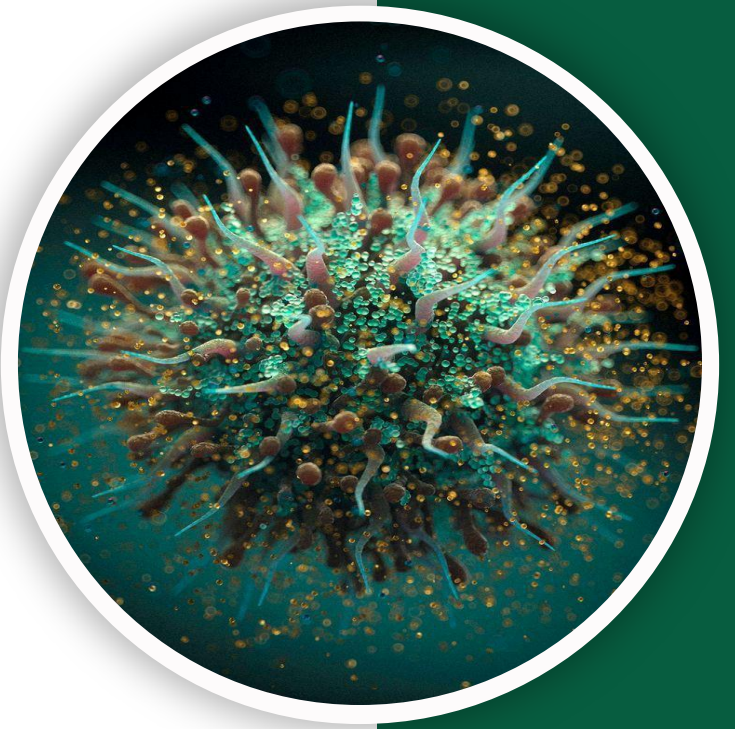
بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

MSS Pathology | FINAL 1

MSS & Skin Tumors (Pt.7)



Written by : DST

Reviewed by : Abdelrahman Moualla

Abdallah Al-Abdallat

RHEUMATOID ARTHRITIS

Meaning it is Pannus forming

- **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:

- ✓ **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).**

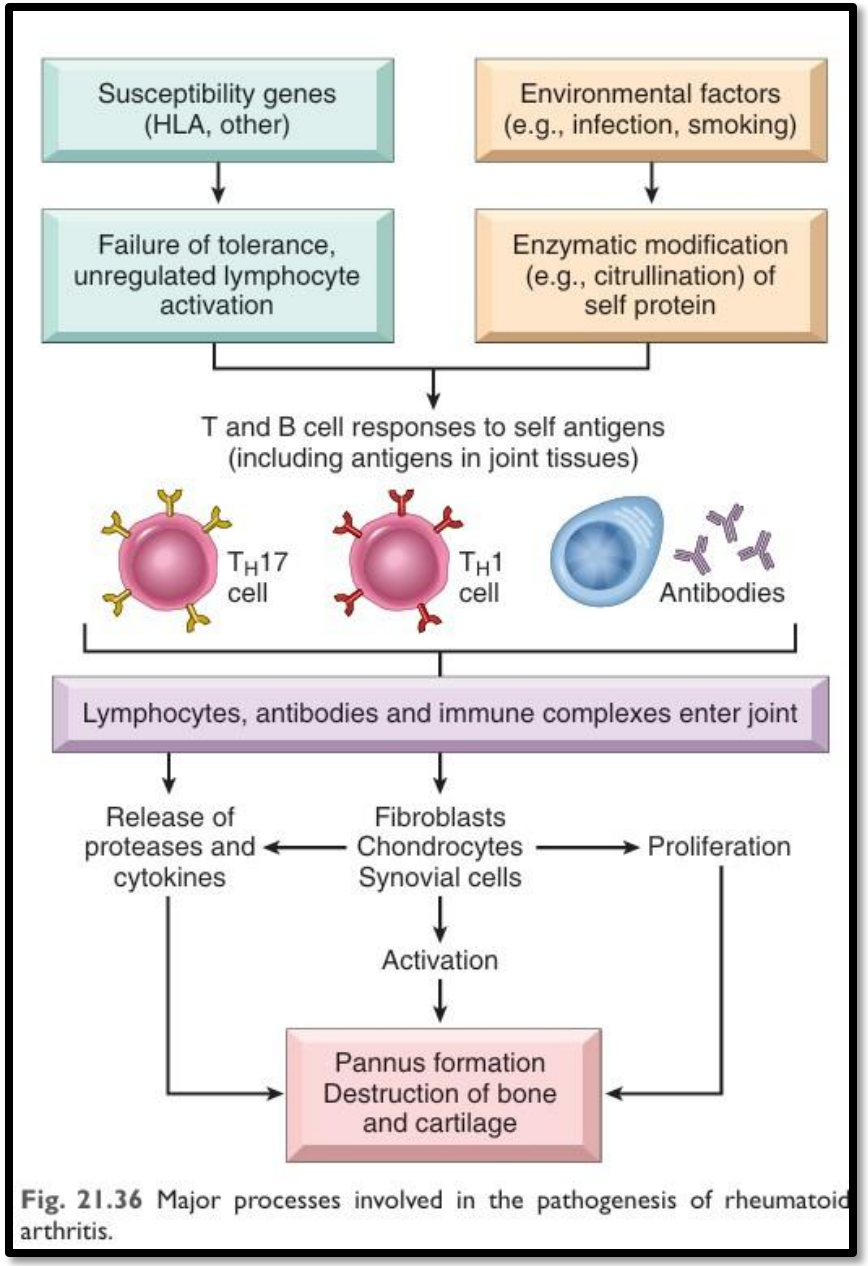


Fig. 21.36 Major processes involved in the pathogenesis of rheumatoid arthritis.

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.

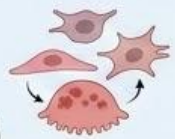
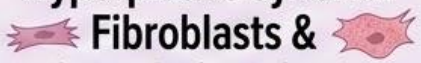
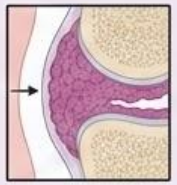
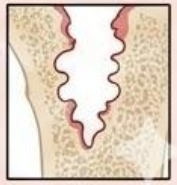
80% of patients with RA have autoantibodies IgG & IgM against the Fc portion (the constant region of the heavy chains) of their own IgG, this is what we call [Rheumatoid factors]("ABs against your own ABs") , meaning that negative rheumatoid factor result does not exclude the disease, because epidemiologically,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

Clarification of the pathogenesis from AI 😉

THE CHAIN OF DESTRUCTION IN RHEUMATOID ARTHRITIS (RA)

THE ACTOR	SPECIFIC COMPONENTS	WHAT THEY DO (THE MECHANISM)	THE DIRECT TARGET
1. THE INITIATORS *(Autoimmune Cells)*	CD4+ T-Cells & Macrophages 	• Infiltrate the joint space and secrete pro-inflammatory cytokines (like TNF-α, IL-1, and IL-6)	**Synovial Cells & Osteoclasts** (Tells them to activate and multiply) 
2. THE STAGING GROUND *(The Pannus)*	Hyperplastic Synovial Fibroblasts & Granulation Tissue 	• Proliferates massively into a thick, invasive mass that physically creeps over the joint surface, choking it off from nutrients.	**The Joint Space** (Acts as the vehicle carrying the destroyers) 
3. THE CARTILAGE DESTROYERS *(Enzymes)*	 Matrix Metalloproteinases (MMPs) & Proteases	• Secreted directly by the pannus. • They chemically dissolve the Type II collagen and proteoglycans.	**Articular Cartilage** (Causes joint space narrowing) 
4. THE BONE DESTROYERS *(Bone Cells)*	Osteoclasts 	• Activated by **RANKL** (produced by T-cells and synovial fibroblasts). • They physically drill into and resorb the subchondral bone.	**Subchondral Bone** (Causes marginal "rat-bite" erosions) 

(OA) AND (RA): MORPHOLOGICAL COMPARISON

Osteoarthritis :

