Seronegative Spondyloarthopathies

DR Sahebari

By: Dr Maryam Sahebari

Definition

- They are a group of *autoimmune disease* which developed in persons with *genetic susceptibility* and characterized with *synovitis* and *enthesopathy*

Reactive arthritis
Ankylosing spondylitis
Psoriatic arthritis
Enteropathic spondyloarthropathy
Undifferentiated spondyloarthropathy

Characteristics

- Relation with HLA-B27
- Familial Aggregation
- Peripheral Arthritis
- Sacroiliitis
- Enthesopathy
- Absence of RF, rheumatoid nodule

Characteristics

- Characteristic exra-articular Involvement
- More prevalent in men

Ankylosing Spondylitis & other SpA

Pathogenesis and Pathology

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- Both genetic and non-genetic risk factors can contribute to As:
- HLA B27 and other MHC related genetic factors
- Innate and adaptive immune responses: Chlamydia, Yersinia, Salmonella

HLA B27

- Among the HLA class B molecules that determine Antigen binding cleft,HLAB27 has a unique B pocket that likely influence the peptide repertoire.
- Among the 30 subtypes of B27 only a few subtypes are associated with As.
- HLA B27 is positive more than 90% of AS patients
- AS in more than 50 to 75% of patients with other SpA
- Only 5 to 15% of the general population are B27 positive

HLA B27

- The overall contribution of B27 to AS susceptibility is 30%.
- The gene is neither necessary nor sufficient to cause the disease.
- Fewer than 5% of HLA-b27 positive individuals develop SpA
- The individual risk is higher in the setting of a positive family history of SpA

Four main theories on the pathogenesisof SpA related to HLAb27

- 1 :The arthritogenic peptide hypothesis :

The basis of this concept is essentially that of molecular mimicry : self peptides displayed by HLA-B27 are targeted by auto-reactive CD8 T cells because they resemble microbial peptides

- 2 : Self Association of B27 Molecule:

Sometimes refolding with different structure in HLAB27 molecule leads to accumulation of this peptide in cells and inflammatory response or presentation on cell surfaces leads to activation of T Cells

Four main theories on the pathogenesisof SpA related to HLAb27

- Enhanced Bacterial Survival:

HLA B27 leads to a less effective elimination of microbes , such as salmonella , in conjunction with any up-regulated production of cytokines.

- Recognition of B27 as an auto-antigen:

HLA B27 itself can be recognized by CD4 T Cells when presented by HLA class II, as an auto-antigen. This is also part of the molecular mimicry hypothesis

Other genes and AS suseptibility

- Fewer than 5% of HLAB27 positive individuals in general population develop one form of SpA over time.
- In contrast only 20% of positive HLAB27 positive relatives of a Patient with SpA will develop SpA.
- The entire effect of HLAB27 is about 30 to 50%
- Other MHC genes: MHCII, MICA, TNF,B60,38,39
- Non MHC genes: IL-1,Il-6, TGFβ, …

Histopathology in Ankylosing Spondylitis:

- The most common sites of inflammation in AS are:
- Sacroiliac joints, vertebral bodies adjacent to intervertebral disks, peripheral joints, gasterointestinal tracts, and eye
- On early sacroilitis: synovitis, mixoid appearing bone marrow, granulation tissue, CD_4 and CD8 T Cells, macrophages, over-expression of TNF alfa

and TGF beta

- Destroyed bone is partly replaced, enchondral ossification results in bony akylosis.

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Synovitis:

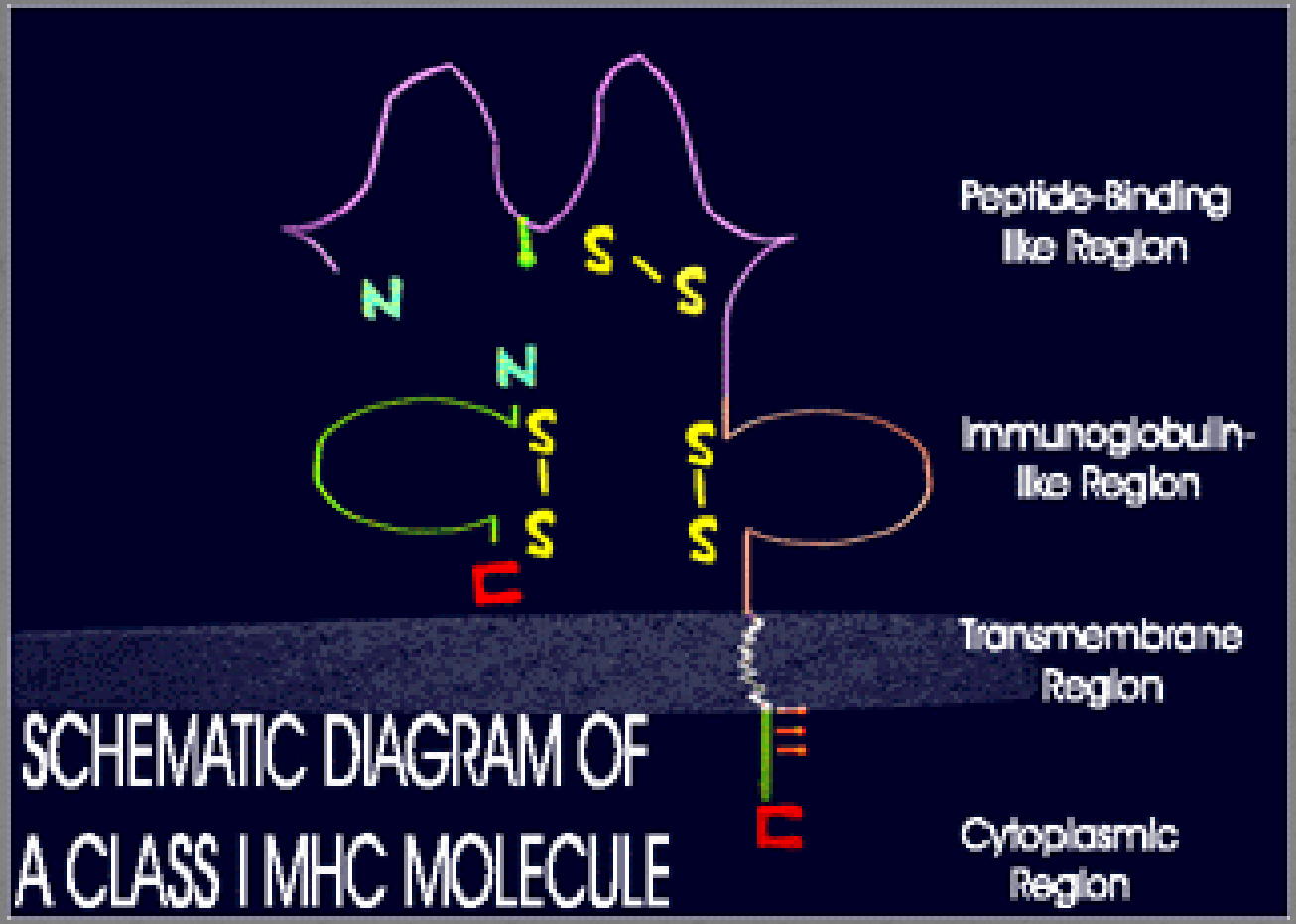
- Increased vascularity, endothelial cell activation, infiltration of CD T cells> CD8 T cells, macrophages , B cells
- **Enthesitis:**
- a hallmark of SpA is characterized by erosive, inflammatory lesion associated with abundance of osteoclasts with infiltration of bone marrow: CD_4 and CD8 T cells and Macrophages

Cytokine expression:

- IL-6 and IL-8 is high in AS patients
- New bone formation:
- The remodeling of bone leading to the squaring of the vertebral bodies in AS is result of acute and chronic synovitis. This is the result of destructive osteitis and repair, this is a consequence of prostaglandin E2 a modulator of bone metabolism

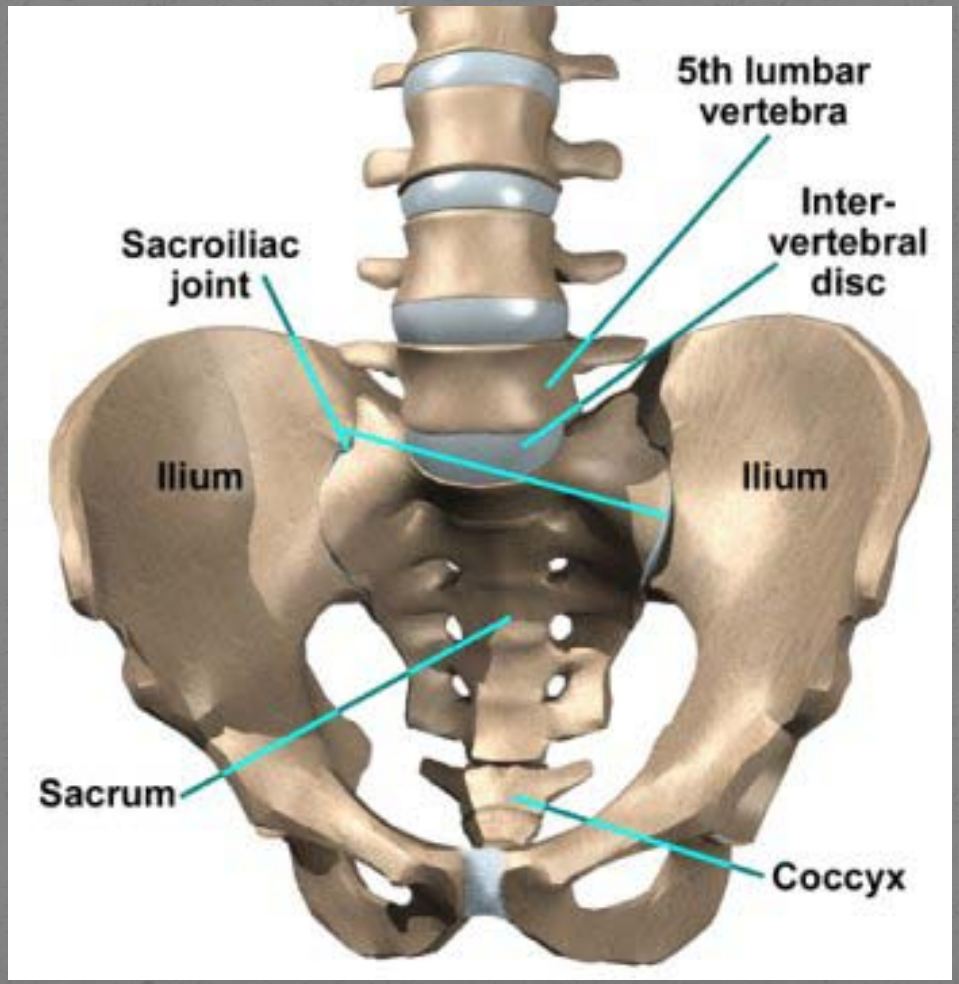
Characteristics

Relation with HLA-B27



Characteristics

Sacroiliitis



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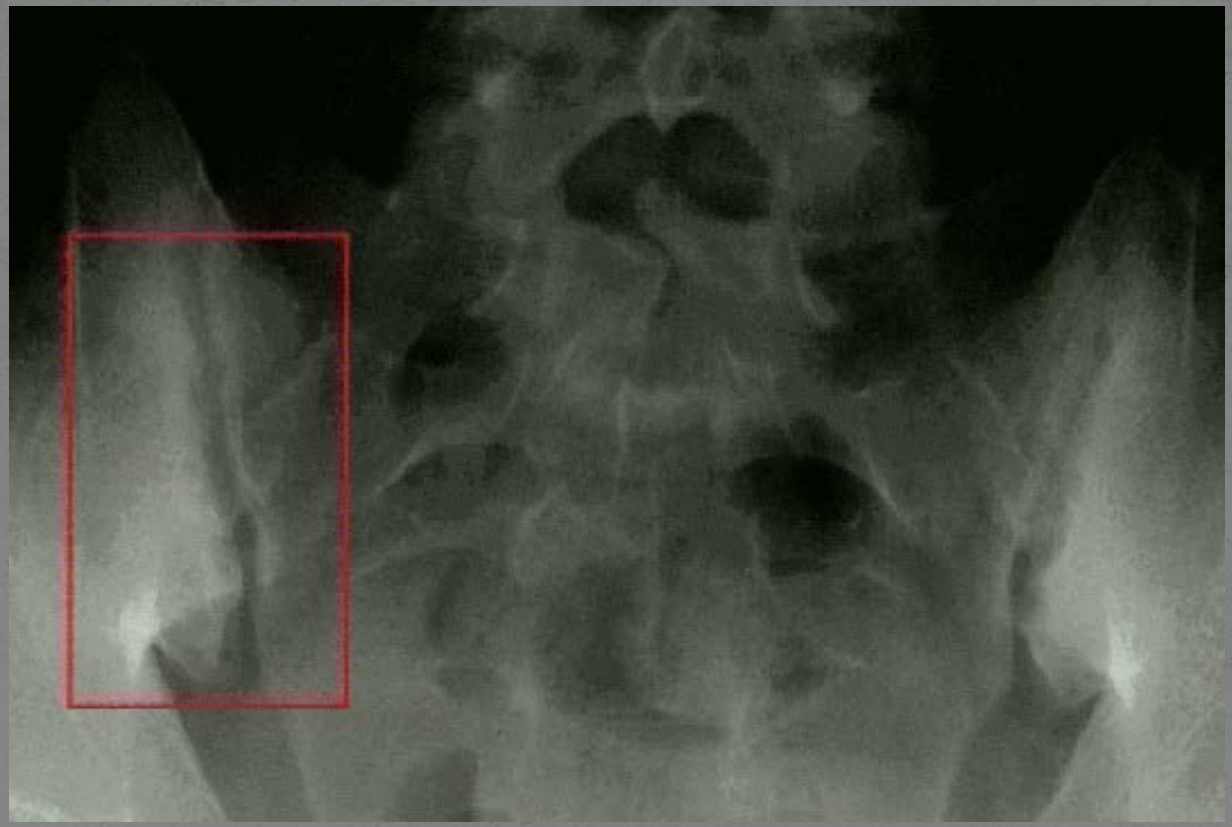

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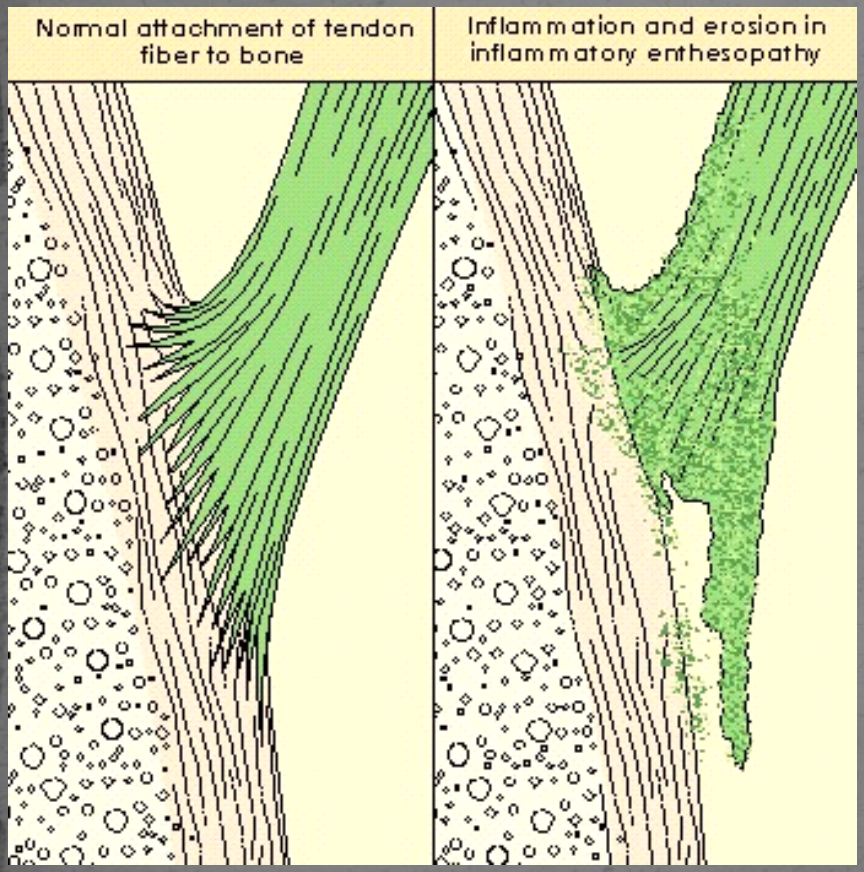
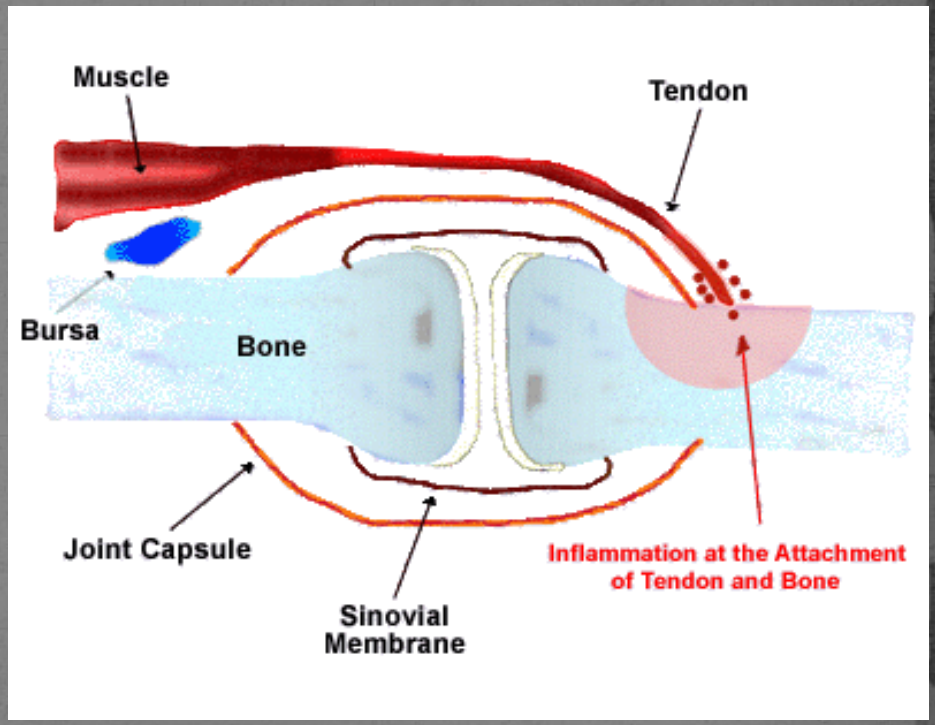
Characteristics

Enthesopathy





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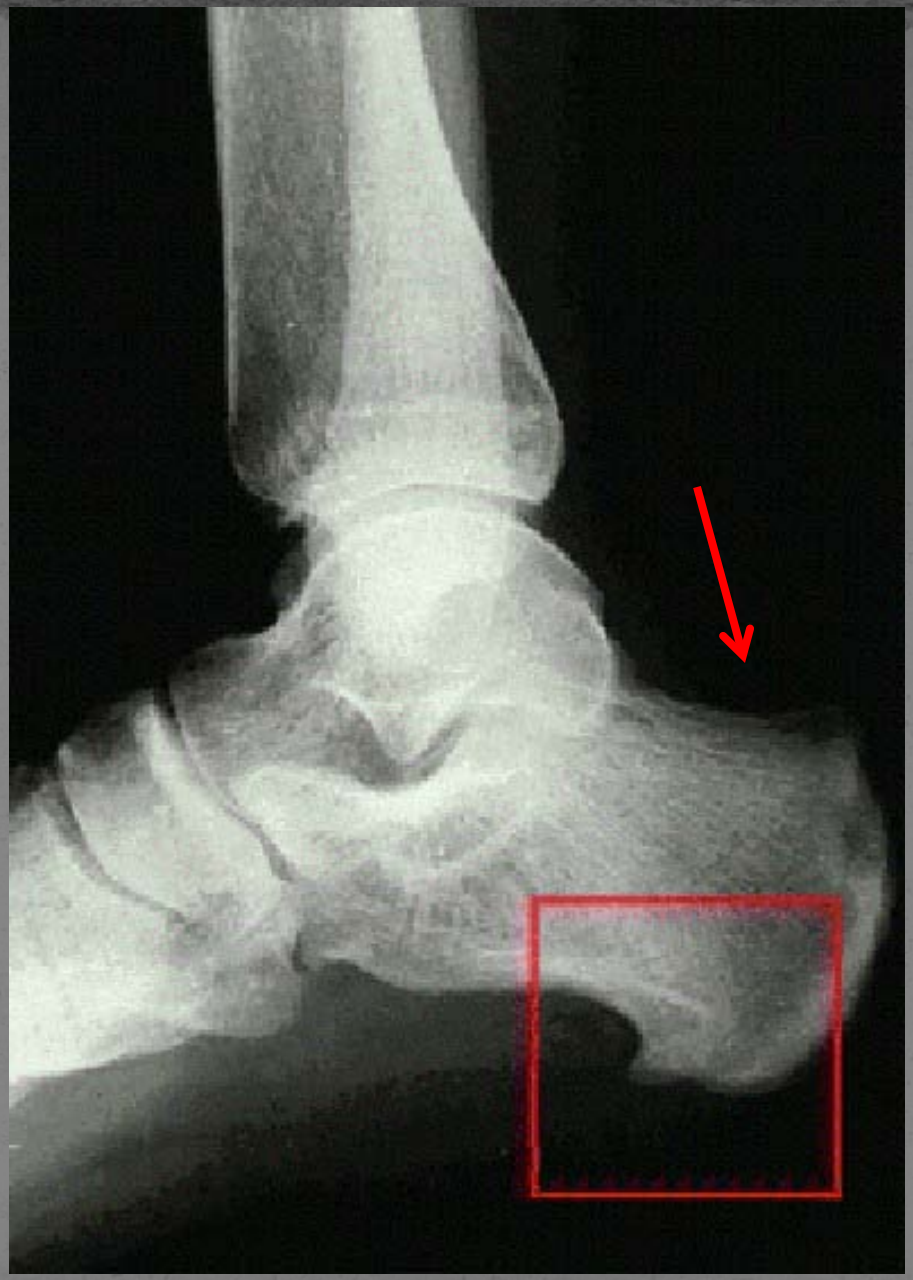

