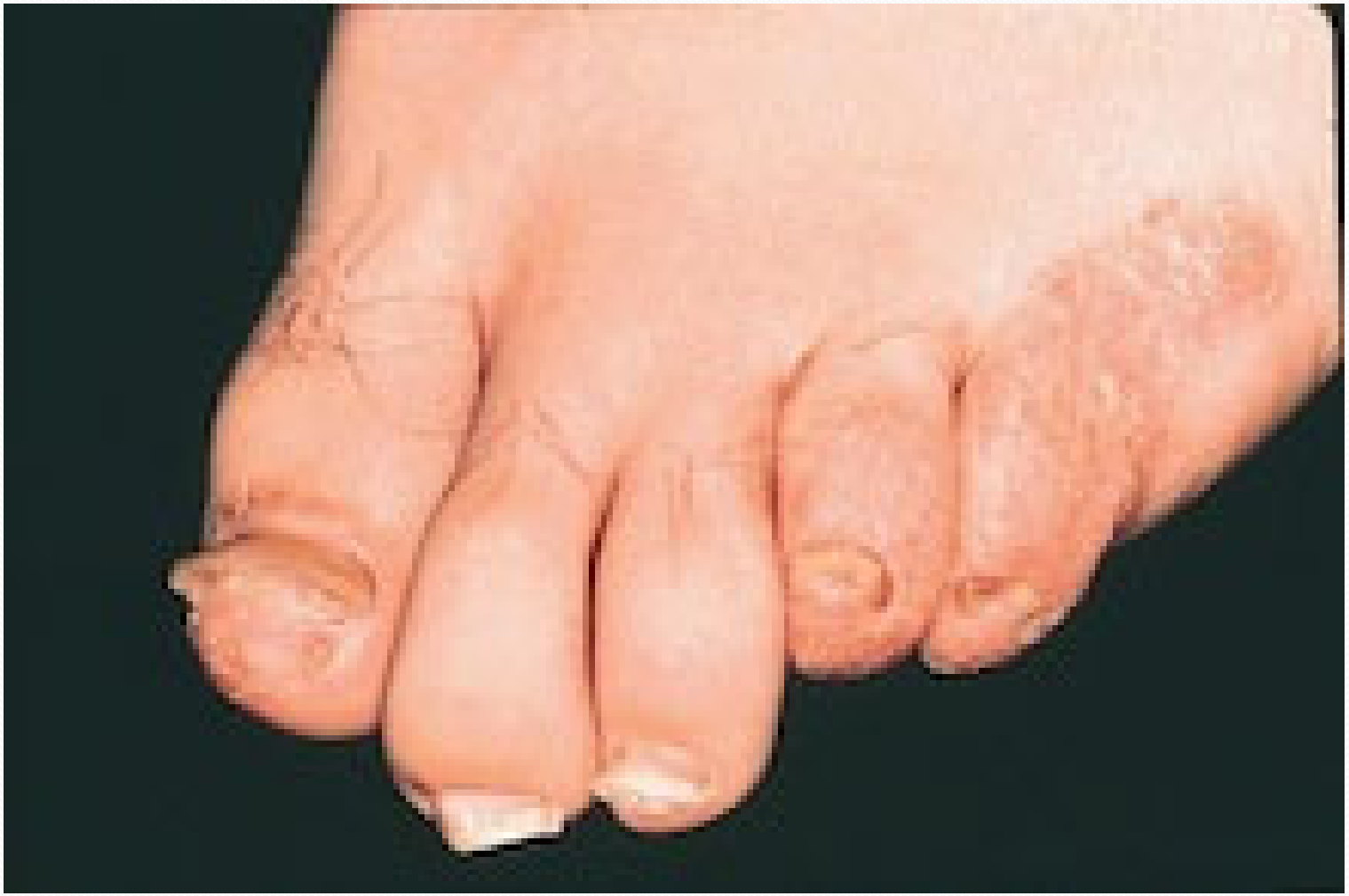
Diagnosing Psoriatic Arthritis

There is no single test to diagnose psoriatic arthritis

- History
- Physical examination
- Imaging of the joints (x-rays, ultrasound, MRI, etc.)
- Laboratory test results

