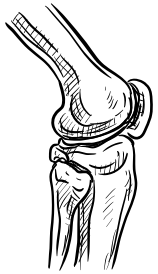
بسم الله الرحمن الرحيم



PATHOLOGY

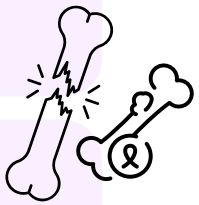
Final | Lecture 2

MSS & Skin Tumors (Pt.7)

Written by: عبد الرحمن السعدي

إيهاب العراكزة

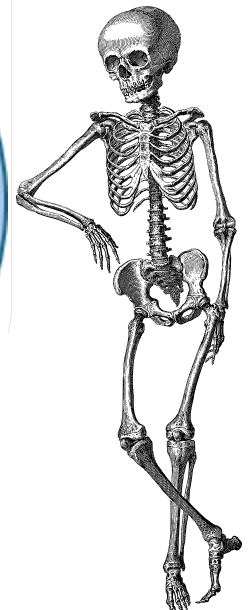
Reviewed by: معاوية الزغول



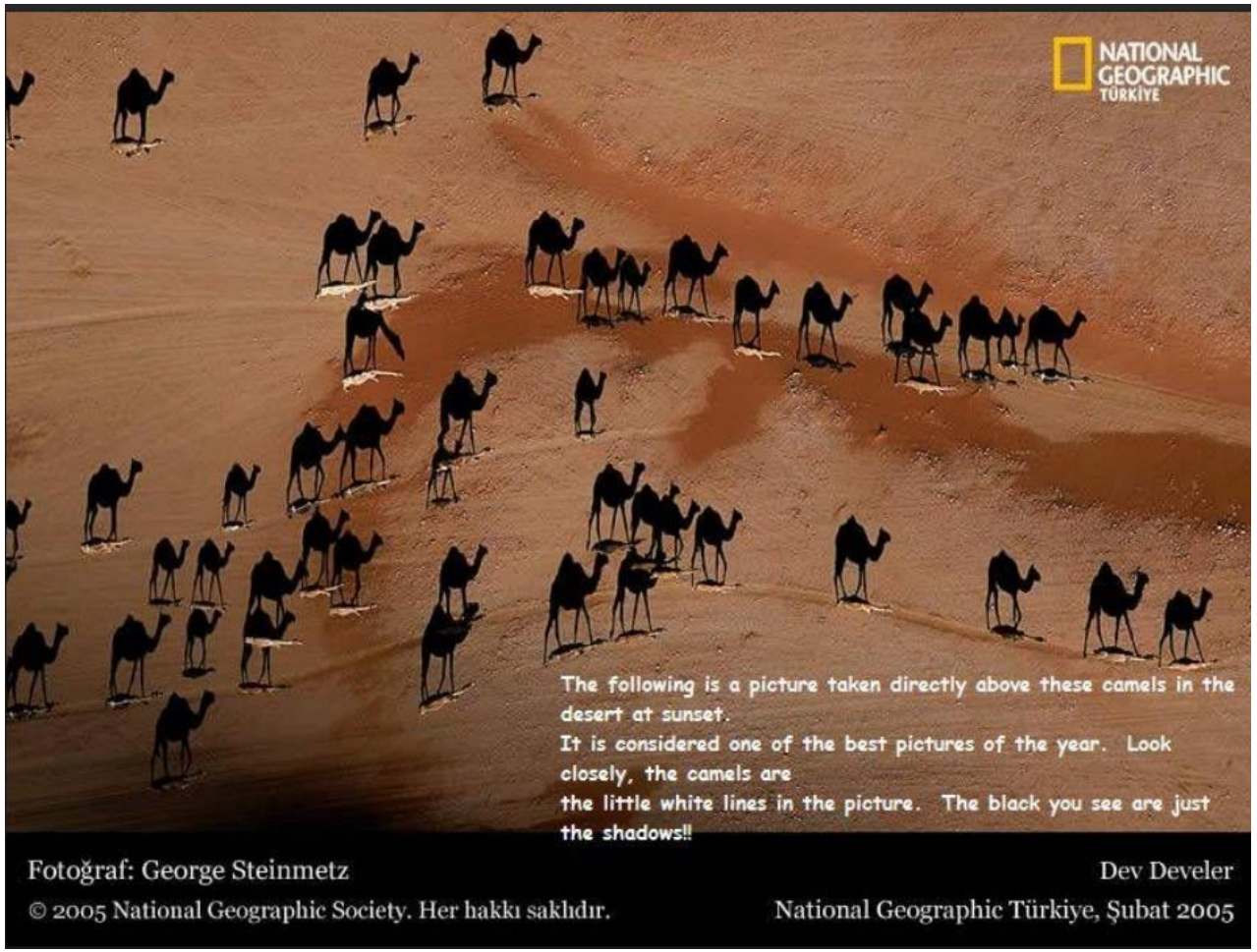
رَمَضَانُ مُبَارَكٌ

وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم

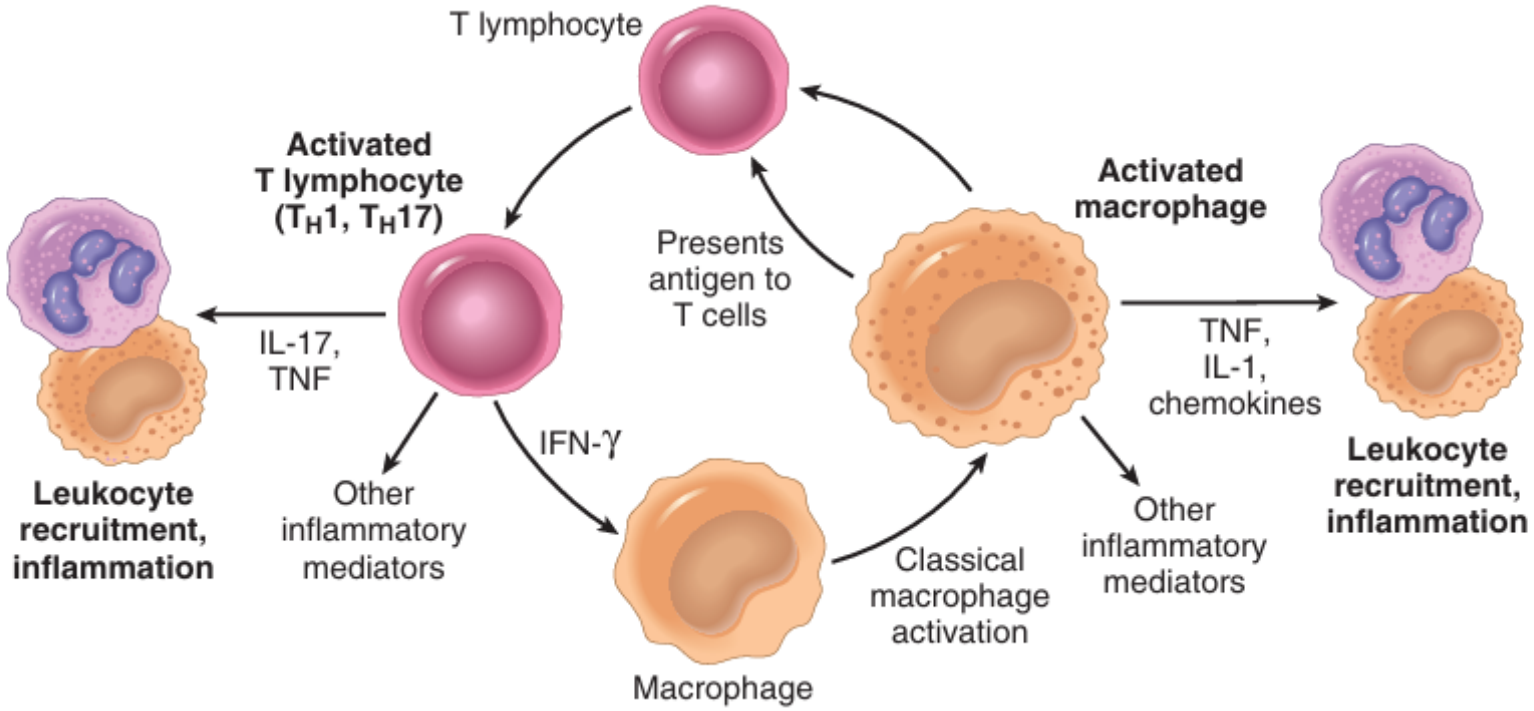
اللهم استعملنا ولا تستبدلنا



You studied previous lecture well?? I bet you can not even solve a single question in these clinical-based problems!!. Click on this photograph which Dr. Mousa admires to accept the challenge or use the link



REMEMBER FROM GENERAL PATHOLOGY



Macrophage–lymphocyte interactions in chronic inflammation. Activated T cells produce cytokines that recruit leukocyte (IL-17, chemokines) and others that activate macrophages (IFN-γ)

JOINTS (BASIC KNOWLEDGE):

- **Provide motion & stability to our skeleton**
- **Synovial (cavitated): synovial joints, wide motion (knee, elbow…)**
- **Non synovial (solid): synarthrosis, minimal movement (skull, sternum…)**
- **Synovial joints covered by hyaline cartilage (70% water, 10% type II collagen, 8% proteoglycans + chondrocytes**
- **Synovial membrane contains type A synoviocytes (differentiated macrophages), and type B synoviocytes (fibroblast-like)**
- **Synov membrane lacks basement membrane**