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REACTIVE ARTHRITIS

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Definition

- Acute, nonsuppurative, sterile, inflammatory arthropathy arising after an infectious process, but at a site remote from the primary infection:

  Enteric infections

  Urogenital infections

- Infectious pathogens cannot be cultured from the joint fluid or synovium

Epidemiology

- Incidence (3.5/100000 men per year)
- Prevalence (1/10000)
- Race (white > black)
- Sex (male > female)
- Age at onset: 18-40 mean 26 year

Pathogenesis

Infectious agent

- Incidences of 1-21% in epidemies of UG and GI infections
- Bacterial antigens have been detected in synovial tissue
- Chlamydia DNA and RNA have been detected in synovial tissue
- In peripheral mononuclear bacterial macromolecules have been found

Pathogenesis

Infectious agent

- **Enteric pathogens :**
  Shigella, Salmonella, Campylobacter, Yersinia

- **Urogenital pathogens:**
  Chlamydia trachomatis, Ureaplasma

- **Respiratory pathogen :**
  Chlamydia pneumonia

- *Genetics (HLA-B27)*

Clinical features

Urogenital infection
. Enteric infection

1-4 weeks

Extra-musculoskeletal symptoms

Musculoskeletal symptoms

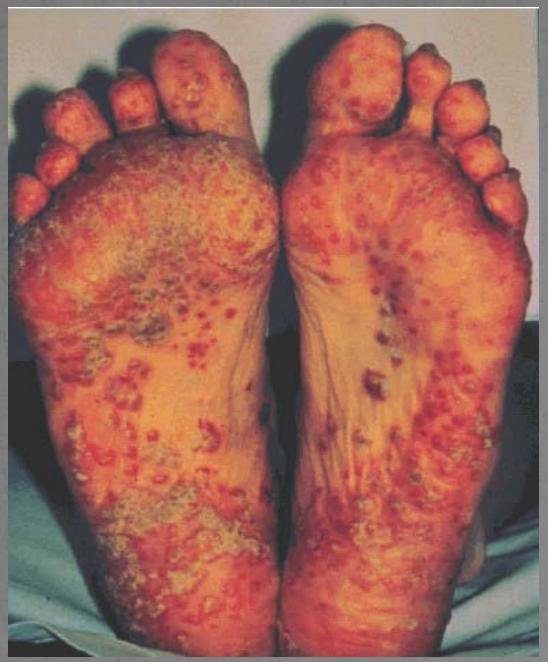
Clinical features

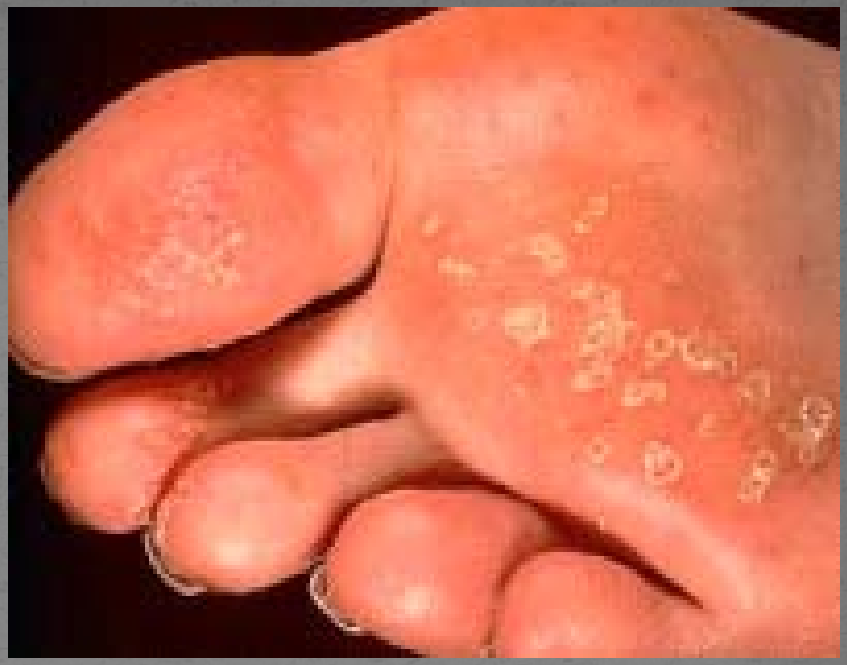
Extra-musculoskeletal symptoms

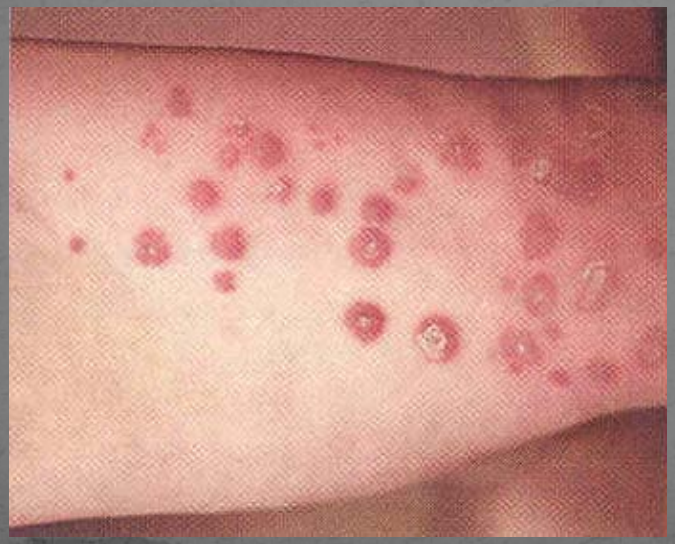
- **Constitutional symptoms**
- **Urogenital lesion**

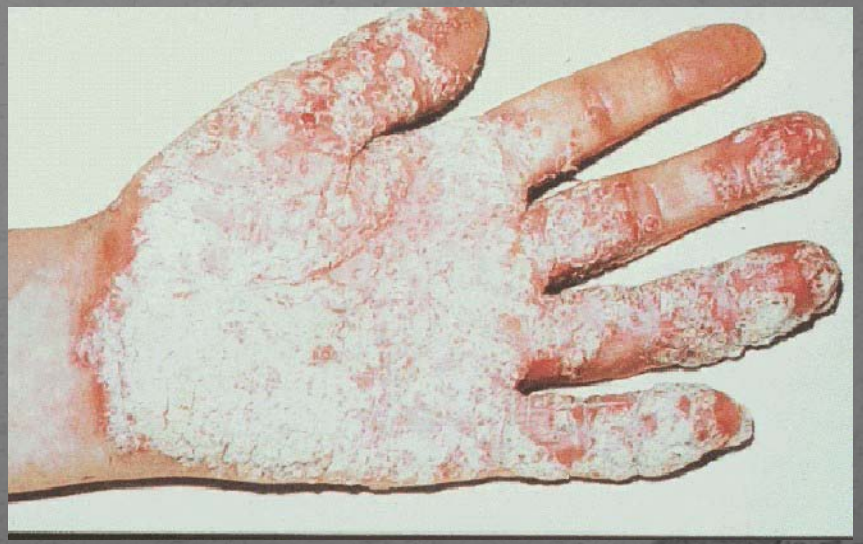
1. ***Urethritis (%46)***
2. ***Prostatitis***
3. ***Epidydimitis***
4. ***Salpingitis***
5. ***Vulvovaginitis***

- **Mucocutaneous lesion (%43)**
- *Keratoderma blenorrhagicum*









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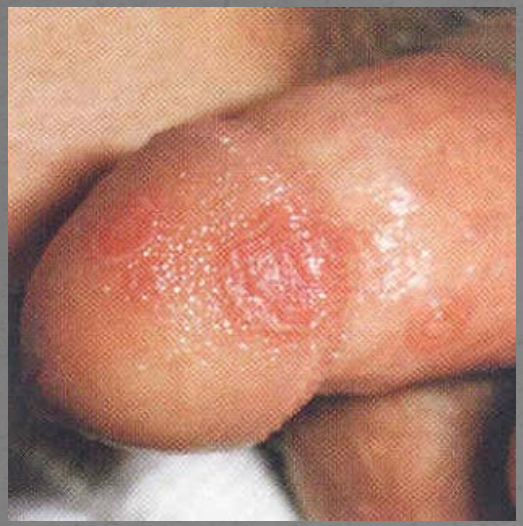
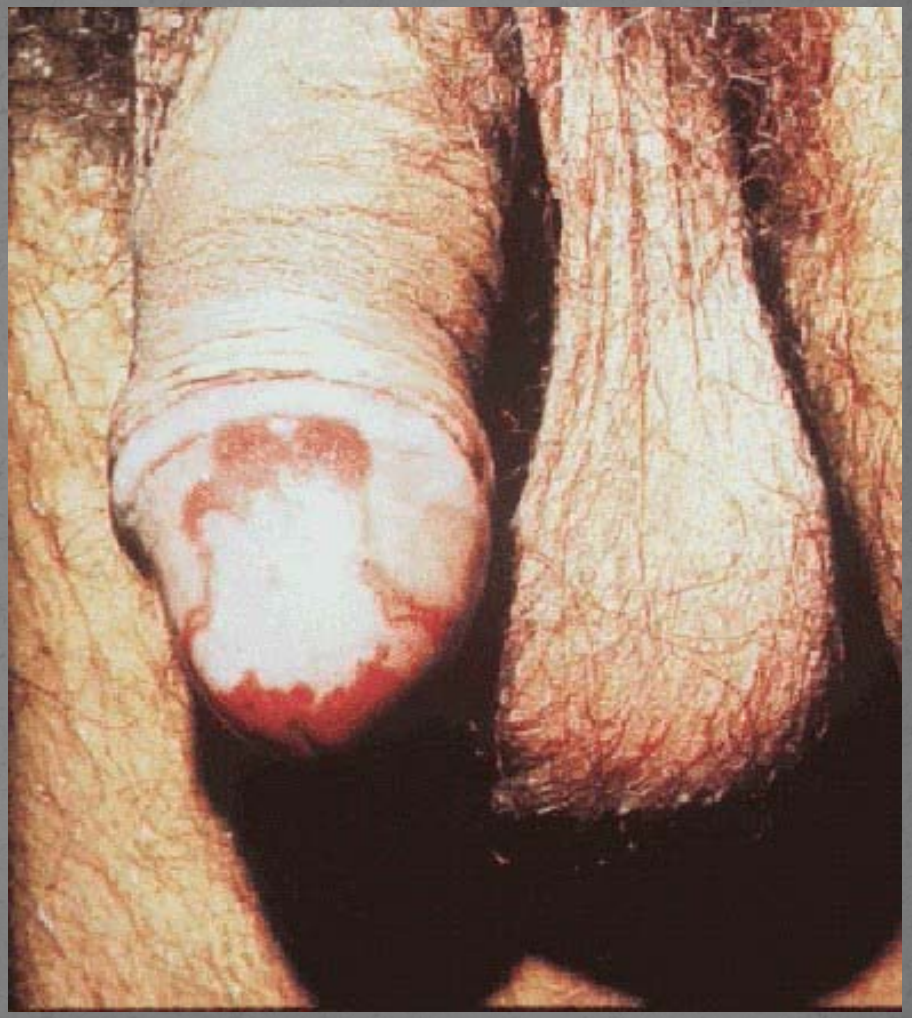
Circinate balanitis





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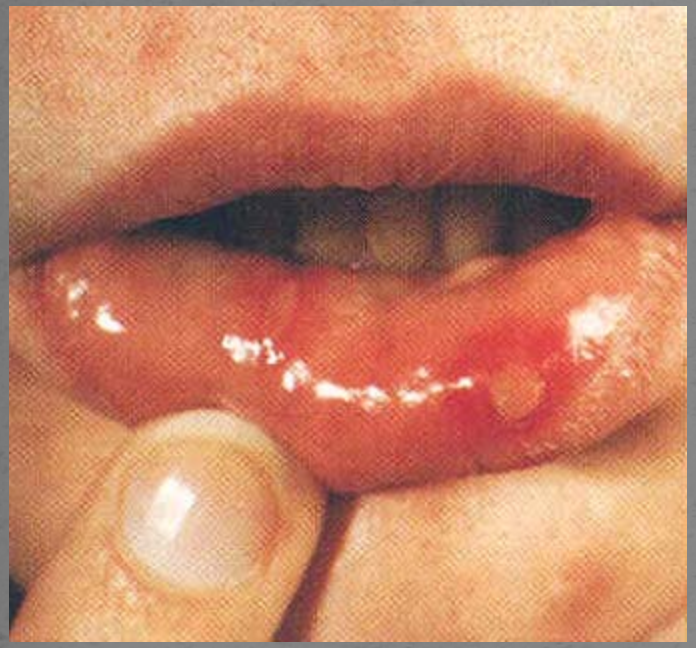
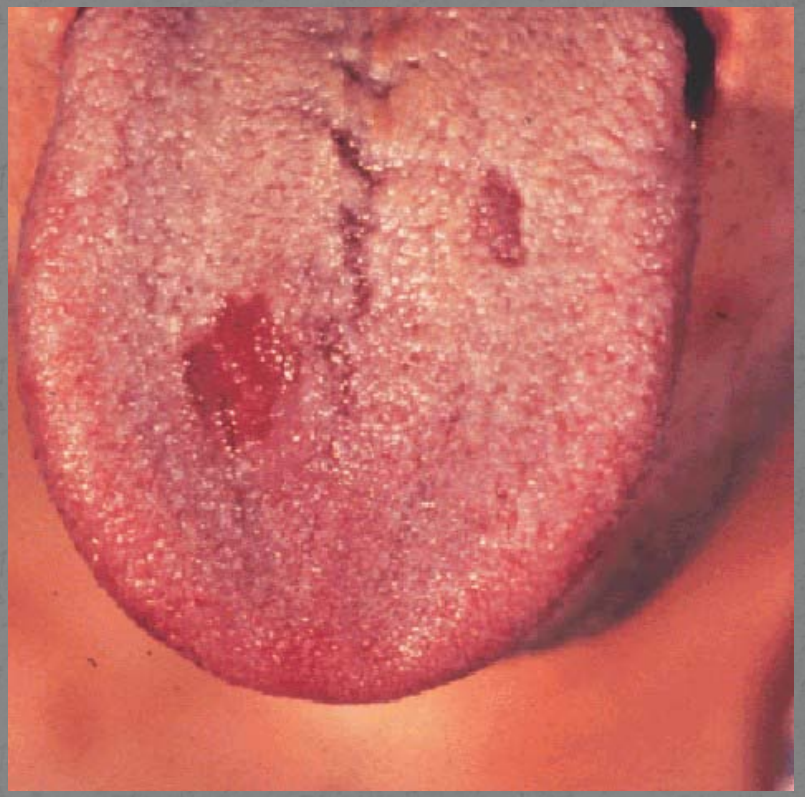
Oral ulcers





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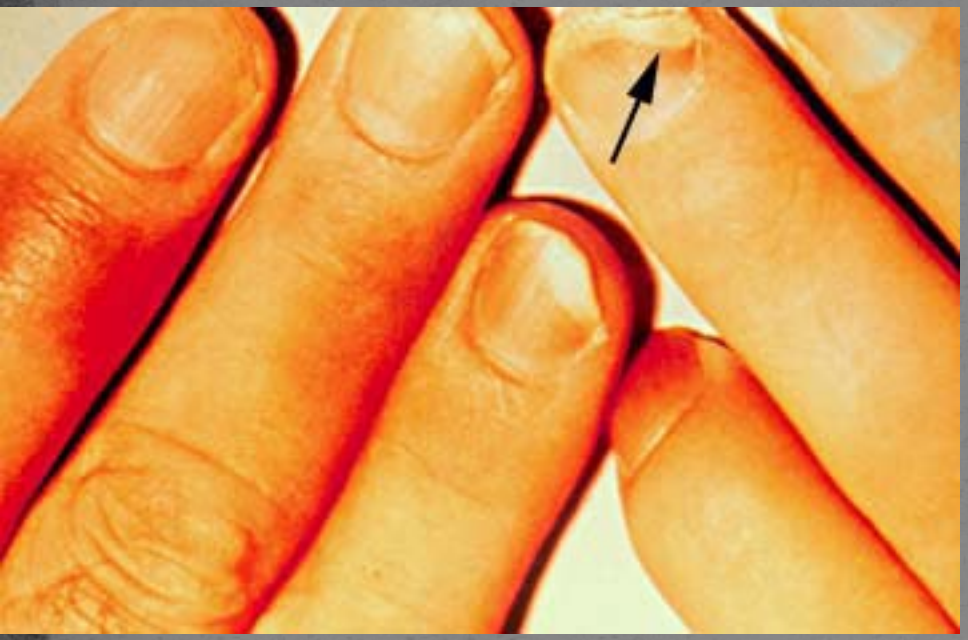
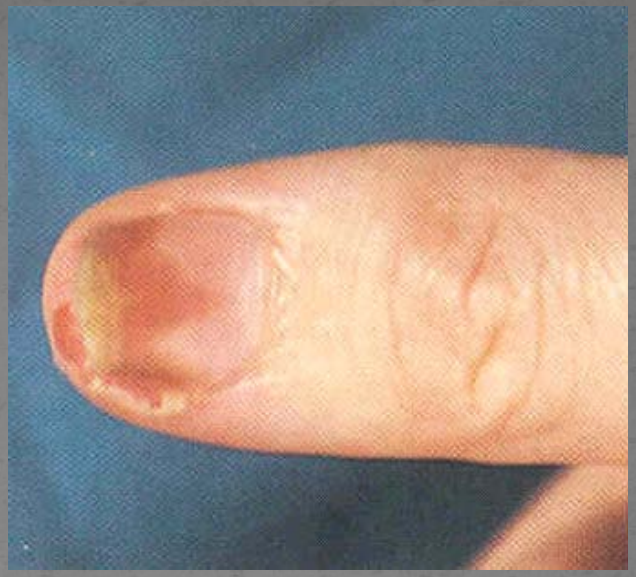
Nail changes