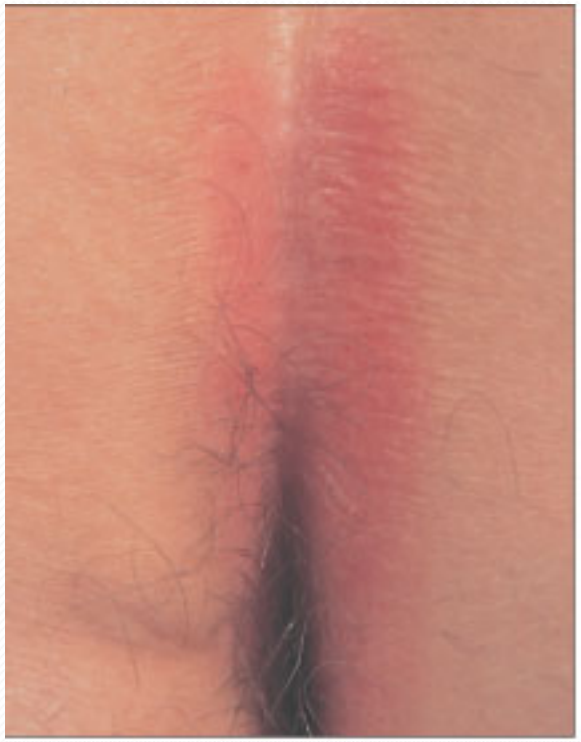
Inflammatory vs. Mechanical Joint Pain

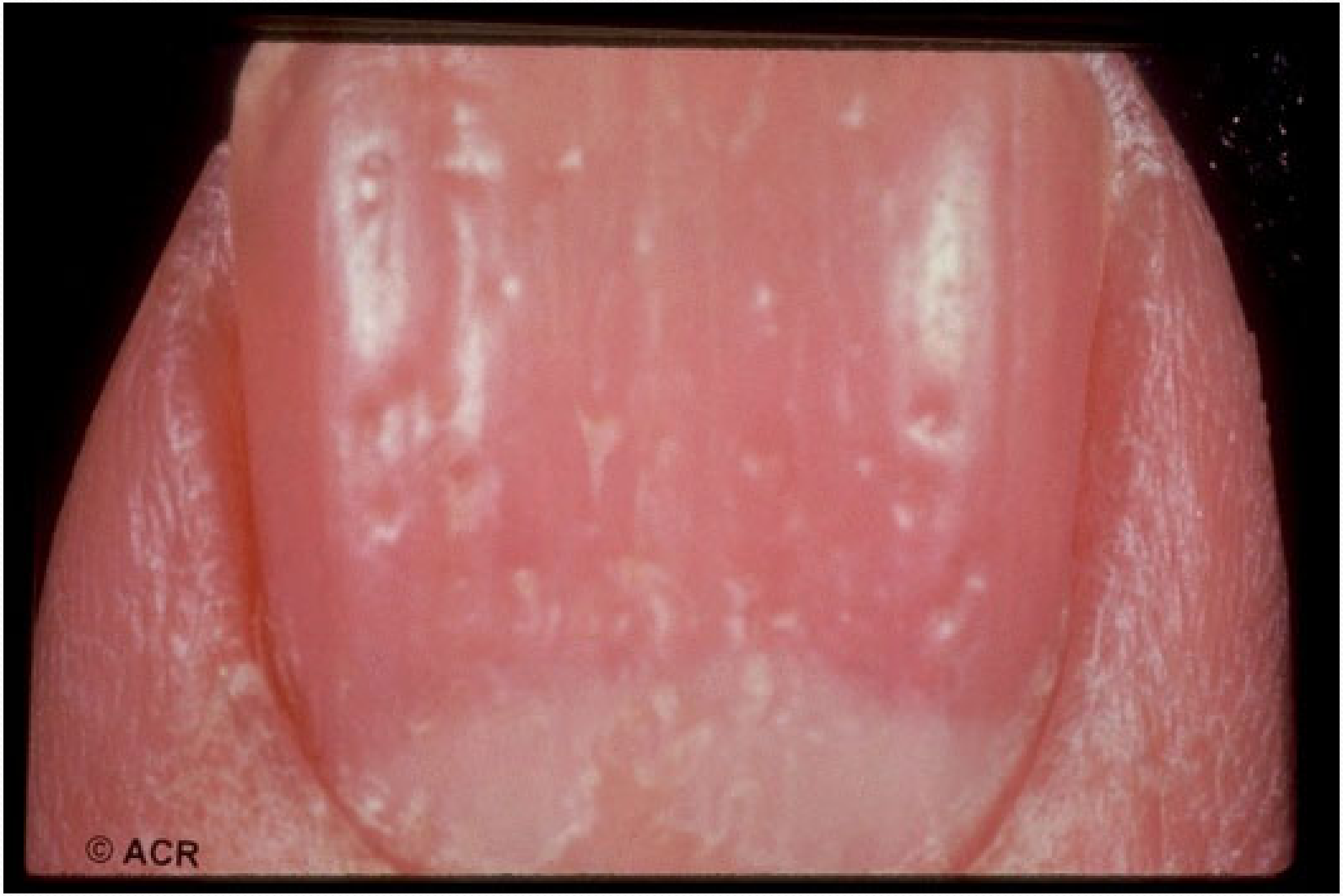
FEATURE	INFLAMMATORY	MECHANICAL
Morning stiffness	> 1 hour	≤ 30 minutes
Onset	Subacute	Variable
Duration	Days to Weeks	Months
Fatigue	Significant	Minimal
Nocturnal pain	Moderate	Mild
Activity	↓ symptoms	↑ symptoms
Rest	↑ symptoms	↓ symptoms
Systemic symptoms	Yes	No



