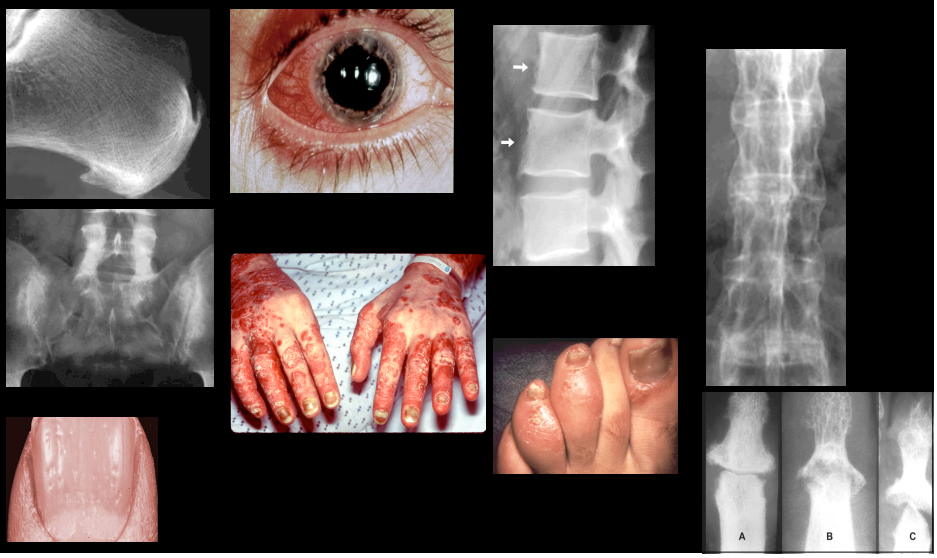
Spondyloarthritis Diseases

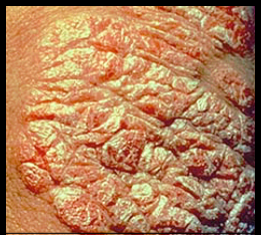
A group of individually distinctive diseases with common, unifying features



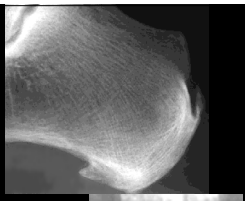
Spondylitis Diseases

- ✔ Ankylosing spondylitis (ASp)
- ✔ Psoriatic arthritis (PsA)
- ✔ Reiter's syndrome (RS) / reactive arthritis (ReA)
- Undifferentiated spondyloarthritis (USpA)
- Enteropathic arthritis (ulcerative colitis, regional enteritis)

Psoriasis



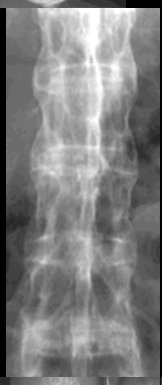
Spondyloarthritis Diseases
Uunifying features



Clinical

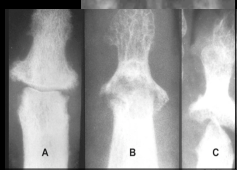
Three main target sites of inflammation

Enthesitis: fibrocartilage insertions of ligaments, tendons & fascia



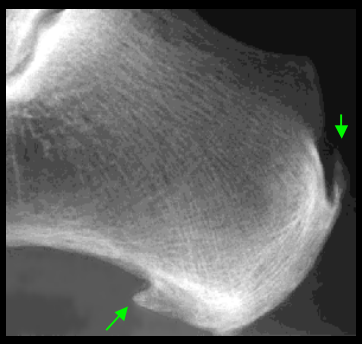
Spondyloarthritis: spine and sacroiliac joints