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

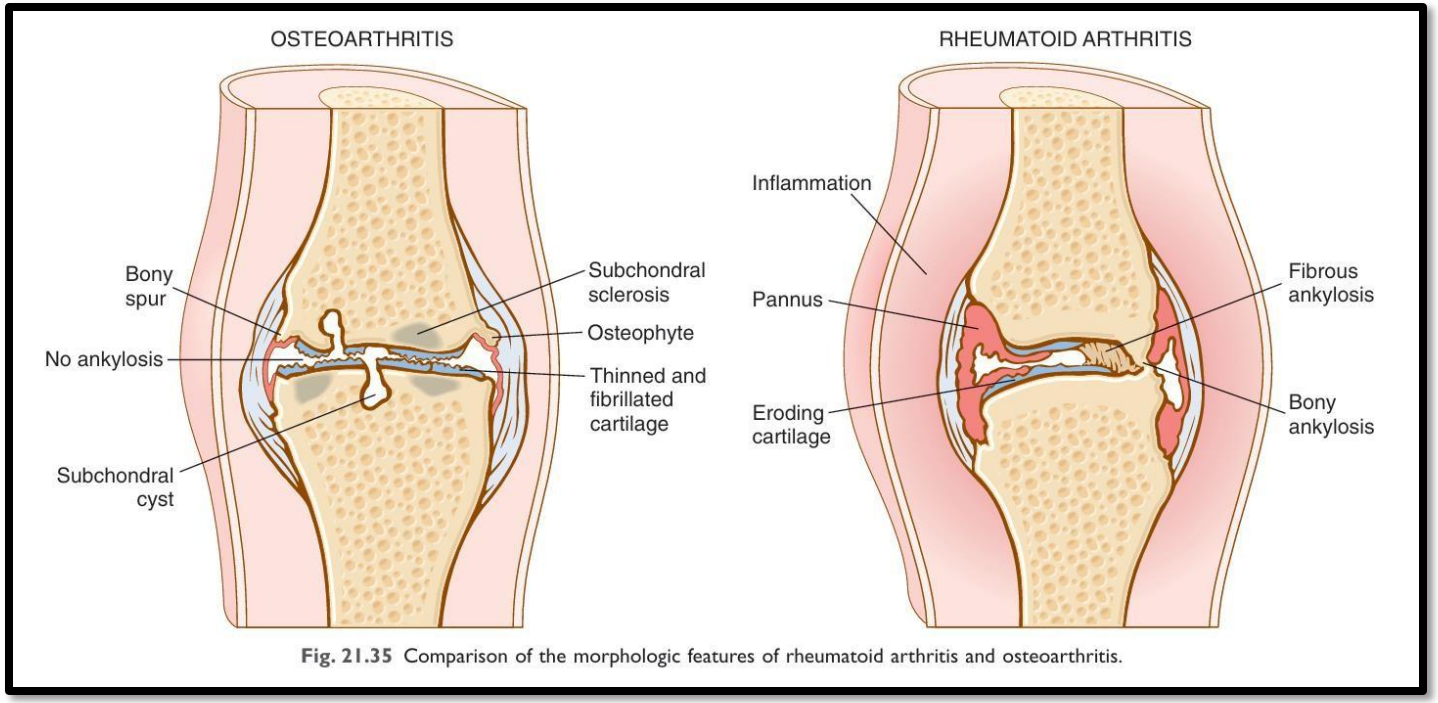


Fig. 21.35 Comparison of the morphologic features of rheumatoid arthritis and osteoarthritis.

Rheumatoid Arthritis :

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

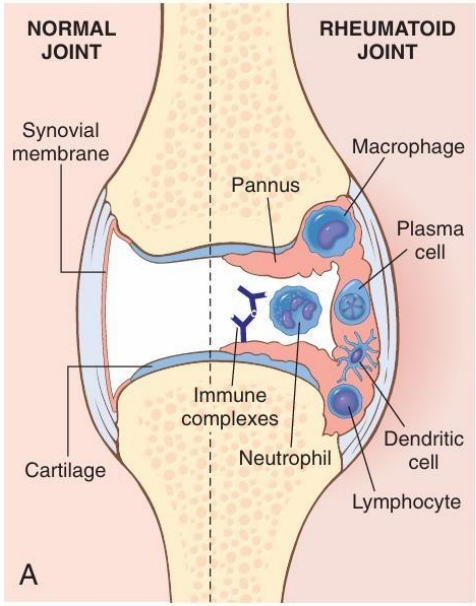
Rheumatoid Arthritis is much less common than Osteoarthritis.