Occult Psoriasis

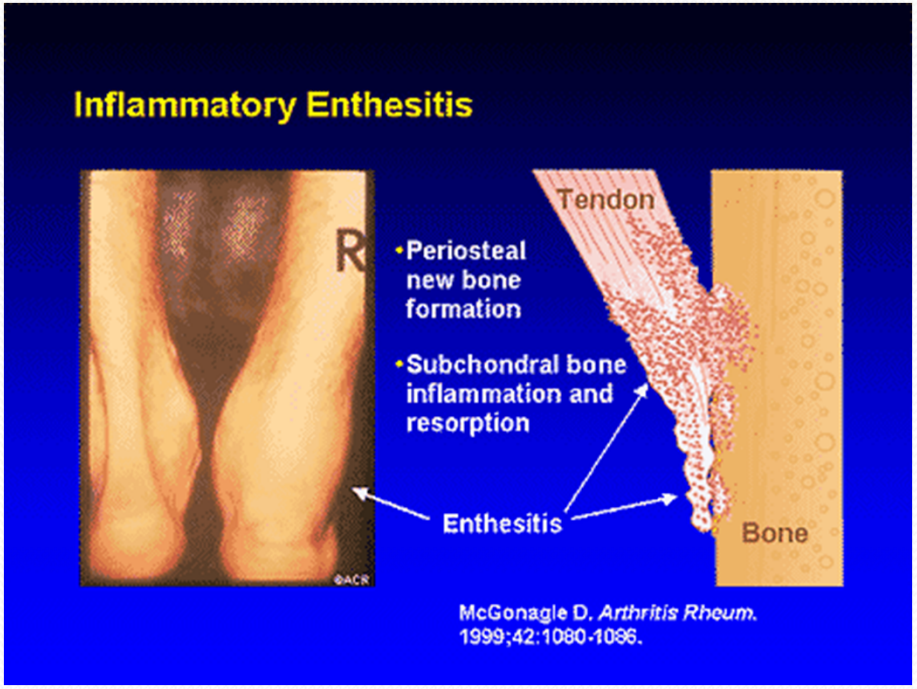
- Umbilicus
- Scalp
- Anus / cleft of the buttocks
- Ears




© ACR

Enthesitis

- Hallmark of the spondyloarthropathies
- Inflammatory process affecting the junction between ligaments/tendons and bone



Classification Criteria for PsA (CASPAR)

Established inflammatory articular disease (joint, spine, entheseal)
plus ≥ 3 points from the following criteria:

Symptom Domain	Criterion
Clinical	PsO (current*, history, or family history)
	Nail changes
	Dactylitis (current or history)
Serology	Rheumatoid factor negative
Radiology	Juxta-articular new bone formation

*Active PsO accounts for two points

Taylor W, et al. *Arthritis Rheum.* 2006;54(8):2665–2673.

TREATMENT

Medications

- NSAIDs
- Conventional DMARDs
- Apremilast
- Biologic DMARDs

NSAID CLASSES

Propionic Acids	Indoles	Oxicams	Phenylacetic Acids	Salicylates	Non-acidic	Cox - 2 Selective
Ibuprofen Naproxen Ketoprofen Oxaprozin	Indomethacin Tolmetin Sulindac	Piroxicam Meloxicam	Diclofenac	Aspirin Salsalate* Trisalicylate*	Nabumetone	Celecoxib

* Non-acetylated Salicylates

Conventional DMARDs in PsA

- **DMARDs:**
  - Decrease pain and inflammation
- **Many are used off-label in PsA**
  - Approved for other inflammatory conditions
- **Modest effects/efficacy on arthritis and skin**
  - Minimal effect on preventing radiological progression
  - No effect on axial disease
- **Risk for adverse events**
- **Significant contraindications**

DMARD = Disease-Modifying Antirheumatic Drug

Raychaudhuri SP, et al. *J Autoimmun*. 2017;76:21–37; Mease PJ, et al. *Drugs*. 2014;74(4):423–441; Kingsley GH, et al. *Rheumatology*. 2012;51(8):1368–1377.

