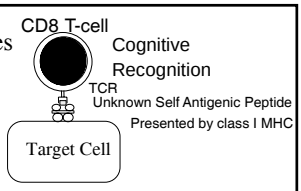
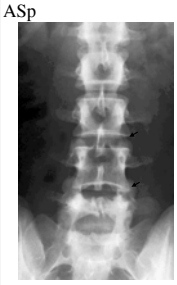
Spondyloarthritis Diseases

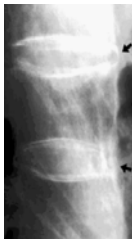


- A group of autoimmune diseases that in common appear mediated by activation of autoreactive CD8 T cells
- Physical stress, inflammation and infection with specific microorganisms trigger the immune response
- Primarily affect joints, skin, eyes and mucous membranes
- Autoantibodies such as ANA or RF are absent

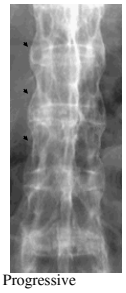
Spondylitis leads to the development of syndesmophytes and ankylosis ASp



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

Spondylitis Diseases

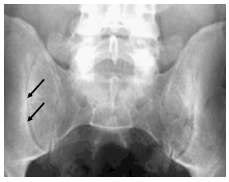
- ✔ Ankylosing spondylitis (ASp)
- ✔ Reiter's syndrome (RS) / reactive arthritis (ReA)
- ✔ Psoriatic arthritis (PsA)

Undifferentiated spondyloarthritis (USpA)

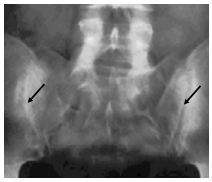
Enteropathic arthritis (ulcerative colitis, regional enteritis)

Psoriasis

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

Spondyloarthritis Diseases-features common to all

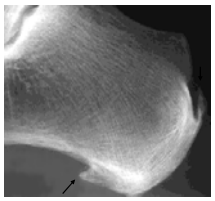
1. Clinical:- Affect joints, skin, eyes and mucous membranes in varying proportions with characteristic joint involvement: Spondylitis (inflammation of vertebral discs), sacroiliitis (sacroiliac joints) and enthesitis (tendon insertions). All with granulomatous fibrosis and new bone formation

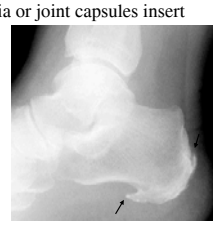
2. Genetic:- Susceptibility to develop disease is associated with inheritance of certain MHC class I alleles, notably HLA-B27

3. Pathogenesis:- Effector/ memoryCD8 T cells are activated and clonally expanded while CD4 T cells or B cells are not involved as shown by increased occurrence of these diseases in AIDS

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, enthesitis, produces 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).

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 during sleep
- Improvement with exercise

Specific Spondyloarthritis Diseases

Ankylosing spondylitis

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

Uniquely high relationship of susceptibility and HLA-B27

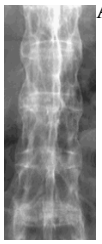
Spondylitis Disorders

Genetic epidemiology

- Strong familial aggregation, identical twin concordance
- HLA-B27 increased, but unevenly, among spondylitis diseases

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

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

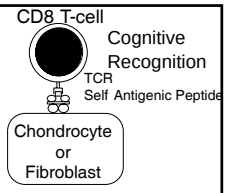


Ankylosing spondylitis

- A progressive autoimmune inflammatory disease characterized by widespread spondylitis and sacroiliitis
- Male: female =3-10:1
- Culminates in boney ankylosis of spine
- Onset, age 10-35 with dull pain in lumbar or gluteal regions
- Hip, shoulder knee arthritis in ~30%
- Epidemiology: >95% of those affected are positive for 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