✓ This membrane lines the inside of joint capsule and secretes synovial fluid into joint cavity.

- **Hyaline cartilage: no blood supply, no nerves, no lymphatics (shock absorber)**

✓ this accounts for the fact that it is rarely to have mets (metastases) to the cartilage.

OSTEOARTHRITIS (DJD):

- **Degeneration of cartilage, not true – *ITIS*** (Nevertheless there are several inflammatory mediators implicated in the process). It is the most common disease of joints. Although the term osteoarthritis implies an inflammatory disease, it is considered an intrinsic disorder of cartilage in which chondrocytes respond to biochemical and mechanical stresses resulting in the breakdown of the matrix and failure of its repair.
- **Primary or idiopathic: aging process** also recurrent traumas (in athletes) **; few joints** (Knee, ankle and hip joint are mostly affected). Primary DJD constitutes most of the cases.
- **Secondary: due to pre-existing diseases** like joint deformity, or a previous joint injury.

✓ Genetic susceptibility also plays a role in the disease.

- **Insidious; increase with age (>50 yr); 40% of people > 70 years are affected**
- **Degeneration of cartilage >> repair and proliferation** of chondrocytes.

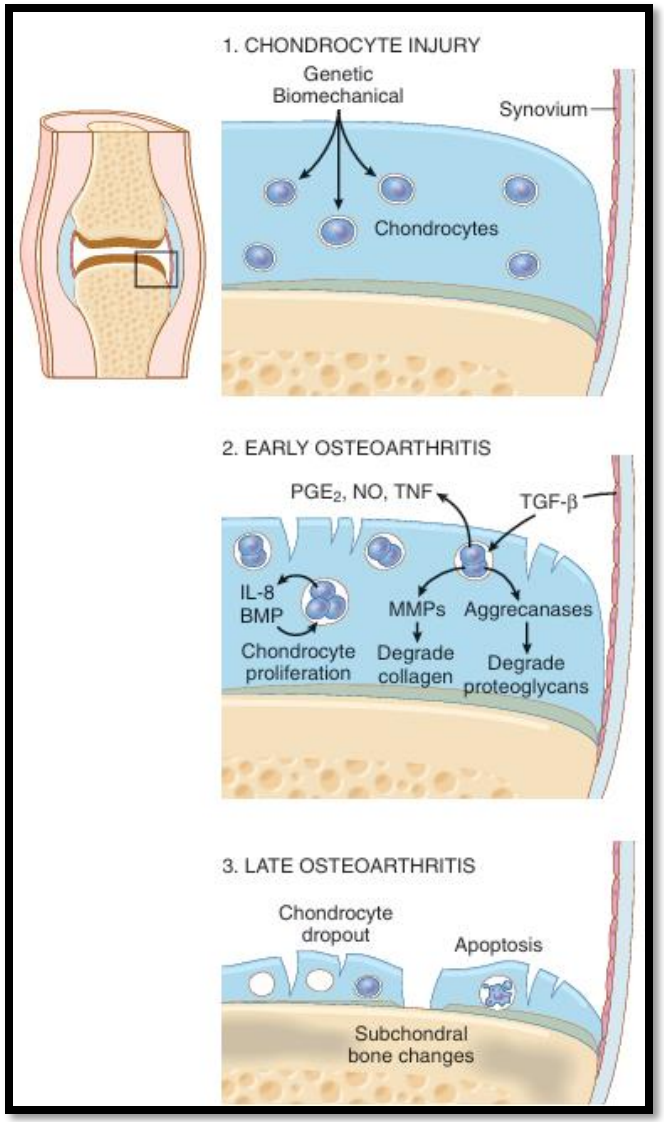
"I have osteoarthritis because I used to play football
a lot in my old days",
Dr. Mousa says.

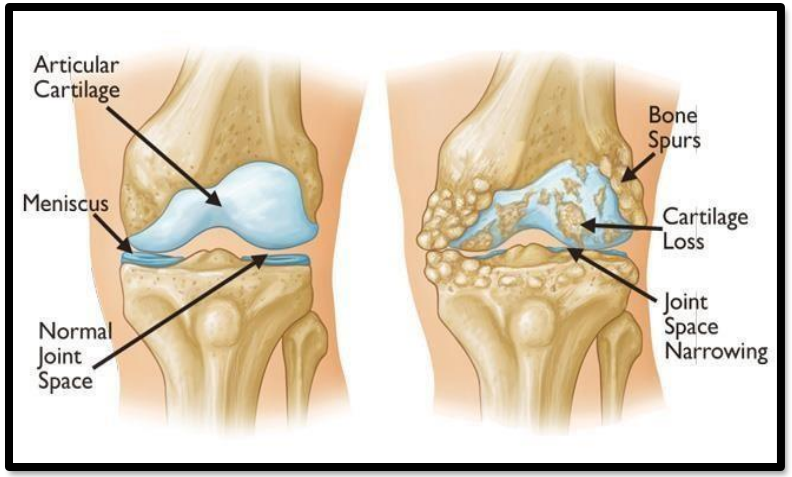
Pay attention to every detail in these figures.