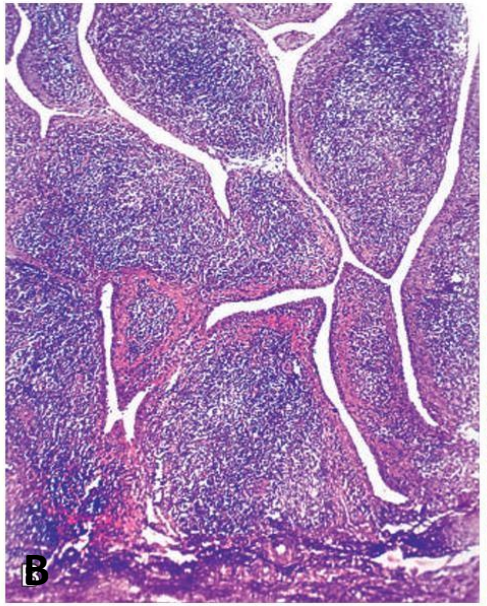
- ✓ ***Figure A***: thickened and edematous synovium with fibroblast and synovial cells proliferation, inflammatory cells infiltrates like lymphocytes, macrophages, and plasma cells with deposition of immune complexes.

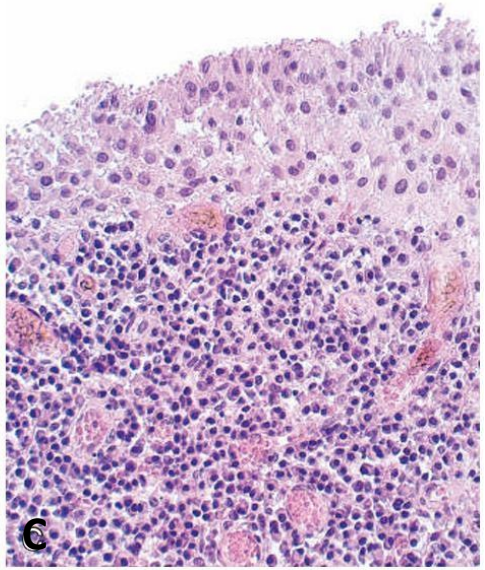
- ✓ ***Figure B***: low magnification showing thickened synovium with severe blue-cell infiltration of inflammatory cells.

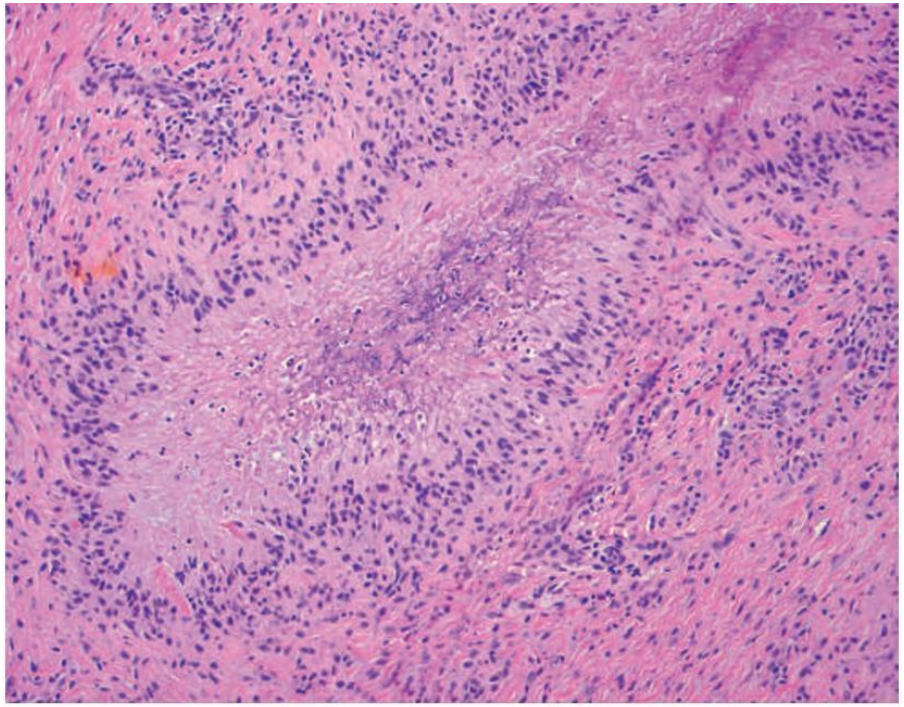
- ✓ ***Figure C***: high magnification showing again infiltration of inflammatory cells.