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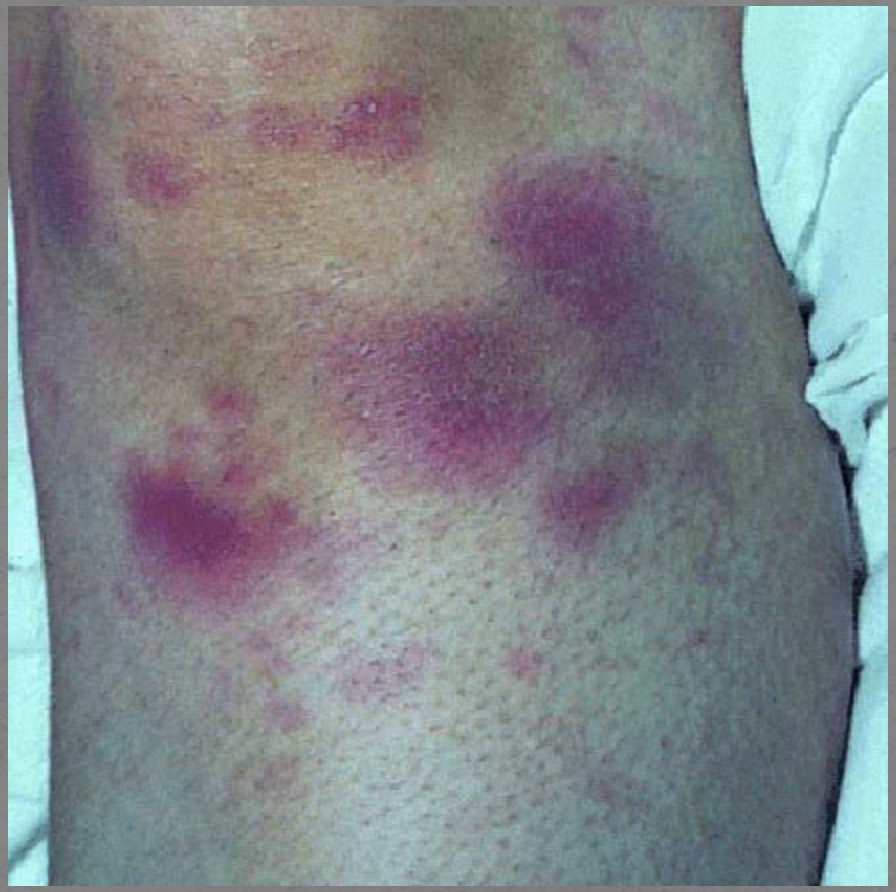
Erythema nodosum



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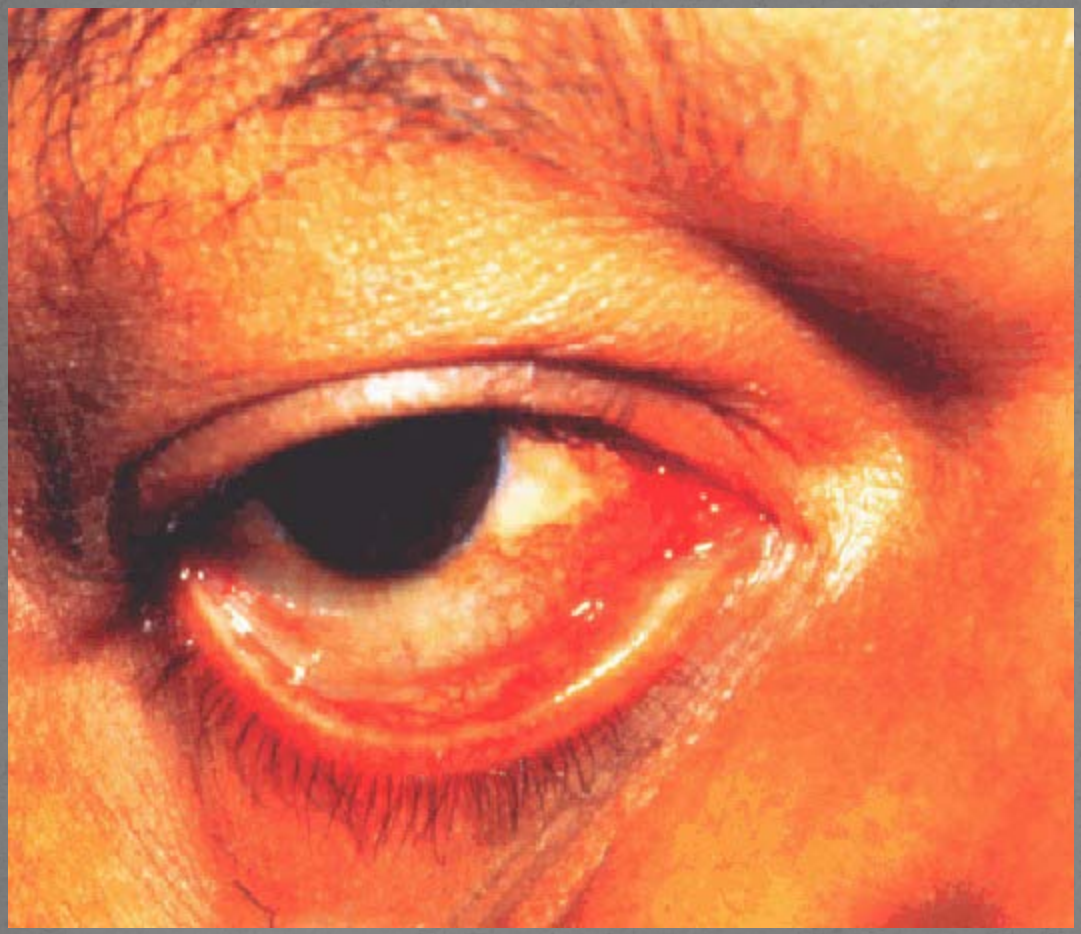
Ocular lesion



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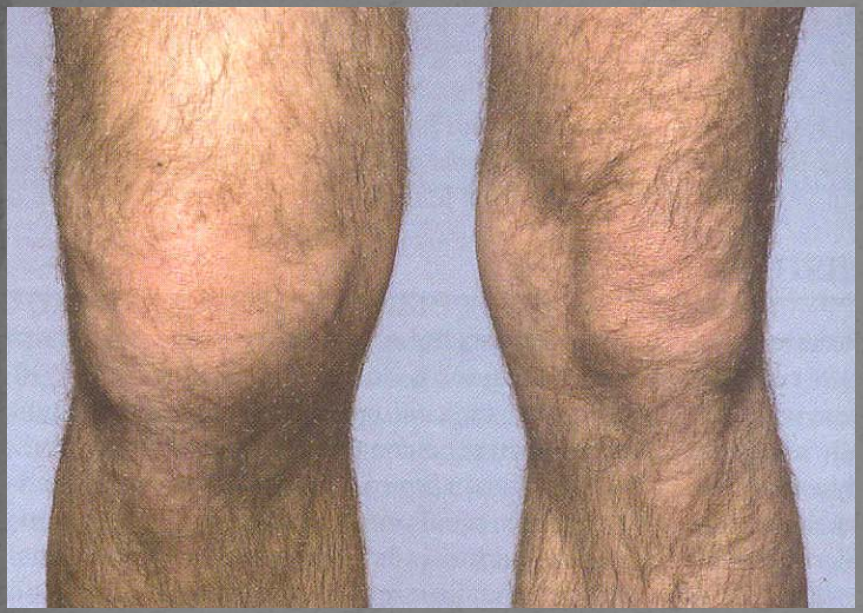
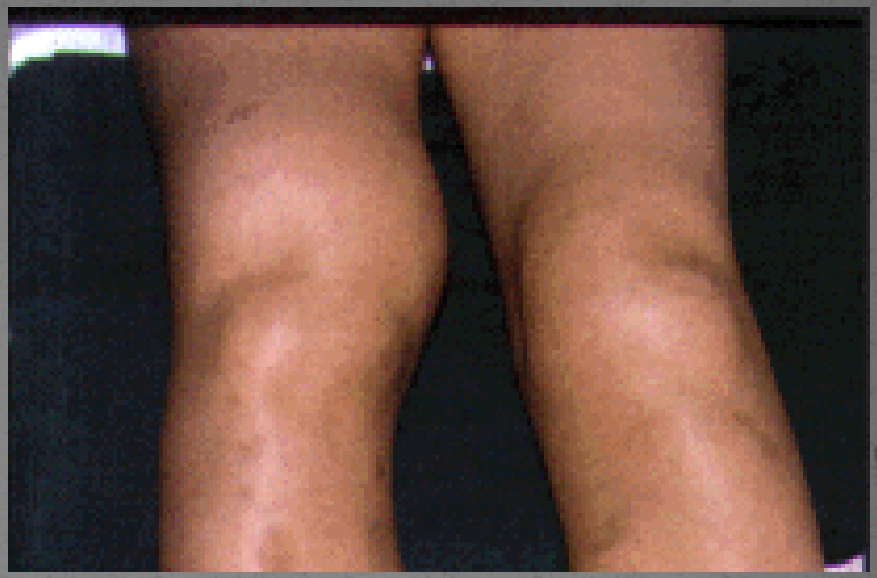
Clinical features

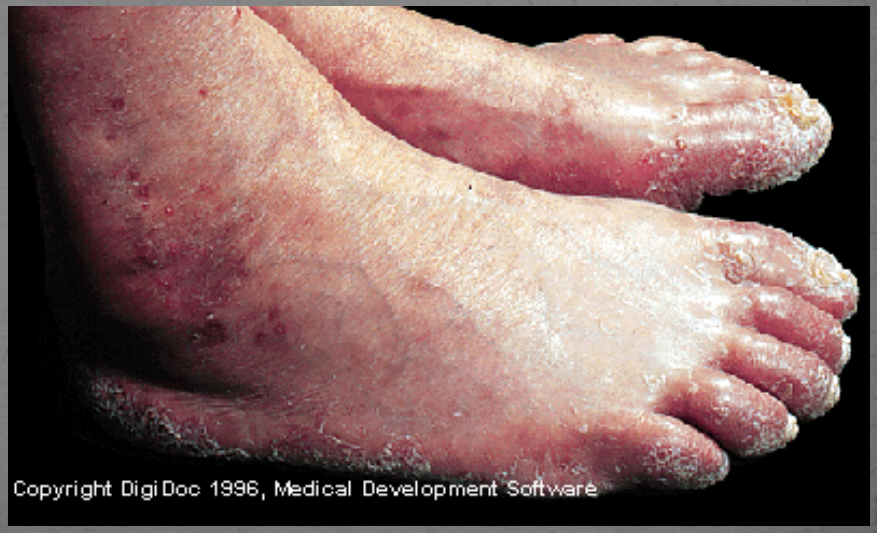
Musculoskeletal symptoms

- **Arthralgia**
- **Arthritis**

1. Acute
2. Oligoarticular, asymmetric, additive
3. More common in knee, ankle, foot
4. Hip arthritis is uncommon
5. Joint is red, warm, and painful but swelling is rare







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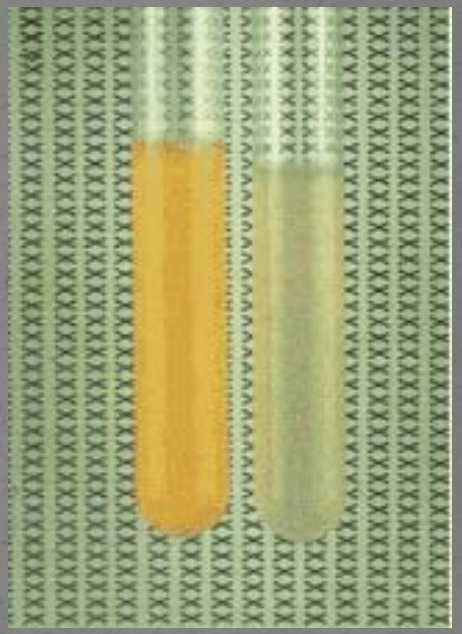
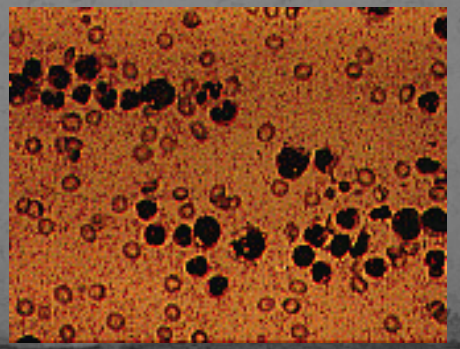
Clinical features

Musculoskeletal symptoms

6. Synovial fluid
   - *Cloudy translucent*
   - *Low viscosity*
   - *WBC 5000-50000*
   - *High protein*
   - *High complement*
   - *Reiter cells*

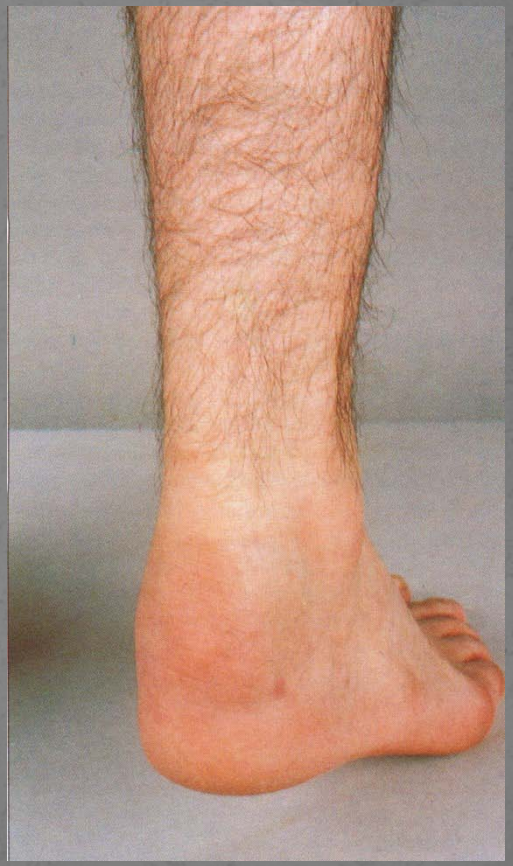




Clinical features

Musculoskeletal symptoms

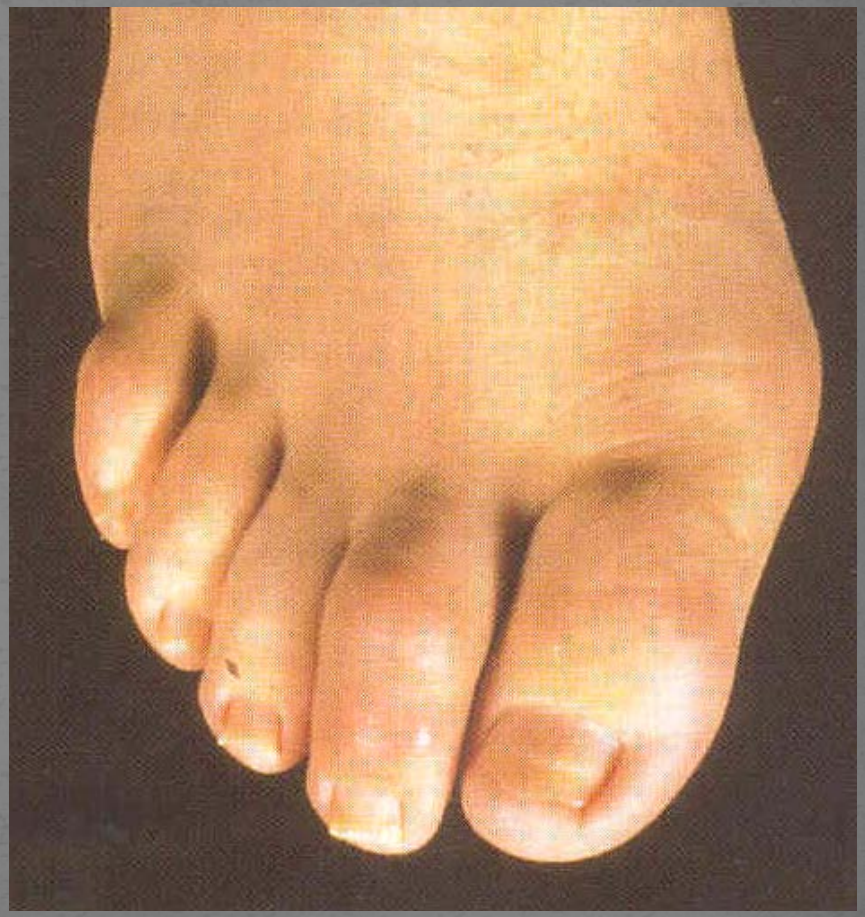
- **Arthralgia**
- **Arthritis**
- **Enthesitis**



Clinical features

Musculoskeletal symptoms

- Arthralgia
- Arthritis
- Enthesitis
- Dactylitis



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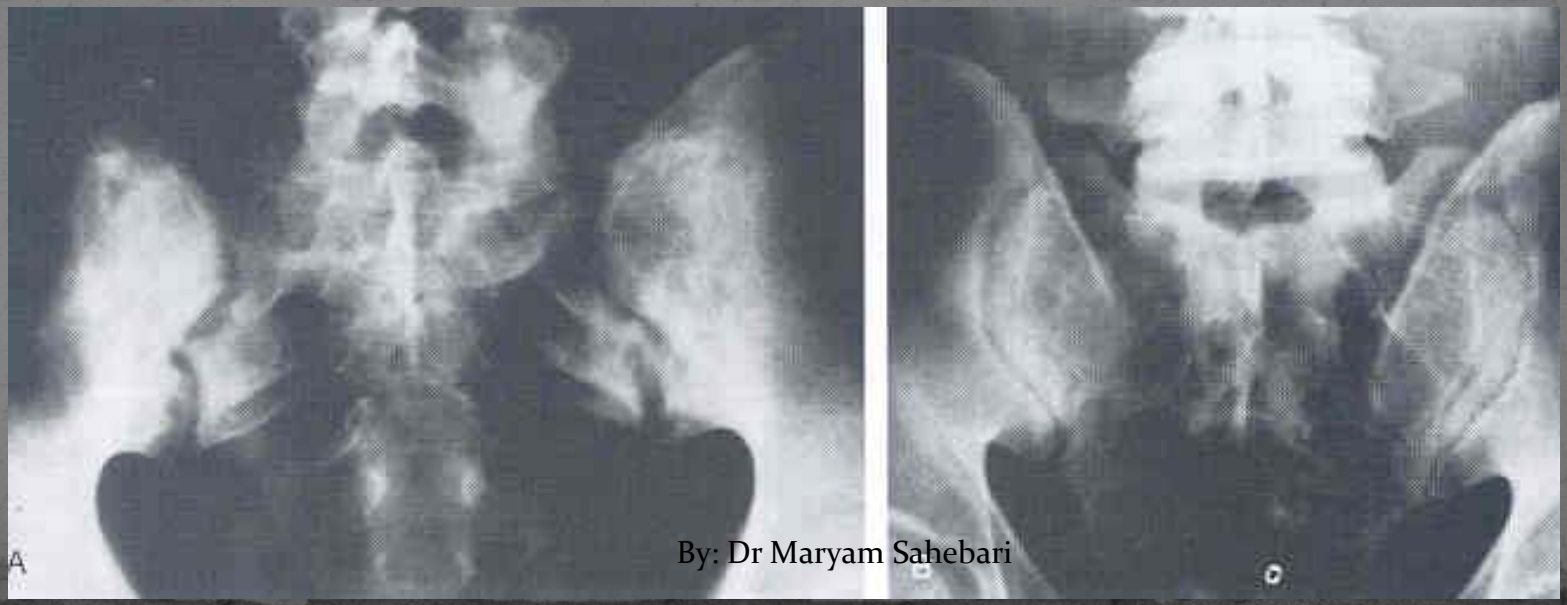
Clinical features

Musculoskeletal symptoms

- Arthralgia
- Arthritis
- Enthesitis
- Dactylitis
- Axial involvement



Laboratory findings

- Anemia, leukocytosis, thrombocytosis
- ESR ↑, CRP+
- Complement ↑
- Ig especially IgA ↑
- HLAB27+ ↑
- RF-, ANA-
- Serologic findings of infection

Radiographic findings

- **In acute phase**

  Only shows soft tissue swelling (effusion, periarticular edema)