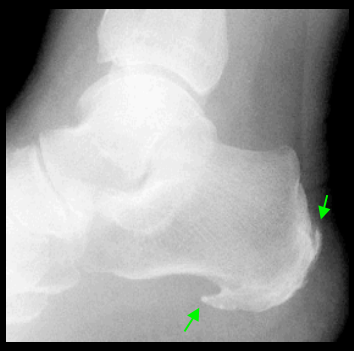
Synovitis: peripheral joints



Enthesitis (enthesopathy): the central inflammatory unit of spondyloarthritis

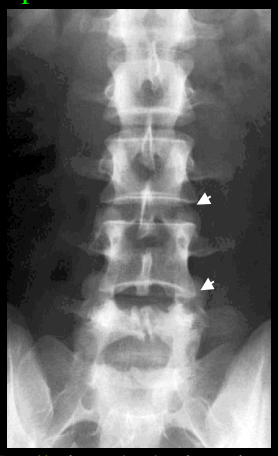
Entheses are the specialized fibrocartilagenous region of bone where ligaments, tendons, fascia or joint capsules insert



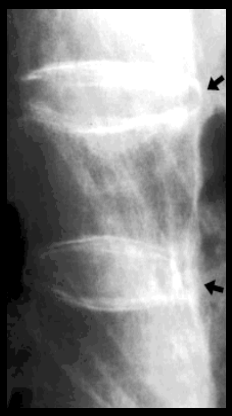


Infiltration of entheses by T cells initiates granulation tissue producing a combination of bone erosions and heterotopic new bone formation
Calcaneal spurs at insertion of plantar fascia and Achilles ligament are classic examples (Lover's heel).

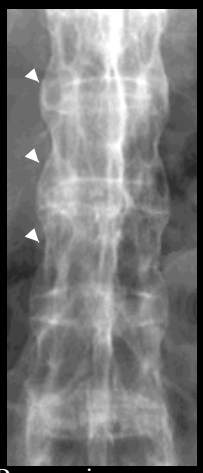
Spondylitis leads to the development of syndesmophytes and ankylosis ASp



T cells invade the junction of annulus fibrosis and vertebral body forming granulation tissue (activated macrophages, T cells and fibroblasts)

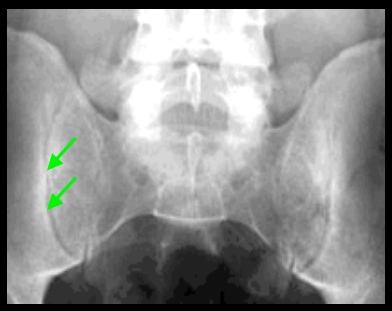


Annulus fibers are eroded, then replaced by fibrocartilage that ossifies to form a syndesmophyte. Subperiosteal new bone formation ensues

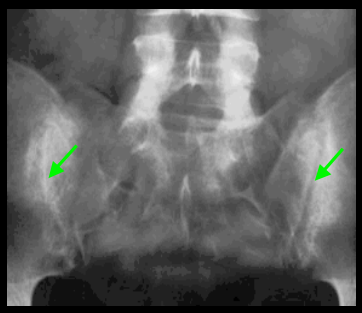


Progressive cartilaginous and periosteal ossification forms a "bamboo spine", osteoporosis develops

Sacroiliitis



The subchondral regions of the synarthrotic SI joints are invaded by T cells leading to the formulation of granulation tissue



The cartilage on the iliac side is eroded first, causing bone plate blurring, joint space "widening" and reactive sclerosis. Ultimately the resultant fibrous ankylosis is replaced by bone, obliterating the SI joint

Inflammatory back pain

Due to the initial inflammation of enthesitis, spondylitis or sacroiliitis

- Onset before age 40
- Insidious persistent (> 3 mo) dull deep buttock or low back pain
- Poorly localized, does not follow nerve root
- Stiffness/pain upon arising in the morning, or awakens from sleep
- Improves with exercise