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









CLINICAL COURSE OF RA:

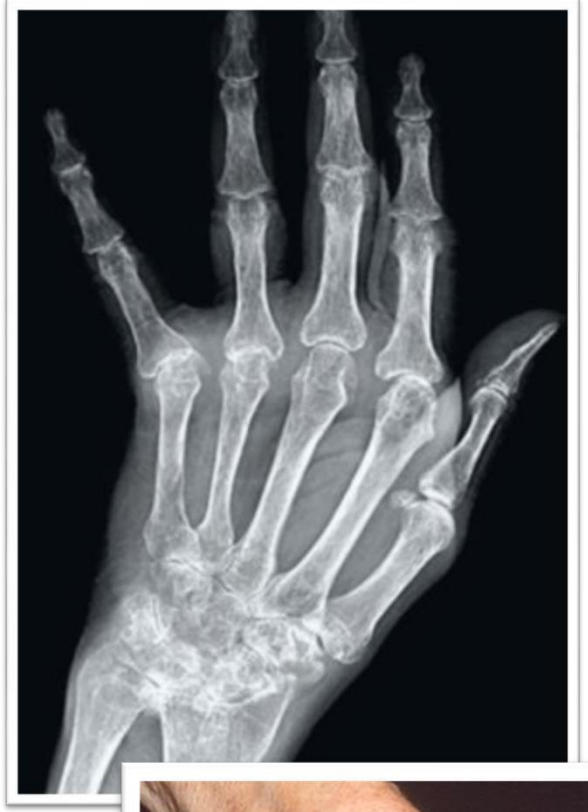
- **Begins slowly and insidiously, polyarthritis** (involvement of multiple symmetrical joints)
- **Symmetrical** (bilateral) **joints : hands, feet, wrists, ankle, MCP** (Metacarpophalangeal) **and proximal IPJ** (Interphalangeal joint) **are commonly affected.**
- **Joints: warm, swollen & painful.**

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

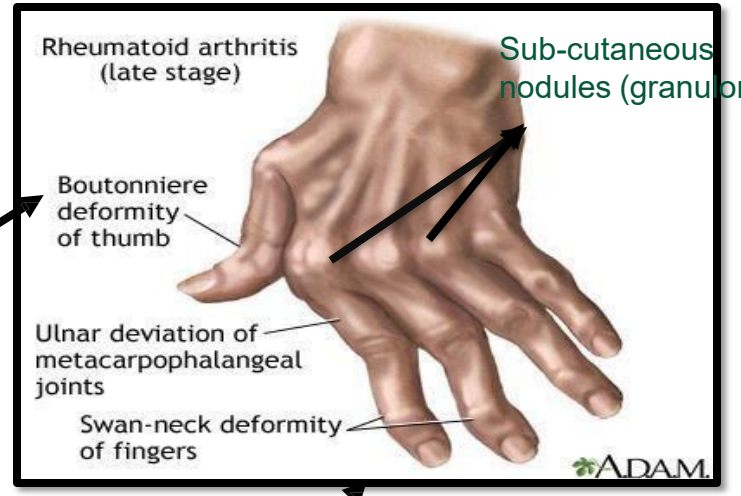
- **Stiffness when inactive and in the morning.**
- **Waxing and waning chronic** (بروح وبيجي)

✓ 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)



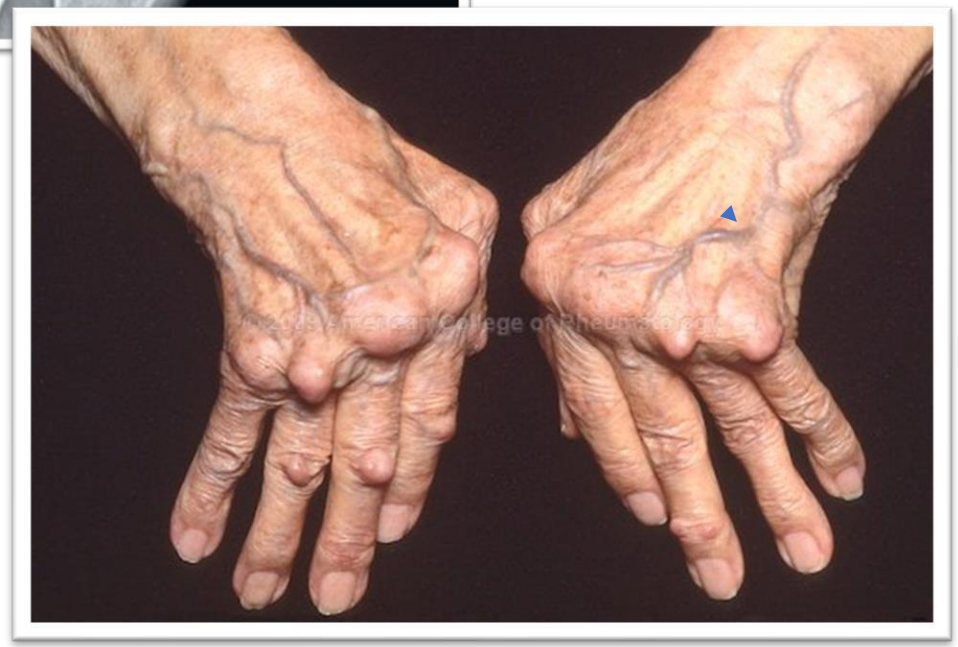
Boutonnière deformity **of the thumb is hyperextension at the interphalangeal (IP) joint of the thumb.**