Apremilast

- Phosphodiesterase 4 inhibitor
- Reduces production of multiple cytokines
- NOT for erosive erosive arthritis
- Consider in patients with multiple co-morbidities
- Good safety profile

Biologic DMARDs

- TNF a inhibitors
  - Adalimumab
  - Etanercept
  - Golimumab
  - Infliximab
  - Certolizumab
- IL-17 inhibitors
  - Secukinumab
  - Ixekizumab

Biologic DMARDs

- IL 12/23 inhibitor
  - Ustekinumab
- IL 23 inhibitor
  - Guselkumab
- T-cell co-stimulation blocker
  - Abatacept
- Janus kinase (JAK) inhibitors
  - Tofacitinib

Targeted Therapies in PsA

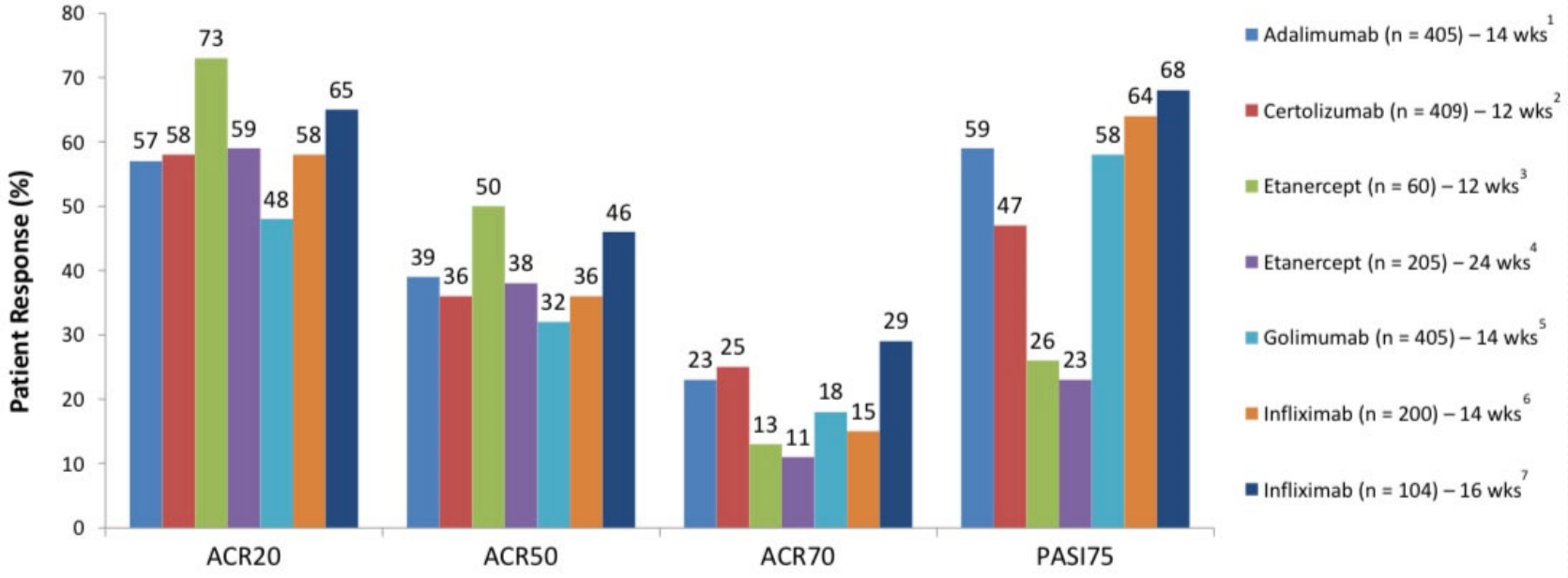
	Therapy	Administration	Key Trials	PsO Indication
Approved Therapies				
CD 80/86	Abatacept	IV Q4W / SC QW	ASTRAEA	No
PDE4	Apremilast	Oral BID	PALACE	Approved
JAK 1/3	Tofacitinib	Oral QD / BID	OPAL	No
TNF-α	Etanercept	SC QW	Ph3 Etanercept in PsA	No
	Infliximab	IV Q8W	IMPACT 2	Approved
	Adalimumab	SC Q2W	ADEPT	Approved
	Golimumab	SC Q4W / IV Q8W	GO-REVEAL, GO-VIBRANT	No
	Certolizumab	SC Q2W / Q4W	RAPID-PsA	Approved
IL 12/23	Ustekinumab	SC Q12W	PSUMMIT 1	Approved
IL 17A	Secukinumab	SC Q4W	FUTURE 2	Approved
	Ixekizumab	SC Q4W	SPIRIT-P1	Approved
Therapies in Phase 3				
JAK 1	Upadacitinib	Oral QD	SELECT-PsA 1 and 2	No
	Filgotinib	Oral QD	PENGUIN-1 and -2	No
IL 23	Guselkumab	SC Q4W / Q8W	DISCOVER	Approved
	Risankizumab	SC Q12W	NCT03675308, NCT03671148	Approved
IL 17A/F	Bimekizumab	SC Q4W	BE-VITAL, BE-COMPLETE, BE-OPTIMAL	Investigational
IL 12/23	Tildrakizumab	SC Q4W / Q12W	NCT03552276	Approved