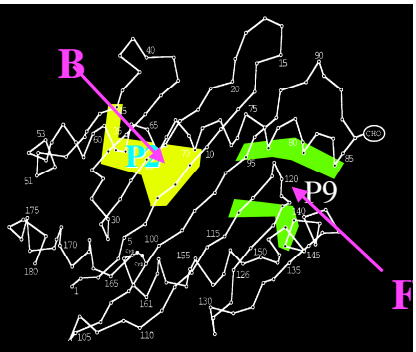
Spondyloarthritis Diseases

Uunifying features

Genetics

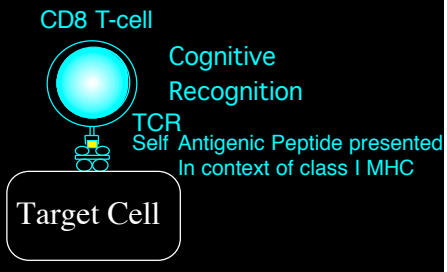
Strong familial aggregation

Identical twin concordance



Susceptibility associated with certain class I MHC alleles

HLA-B27 is a common denominator

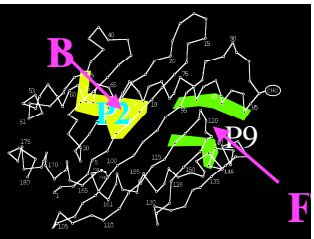


Class I-associated autoimmune diseases

Spondyloarthritis Diseases

Unifying features

Genetics



- HLA-B27 increased, but unevenly, among spondylitis diseases

	HLA-B27 frequency (%)
Ankylosing spondylitis	95
Reiter's syndrome (reactive arthritis)	60-70
Psoriatic arthritis	20
Ethnically matched controls	3-8

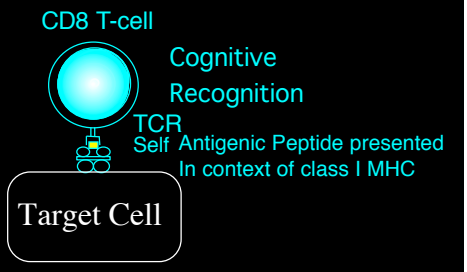
- Other class I alleles may also be involved, especially in PsA and RS

Spondyloarthritis Diseases

Uunifying features

Mechanism

Appear to primarily result from the activation of autoreactive CD8 T cells that recognize self peptides in the context of class I MHC molecules

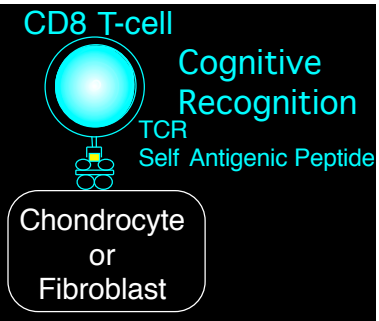


Autoantibodies such as ANA or RF are not present, hence they are sometimes called "seronegative arthritides"

Pathogenesis incompletely understood but seems to be at the interface of triggering CD8 T cell clones of the adoptive immune system by receptors recognizing innate immune system ligands

Spondylitis Disorders

CD8 T cell effector mechanisms of tissue injury



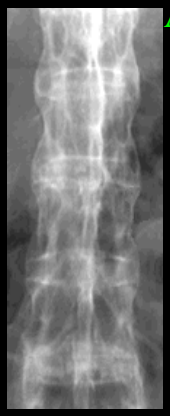
- Activated CD8 T cells injure target cell and release cytokines including γ-IFN that reprogram gene expression of nearby cells
- CD8 T cells are CD28-negative, memory / effector cells that receive a "signal 2" from engagement of NK receptors by stress-induced ligands
- The identity of autologous peptides /proteins driving the response is still unknown…aggrecan?
- Macrophages activated by γ-IFN release cytokines (TNF-α)
- Fibroblasts usually have fibrogenic and osteoblastic program activated

Specific Spondyloarthritis Diseases

Ankylosing spondylitis

First disease shown to be related to occurrence of a particular HLA allele

Uniquely high relationship between susceptibility and HLA-B27



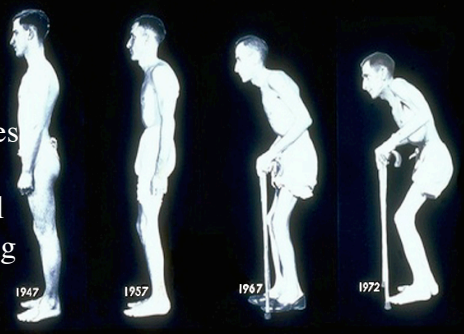
Ankylosing spondylitis

- A progressive autoimmune inflammatory disease characterized by widespread spondylitis and sacroiliitis
- Male: female =3-10:1
- Culminates in boney ankylosis of spine
- Onset, age 10-25 with dull pain in lumbar or gluteal regions
- Hip, shoulder knee arthritis in ~30%