رقبة البجعة

Swan-neck deformity **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):

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

- **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 CONTRAST TO ADULTS RA; JIA IS CHARACTERIZED BY:
Oligoarthritis is more common (in JIA only one or two joint affected at most)(= multiple JIA occurring is less probable than multiple RA occurring)
Systemic disease is more common (thus diagnosis is easier)(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

(Arthritic diseases that lack rheumatoid factor in serum)

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

[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.]

HETEROGENOUS GROUP OF DISEASES THAT SHARE THE FOLLOWING FEATURES:
Absence of rheumatoid factor
Ligaments pathology rather than synovium (Ligamentitis rather than synovitis)
Sacroiliac joints mainly (Sacroiliitis is a common feature of Seronegative spondyloarthropathies
Association with HLA-B27 Gene
Bony ankylosis (fusion) in severe cases

SERONEGATIVE SPONDYLOARTHROPATHIES

(Arthritic diseases that lack rheumatoid factor in serum)

Feel free to skip this paragraph if you do not want to be a good clinician: (not required indeed, but highly recommended from Dr. Mousa).

See sacroiliac joint examination

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.

SERONEGATIVE SPONDYLOARTHROPATHIES

❖Ankylosing Spondylitis:

- **Ankylosing spondylitis is the most common prototype of Seronegative spondyloarthropathies.**
- **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 .**

SERONEGATIVE SPONDYLOARTHROPATHIES:

These are the most common diseases of heterogroups of 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. (Distal Interphalangeal joint)

(5% of patients with Psoriasis will have Psoriatic Arthritis.)

“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

SUPPURATIVE ARTHRITIS (Septic Arthritis)

- It is a Bacterial infection characterized by pus formation and inflammation within the joint space. It often occurs in conjunction with acute osteomyelitis. For example, if osteomyelitis affects the distal femur, the adjacent knee joint is commonly involved due to the proximity and shared blood supply. However, septic arthritis can also occur independently without any bone involvement.

- Most common route of infection is Hematogenous spread

- Can be causes in infants < 2 years by H. influenza, and in older children + adults by S. aureus, and in young adults by gonococcus.
- Sickle cell disease patients are more prone to salmonella

SUPPURATIVE ARTHRITIS (Septic Arthritis)

- **Clinically: The condition presents sudden acute pain, swollen and warm joints, mainly knee, with systemic manifestation (fever, leukocytosis, elevated ESR(Erythrocyte Segmentation Rate))**

- **Dx s Rx: aspiration of joint; antibiotics (Prompt diagnosis is essential, as delayed treatment can lead to joint destruction.**

LYME ARTHRITIS

- Lyme disease is caused by spirochetes, specifically bacterium **Borrelia burgdorferi**, which has an interesting story behind its name (Click HERE).
- This disease is a bacterial-induced arthritis that is rare in our country but is more commonly observed in the Northeastern United States. The higher prevalence in that region is due to the presence of ticks, which act as vectors transmitting the organism through their bites.