SC = Subcutaneously; BID = twice per day

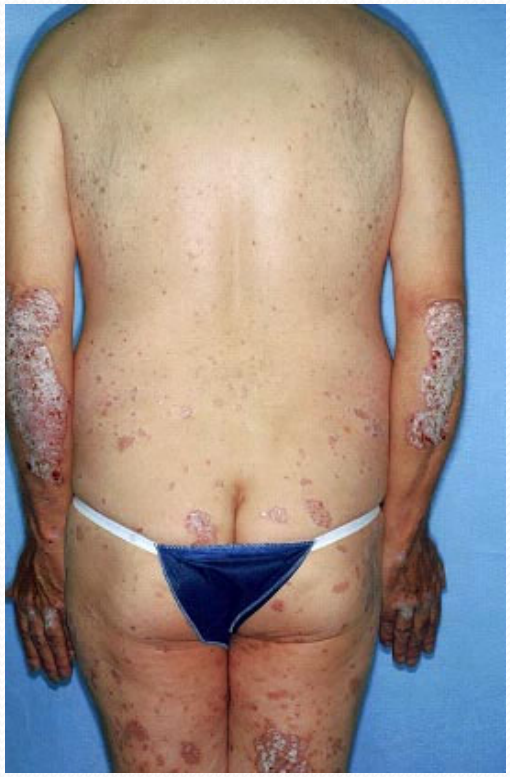
FDA Approved Therapies. Available at https://www.fda.gov/drugs. Accessed 2/26/2020; Clinical Trials. Available at https://clinicaltrials.gov/. Accessed 2/26/2020.

Anti-TNF Therapies in PsA: ACR and PASI Responses

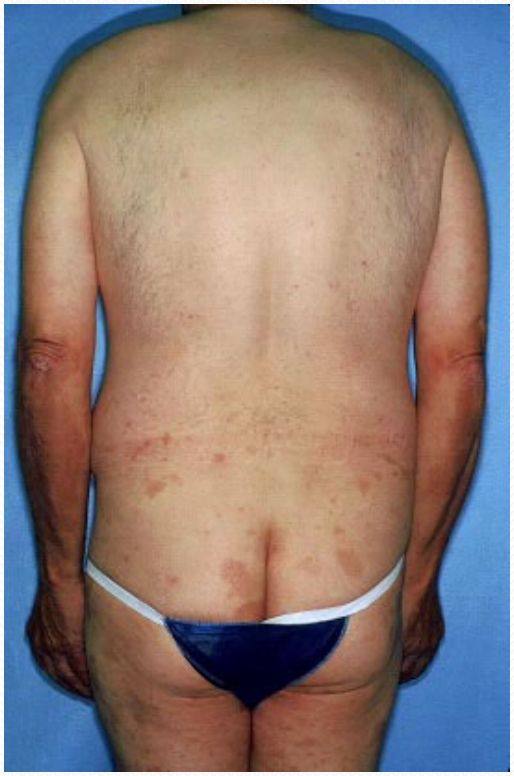
Please note: data presented in this graph come from different trials and are not directly comparable.



1. Mease PJ, et al. *Arthritis Rheum.* 2005;52(10):3279–3289. 2. Mease PJ, et al. *Ann Rheum Dis.* 2014;73(1):48–55. 3. Mease PJ, et al. *Lancet.* 2000;356(9227):385–390. 4. Mease PJ, et al. *Arthritis Rheum.* 2004;50(7):2264–2272. 5. Kavanaugh A, et al. *Arthritis Rheum.* 2009;60(4):976–986. 6. Antoni C, et al. *Ann Rheum Dis.* 2005;64(8):1150–1157. 7. Antoni CE, et al. *Arthritis Rheum.* 2005;52(4):1227–1236.

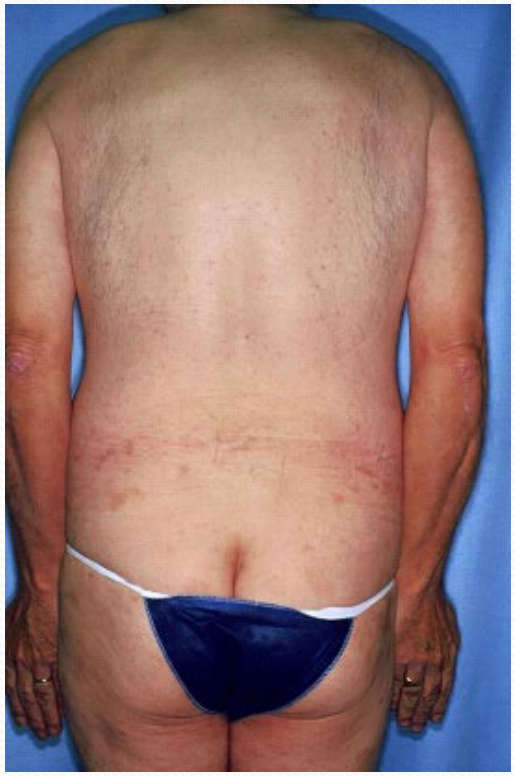


PASI score 15.4



PASI score 3.3

(>PASI 75 response)