- Epidemiology: >95% of those affected are HLA-B27 Disease prevalence follows distribution of HLA-B27 alleles, highest in circumpolar regions in Europe and Asia
- Affects 1-3% of HLA-B27 individuals,
- No evidence for triggering by microorganisms

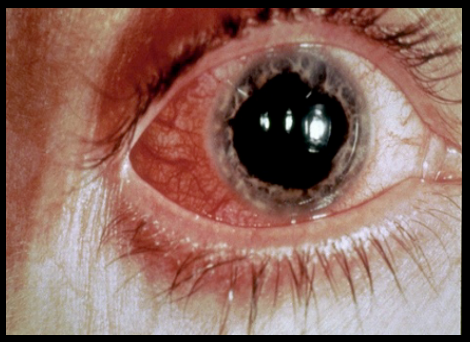
Ankylosing spondylitis - Course

- Begins with sacroiliitis
- Inflammatory back pain and tenderness or pain at central entheses (iliac crests, ischeal tuberosities) progresses and ascends over several months to ~10 years, with increasing stiffness and loss of mobility



- Postural changes include loss of lumbar lordosis, buttock atrophy and thoracocervical kyphosis, chest expansion compromised
- Peripheral joints, notably the hips may develop flexion contractures or ankylosis. Compensatory knee flexion
- Peripheral arthritis (~30%) and peripheral enthesopathy (~30%) may dominate the early phase of disease, while bony ankylosis predominates later

Ankylosing spondylitis - systemic involvement



• Acute anterior uveitis may occur at any time (25%). High potential for syncheae and glaucoma

• Apical pulmonary fibrosis often with cavitation, uncommon (<<5%)

• Restrictive pulmonary disease due to costovertebral ankylosis,~ 10%

• Symptomatic complete heart block due to interventricular septum inflammation and /or aortic insufficiency due to granulomatous aortitis occurring in ~5% of patients. These may appear early, even developing in HLA-B27 individuals without detectable spondylitis

Ankylosing spondylitis- different types of HLA-B27

HLA-B27 alleles differ from one another in polymorphic amino acids, in ethnic distribution and, importantly, whether they determine disease susceptibility

Allele	Features	Ank.Spon
B*2701	Rare	Yes
B*2702	10% of AS in Europe and Middle East	Yes
B*2703	Rare West African allele	Yes
B*2704	Major HLA-B27 allele in China and India	Yes
➔ B*2705	90% of AS, circumpolar Caucasians & Asians	Yes
B*2706	SE Asia	**No**
B*2707	Minor allele in SE Asia, China and India	Yes
B*2708	Rare, UK and Azores	Yes
B*2709	Sardinia	**No**

A self-peptide likely drives ankylosing spondylitis

HLA-B27 alleles share the same P2 "B"pocket, but differ from one another in the "F" P9 pocket

		P9 Pocket				
Allele	59	77	80	116	114	Ank.Spon
B*2701	Tyr	Agn	Thr	Asp	His	Yes
B*2702	Tyr	Agn	Ile	Asp	His	Yes
B*2703	His	Asp	Thr	Asp	His	Yes
B*2704	Tyr	Ser	Thr	Asp	His	Yes
➔ B*2705	Tyr	Asp	Thr	Asp	His	Yes
B*2706	Tyr	Ser	Thr	**Tyr**	**Asp**	No
B*2707	Tyr	Asp	Thr	Asp	His	Yes
B*2708	Tyr	Ser	Ile	Asp	His	Yes
B*2709	Tyr	Asp	Thr	**His**	His	No

Current theories of why HLA-B27 predisposes to Ankylosing Spondylitis

Peptide binding properties of HLA-B27

Distinctive chemical state of HLA-B27 molecules

Transgenic rats expressing >100 copies of HLA-B27 develop a disease with some features of ankylosing spondylitis

HLA-B27 may misfold and elicit an altered protein stress response

Ankylosing Spondylitis

Therapies

Physical medicine: posture and mobility

Antiinflammatory (NSAIDS)