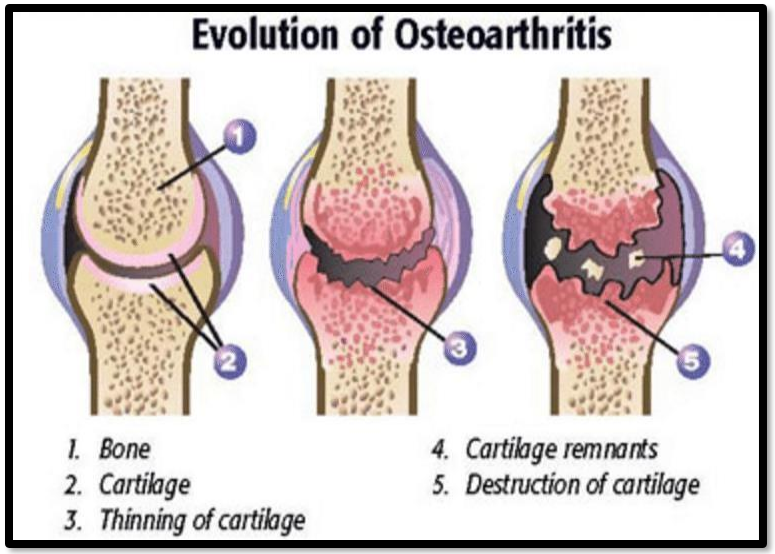
1- Chondrocyte injury due to repeated biochemical and mechanical stresses with genetic susceptibility is some individuals.

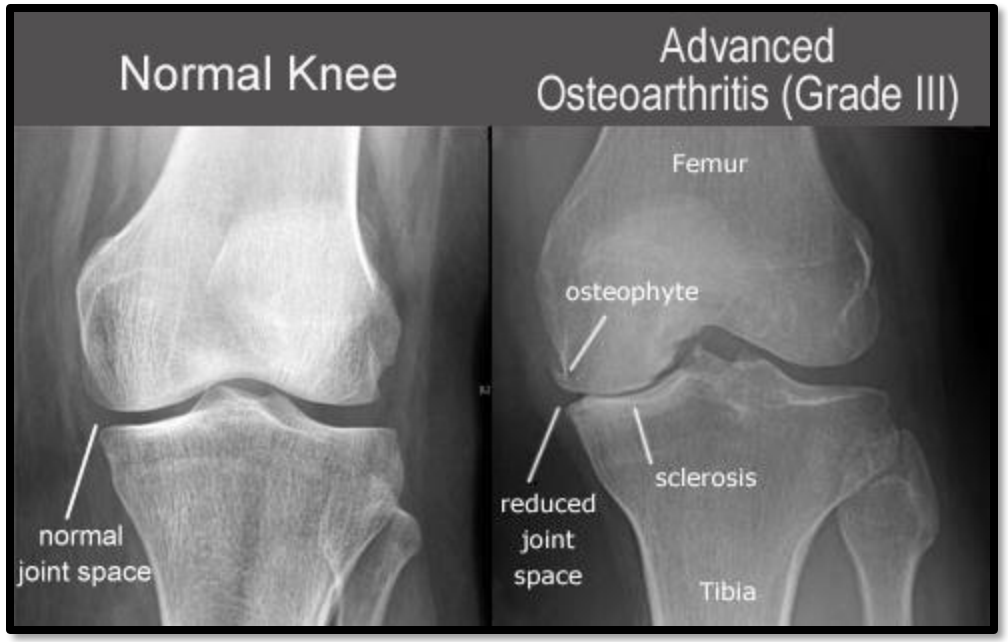
2- several inflammatory mediators are secreted by chondrocytes and synoviocytes like PGE2, NO, TNF, TGF-β, also, enzymes like MMPs and aggrecanases that degrade the matrix.

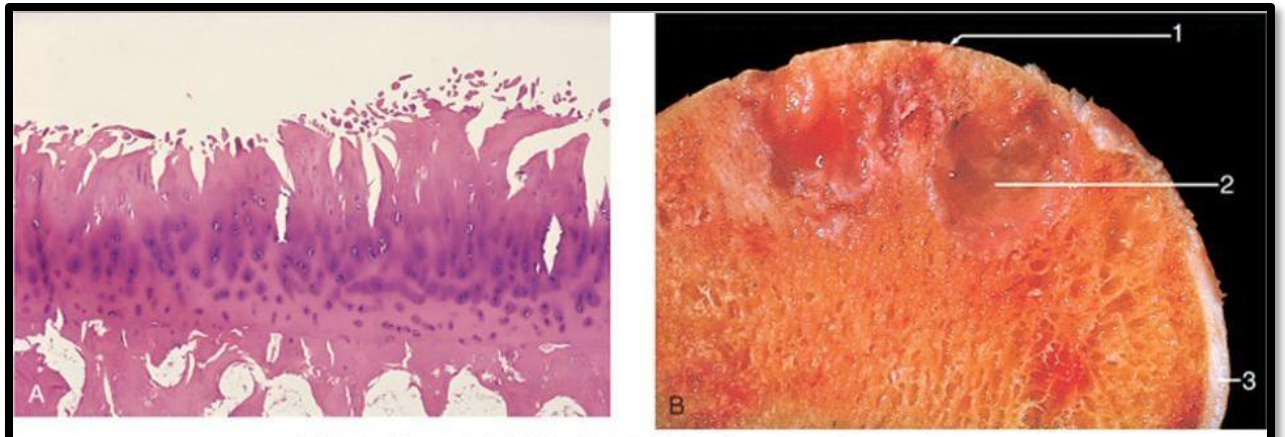
3- This process continues for months and years. Degradation exceeds repair and ultimately, chondrocyte apoptosis and severely damaged matrix will occur.