- **In chronic phase**

  Periarticular osteoporosis

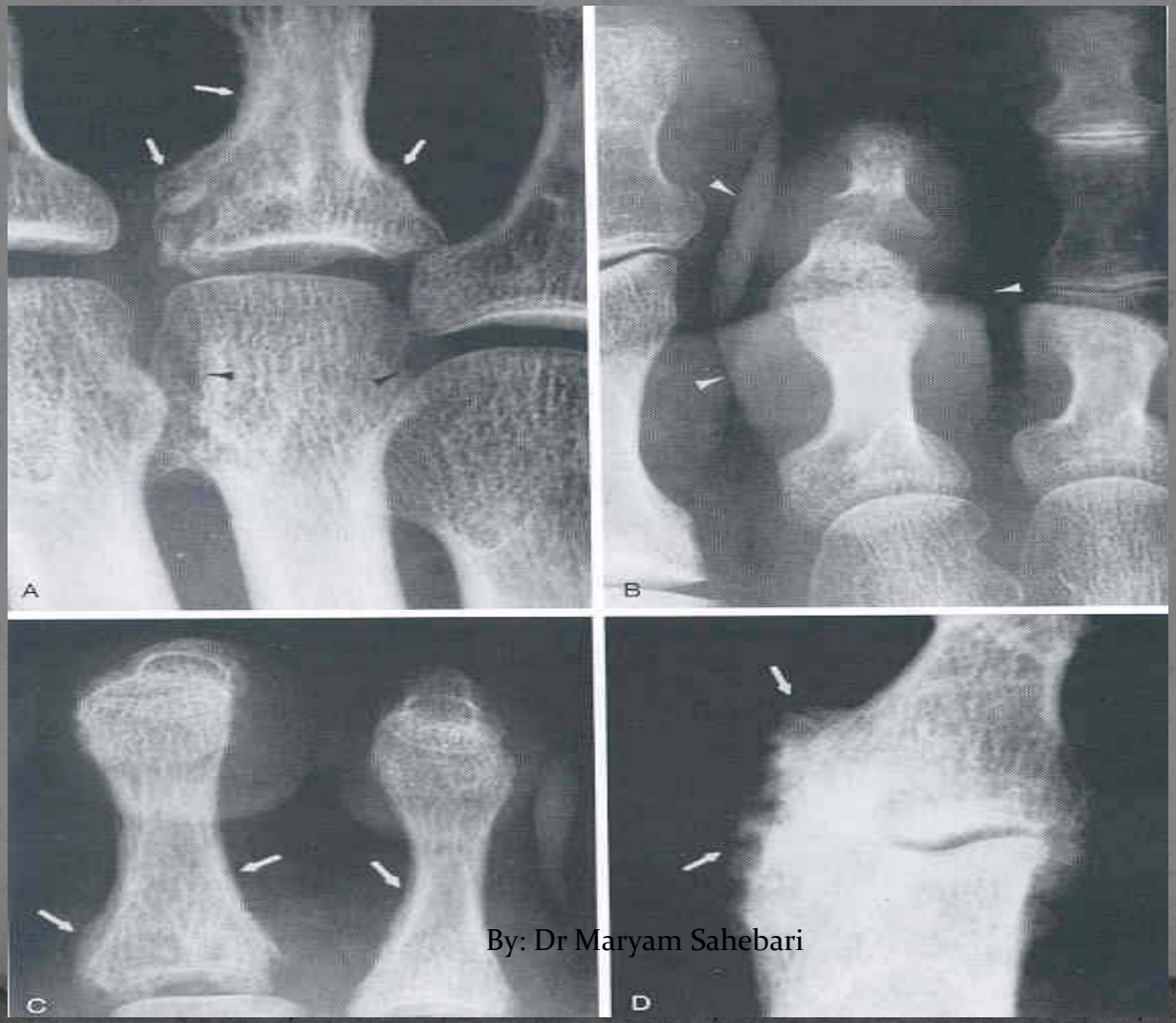
  Erosion

  Bony proliferation

  Joint space loss

Radiographic findings

Peripheral joints



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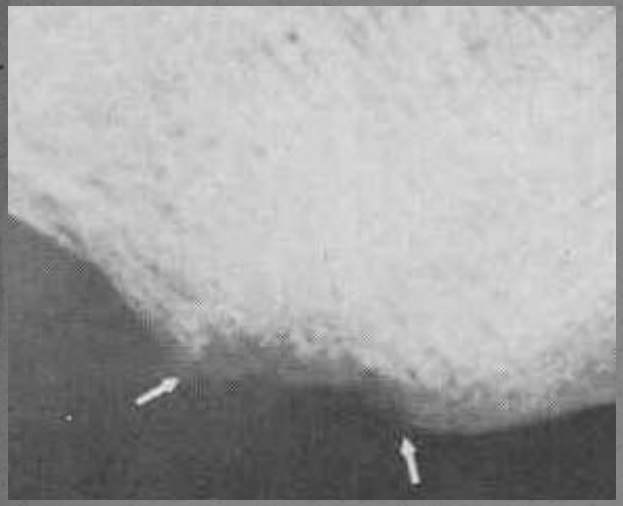
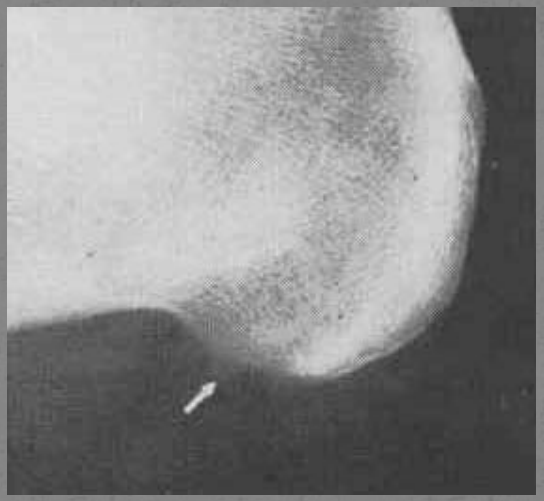
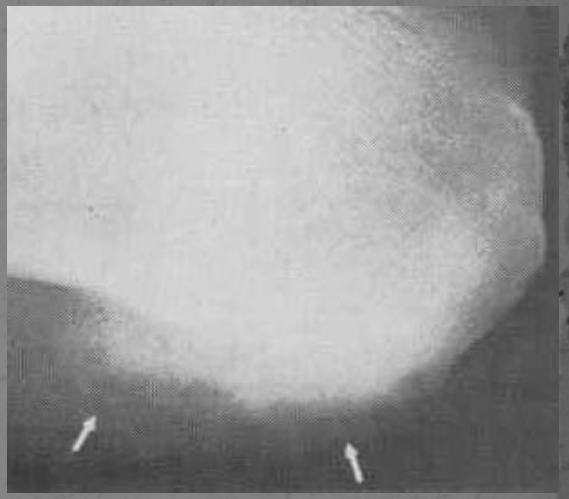
Radiographic findings

Enthesitis







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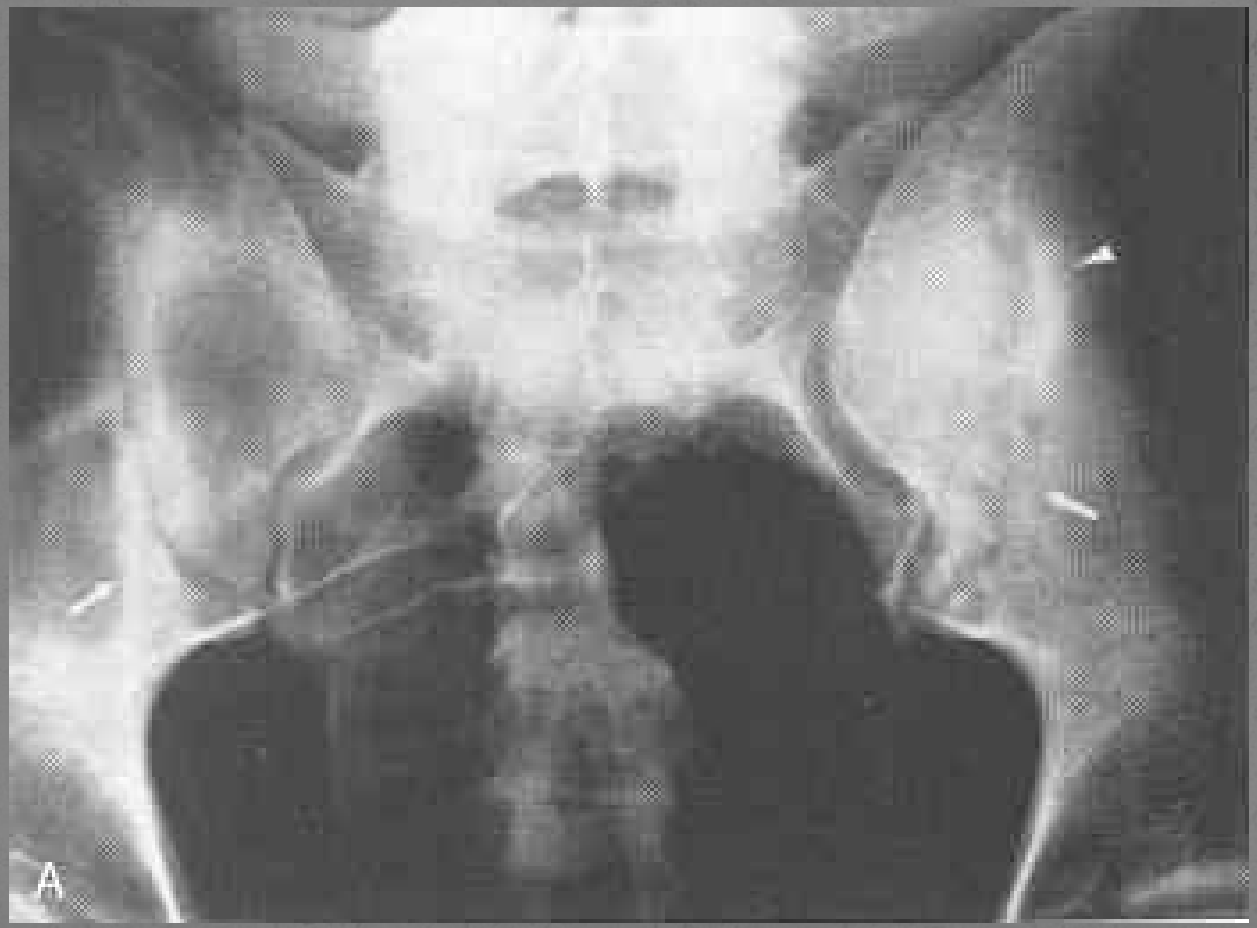
Radiographic findings

Axial



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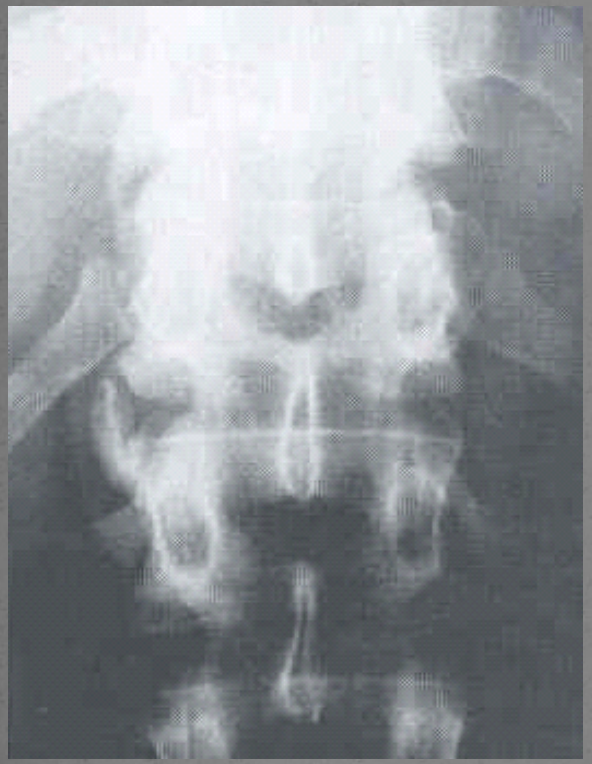
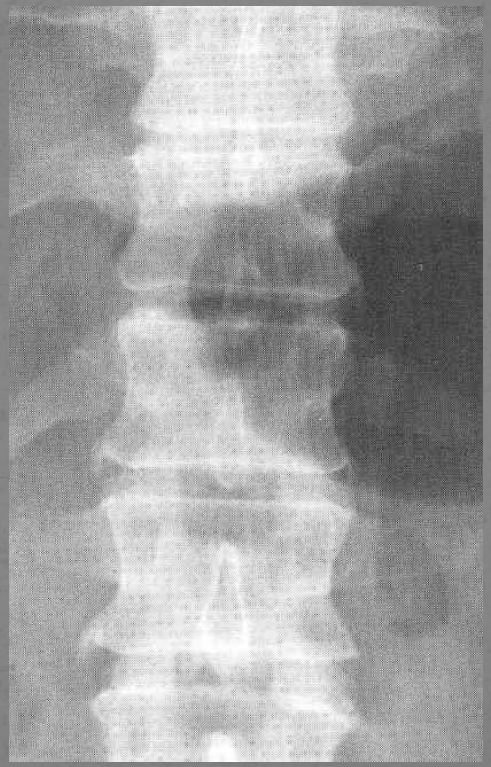
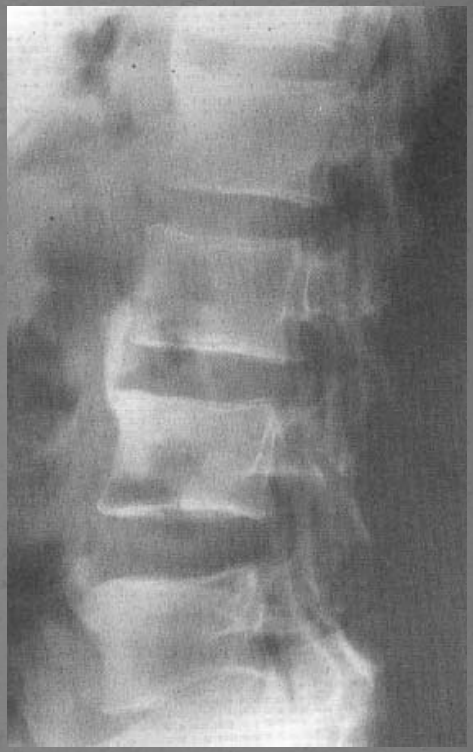
Radiographic findings

Axial







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Course

Urogenital infection
Enteric infection

1-4 weeks

Extra-musculoskeletal symptoms

Musculoskeletal symptoms

Weeks-3 months

Chlamydia infection, Males, B27+

Remission

Chronic arthritis
. Sacroilitis

Relapse

Permanent
.remission

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Diagnosis

- Oligoartritis or inflammatory low back pain
- History of symptomatic urethritis, cervicitis, or enteritis
- Positive test for bacteria

Treatment

- NSAIDs (only during symptomatic periods)
- Corticosteroid (intra-articular)
- DMARDs
- Anti TNFα
- Antimicrobial agents:

  Short duration therapy (if infection is present)

  Prolonged therapy for chlamydia (?)

  Prolonged therapy for others (no)

Prognosis

- **Predictive factors of Poor prognosis :**

1. Hip arthritis or
2. Three of:
    - ESR>30
    - Poor efficacy of NSAIDs
    - LOM of lumbar axis
    - Dactylitis
    - Polyarthritis
    - Onset before 16


بنام آنکه یادش آرام کنندهٔ قلب هاست
By: Dr Maryam Sahebari
20/9/2009

PSORIATIC ARTHRITIS

By: Dr Maryam Sahebari

Definition

- Psoriatic Arthritis (PsA) is an inflammatory arthritis associated with psoriasis

What is psoriasis?

- Psoriasis is a skin disease which characterized by dry, well circumscribed, silvery scaling papules and plaques of various size
- It is due to increased epidermal cells proliferation
- Onset is usually between ages 10-40
- Family history of disease is common

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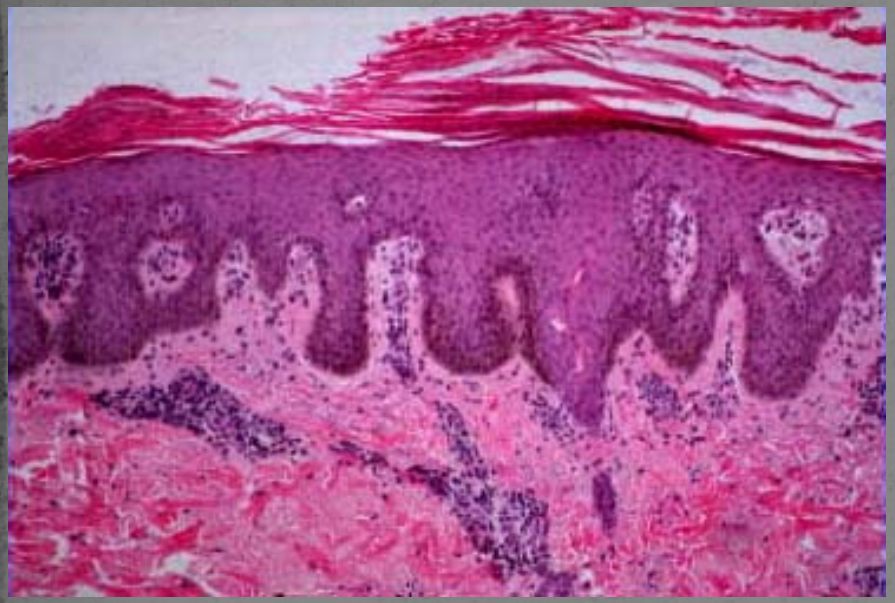

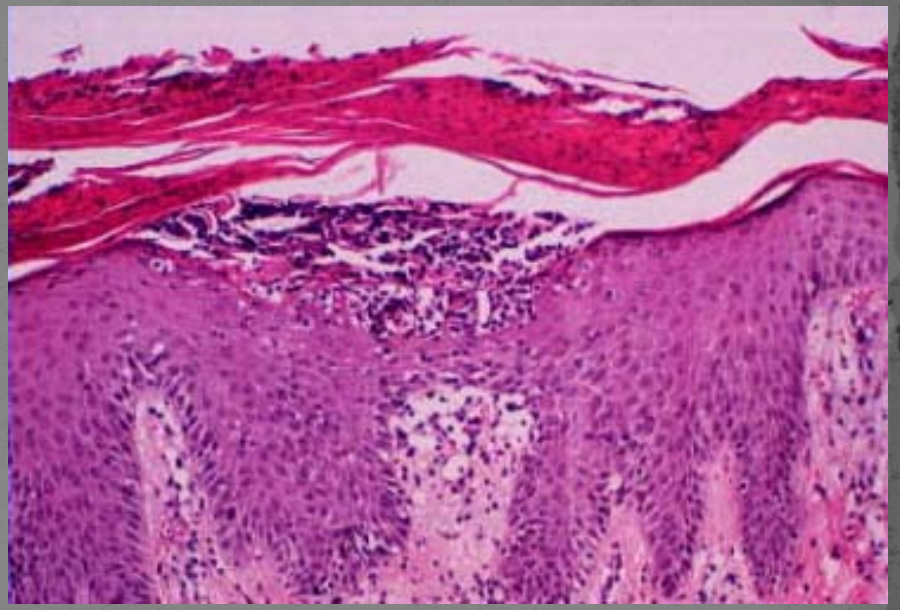

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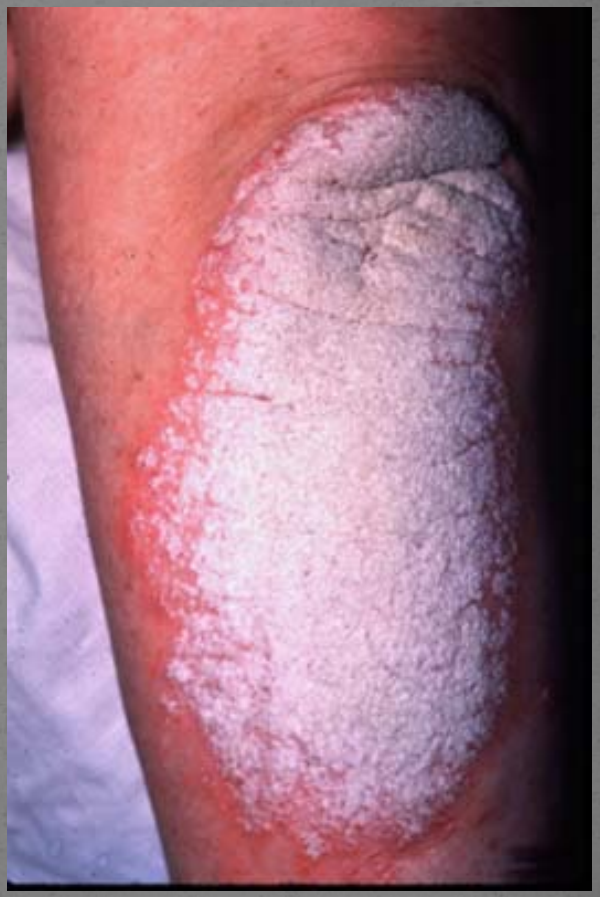
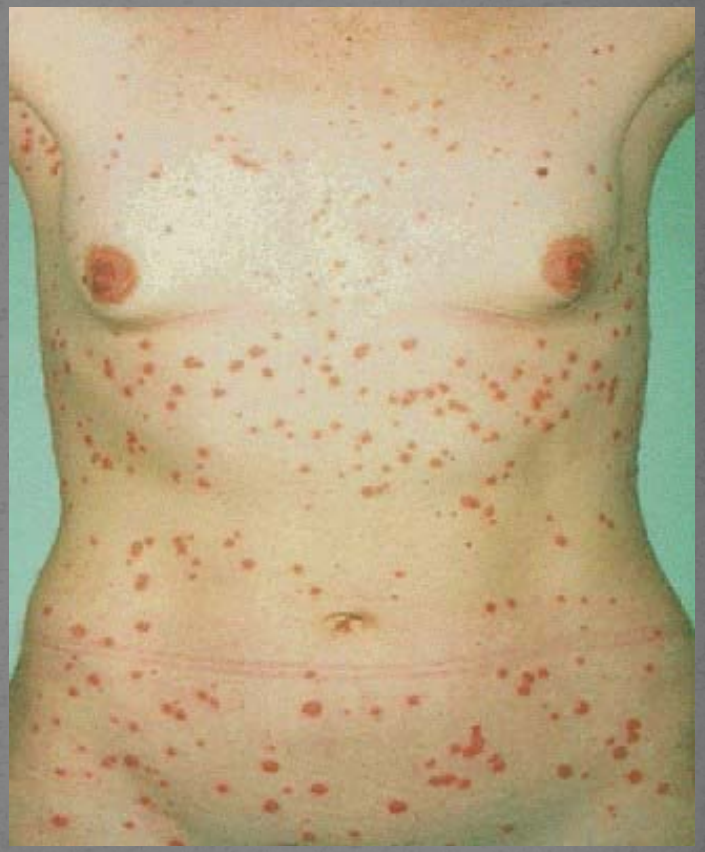
Subtypes