PASI score 1.5

(≥PASI 90 response)

Courtesy of Michael Heffernan, M.D., Washington University

Perioperative Care:
Pitfalls and Problems Preparing for Surgery

Case

- 35 year old white male
  - Psoriasis for 8 years
  - Sjogren's syndrome
  - Gout for 3 years
- Referred for surgical options

- Meds:
  - Prednisone 7.5mg/d
  - Ibuprofen 800 bid/tid
  - MTX 20mg/week
  - Adalimumab 40mg q 2 week
  - Buprenorphine 15mcg/hr
  - Hydrocodone 5/325 mg 0-2/d
  - Pilocarpine 5mg qid
  - Allopurinol 300mg/d
- Exam:
  - Limited ROM B wrists
  - Left mid-foot with tenderness with palpation and swelling

The Questions

- What needs to be started/stopped before surgery and when?
- What needs to be started/stopped during surgery?
- What needs to be re-started/started or stopped after surgery and when?

Steroids

- Surgical problems:
  - Impaired wound healing
  - Increased friability of skin and superficial blood vessels
- Adrenal gland suppression:
  - Prolonged use of glucocorticoids may suppress the normal increase in endogenous cortisol that is needed due to surgical stress. Supplementation of glucocorticoids may therefore be needed to mimic the body's own response to stress.
- Moderate surgical stress:
  - Hydrocortisone 50 or 100 mg IV on call to the OR then
  - Taper down over 1 -2 days to preoperative daily oral dose
- Severe surgical stress:
  - Hydrocortisone 100 mg IV on call to the OR then
  - Hydrocortisone 100 mg IV q 8 hours for 24 hours (post op day 1) then
  - Hydrocortisone 50 mg IV q 8 hours for 24 hours (post op day 2) then
  - Hydrocortisone 100 mg x 1 dose (post op day 3) then
  - Preoperative daily oral dose

NSAIDS

- NSAIDs reversibly inhibit platelet function
  - Discontinue 3-4 half-lives of the medication prior to surgery[1]
- Aspirin irreversibly inhibits platelet function
  - Discontinue at least one week prior to surgery to allow production of NEW platelets
- Selective cyclooxygenase 2 (COX-2) inhibitors do not interfere with platelet function
  - No increased risk of bleeding.
  - May have a role in wound healing and can affect renal function
  - "Use cautiously" in the peri-operative period[1]
- "Brief peri-operative use"[2] (mean duration of 3 days postop.) N=10,873
  - NOT associated with increased risk for MI compared with not using NSAIDs following TKR and THR (odds ratio 0.95, 95% CI 0.5-1.8)
  - NSAID use was associated with a reduced hospital length of stay (98 versus 115 hours)

1. Perioperative management of the rheumatic disease patient
Bull Rheum Dis. 2002;51(6)
2. Association of perioperative use of nonsteroidal anti-inflammatory drugs with postoperative myocardial infarction after total joint replacement
Reg Anesth Pain Med. 2012 Jan;37(1):45-50

Disease Modifying Anti-Rheumatic Drugs (DMARDs)

- Theoretic increased risk of infection if continued[1]
- MTX through the peri-operative period found to be SAFE in 8 published trials in RA undergoing elective orthopedic surgery[2]
- Largest RCT[3] showed continued MTX associated with LESS infection and LESS flares and NO change in healing
- Other DMARDs (penicillamine, cyclosporine, anti-malaria) and prednisone found to have increased risk of infection

1. Disease modifying treatment and elective surgery in rheumatoid arthritis: the need for more data.
Ann Rheum Dis. 2004;63(5):602.
2. The place of methotrexate perioperatively in elective orthopedic surgeries in patients with rheumatoid arthritis.
Clin Rheumatol. 2008;27(10):1217
3. Methotrexate and early postoperative complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery.
Ann Rheum Dis. 2001;60(3):214

Biologics

- Agents that interfere with or deplete cytokines or B lymphocytes
- Little evidence available regarding optimal timing in the pre- and peri-operative period so "expert opinion" has been to hold the medications
- Retrospective studies of elective TKR,THR, cardiac or abdominal surgeries showed NO change in short term infection rates (30 day), readmission or mortality if continued compared to holding[2,4]
- Retrospective analysis of patients on abatacept did NOT have more post-op complications when infusion was continued[3]

1. Perioperative management of biologic agents used in treatment of rheumatoid arthritis. Am J Ther. 2011;18(5):426

2. Perioperative timing of infliximab and the risk of serious infection after elective hip and knee arthroplasty. Arthritis Care Res. 2017; 1 (27): 1002 (abstract)

3. Safety of surgery in patients w rheumatoid arthritis treated by abatacept: data from the French Orencia in RA Registry. Rheumatology (Oxford).2017 56 (4): 629-37.