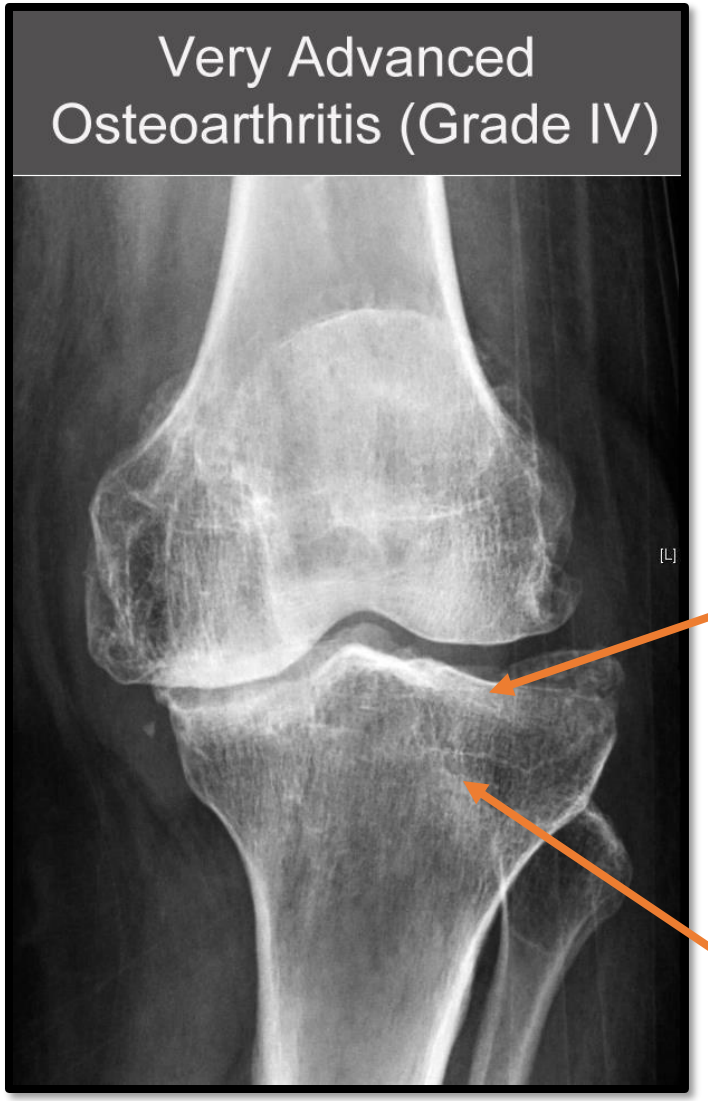






© Elsevier. Kumar et al: Robbins Basic Pathology 8e - www.studentconsult.com

- Osteoarthritis. **A,** Histologic demonstration of the characteristic fibrillation of the articular cartilage. **B,** Severe osteoarthritis with 1, Eburnated articular surface exposing subchondral bone. 2, Subchondral cyst. 3, Residual articular cartilage



Notice the subchondral sclerosis (whitish areas) and the severely narrowed joint.

Subchondral cysts

Pay attention to every detail in these figures.

MORPHOLOGICAL FEATURES OF OSTEOARTHRITIS

Early stages:

- ✓ Damage to cartilage due to biochemical and mechanical stresses producing fissures and clefts known as fibrillation of articular cartilage.

Late stages:

- ✓ With continuous degeneration and erosion, cartilage thickness is significantly reduced exposing the subchondral bone.
- ✓ Pieces of cartilage and subchondral bone tumble into the joint space, forming ***loose bodies***.
- ✓ ***Bone eburnation*** because of friction between the opposing exposed articular bony surfaces resulting in polished bone.
- ✓ Reduced joint space.
- ✓ Irritation of the subchondral bone.
- ✓ Subchondral or ***cortical sclerosis***.
- ✓ Developing of ***subchondral cysts*** with hemorrhage.
- ✓ Emergence of outgrowths called ***bone spurs or osteophytes***.

OA(DJD) CLINICALLY

- **Joint pain worsens with use, morning stiffness, crepitus & range limitation** (it hurts when the joint is hyper-flexed or hyperextended), **radicular pain, osteophytes impingement on vertebrae, muscle spasm & atrophy**

✓ Crepitus is the cracking and popping sounds you hear or feel from the affected joint once flexed and extended just by palpating it.

- **No magic preventive strategies (wt loss?)**

✓ As a clinician, if you have an obese patient suffering from DJD, weight loss is mandatory.

- **Trx: pain control, decrease inflammation (NSAIDs), intra-articular steroids, or joint replacement for severe cases**
- **Large health cost on countries**

RHEUMATOID ARTHRITIS

- **Chronic inflammatory disease; autoimmune in nature; attacks joints with nonsuppurative proliferative and inflammatory synovitis; leading to destruction of joints and adhesions (ankylosis) (fusion of the joint) ; systemic disease (skin, heart, vessels & lungs).**

✓ The underlined words are the buzzwords regarding rheumatoid arthritis (extremely important). The main target here is the synovium with a true inflammatory reaction, and the disease is *systemic* involving various other organs, unlike DJD indeed, where we have destruction of the cartilage (the main target) in joints solely, without a real inflammatory process. However, DJD remains the most common disease of the joint.

- **1% prevalence in USA; F:M = 3:1; 4^{th}-5^{th} decade**
- **Genetic predisposition (some families have more rheumatoid arthritis than others) plus environmental factors play a role in the development, progression and chronicity of the disease**

PATHOGENESIS:

Pay attention to every detail in this figures.

- ✓ **The pathogenesis in rheumatoid arthritis is multifactorial process.**
- ✓ **Environmental factors including infection and smoking lead to citrullination of self proteins, the process by which arginine is post-translationally converted to citrulline in normal proteins producing altered or atypical self-antigens.**
- ✓ **Some genes like *Human Leukocyte Antigen (HLA)* confer susceptibility to this disease, probably by failure to discriminate between foreign and self-antigen (failure of tolerance) and the unregulated lymphocyte activation.**
- ✓ **All these factors eventually lead to the activation of T lymphocytes (*T_H1 and T_H17*) and B lymphocytes (*plasma cells and antibodies production*), carrying an autoimmune rection against self-antigens.**
- ✓ **Immune cells, antibodies and immune complexes enter the joint, triggering the activation and the proliferation of fibroblast, chondrocytes and synoviocytes, and the release of cytokines and proteases to induce the inflammation, causing destruction to the bone, cartilage and the synovium, and *pannus formation* (further discussed).**