- Psoriasis volgaris (85%)



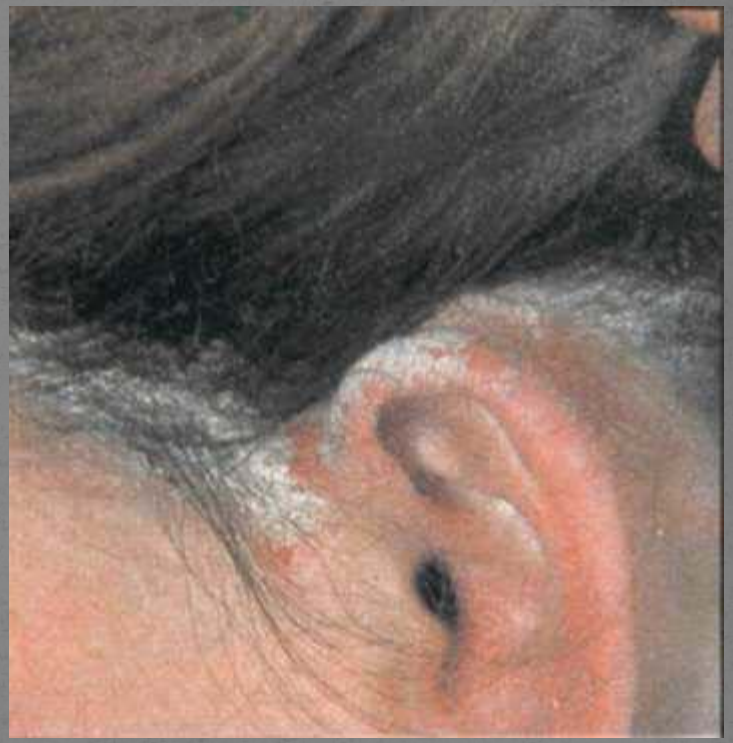
Subtypes

- Psoriasis volgaris (85%)
- Gutate psoriasis



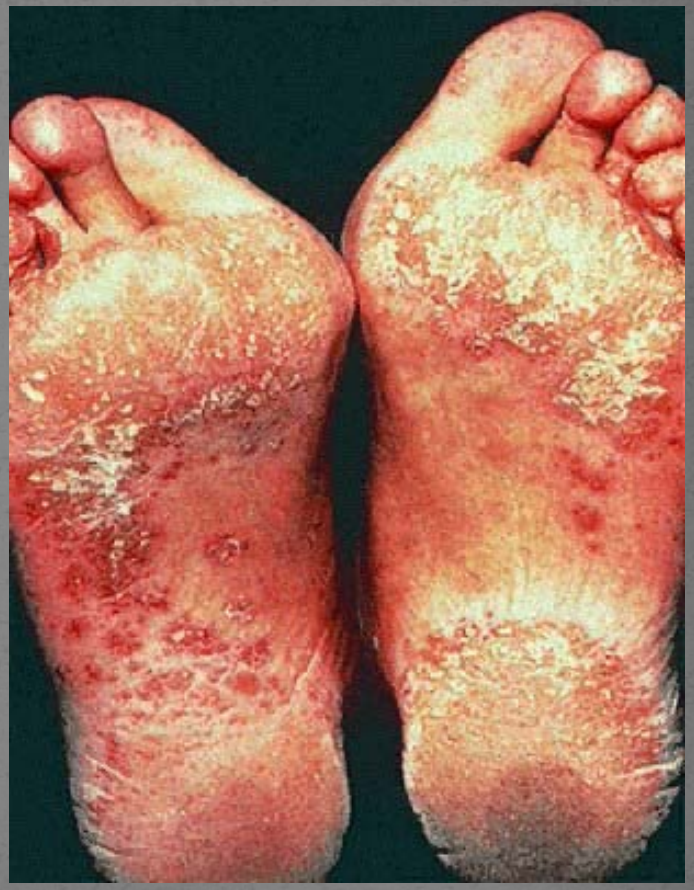
Subtypes

- Psoriasis volgaris (85%)
- Gutate psoriasis
- **Seborrheic psoriasis**



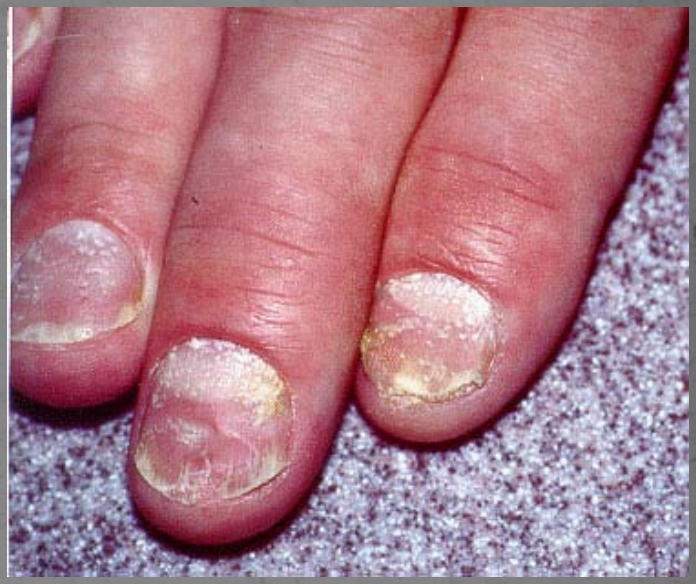
Subtypes

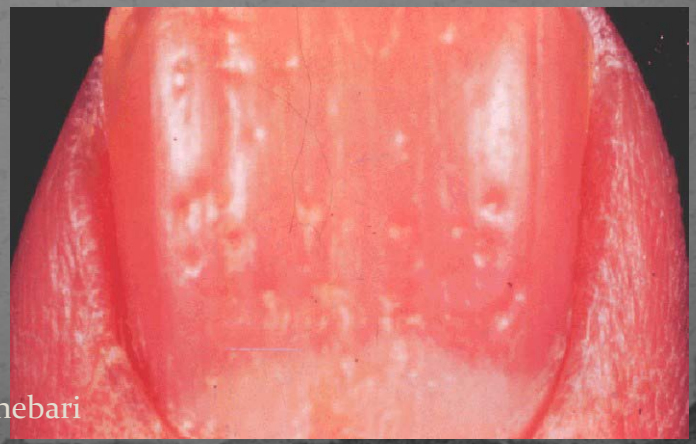
- Psoriasis volgaris (85%)
- Gutate psoriasis
- Seborrheic psoriasis
- **Pustular psoriasis**



Subtypes

- Psoriasis volgaris (85%)
- Gutate psoriasis
- Seborrheic psoriasis
- Pustular psoriasis
- Follicular psoriasis
- Erythrodermic psoriasis
- **Nail psoriasis (41%)**





History

- The association between arthritis and psoriasis was first made by Aliber in 1818
- The term psoriatic arthritis was first made by Pierre Bazin in 1860
- In the late 19th and early 20th was no general consensus that PsA was discrete entity
- Moll and Wright in 1972 described PsA classification

Is PsA a discrete disease?

- Prevalence of arthritis in population is 2-3% but in psoriatic patients is 7-42%
- Prevalence of psoriasis in population is 0.1-2.8% but in patients with arthritis is 2.6-7%
- PsA is different from RA

Is PsA a discrete disease?

- Similar histopathologic changes in skin lesions and synovium

1. Activation and proliferation of tissue specific cells (keratinocytes, synoviocytes)

2. Inflammatory cells accumulation: T cells, B cells, Neutrophiles, Macrophages

3. Angiogenesis

Epidemiology

- Peak age of onset for PsA is 30 to 55 years
- M/F ratio is equal but this ratio varies in different subset of disease
- Overall prevalence for psoriasis is %0.1 to %2.8 and arthritis occurs in %5-40 of people with psoriasis

Etiology and pathogenesis

Triggering Agent

Neuroendocrine axis **Genetic Background**

Inflammatory Response

PsA

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Genetic association

- The concordance between monozygotic twin is high (about %70)
- Family studies suggest an approximate 50 fold increased risk of PsA in first degree relatives
- HLA-class I (B17,B16,B13,B27,CW0602) and HLA-class II (DR4,DR7) are associated with PsA

Immune system

- **Evidence for T cells role in pathogenesis**

1. Infiltration of activated T cells proceeds plaque formation
2. Infiltration of CD8 cells in epidermis and synovial fluid, CD_4 cells in dermis
3. Th1 cytokines (IFNγ, TNFα, IL1, IL2, IL8) dominancy
4. Remission of psoriasis with anti T cell therapies (cyclosporin)

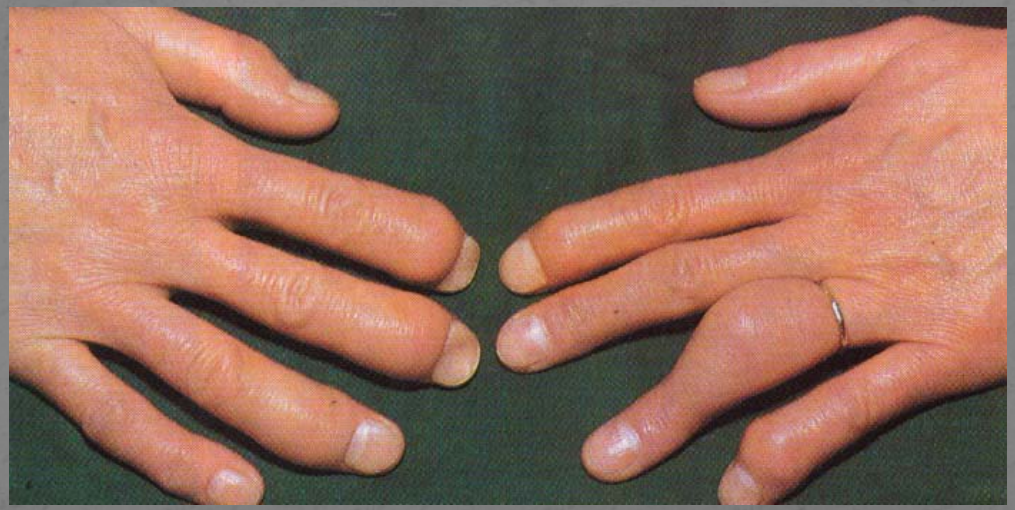
Clinical Features

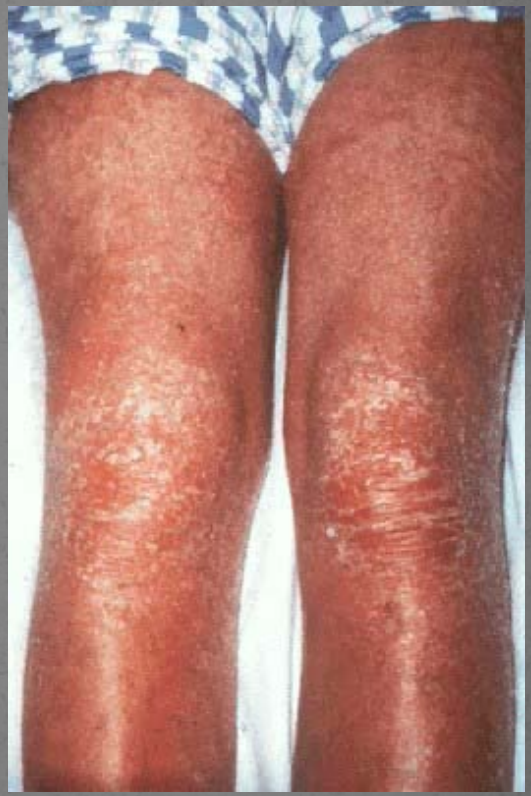
- In the majority of patients there is a lag of approximately two decades between the onset of psoriasis and the evolution of PsA
- Psoriasis antedated the arthritis in %70 of patients and followed it in %15 and isochronous onset in %15.
- There is no relation between type of psoriasis and PsA

Clinical Features

Musculoskeletal

- Arthritis (95%)

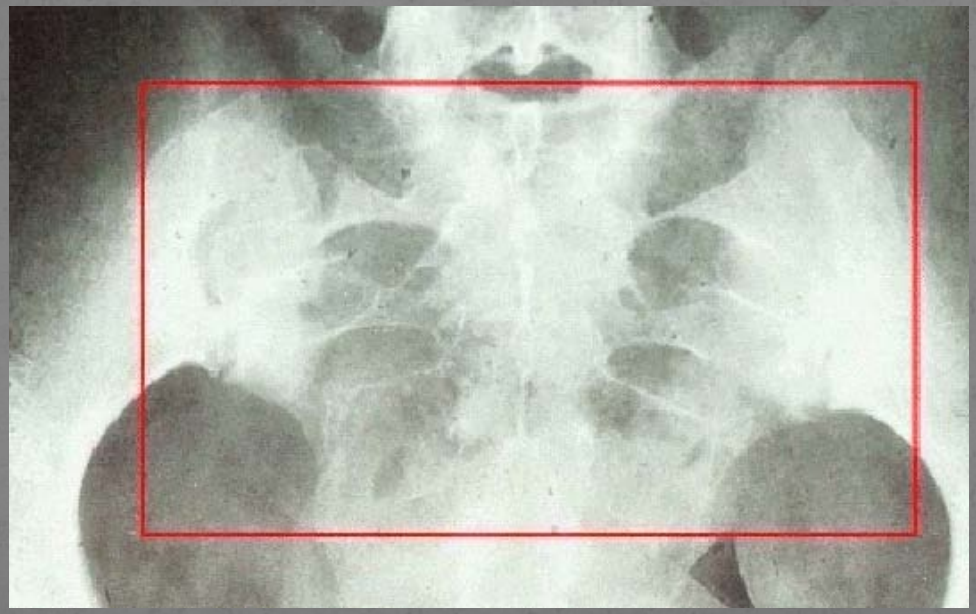


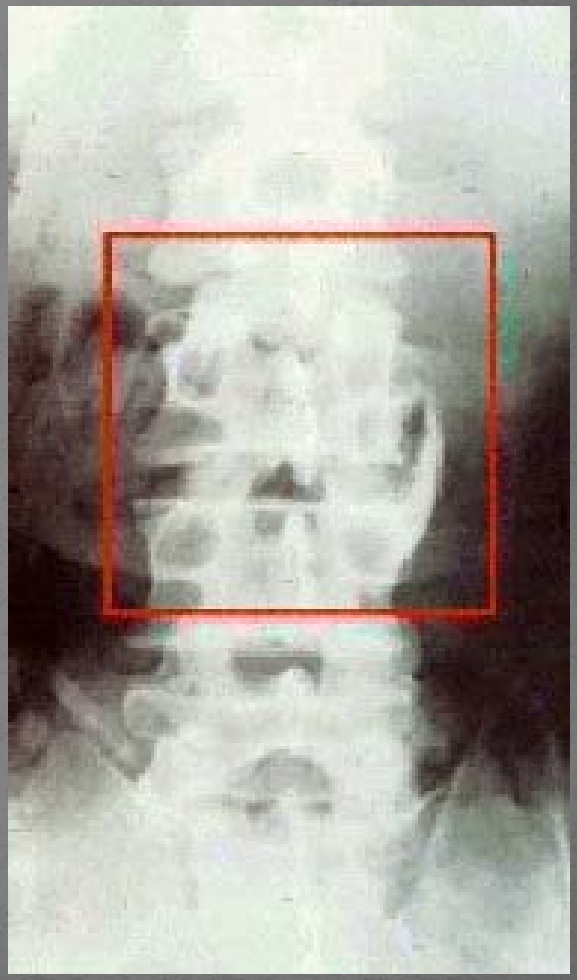


Clinical Features

Musculoskeletal

- Arthritis (95%)
- Spondylitis (20-40%)





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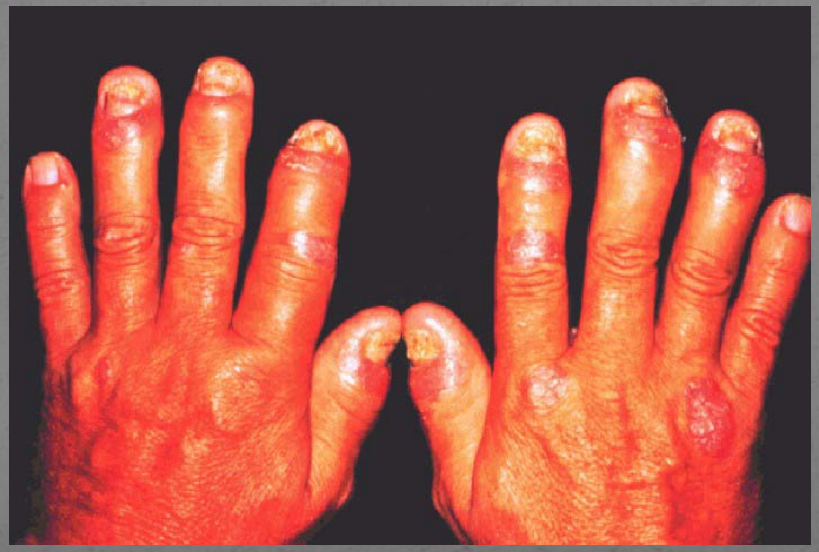
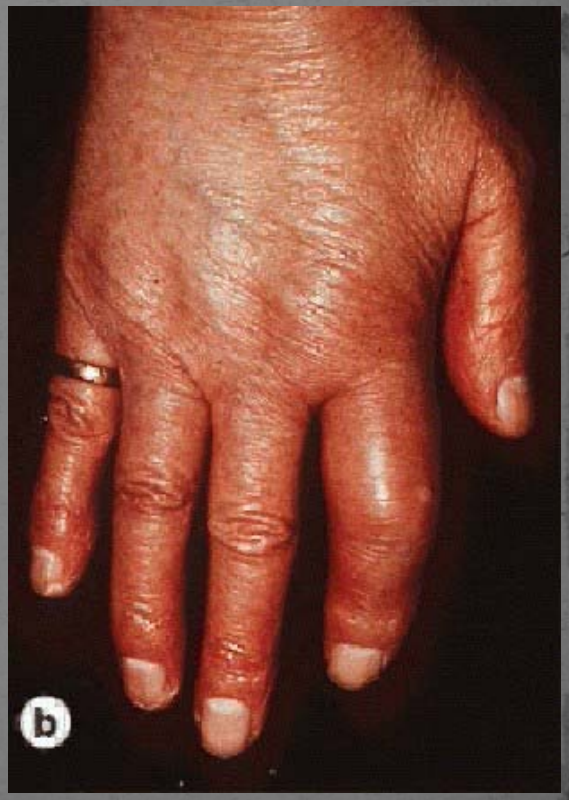
Clinical Features

Musculoskeletal

- Arthritis (95%)
- Spondylitis (20-40%)
- Dactylitis (%30)