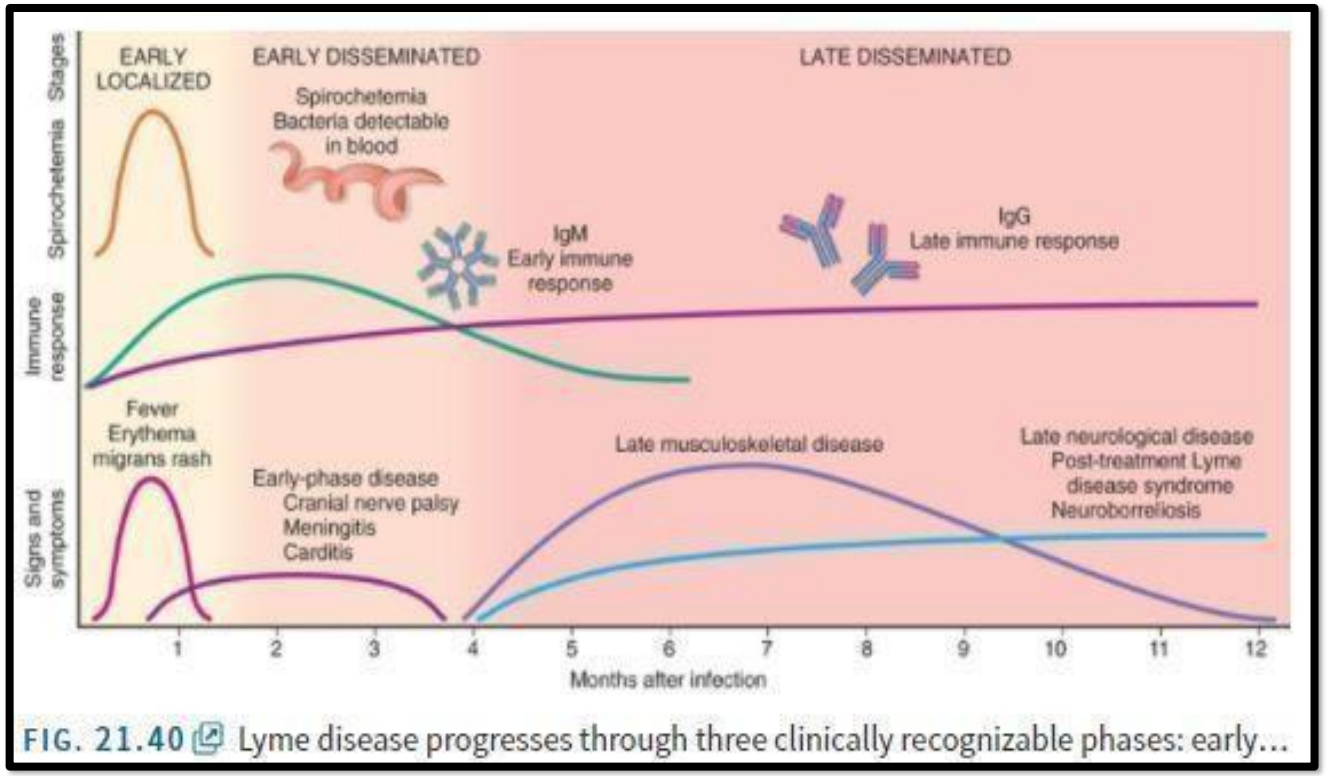


FIG. 21.40 Lyme disease progresses through three clinically recognizable phases: early...