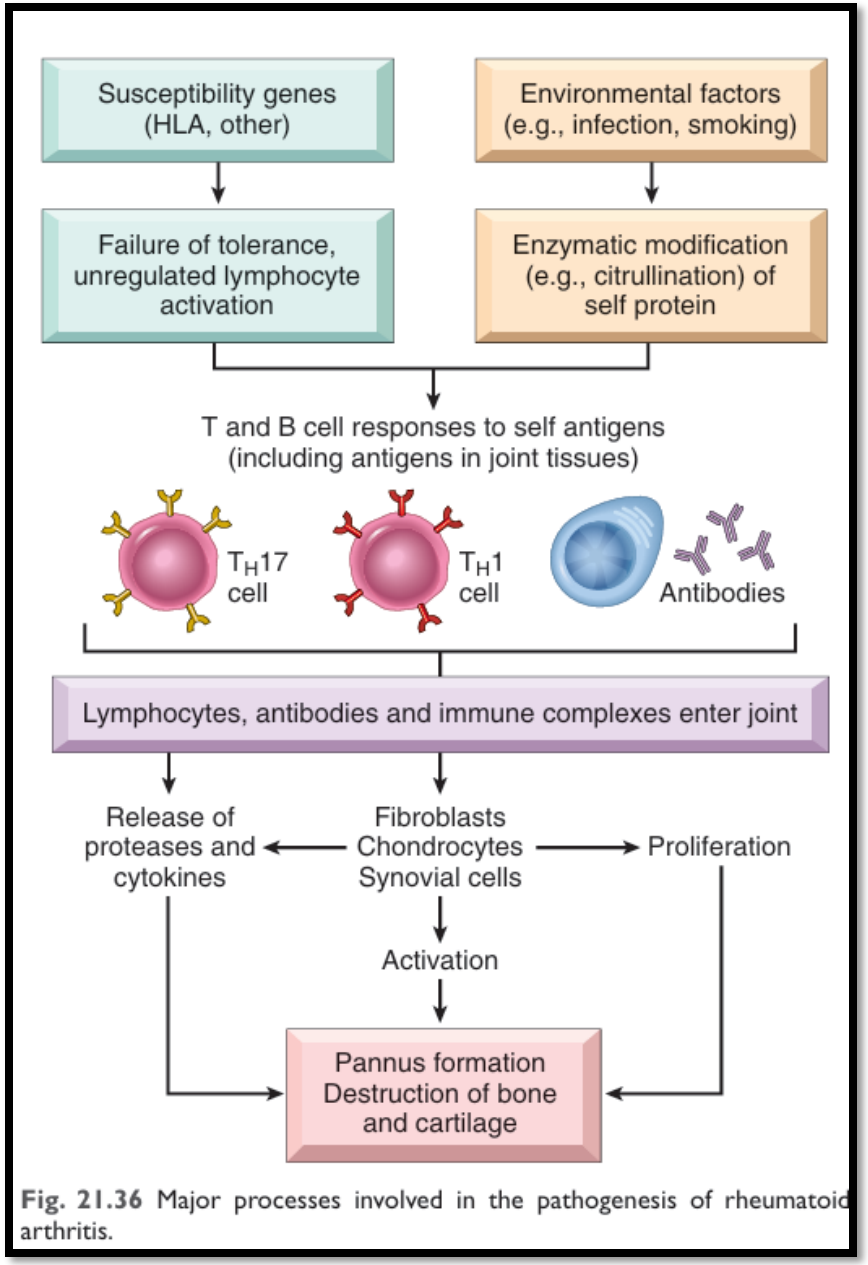


Fig. 21.36 Major processes involved in the pathogenesis of rheumatoid arthritis.

PATHOGENESIS:

IFN-γ from T_H1	Activates macrophages & synovial cells
IL-17 from T_H 17	Recruits neutrophils and monocytes
RANKL from T cells	Stimulates osteoclasts & bone Resorption (leads to bone destruction)
TNF & IL-1 from macrophages (activated by INF-γ from T_H1), TNF is believed to be the major player in this process.	Stimulates residents synoviocytes to secrete proteases that destroy hyaline cartilage

"The details of this slide are extremely important and you will be asked about it", Dr. Mousa adds.

80% of patients with RA have autoantibodies IgG & IgM against the Fc portion (the constant region of the heavy chains) of their own IgG, this is what we call [Rheumatoid factor], meaning that negative rheumatoid factor result does not exclude the disease, because epidemiologically, 20% of the patients who have RA are negative for this marker.

70% of patients with RA have Anti-Citrullinated Protein Antibodies (ACPA)

Both tests confer a good sensitivity to detect the disease.

(OA) AND (RA): MORPHOLOGICAL COMPARISON

Osteoarthritis :

- ✓ The primary target is the cartilage.
- ✓ Thinned and fibrillated cartilage.
- ✓ Subchondral sclerosis.
- ✓ Osteophytes or bone spurs.
- ✓ Subchondral cysts.
- ✓ No ankylosis (fusion).

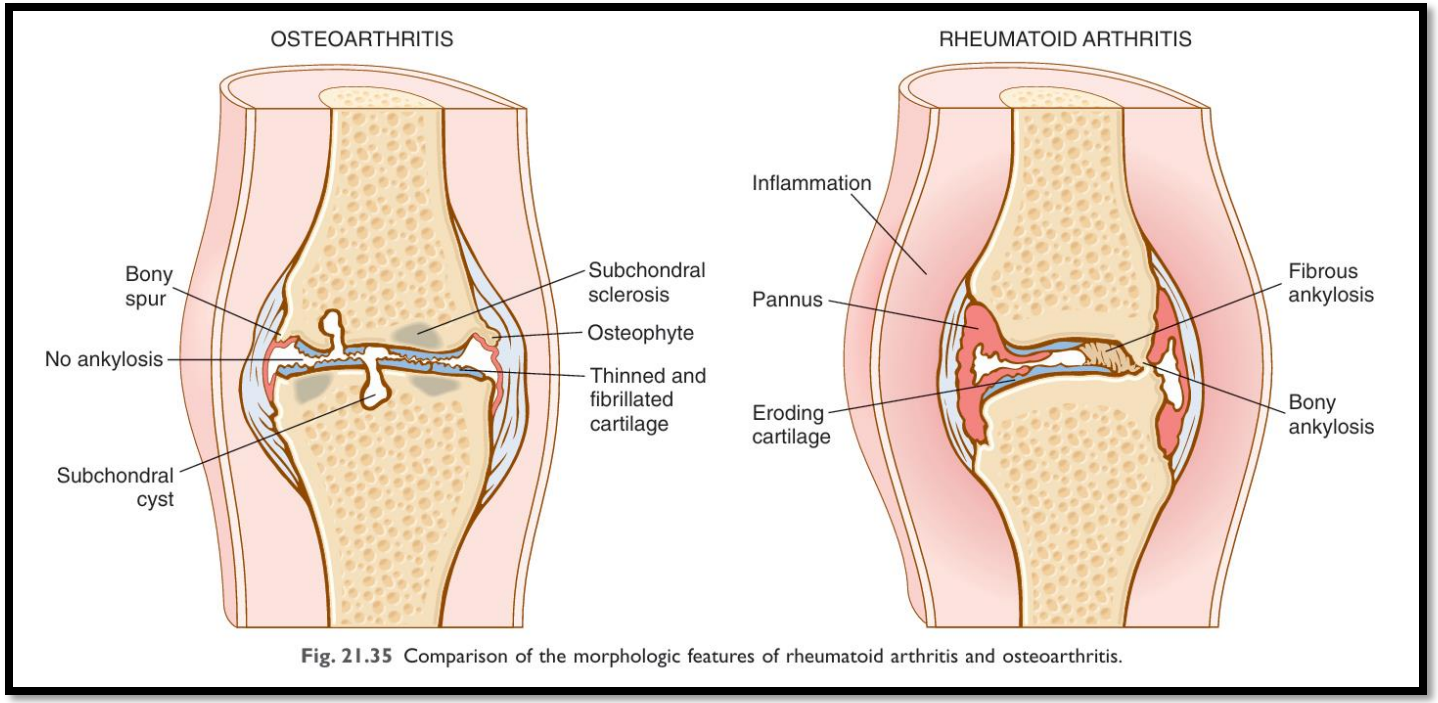


Fig. 21.35 Comparison of the morphologic features of rheumatoid arthritis and osteoarthritis.

Rheumatoid Arthritis :

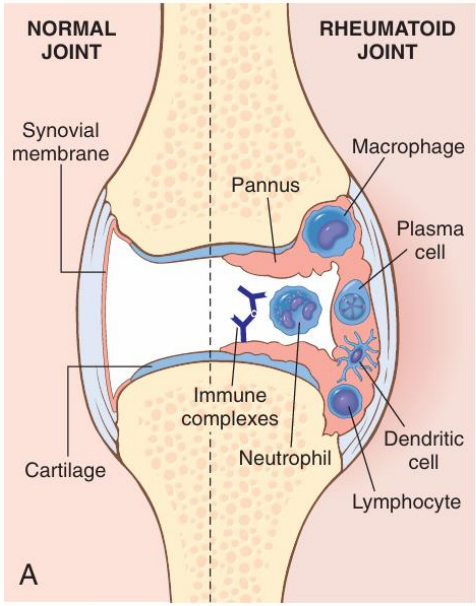
- ✓ Non-supportive synovitis, so the main target is the synovium not the cartilage, the cartilage will be destroyed secondarily.
- ✓ Pannus formation (mass of edematous synovium, inflammatory cells, granulation tissue, and fibroblasts)
- ✓ Bony and fibrous ankylosis in severe cases.