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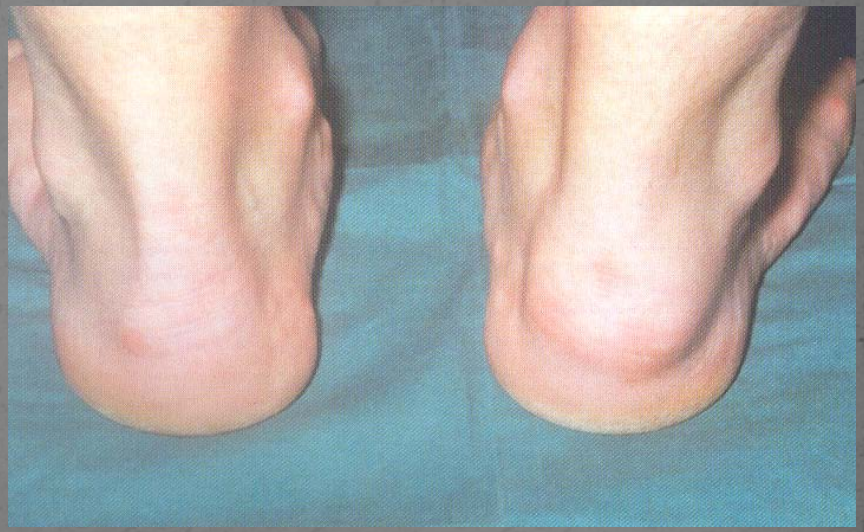
Clinical Features

Musculoskeletal

- Arthritis (95%)
- Spondylitis (20-40%)
- Dactylitis (%30)
- Enthesitis



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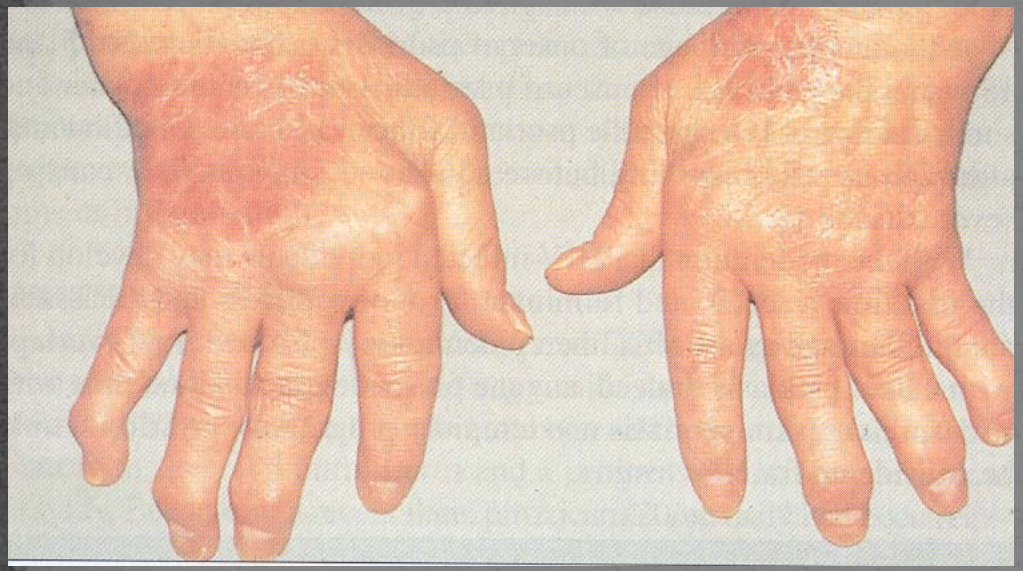
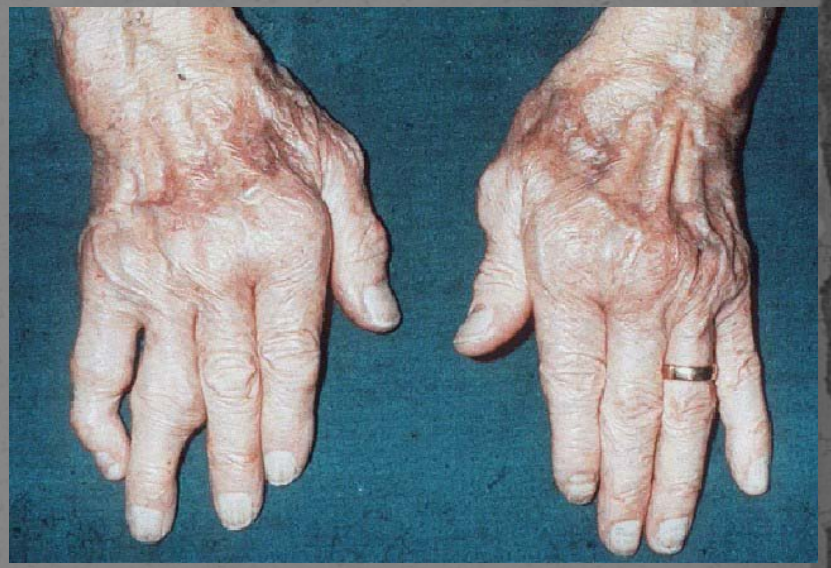
Clinical subgroups of PsA

Symmetric polyarthritis





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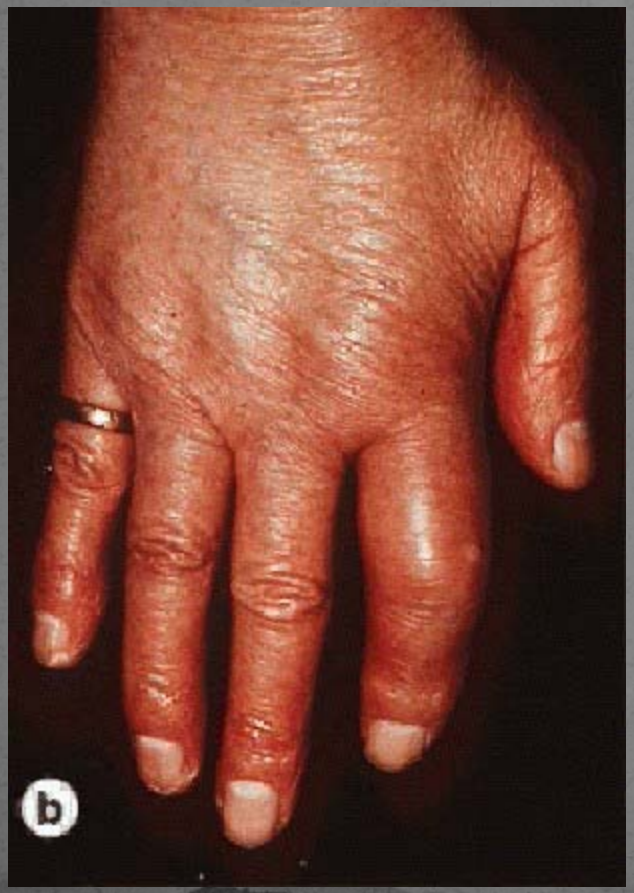
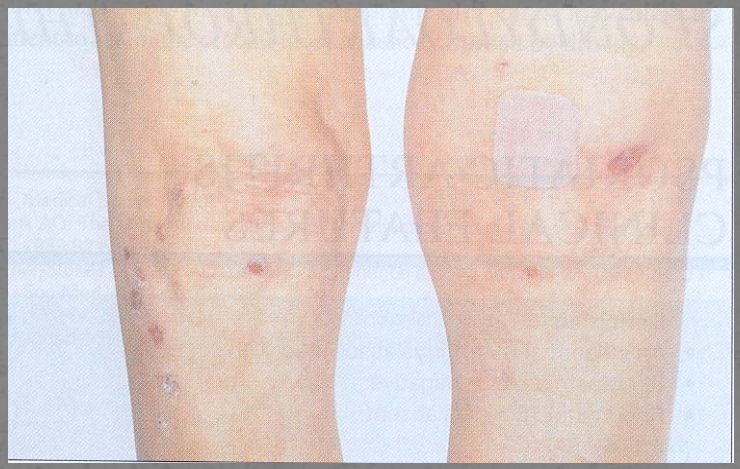
Asymmetric oligoarthritis with dactylitis (16-53%)





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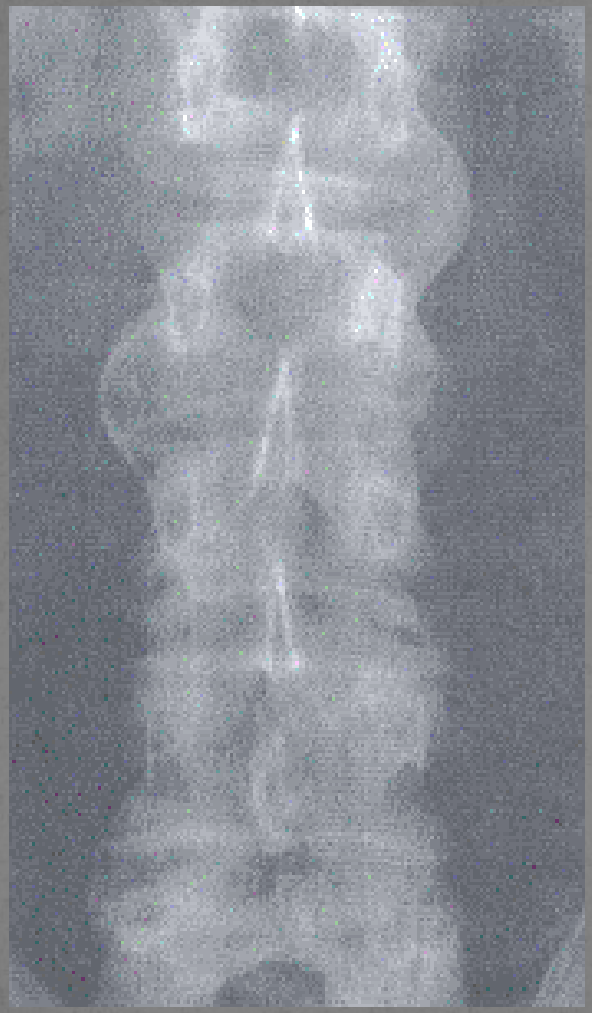
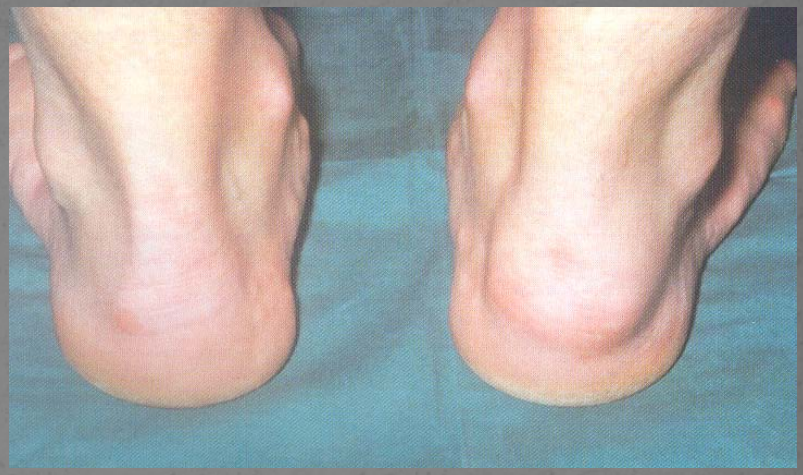
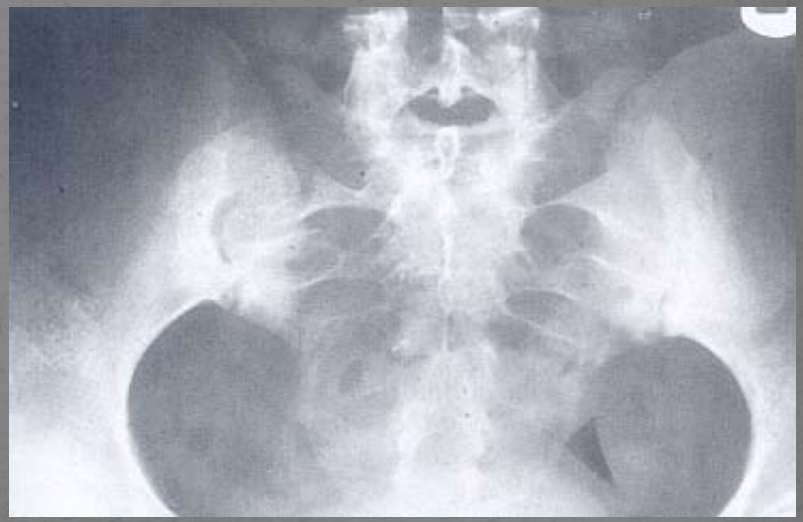
Axial involvement (13-37%)







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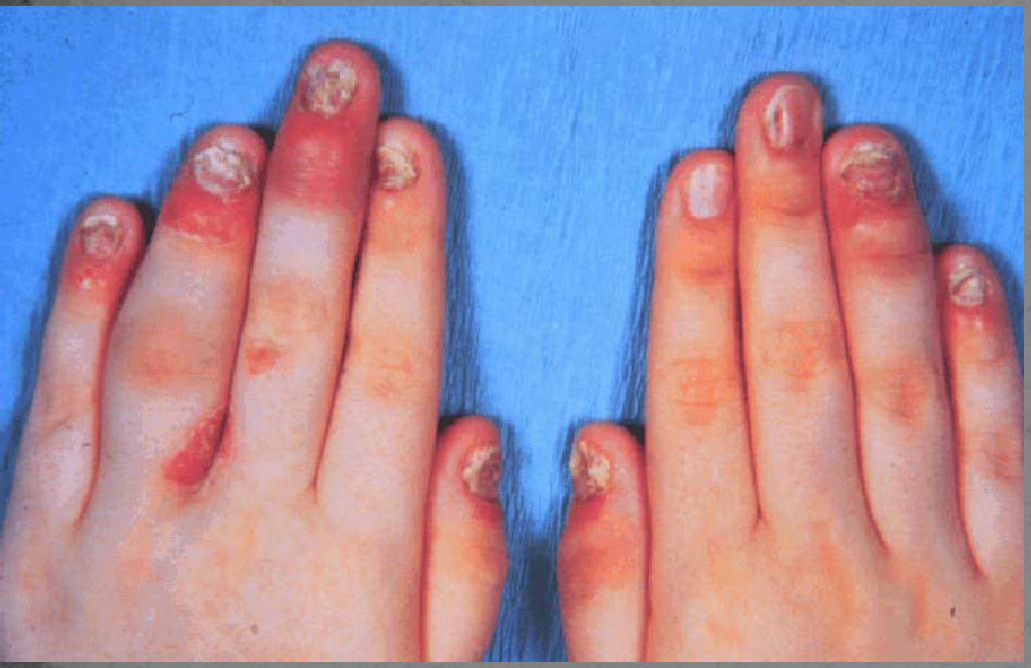
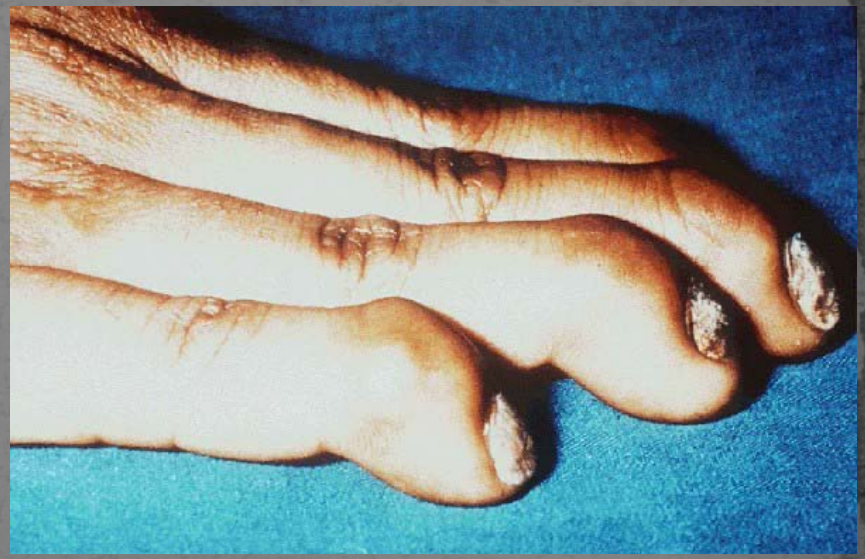
Classic PsA confined to DIP joints (1-17%)





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Clinical Features

Extra musculoskeletal

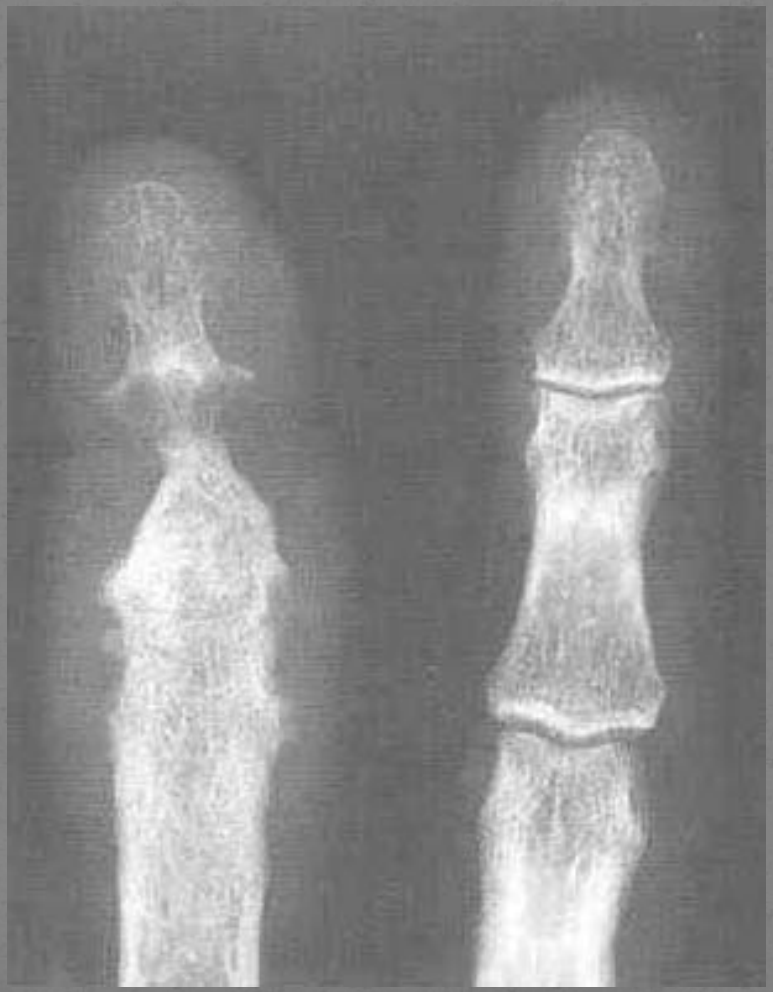
- Nail lesion (90%)
- Inflammatory eye disease (30%)
- Valvular regurgitation
- IgA nephropathy
- Pulmonary fibrosis
- Amyloidosis

Laboratory findings

- There is no diagnostic laboratory test for psoriatic arthritis
- ESR elevation, CRP+ (60%)
- RF is negative but low titers are detected in 5-10%
- Hyperuricemia (%10 to %20).