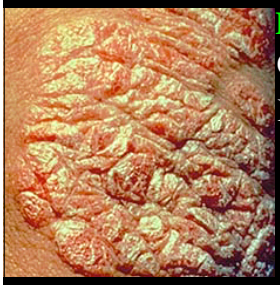
TNF blockers

Psoriasis / Psoriatic Arthritis

Psoriasis is characterized by retardation in kertinocyte differentiation induced by the presence of activated T cells that are seemingly driven by keratinocyte peptides presented by class I molecules

Psoriatic arthritis is an often clinically distinctive complex of spondloarthritis occurring in the setting of psoriasis. It may involve the spine or peripheral joints in a variety of patterns

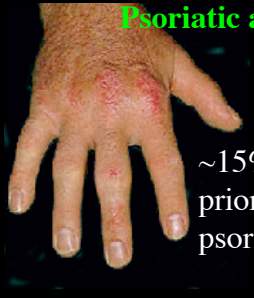
Initiated or exacerbated by stress or non specific infection



Psoriasis
Onset age 15-30 yrs
Prevalence ~3%

10-20%
0-20+ years
between Ps & PsA

Psoriatic arthritis



~15% no prior psoriasis

Clinical Diagnostic Features of Psoriatic Arthritis

Characteristic features:

- Psoriasis present
- Enthesitis
- Ankylosed joints, e.g. hallux rigidus
- Juxta-articular new bone formation
- Sacroiliitis and/or spondyloarthritis
- DIP joint arthritis
- Onychodystrophy
- Dactylitis

Supporting features:

- Convincing past history and/or family history for psoriasis
- Peripheral arthritis, often asymmetrical at onset

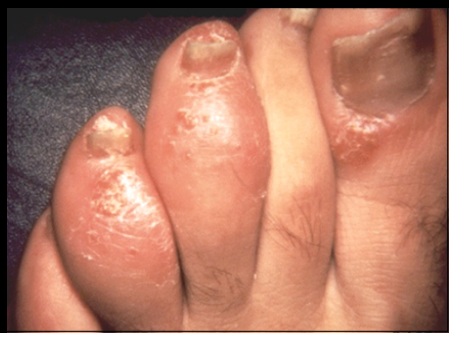
Exclusions:

- Fibromyalgia, seronegative or seropositive rheumatoid arthritis
- Intercurrent arthritides, e.g. Lyme disease
- Repetitive motion-induced musculoskeletal syndromes

Psoriatic arthritis

Dactylitis (Sausage digit) widespread inflammatory edema due to

- DIP and PIP arthritis of same ray
- Enthesitis
- Tenosynovitis flexor > extensor
- Periostitis
- Onychodystrophy



Acral dystrophic state

Psoriatic arthritis - features

•Presentation: with obvious skin lesions, sometimes with subtle skin involvement (eg, scalp, umbilicus, intergluteal cleft, ear), only nail manifestations, or no psoriasis; usually between ages 25 and 45

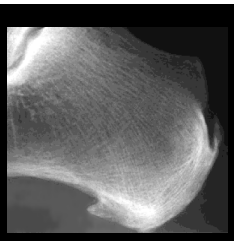
•Early onset psoriatic arthritis occurs in a setting of strong family history

•Onset typically insidious with stiffness predominating, but may be acute mimicking gout if localized to the foot or toe, sometimes seeming to following a joint injury

•Dactylitis and pitting edema of the hands or feet, sometimes asymmetrical, secondary to enthesitis and tenosynovitis, and or inflammatory back pain at onset

•Sex: Men and women are affected equally

Enthesitis



•May be quite subtle and relatively easy to overlook

•Nonspecific foot pain, "tennis elbow" in the non dominant hand, or isolated posterior tibial tendinitis

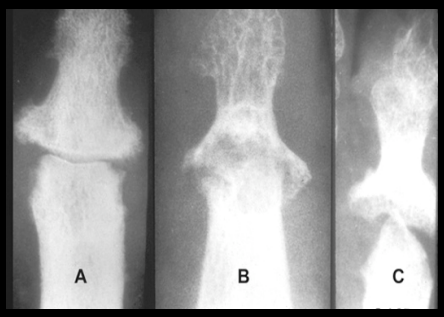
•When more widespread and symmetric, the distribution differentiates it from posttraumatic or occupational tendon injury