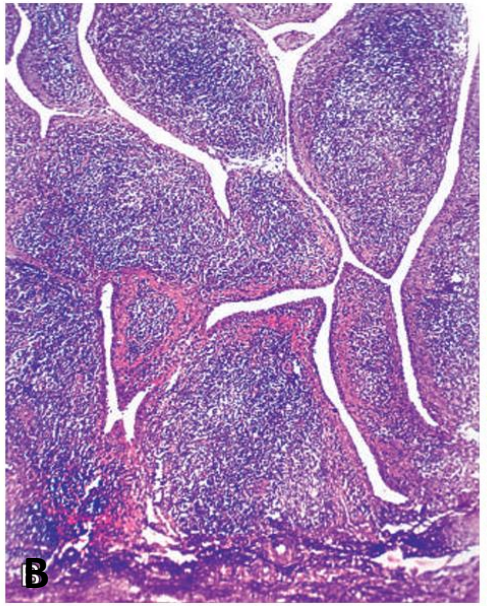
- ✓ ***Figure A***: thickened and edematous synovium with fibroblast and synovial cells proliferation, inflammatory cells infiltrates like lymphocytes, macrophages, and plasma cells with deposition of immune complexes.

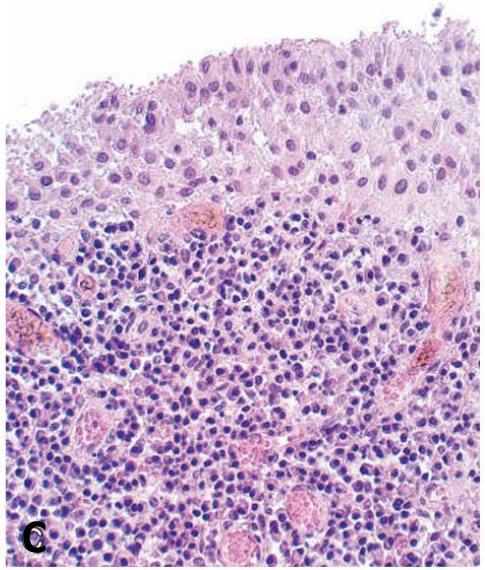
- ✓ ***Figure B***: low magnification showing thickened synovium with severe blue-cell infiltration of inflammatory cells.

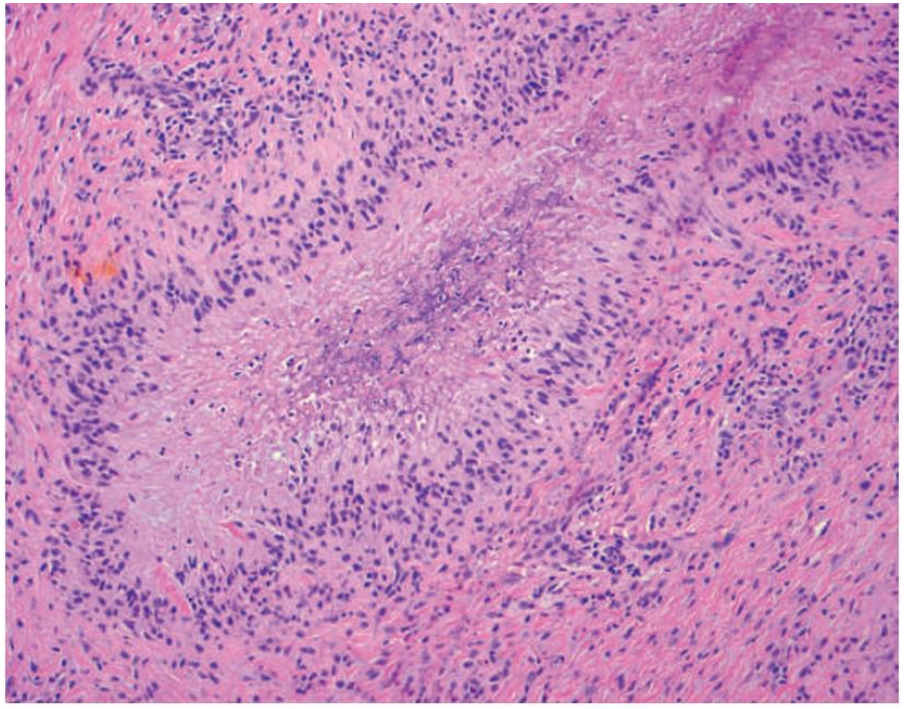
- ✓ ***Figure C***: high magnification showing again infiltration of inflammatory cells.

- ✓ ***Figure below***: chronic granulomatous inflammation. This is referred to as rheumatoid *granuloma* or *nodule* usually found in the pannus region, containing activated epithelioid histiocytes with central necrosis.









CLINICAL COURSE OF RA:

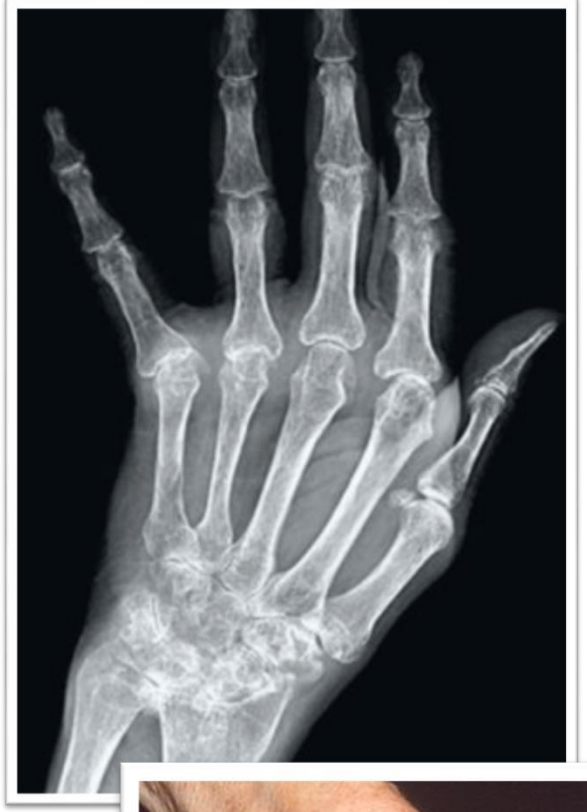
- **Begins slowly and insidiously, polyarthritis** (involvement of multiple symmetrical joints)
- **Symmetrical** (bilateral) **joints : hands, feet, wrists, ankle, MCP** (Metacarpophalangeal) **and proximal IPJ** (Interphalangeal joint) **are commonly affected.**
- **Joints: warm, swollen & painful.**

✓ However, the pain is relieved with use, unlike the exacerbation of pain with movement in osteoarthritis.

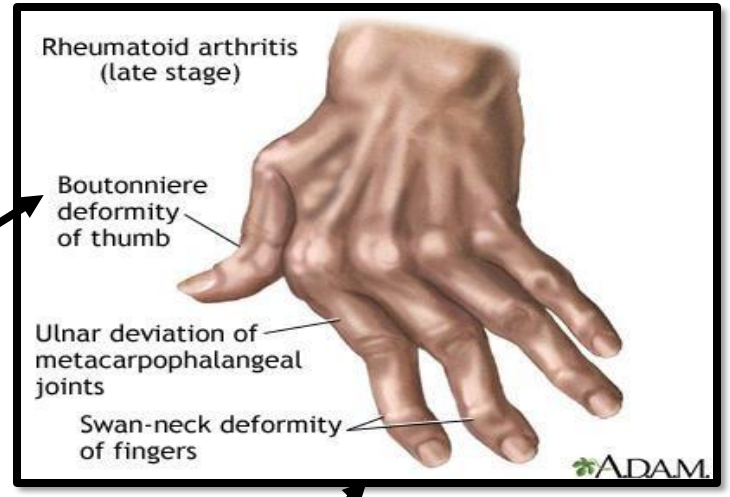
- **Stiffness when inactive and in the morning.**
- **Waxing and waning chronic**

✓ Symptoms may intensify (wax) and then subside (wane). The symptoms must persist for 6-8 weeks to diagnose the disease, with the appropriate clinical and serological features indeed.