4. George MD, Baker JF, Winthrop KL, *et al*. Immunosuppression and the risk of readmission and mortality in patients with rheumatoid arthritis undergoing hip fracture, abdominopelvic and cardiac surgery. *Annals of the Rheumatic Diseases* Published Online First: 24 March 2020. doi: 10.1136/annrheumdis-2019-216802.

Opioids and Buprenorphine

- Buprenorphine: semisynthetic opioid
  - Partial mu-opioid receptor agonist (1000 times greater affinity compared with morphine) and antagonist at the kappa-opioid receptor
  - Increasingly used to treat narcotic addiction and chronic pain
  - 2 formulations (pill and patch)
  - High affinity for opioid receptors, buprenorphine may reduce effectiveness of other opioids[1-2]
- Half-life is 20 to 70 hours (mean 37 hours)
- The analgesic effects and respiratory depressive effects of buprenorphine are both limited by a "ceiling"
  - Increasing the dose beyond a certain point shows NO further increase in either analgesia or respiratory depression
- STOP a week before surgery

1. Buprenorphine (Butrans): new tricks with an old molecule for pain management. Clin J Pain. 2008 Feb;24(2):93-7
2. Buprenorphine/naloxone (Suboxone): a review of its use in the treatment of opioid dependence. Drugs. 2009;69(5):577-607.

Other Associated Conditions: Sjogren's

- Pilocarpine (cholinergic agonist)
  - Should NOT be given peri-op
  - Risk of bronchospasm, bradycardia, involuntary urination, vomiting, hypotension, and tremor
- Lubricating gel & artificial tears
  - SHOULD be given during and after anesthesia
  - Prevent corneal drying & abrasion

Other Associated Conditions: Gout

- Don't stop uric acid lowering therapy!!!
  - Allopurinol
  - Febuxostat
  - Colchicine

Table 1

Summary of Recommendations for Perioperative Management of Rheumatoid Arthritis Drugs[110]

Medication	Half-life	Recommendation
NSAIDs	2–17 hr	Therapy should be discontinued within 1 wk before surgery. Aspirin should be discontinued at least 72 hr before surgery.
Methotrexate	0.7 to 5.8 hr	Continue perioperatively.
Sulfasalazine	5 hr	Discontinue therapy 1 wk before surgery.
Azathioprine	7.6 hr	Discontinue therapy 1 wk before surgery.
Leflunomide	Approximately 2 wk	Can be discontinued 1–2 d before surgery, with cholestyramine used to remove active metabolite; may be reinstated 1–2 wk postoperatively.
Hydroxychloroquine	1–2 mo	Therapy can continue up to and including the day of surgery.
Etanercept	4.3 d	Hold for at least 1 wk before surgery. Reinstate 1–2 wk postoperatively.
Infliximab	8–10 d	Hold for 4 wk before surgery; may be reinstated 1–2 weeks postoperatively (with no sign of infection).
Golimumab	8–10 d	Hold for 4 wk before surgery; may be reinstated 1–2 weeks postoperatively (with no sign of infection).
Tocilizumab	12–14 d	Hold for 1 mo before surgery.
Abatacept	12–14 d	Hold for 1 mo before surgery.
Adalimumab	12–14 d	Hold for 1 mo before surgery.
Certolizumab	12–14 d	Hold for 1 mo before surgery.
Rituximab	21 d	Hold for 2 mo before surgery.