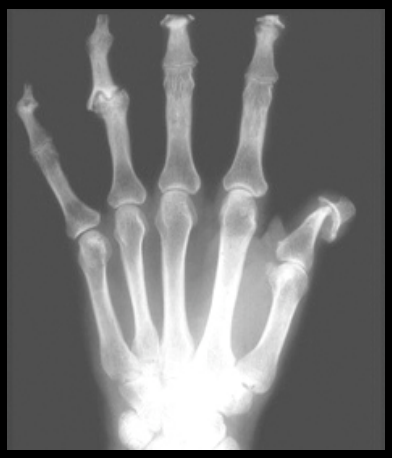
•Can be fulminant and combined with intense tenosynovitis

Psoriatic arthritis-peripheral synovitis patterns

- Asymmetric oligoarthritis of small and medium-sized joints
  - Classic, with time more joints accumulate, blurring asymmetry
  - Digits of the hands and feet often affected first, characteristically with dactylitis
- DIP arthritis joints, where it characteristically also involves nails
  - Classic and unique to psoriatic arthritis, but not common as isolated form, primarily males
  - Associated paronychia and swelling of the digital tuft may make appreciation of arthritis difficult; DDx Heberden's nodes
- Arthritis mutilans
  - Osteolytic dissolution of joint with redundant overlying skin and telescoping digits (opera-glass hand)
  - Typical but uncommon, males and in early-onset disease

Progression of DIP arthritis





Narrowed joint space & condylar erosions

Reactive sub periosteal new bone

Pencil in cup appearance

Psoriatic Arthritis-Nail Involvement

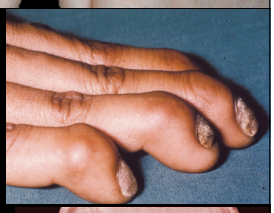
~80-85% inPsA, vs. 20-30% in Ps

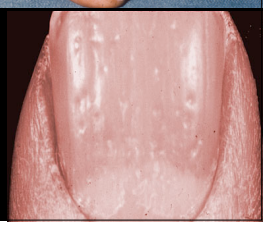
Nail matrix abnormalities

- Pitting
- Onychodystrophy, crumbling
- Transverse ridging (Beau's lines)
- Subungual hyperkeratosis
- Leukonychia
- Onycholysis
- Ectatic capillaries

Acral dystrophic state

- Nail matrix abnormalities
- Acrokeratosis
- Often seen in digit involved with DIP arthritis





Psoriatic arthritis-peripheral synovitis patterns

- Symmetric polyarthritis

  Most common reported pattern at onset, but if isolated has lowest specificity for PsA

  Not easily distinguished from coincident rheumatoid arthritis, especially seronegative

  Hands, wrists, ankles, and feet

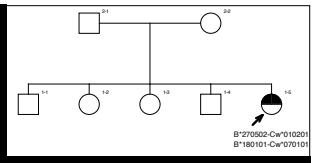
  Female preponderance

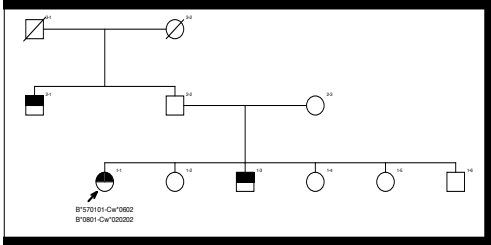
  Differentiated from RA by enthesopathy and dactylitis, DIP joint involvement, relative asymmetry, new bone formation, pencil in cup deformity, absence of subcutaneous nodules, and negative RF

  In absence of distinguishing features not a criterion of certain PsA

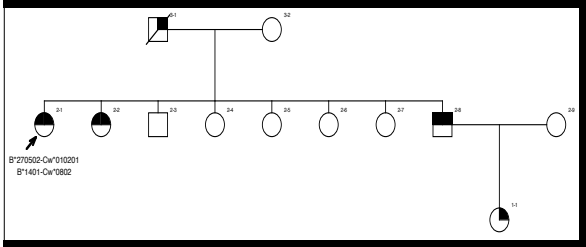
Important to distinguish RA from PsA because steroids contraindicated

PsA inheritance





~40% have strongly positive family histories, most often with first degree relatives affected by psoriasis