General radiographic findings

Soft tissue swelling and severe erosion



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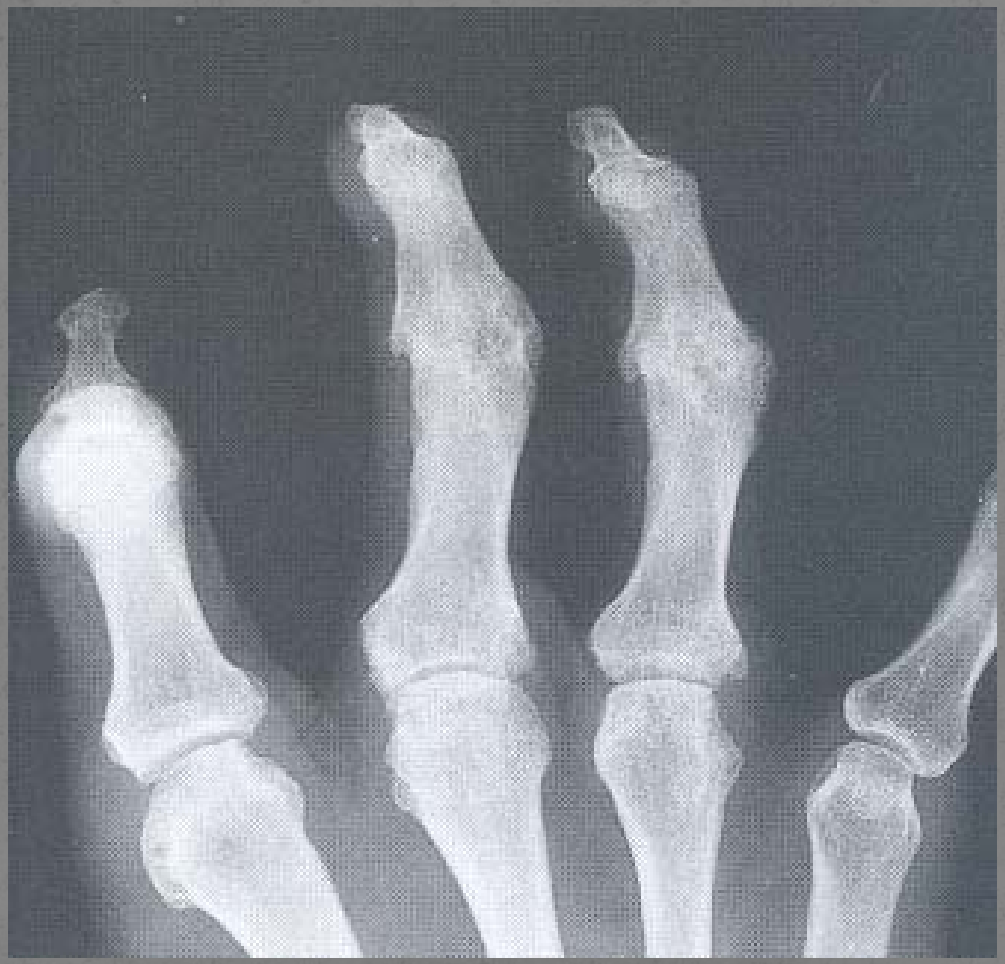
General radiographic findings

Osteoprosis generally absent



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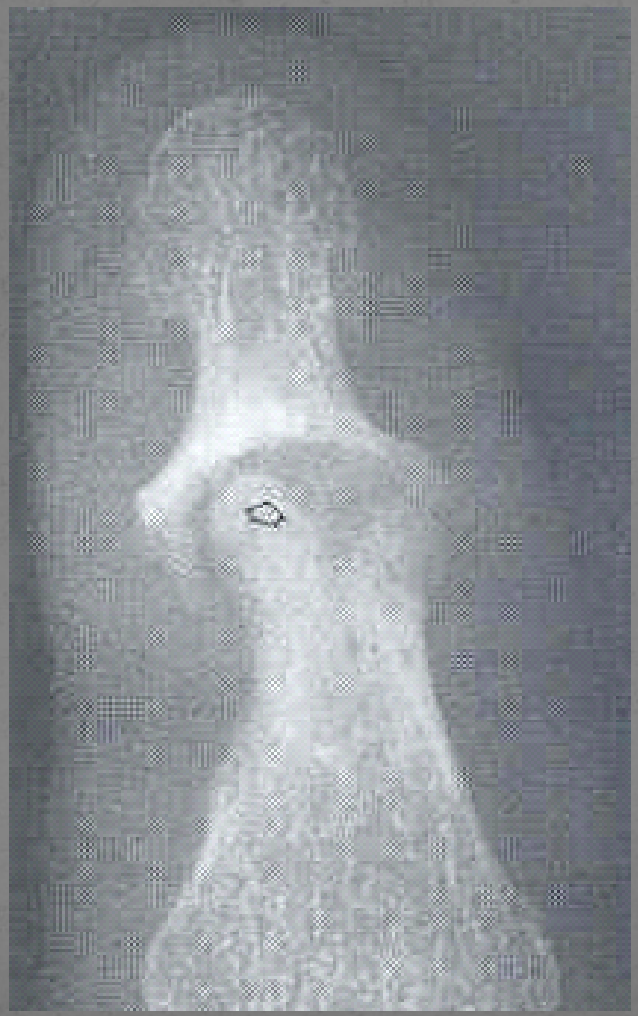
General radiographic findings

Bone erosions



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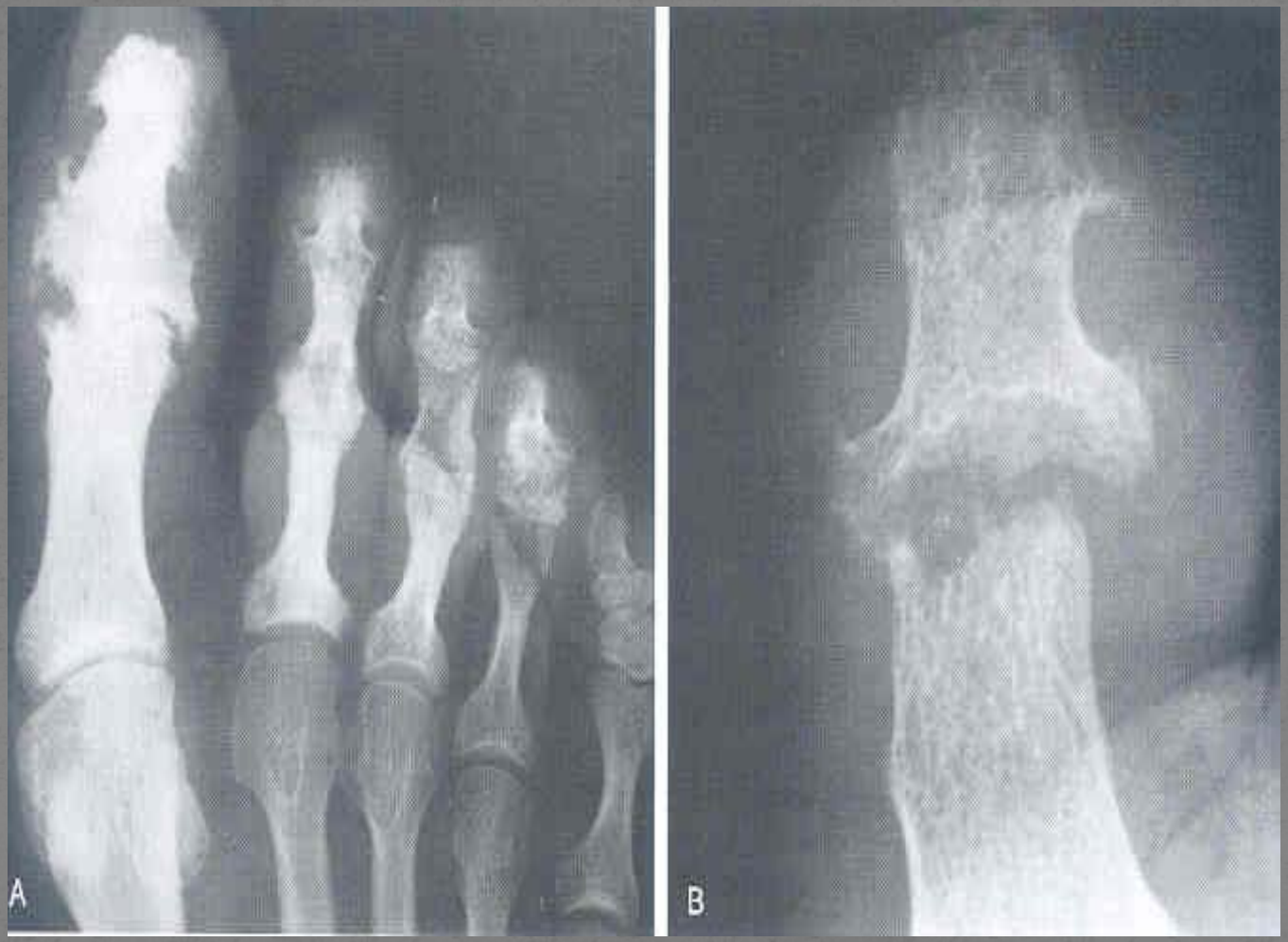
Forefoot



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Clinical course and outcome

- The course of PsA is usually characterized by flares and remission
- PsA is a mild disease and that only a minority of patients (< %5) progress to arthritis mutilans
- Poor prognostic factors:

Family history of PsA

Onset before age 20

HLA-DR3 or DR4

Erosive or polyarticular disease

Extensive skin involvement

Treatment

- NSAIDS
- Intra articular steroid
- Systemic corticosteroid
- MTX
- Sulfasalazin
- Cyclosporin A
- HCQ
- Gold
- Anti- TNF-a

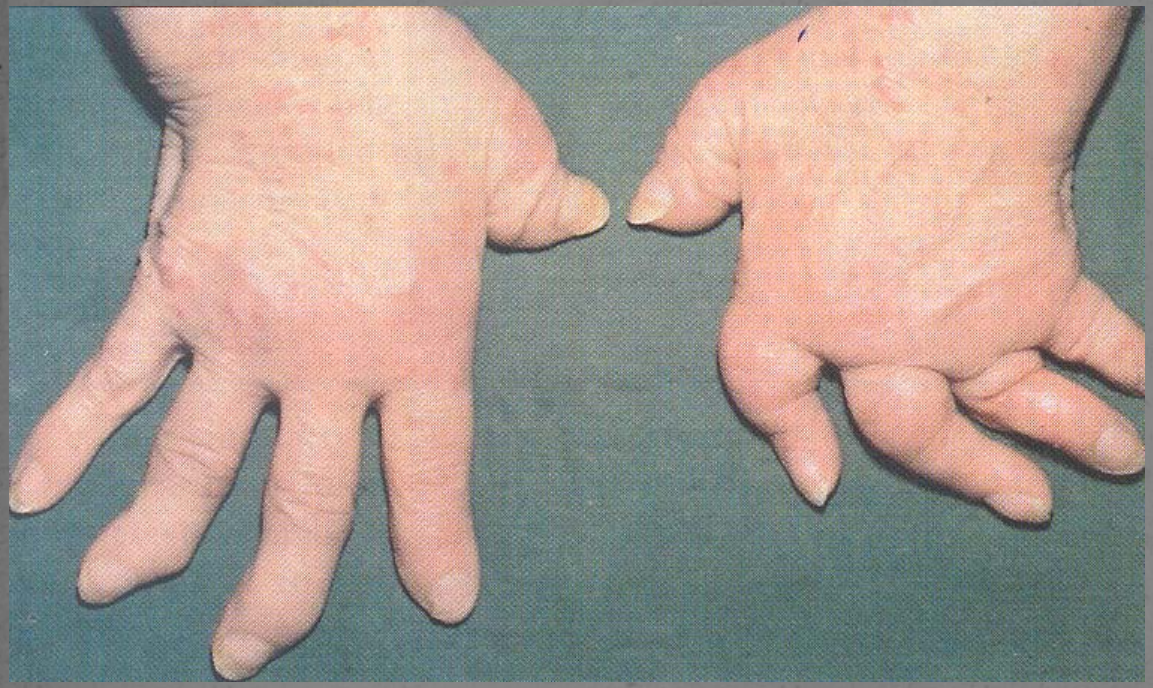
Clinical Features

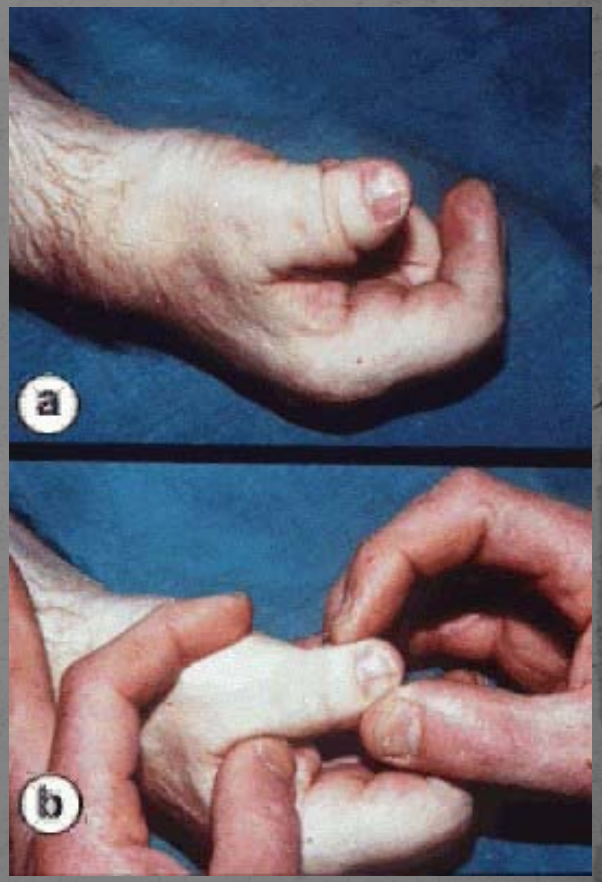
- In the majority of patients there is a lag of approximately two decades between the onset of psoriasis and the evolution of PsA
- Psoriasis antedated the arthritis in %70 of patients and followed it in %15 and isochronous onset in %15.
- There is no relation between type of psoriasis and PsA

Clinical subgroups of PsA

- Symmetric polyarthritis similar to RA (33-78%)
- Asymmetric oligoarthritis with dactylitis (16-53%)
- Axial involvement (13-37%)
- Classic PsA confined to DIP joints (1-17%)
- Arthritis mutilans (2-16%)

Arthritis mutilans





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ENTEROPATHIC SPODYLO ARTHROPATHY

By: Dr Maryam Sahebari

Definition

- Inflammatory joint disease is consider an enteropathic arthritis if the GI tract is directly involved in the pathogenesis

Definition

- **Enteropathic spondyloarthropathy characterized with:**
  - Intestinal involvement
  - Axial involvement (Sacroillitis, spondylitis)
  - Inflammatory peripheral arthritis
  - Enthesopathy
  - RF negative
  - Familial aggregation
  - Association with HLA- B27
  - Exra musculoskeletal involvement

Peripheral arthritis

- In 10-20% of IBD, more common in Crohn
- M:F=1
- Pauciarticular, asymmetric, in lower limb
- Nondestructive, attack subside in 6 weeks
- Enthesopathy especially Achilles or plantar fascia
- Sausage –like fingers
- Clubbing

Peripheral arthritis

- Intestinal symptom antedate or coincident
- Course of arthritis related to intestinal disease
- Total colectomy is associated with remission of arthritis in half of patients with ulcerative colitis
- Sometimes the arthritis may begin after surgery (due to bypass)

Axial involvement

- In 10-20% of IBD
- M:F=1
- May precede the onset of IBD or appear later
- Do not vary with intestinal disease activity
- Similar to classic ankylosing spondylitis

Treatment

- NSAID
- Intraarticular corticosteroid
- Sulfasalazine: peripheral arthritis , IBD
- Oral corticosteroid: peripheral arthritis, IBD
- Methotrexate : refractory IBD
- Azathioporine , cyclosporine
- Infliximab : intestinal symptom of crohn

SpA: European SpA Study Group (ESSG) Criteria

PLUS 1 or more of the following:

- Alternate buttock pain
- Sacroiliitis
- Positive family history
- Psoriasis
- Inflammatory bowel disease
- Urethritis or cervicitis or acute diarrhea occurring within 1 month before the onset of arthritis

Dougados M, et al. *Arthritis Rheum.* 1991;34:1218-1227.

AS

- Inflammatory low back pain:
- Chronic pain lasting more than 3 months
- Night pain
- Resolving with activity and worsening with rest
- Morning stiffness more than 0.5 hour
- Limited chest expansion
- Limitation of motion
- Positive findings of sacroilitis on Xrays

Testing Spinal Mobility: Schober's Test

Two midline vertical marks 10 cm apart starting at the posterior superior iliac spine (dimples of Venus).

Re-measure with lumbar spine at maximal flexion. Less than 4-5 cm change is abnormal.

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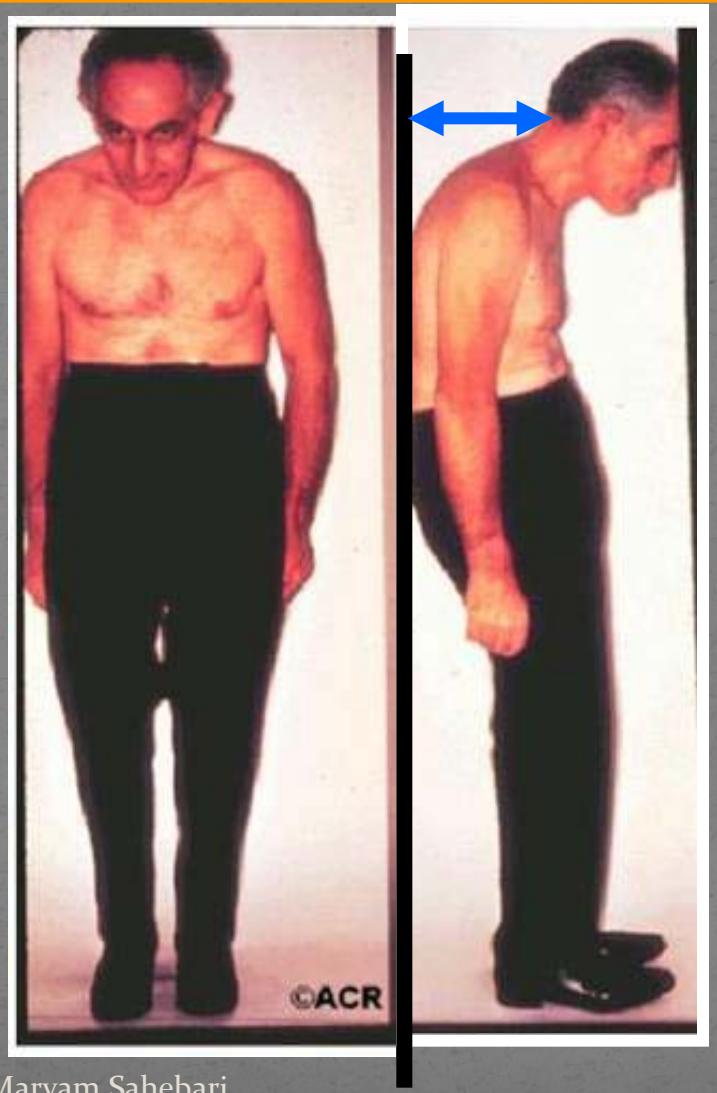
Increased Occiput-to-wall distance

Measure the distance of the patient's occiput to the wall with full neck extension. Normal is 0 cm.