- **Ulnar deviation** (see next slide)
- **Trx: Steroids, MTX** (Methotrexate, immunosuppressive drug), **Anti-TNF** (remember that TNF is strongly implicated in the inflammatory process)

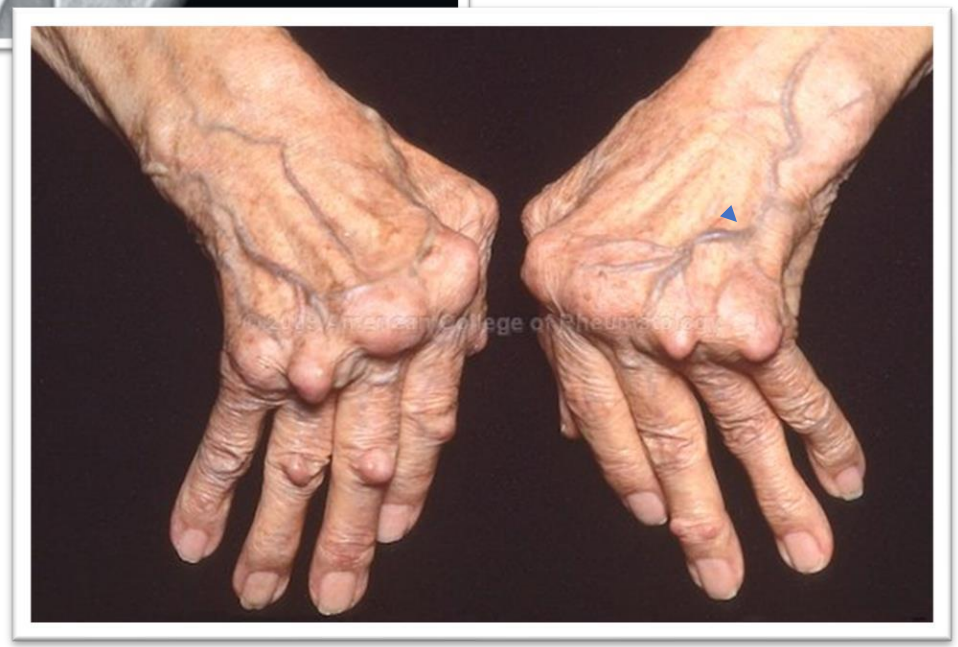


Boutonnière deformity **of the thumb is hyperextension at the interphalangeal (IP) joint of the thumb.**



Swan-neck deformity **(تشوه عنق البجعة) of fingers is a condition in which the fingers develop a distinctive zig-zag pattern like swan neck due to:**

1. Hyperextension of the proximal interphalangeal (PIP) joint.
2. Flexion of the distal interphalangeal (DIP) joint.



This is *ulnar deviation* of symmetrical MCP joints where fingers are displaced towards the ulna (medially), this is characteristic of RA. Also notice the swollen joints.

JUVENILE IDIOPATHIC ARTHRITIS (JIA):

- **Heterogeneous group** of diseases **; arthritis of unknown cause ; <16 years** (hence *juvenile*, affects children) **for at least 6 weeks** (the symptoms must be there for at least 6 weeks to confirm the diagnosis)
- **Pathogenesis is similar to adult RA**
- **Prognosis variable; only 10% will have serious functional disability,** So *JIA* is milder than adult *RA*

"In my old days in 80s and 90s, it was called: (Juvenile Rheumatoid Arthritis)", Dr. Mousa remarks.

IN CONTRAST TO ADULTS RA; JIA IS CHARACTERIZED BY:
Oligoarthritis is more common (only one or two joint affected at most)
Systemic disease is more common (still both are systemic)
Large joints are affected more than small joints (mostly affects knee ,ankle and elbow joints more than small joints of the hand and feet)
Rheumatoid nodules and Rheum Factor are usually absent (mostly JIA patients are negative for rheumatoid factor test on contrary to RA patients)
Anti Nuclear Antibody (ANA) seropositivity is common (usually negative in adult RA)

SERONEGATIVE SPONDYLOARTHROPATHIES

Feel free to skip this paragraph if you do not want to be a good clinician:
See sacroiliac joint examination in mayo clinic (not required indeed, but highly recommended from Dr. Mousa).
To examine for sacroiliac joint disease, have the patient lie on their back, then ask them to place their right leg over the left leg, with the right leg flexed and the left leg extended. While standing above the patient, apply pressure to perform hyperextension at the knee joint, pushing it downwards. If the patient experiences significant pain, especially from the hip area, it suggests some problem in sacroiliac joint.

Autoimmune T cell response to unidentified antigen (possibly infectious agent) that cross react with self musculoskeletal antigens

HETEROGENOUS GROUP OF DISEASES THAT SHARE THE FOLLOWING FEATURES:
Absence of rheumatoid factor, also negative for ANA.
Ligaments pathology rather than synovium (Ligamentitis rather than synovitis)
Sacroiliac joints mainly
Association with HLA-B27 gene
Bony ankylosis (fusion) in severe cases

- Ankylosing spondylitis: most common prototype.
- Destructive arthritis and bony damage and ankylosis of sacroiliac joint, main joint involved.
- 90% HLA-B27
- Anti IL-17 has shown some efficacy as treatment, probably because *IL-17* is one of the major players in the process.

Cross reactivity refers to the process by which an antigen (in this case foreign antigen) evokes and stimulates an immune response that is misdirected towards another antigen (in this case self-antigen), probably due to structural similarities between both antigens.

SERONEGATIVE SPONDYLOARTHROPATHIES:

One can notice how infections and cross reactivities are strongly associated with seronegative arthropathies.

- **Ankylosing Spondylitis:** (The most common one)
  - Adolescent boys, HLA B27, axial joints (sacroiliac)
- **Reiter Syndrome:** Also known as ***Reactive Arthritis***.
  - Triad of arthritis, urethritis/cervicits & conjuctivitis
  - Autoimmune but initiated by bacterial infection. ← Usually, sexually transmitted infections.
- **Enteropathic Arthritis:**
  - Secondary to bowel infections (salmonella, shigella)
  - HLA B27 positive
- **Psoriatic Arthritis:**
  - 5% of patients, starts in DIP joints, similar to RA.

5% of patients with Psoriasis will have Psoriatic Arthritis.

Distal Interphalangeal joint

“Read it on your own”, Dr. Mousa reflects.