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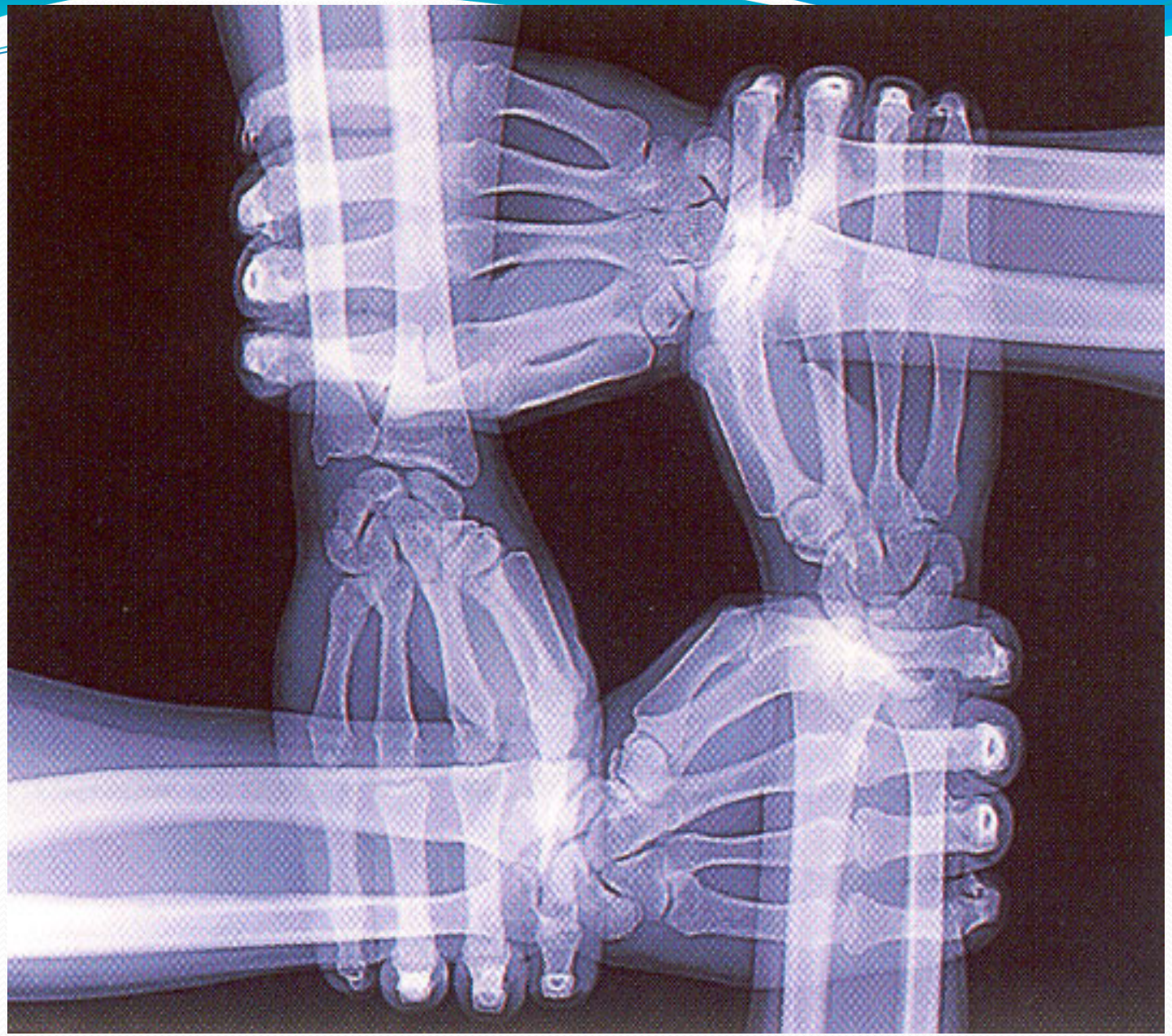

Genetics of Psoriatic Arthritis

High prevalence of:

HLA B27 (subtypes B*2701-2759)

HLA DQ8.1 (DQA1*0301:DQB1*0302)

Table 1. Major Psoriatic Gene Variants and Loci with Independent Replication.

Gene or Locus	Chromosomal Location	Odds Ratio for Disease	Comments	Other Disease Association	Reference
PSORS1	6p	6.4	Contains HLA-Cw6 (putative immune function) as major candidate gene and corneodesmosin	None	Trembath et al.,[8] Nair et al.,[9] Nair et al.[10]
PSORS2	17q	—	Putative role in immune synapse formation	None	Helms et al.[11]
IL12B	5q	1.4	T-cell differentiation	Crohn's disease	Cargill et al.,[12] Capon et al.,[13] Tsunemi et al.[14]
IL23R	1p	2.0	T-cell differentiation	Crohn's disease, ankylosing spondylitis, psoriatic arthritis	Nair et al.,[9] Cargill et al.,[12] Capon et al.,[13] Rahman et al.,[15] Rahman et al.,[16] Burton et al.[17]
ZNF313 (*RNF114*)	20q	1.25	Ubiquitin pathway	None	Nair et al.,[9] Capon et al.[18]
CDKAL1	6p	1.26	Unknown	Crohn's disease, type 2 diabetes mellitus	Wolf et al.,[19] Li et al.[20]
PTPN22	18p	1.3	T-cell signaling	Type 1 diabetes mellitus, juvenile idiopathic arthritis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune thyroid disease	Li et al.,[20] Hüffmeier et al.,[21] Smith et al.[22]
Interleukin-4–interleukin-13 cytokine-gene cluster	5q	1.27	T-cell differentiation	Crohn's disease (distinct variant)	Nair et al.,[9] Chang et al.[23]
LCE3B/3C	1q	1.31	Epidermal differentiation		de Cid et al.,[24] Zhang et al.[25]