λ_R= 55 (assuming prevalence 0.1%)

λ_R= 12.2 (assuming prevalence 0.45%)

Mixed multifactorial pattern, partially dominant mode of inheritance, incompletely penetrant

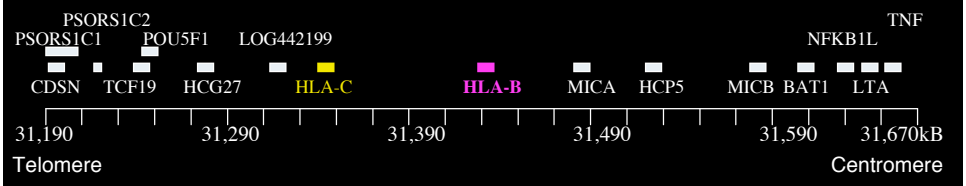
Psoriatic arthritis genetics

Multiple studies implicate several class I HLA alleles

Genetic Heterogeneity

Psoriasis susceptibility HLA alleles: HLA-Cw*0602, (*Psors 1*) ~ 60% in most series, and a group of HLA-B alleles that are in linkage disequilibrium: HLA-B57, HLA-B37, HLA-B13

HLA-B alleles HLA-B27, HLA-B38, HLA-B39 (not strongly associated with psoriasis, no common HLA-C allele in linkage disequilibrium)



Psors1

Psoriatic Arthritis Therapy

NSAIDS + Methotrexate

Anti TNF-α receptor blockade

No systemic steroids!

Specific Spondyloarthritis Diseases

Reiter's syndrome /Reactive arthritis

Directly triggered by specific pathogenic microorganisms in susceptible persons that carry HLA-B27

First example of a MHC allele controlling an immune response in humans (1974 Brewerton)

Reiter's syndrome /Reactive arthritis

"On August 21, 1916 a lieutenant in the Prussian army developed abdominal pain and diarrhea. This episode last 48 hours and was followed by a latent period of 7 days at which time urethritis and conjunctivitis occurred.

"The following day he developed polyarthralgias and arthritis of the knees, ankles, elbows, wrists and several interphalangeal joints.

"Within a few days the symptoms remitted and the patient remained well for 3 weeks.

"A relapse followed with a recurrence of urethritis and uveitis".

H. Reiter (Andre Calin)

Triad of Reiter's syndrome

Reiter's syndrome /Reactive arthritis - features

• Onset 7- 30 days after self limited specific enteric or venereal infection

• Course-Initial episode usually regresses completely after weeks to months, but occasionally can return in a series of sometimes increasingly intense recrudescences and become sustained and chronic

• Peripheral arthritis: acute, highly inflammatory asymmetric arthritis involving knees, ankles, toes, and fingers.
- All affected joints usually synchronous in abrupt fulminant onset
- Usually an oligoarthritis with 2-4 joints involved

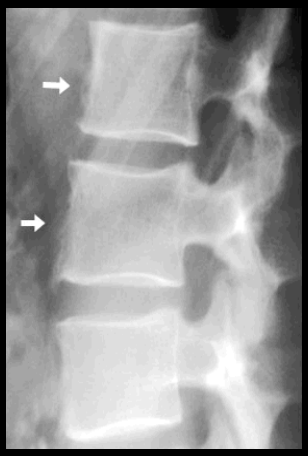
• Enthesitis - notably plantar fascia and Achilles tendon (40%)

• Dactylitis (Sausage digit) (40%)

• Sacroiliitis, stuttering spondylitis with asymmetric involvement of only one or two vertebral units (50%). More extensive vertebral "squaring"

Reiter's syndrome-Reactive arthritis

Sub periosteal new bone formation a major feature



Infiltration of lymphocytes followed by fluffy reactive new bone formation, similar to process occurring in entheses.