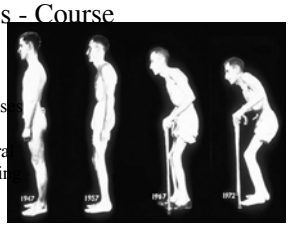
Spondylitis Disorders

CD8 T cell effector mechanisms of tissue injury



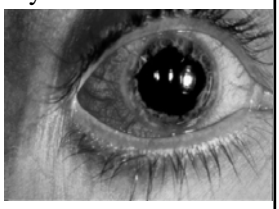
- Activated CD8 T cells injure target cell and release cytokines including γ-IFN that reprogram gene expression of nearby cells
- CD8 T cells are CD28-negative, memory / effector cells that receive a "signal 2" from engagement of NK receptors by stress-induced ligands
- The identity of autologous peptides /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

Ankylosing spondylitis - Course



- Begins with sacroiliitis
- Inflammatory back pain and tenderness or pain at central enthes (iliac crests, ischeal tuberosities) progresses and ascends over severa months to ~10 years, with increasi 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 in the latter

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

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- 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, Italy	**No**

Specific Spondyloarthritis Diseases

Reiter's syndrome /Reactive arthritis

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

A clue to the identity of a driving peptide

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

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

• 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"

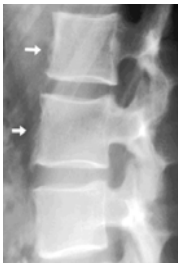
Reiter's syndrome vs. Reactive arthritis

Reiter's syndrome - triad of usually explosive arthritis, conjunctivitis and urethritis with keratodermic skin and nail lesions

Reactive arthritis - a somewhat milder and more self-limited post infectious arthritis without evidence of skin or eye involvement or urethritis

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- role of specific infection

Induction by particular pathogens

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

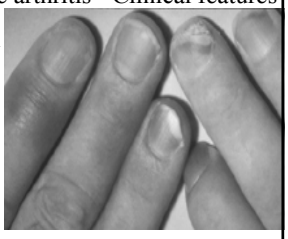
- *Salmonella typhimurium*, and occasionally *S. paratyphi* or *S. heidelbergii*
- *Shigella flexneri* 2a and 2b, but not after *S. sonnei*
- *Yersinea enterocoliticas*
- *Campylobacter jejuni* or *C. fetus*

These organisms typically invade intestinal and other cells, perhaps resulting in the expression of arthritogenic peptides in class I MHC

Develops 7-30 days after venereal infection with

- *Chlamydia trachomatis* or *C. psittaci*

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

Epidemiology Reiter's syndrome /Reactive arthritis

Two situations:

1. In previously healthy individuals, disease increasingly common as proceed North in Europe and Asia with highest prevalence circumpolar

- HLA-B27 marks the most susceptible individuals; 7% of Northern European Caucasoids, increasing in frequency in Northern peoples; 25-40% of Alaskan Inuit and Northern Asians, e.g. Chuckchis

2. Poorly treated HIV-1 infection, Subsaharan Africa

- HLA-B27 O% in Zimbabwe, where reactive arthritis is a major health problem in setting of HIV

Reiter's syndrome /Reactive arthritis

• Penetrance high: > 50% of HLA-B27 individuals develop RS / RA during major epidemics of dysentery by arthritogenic organisms

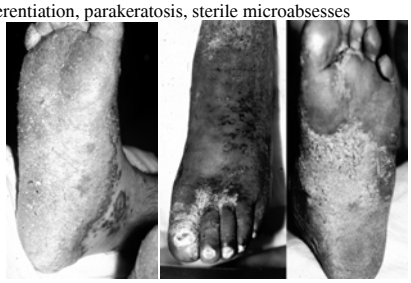
• HLA-B7 and HLA-B22 are the non HLA B-27 alleles in Northern European Caucasoids most often associated with susceptibility

• The 7-30 day delay in disease development after infection suggests clonal expansion and induction of a memory/effector T cell population

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



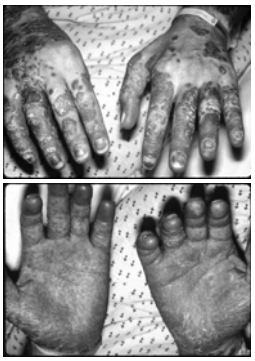
Reiter's syndrome-Reactive arthritis -Mechanism

Disruption of tolerance of autoreactive CD8 T cells likely occurs through a combination of mechanisms:

• Activation of dendritic cells in initial immune response to infection provides co-stimulatory signals that may disrupt tolerance of other intrinsically self-reactive T cells

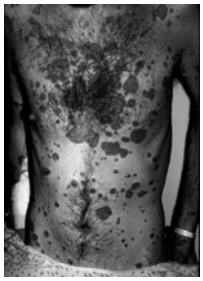
• Molecular mimicry - The same T cell clones involved in attack on microorganisms expand and initiate attack on body cells expressing target proteins that contain peptides that mimic the amino acid sequence found in the microorganisms

• Activation of memory / effector T cells -inflammation provides "danger" signals that foster the expression of NK and other innate immune system receptors on CD8 T cells, as well as upregulating expression of ligands for these receptors



Reiter's syndrome

Progression to psoriasis pattern of skin disease in AIDS



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

• Ankylosing spondylitis not seen with AIDS

• Sometimes the Reiter's syndrome was the first evidence of HIV-1 infection 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 suggested that these spondylitis diseases arise from clones of previously expanded *memory* rather than from naïve CD8 T cells

(Rheumatoid arthritis and SLE are ameliorated in advanced AIDS)

Possible events in advanced HIV-infection that foster development of Reiter's syndrome / psoriatic arthritis

•Increased microbial persistence, and difficulty clearing enteric infections, e.g. Salmonella colonization

•Increased cytokines, including IL-15 that enhance expression of NK receptors and ligands

•Increased T cell activation

•Diminished regulatory cell numbers

Specific Spondyloarthritis Diseases

Psoriatic Arthritis

Often triggered by physical stress or injury, and non specific inflammation

Psoriatic arthritis-patterns

- Symmetric polyarthritis generally similar to rheumatoid arthritis

  Affects hands, wrists, ankles, and feet

  Generally milder than RA, more stiffness less tenderness

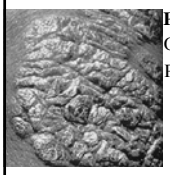
  Differentiated from RA by presence of enthesopathy, onychodystrophy, dactylitis, and DIP joint involvement, absence of subcutaneous nodules, or rheumatoid factor (negative RF test)

Psoriasis / Psoriatic Arthritis

Psoriasis: T cells driven by keratinocyte peptides infiltrate basal layers of skin and retard kertinocyte differentiation resulting in formation of plaque-type lesions of immature keratinocytes

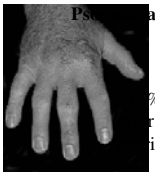
Psoriatic arthritis: an often clinically distinctive complex of enthesitis and arthritis that occurs in the setting of psoriasis

It may involve the spine or peripheral joints in a variety of patterns, and is initiated or exacerbated by stress or non specific infection



Psoriasis
Onset age 15-30 yrs
Prevalence ~3%

10-30%
10 years



Ps arthritis

% no
r
iasis

Psoriatic arthritis-patterns

- Asymmetric oligoarthritis of small and medium-sized joints

  Classic type- e.g. two PIP joints in one hand, a MCP joint in the other

  Digits of the hands and feet often affected first, characteristically with dactylitis (sausage digits)

- DIP arthritis, characteristically seen with nail dystrophy

  Classic and unique to psoriatic arthritis, but found in only ~5% of patients, primarily males

  Paronychia and swelling of the digital tuft may make appreciation of arthritis difficult; DDx Heberden's nodes

Psoriatic arthritis

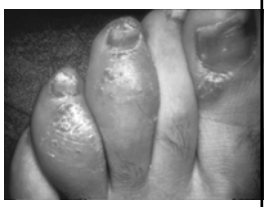
Dactylitis (Sausage digit)

Enthesopathy, fasciitis, tenosynovitis

Spondylitis or sacroiliitis (40%)

Conjunctivitis (20%)
Anterior uveitis (10%)

Systemic features:leukocytosis, fever, night sweats, anemia



Patterns of Peripheral Arthritis (any peripheral joint)

- Symmetric polyarthritis generally similar to rheumatoid arthritis
- Asymmetric oligoarthritis of small and medium-sized joints
- DIP arthritis joints, where it characteristically also involves nails
- Arthritis mutilans