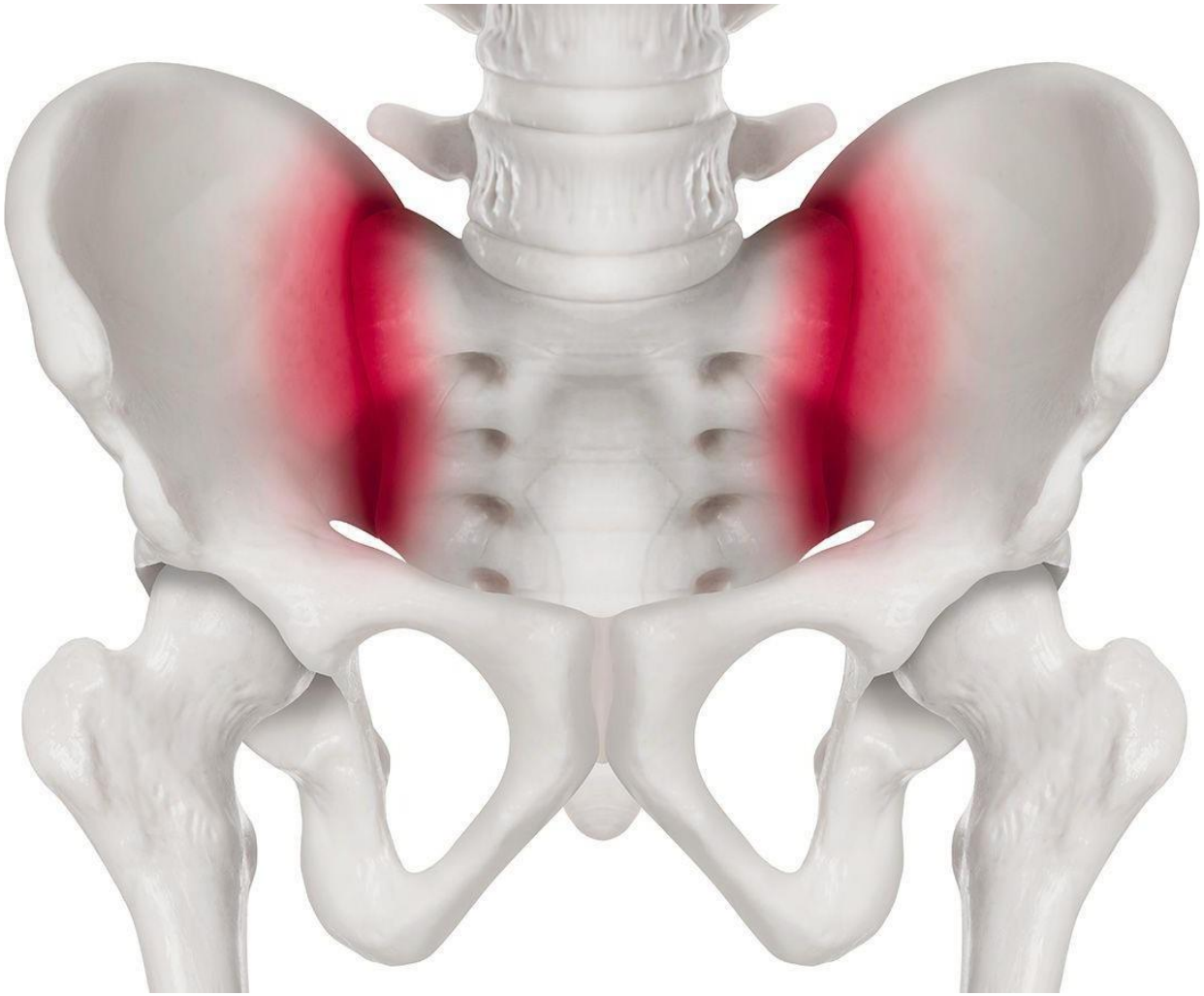
These are the stages of Lyme Arthritis, The prof. didn't much focus on them, yet he said they are important in external exams (USMLE and else...)

CRYSTAL-INDUCED ARTHRITIS

- **Crystals deposited (precipitated) in joints trigger inflammatory reaction that destroys cartilage, causing disease.** (It can present as an acute condition, chronic condition, or begin acutely and then progress into a chronic phase over time)

- **Endogenous Crystals (produced inside your body) cause 2 diseases:**
  1. **GOUT, Caused by Monosodium urate, MSU**
  2. **PSEUDOGOUT, Caused by Calcium pyrophosphate dihydrate (CPPD)**

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



رسالة من الفريق العلمي:

﴿ إِنَّآ أَنزَلۡنَٰهُ فِي لَيۡلَةِ ٱلۡقَدۡرِ ۝ وَمَآ أَدۡرَىٰكَ مَا لَيۡلَةُ ٱلۡقَدۡرِ ۝ لَيۡلَةُ ٱلۡقَدۡرِ خَيۡرٞ مِّنۡ أَلۡفِ شَهۡرٖ ۝ تَنَزَّلُ ٱلۡمَلَٰٓئِكَةُ وَٱلرُّوحُ فِيهَا بِإِذۡنِ رَبِّهِم مِّن كُلِّ أَمۡرٖ ۝ سَلَٰمٌ هِيَ حَتَّىٰ مَطۡلَعِ ٱلۡفَجۡرِ ﴾

عن أبى هريرة رضى الله عنه أن النبى ﷺ قال: "من قام ليلة القدر إيمانا واحتسابا غفر له ما تقدم من ذنبه" و وفى رواية "غفر له ما تقدم من ذنبه وما تأخر".

وقالت عائشة رضى الله عنها: يا رسول الله إذا وافقت ليلة القدر فما أدعو ؟ فقال: "قولى: اللهم إنك عفو تحب العفو فاعف عنى"

أفكار ذهبية خلال العشر الأواخر من رمضان

هذا ملف يحتوى على أفكار لأعمال بسيطة، لكنها عظيمة الأجر ، وإن صادف قيامك ليلة القدر فذلك فوز عظيم لك ، فاجتهد فى الخير والصدق كل يوم.

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			