May produce "square" vertebrae and other features of paravertebral ossification

Some similarities to ankylosing spondylitis, but different

Reiter's syndrome /Reactive arthritis - Clinical features

- Onychodystrophy with hyper- and para-keratosis. Often subungual
- Conjunctivitis (often first manifestation). Uveitis may appear in recurrent disease
- Non specific urethritis
- Painless circinate balanitis and mucosal ulcers, prostatitis
- Heart - 10% of chronic phase patients develop heart block (1^{o}) from IV septum inflammation and /or aortic valve insufficiency due to granulomatous aortitis at aortic ring, rarely see aortic dissection

Reiter's syndrome- role of specific infection

Induction by particular pathogens, intriguing host-pathogen relationships

Develops 7-30 days after enteric infection with certain Gram neg. rods

- *Salmonella typhimurium*, and occasionally *S. paratyphi* or *S. heidelbergii*
- *Shigella flexneri* 2a and 2b, but not *S. sonnei*
- *Yersinea enterocoliticas*
- *Campylobacter jejuni* or *C. fetus*

These organisms typically invade and kill intestinal M cells, perhaps resulting in the expression of arthritogenic peptides in class I MHC by dendritic cell cross presentation (?)

Develops 7-30 days after venereal infection with

- *Chlamydia trachomatis* or *C. psittaci*

Obligate intracellular eubacteria

HIV and the spondylitis diseases

• Early in the course of the HIV epidemic, a marked increase in instances of very severe Reiter's syndrome or psoriatic arthritis-psoriasis appeared in North America in patients with frank AIDS. This is still a major problem in Africa and parts of Asia

• However, intriguingly, ankylosing spondylitis not seen with AIDS

• Sometimes the Reiter's syndrome or psoriatic arthritis was the first finding and therapy with immunosuppressant drugs accelerated AIDS

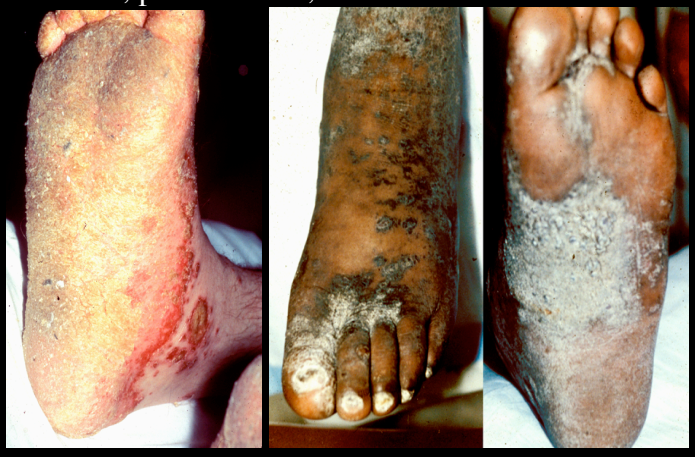
• The paradox of a disease treated with immunosuppression appearing *de novo* in a profound immune deficiency state was an experiment of nature that eliminated the role of CD4 T cells from the pathogenesis of RS /PsA

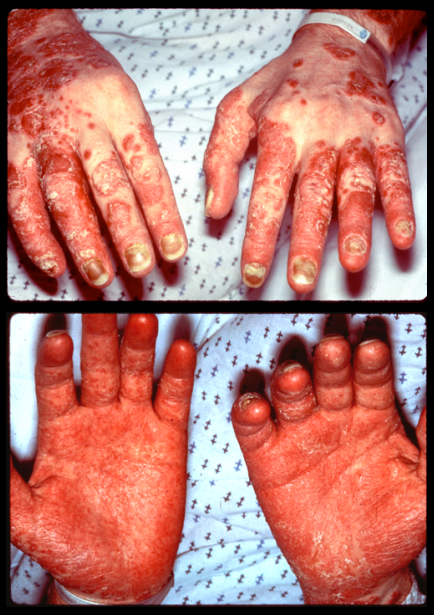
• It also suggested that these spondylitis diseases arise from clones of previously expanded memory rather than naïve CD8 T cells

(Rheumatoid arthritis and SLE are ameliorated in advanced AIDS)

Reiter's syndrome in the setting of AIDS

- Keratodermia blenorrhagicum- pustular psoriasis-like lesions of palms and soles
- Psoriasis - like lesions (T cell infiltration, keratinocytes HLA-DR $^{+}$ with delayed differentiation, parakeratosis, sterile microabsesses





Reiter's syndrome

Progression to psoriasis pattern of skin disease in AIDS