Psoriatic arthritis-patterns

- Arthritis mutilans

  Osteolytic dissolution of joint with redundant overlying skin and telescoping motion of the digit (opera-glass hand)

  Distinctive but uncommon

- Spondylitis (5%) or sacroiliitis (40%)

  Isolated or can also occur with other patterns of psoriatic arthritis joint involvement

  Vertebral involvement differs from that of AS: Vertebrae asymmetrically affected with nonmarginal asymmetric syndesmophytes, paravertebral ossification, vertebral fusion with disk calcification, atlantoaxial joint involvement with odontoid erosion and subluxation

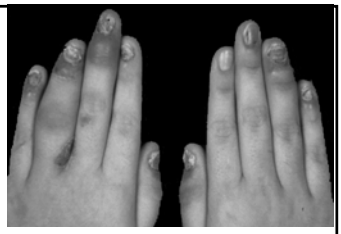
Psoriatic Arthritis Genetics

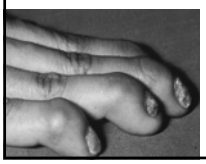
- Concordance rate among monozygotic twins of 35-70%, versus 12-20% for dizygotic twins
- ~40% have strongly positive family histories, most often with first degree relatives affected by psoriasis
- Sex: Men and women are affected equally
- Imprinting: If a parent and child are affected, 85% of time the affected parent will be the father
- Often have psoriasis HLA susceptibility alleles: HLA-Cw*0602, and HLA-B57, HLA-B37, HLA-B13 alleles that are in linkage disequilibrium with HLA-Cw*0602
- Additionally HLA-B27, HLA-B38, HLA-B39

Psoriatic Arthritis

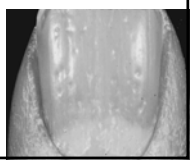
Nail involvement ~80%

Often seen in digit involved with DIP arthritis





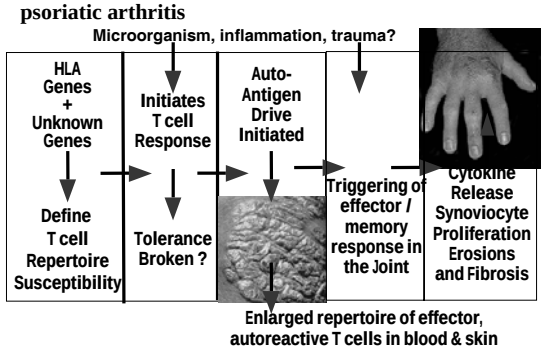
- Onycholysis
- Transverse ridging
- Onychodystrophy
- Pitting
- Acrokeratosis



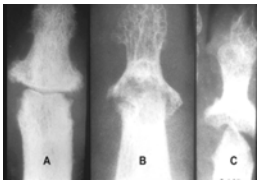
Psoriatic arthritis

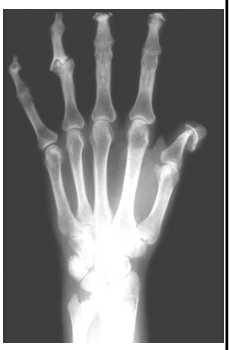
- Psoriasis usually precedes or occurs synchronously with arthritis
- Psoriasis varies from obvious skin lesions to subtle involvement (eg, scalp, umbilicus, intergluteal cleft, ear), or only nail manifestations
- In ~15%, arthritis appears before psoriasis - a family history of psoriasis or presence of enthesopathy, spondylitis, and characteristic features, e.g. DIP disease suggests diagnosis
- Onset typically insidious with stiffness predominating, but occasionally may be acute and severe mimicking gout
- Course: usually characterized by flares and remissions
- Controversy over percentage progressing to joint destruction ~10%, ankylosis more common (Hallux rigidus)

Hypothetical scheme for stages in the pathogenesis of psoriatic arthritis



Psoriatic Arthritis





Progression of DIP arthritis

Narrowed joint space & condylar erosions

Reactive sub periosteal new bone

Pencil in cup appearance