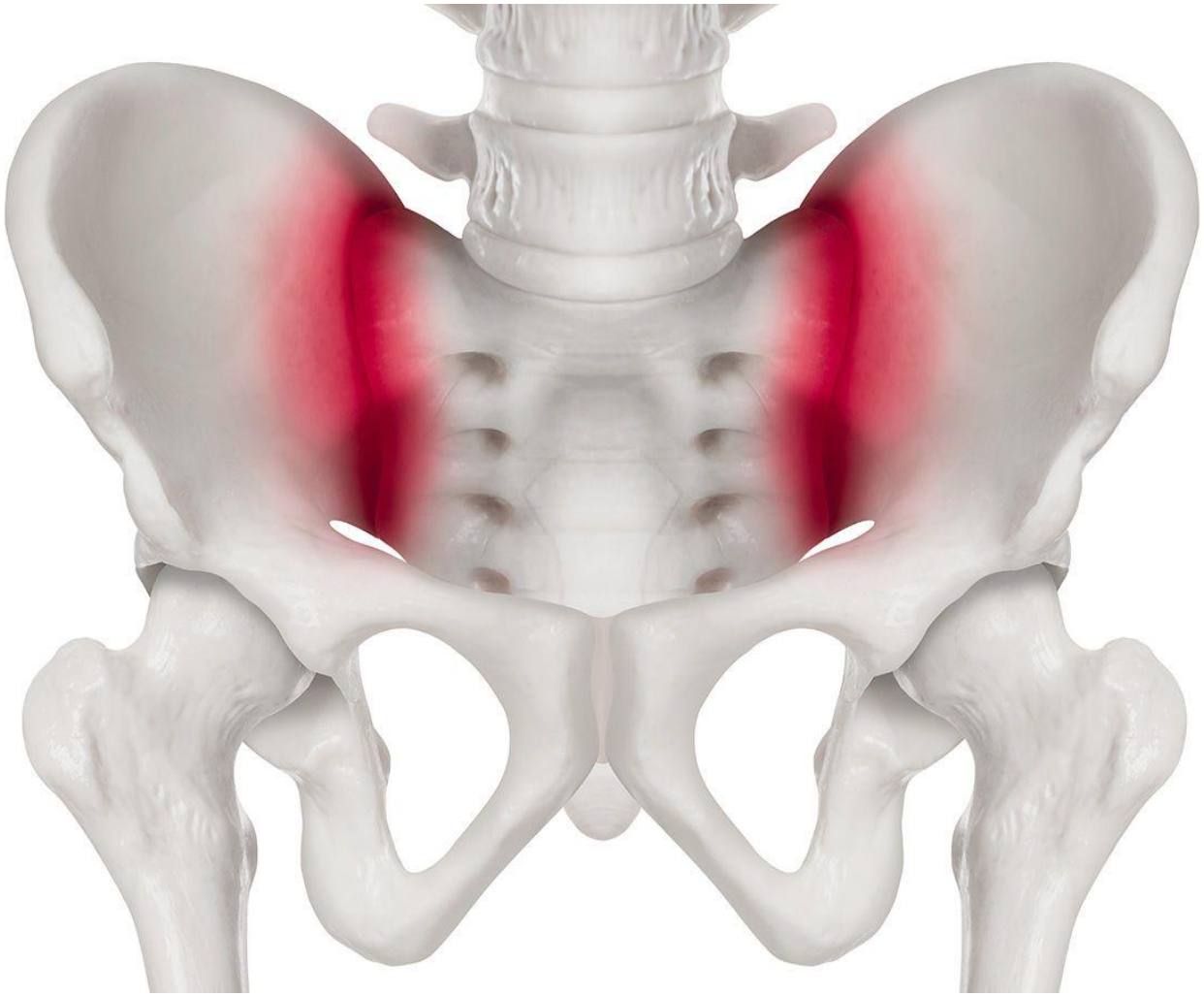
Spondyloarthropathies: Subtype Classification

Ankylosing Spondylitis	Psoriatic Arthritis	Enteropathic (IBD-associated)	Reactive Arthritis	Undifferentiated SpA
Most common subtype along with uSpa 2.5:1 male:female Gradual onset of IBP Acute anterior uveitis most common extra-articular manifestation Can lead to sacroiliac fusion and spinal syndesmophyte formation	Between 10% and 40% of patients with psoriasis develop PsA, depending on study population and psoriasis severity Most phenotypically diverse SpA with 5 subtypes Skin disease precedes joint disease in approximately 70% of cases	5% to 29% of patients with IBD develop arthritis Peripheral arthritis (not axial) can parallel bowel inflammation and can occur in up to 20% of patients Spondylitis occurs in 3% to 6%	Typical acute asymmetric oligoarticular (<4 joints) arthritis 1-3 months after gastrointestinal and genitourinary infection Characteristic triad of urethritis, conjunctivitis, and arthritis seen in < 35% of patients Keratoderma blennorrhagica and circinate balanitis	Most common subtype along with AS Typically used to describe patients not fulfilling criteria of any one SpA but presenting with IBP and other extra-articular SpA manifestations Up to 50% of uSpA will develop into AS

uSpA = undifferentiated SpA; IBP = inflammatory back pain; PsA = psoriatic arthritis; IBD = inflammatory bowel disease; AS = ankylosing spondylitis

Click on the sacroiliac joint pain to test your self on this lecture or use this link

فريق العمل يتمنى لكم عيد فطر سعيد.



For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

Recommended video from Dr. Mousa, especially the last one:

1. **OA:** https://youtu.be/BBqjltHNOrc https://youtu.be/pnKaBMvVUs0

2. **RA:** https://youtu.be/Yc-9dfem3lM https://youtu.be/ld8PhyAHov8

3. **Comparison between OA and RA:** https://youtu.be/6lx_774GuTw

Now take this joke and spread joy and fun: There were two guys who locked in a lunatic asylum, and one night, one night they decided they did not like that anymore, the decided to escape, so they made it up to the roof and there, just across this narrow gap, they see rooftops, stretching across town stretching to freedom, now the first guy he jumps right across no problem, but his friend, no way!!, he is afraid of falling, so the first guy he has an idea, he says: "hay, I got this flashlight with me, I will shine it across the gap between the building so you can walk across the beam and join me", but the second guy says: "what you think I am?? crazy!!, you just turn it off when I am halfway across!!.". **You are supposed to laugh at the end of the joke.**

في كل لحظة تمر، هناك أرواح تصعد إلى بارئها تحت الركام، وأمهات يودعن أبناءهن بقلوب يعتصرها الألم، وأطفال ينامون على صوت القصف بدلًا من الأناشيد. غزة تنزف، وأهلها يقفون بوجه الموت بصدور عارية، بينما العالم ينظر في صمت. لكن، وسط هذا الظلام، يبقى في القلب يقين بأن الحق لا يموت، وأن الظلم وإن طغى زائل لا محالة. غزة ليست وحدها، فقضيتها في أعناقنا جميعًا. إن لم نستطع إيقاف القصف، فلا نعجز عن رفع الدعاء، وإن لم نملك سلاحًا، فليكن علمنا وعملنا سلاحًا. لا نخذلكم يا أهل غزة، فأنتم في القلب والوجدان، وصمودكم مدرسة تعلمنا معنى العزة والإباء. قال الله تعالى: "وَجَاهِدُوا فِي اللَّهِ حَقَّ جِهَادِهِ" (الحج: 78). واجبنا اليوم أن نجاهد بعلمنا أولًا، فنجعل من معرفتنا نورًا يبدد الظلم. ثم نجاهد بأنفسنا وأموالنا، نصرةً لمن يقفون في وجه العدوان، ثابتين رغم الجراح.