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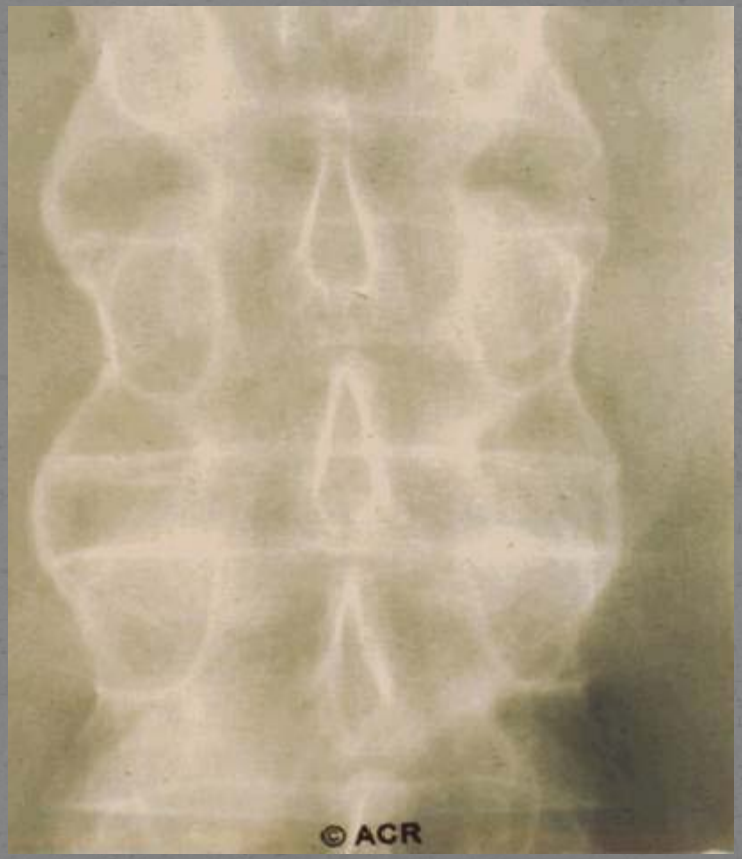
Radiographic changes sacroiliac joi

Early – erosion

Late – fusion

Radiographic changes “Bamboo Spine”



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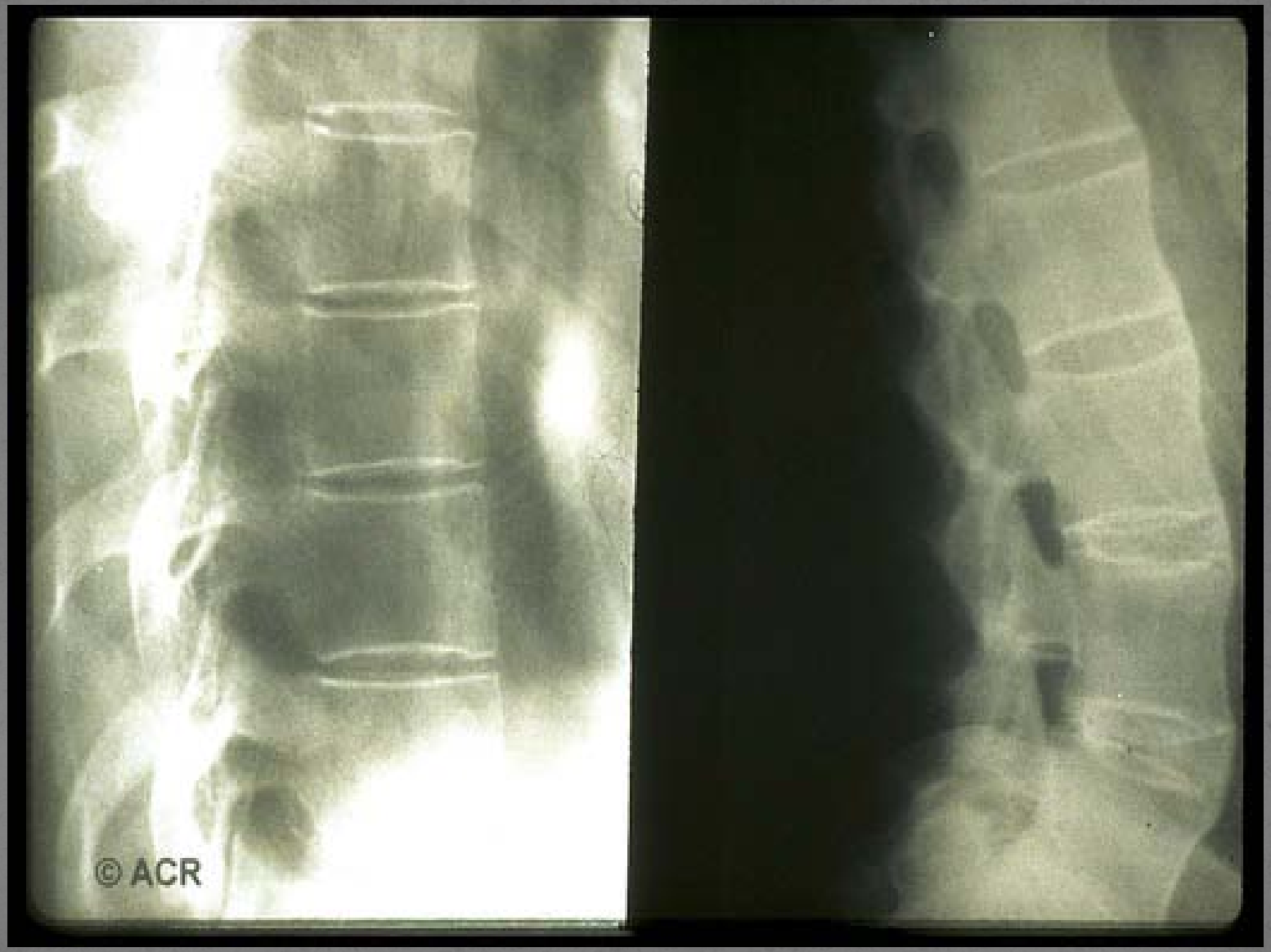

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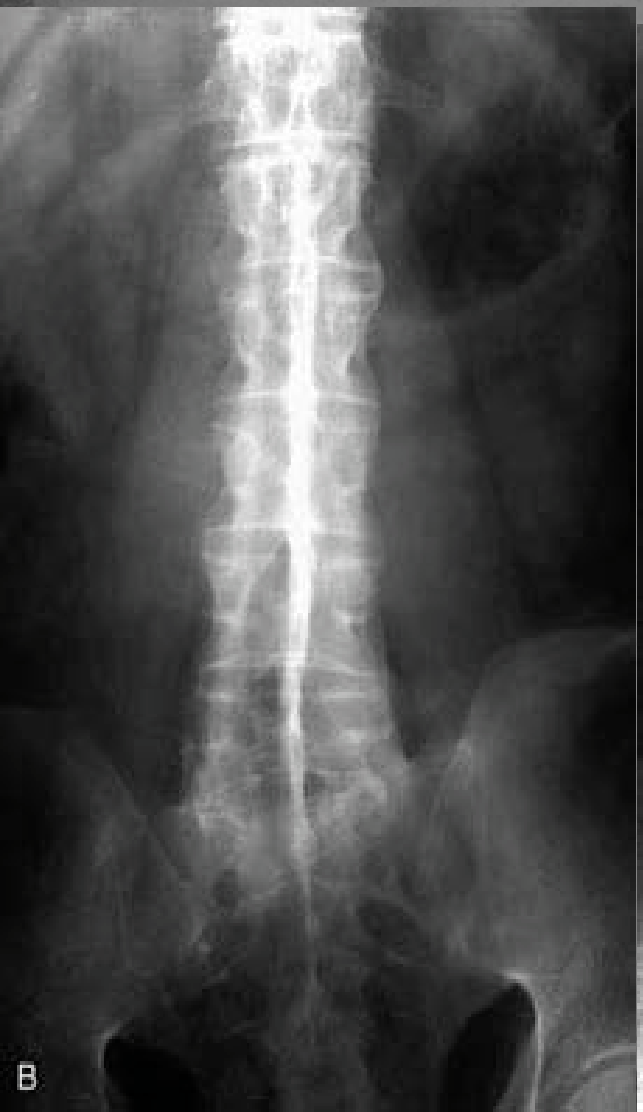
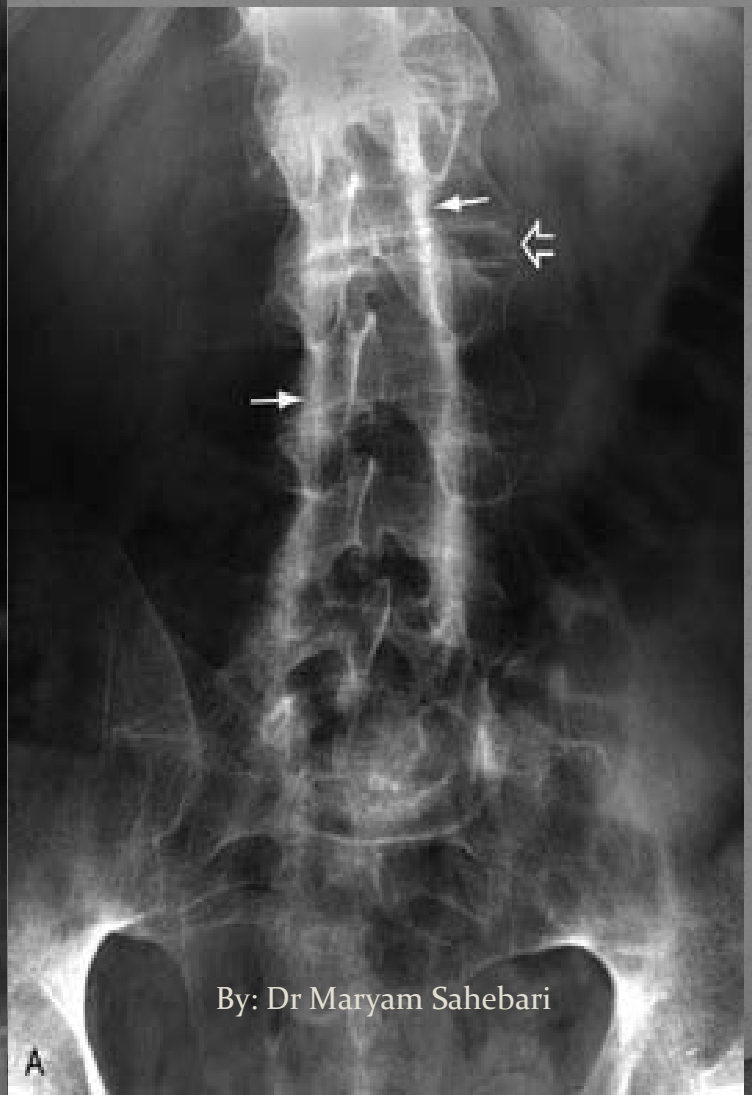
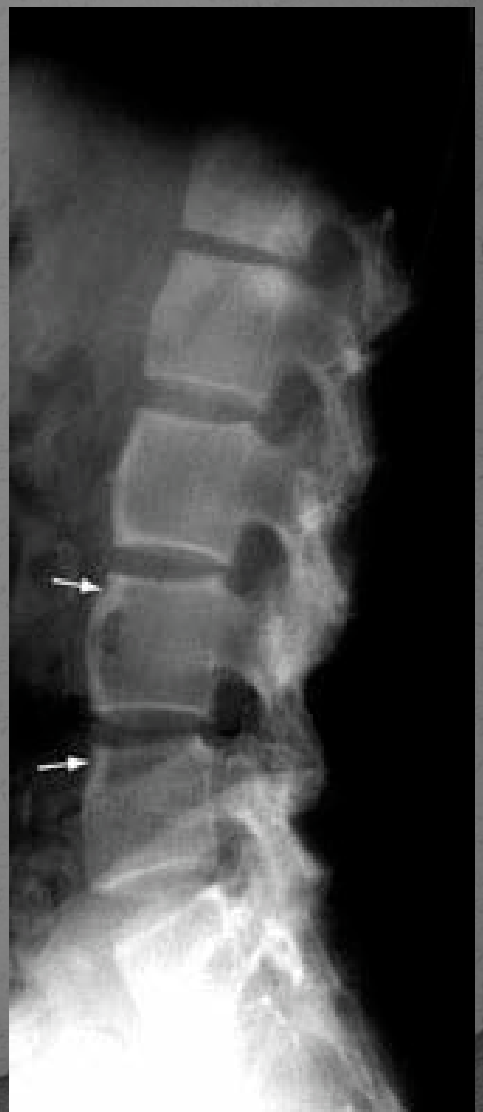
LIGAMENT OSSIFICATION

ROMANUS







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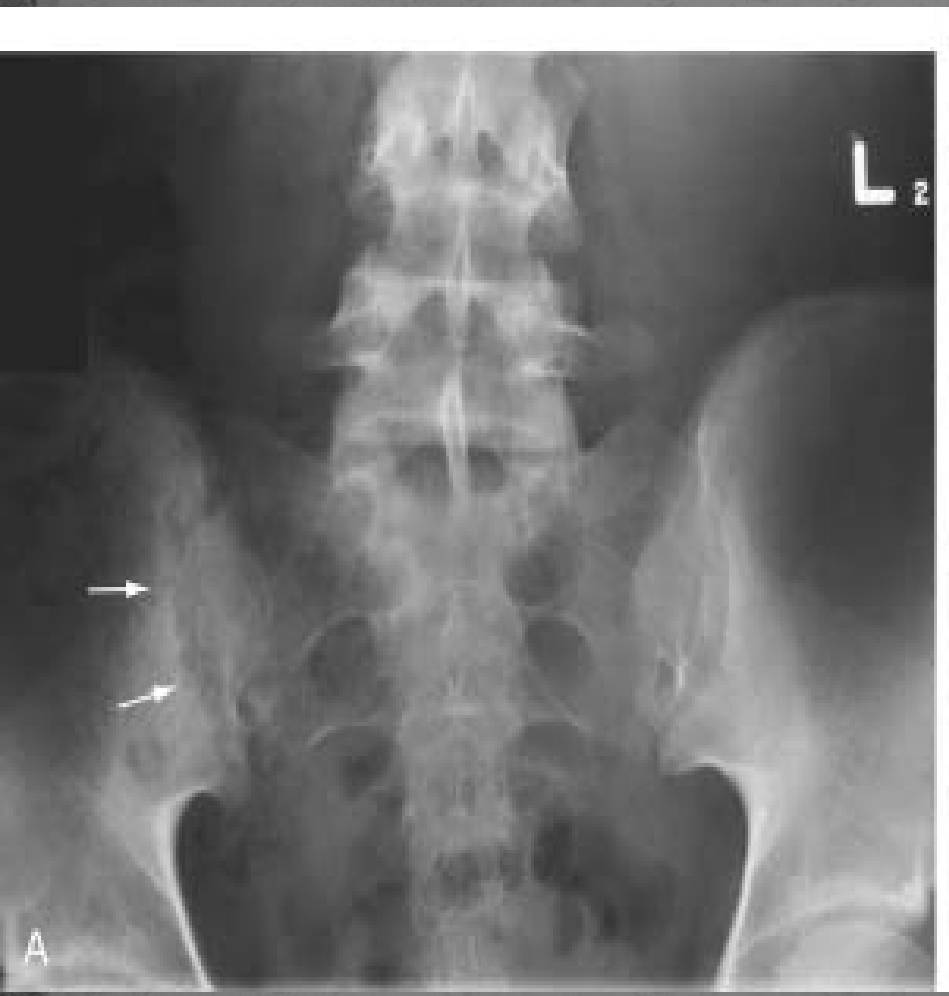
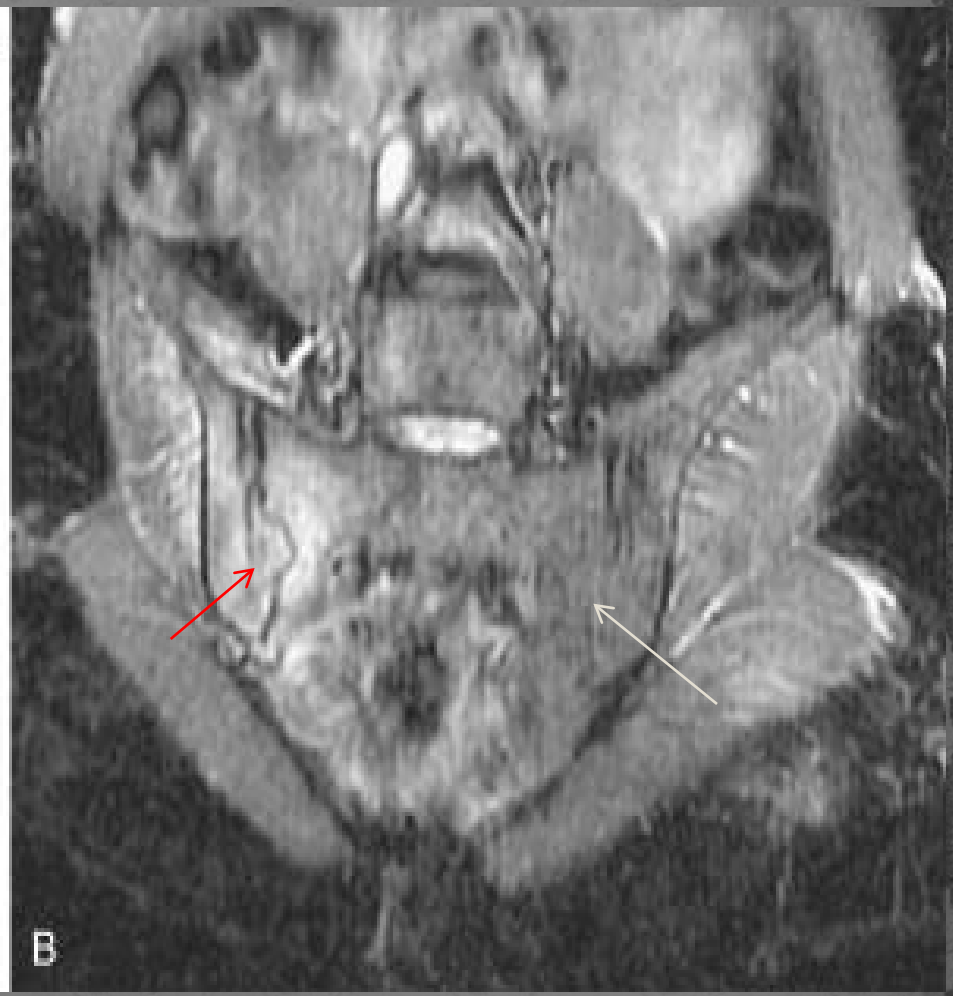
MRI is a good modality for early diagnosis





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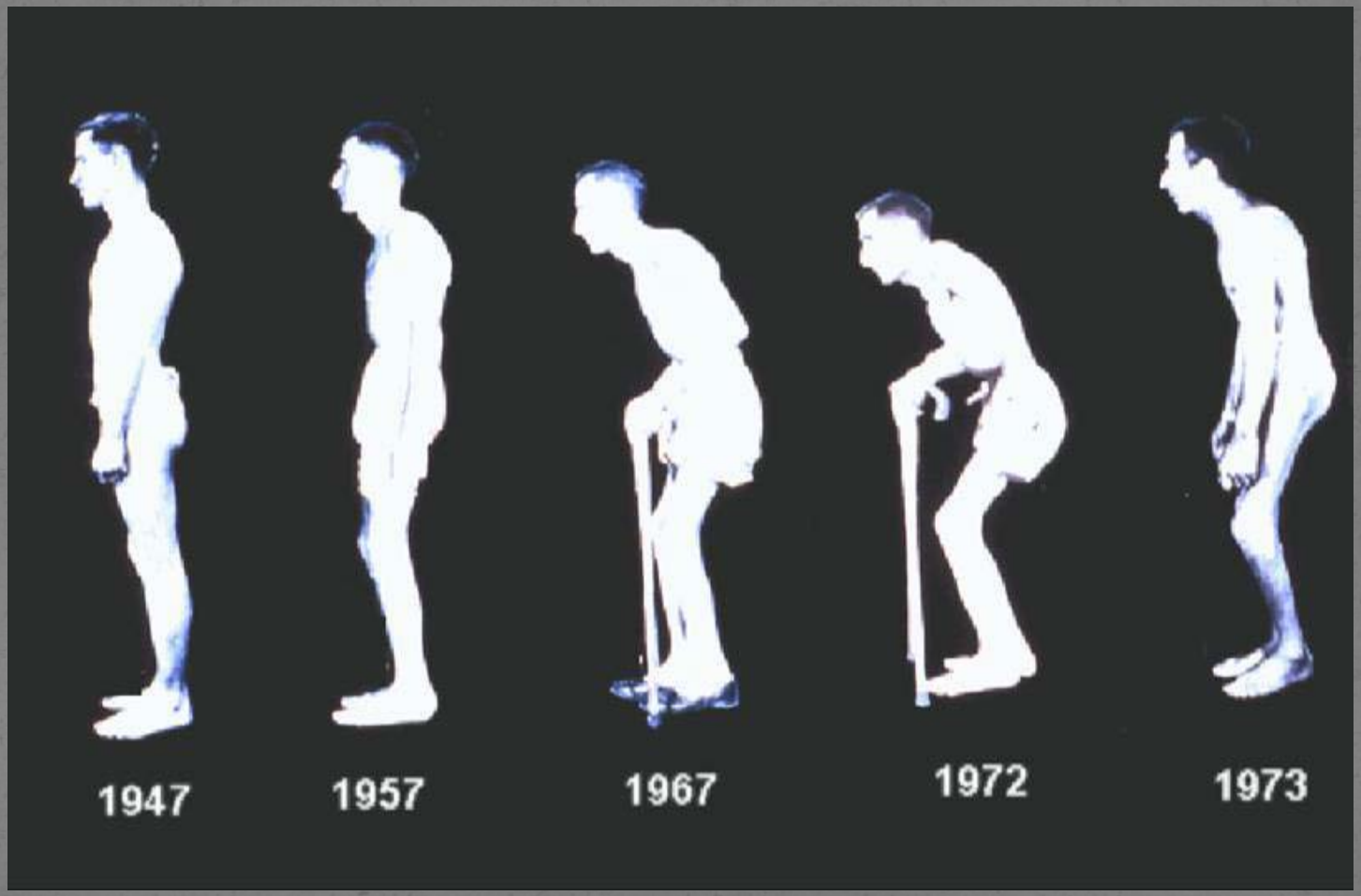
Postural changes of Ankylosing Spondylitis



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Extraskeletal manifestations of Ank Spond

Acute anterior uveitis in 25% of patients

Cardiac :Aortic insufficiency
Conduction defects

Lung : apical fibrosis

Neurologic :Spine fracture dislocation
Cauda equina syndrome

GI: IBD like manifestations
Kidney: IgA nephropathy, NSAID nephropathies, Amyloidosis

By: Dr Maryam Sahebari

Management of SNSAs

Continued activity and Physical therapy with special emphasis on postural training.

Similar to other non crystalline inflammatory arthropathies (RA)

- NSAIDs
- Sulfasalazine
- Methotrexate, Leflunomide
- TNF inhibitors

SNSA:Clinical spectrum

	AS-	RS/ReA -	EntA -	PsA
B27	>90%	80	50	15-50
Axial	+++	++	+	+
Eye,heart	+++	++	+	+
Muco/Cut	0	++	++	+++


16/7/2007
By: Dr Maryam Sahebari