Non-Infectious Arthritis

Lecture: 4th for females, 5th for males.
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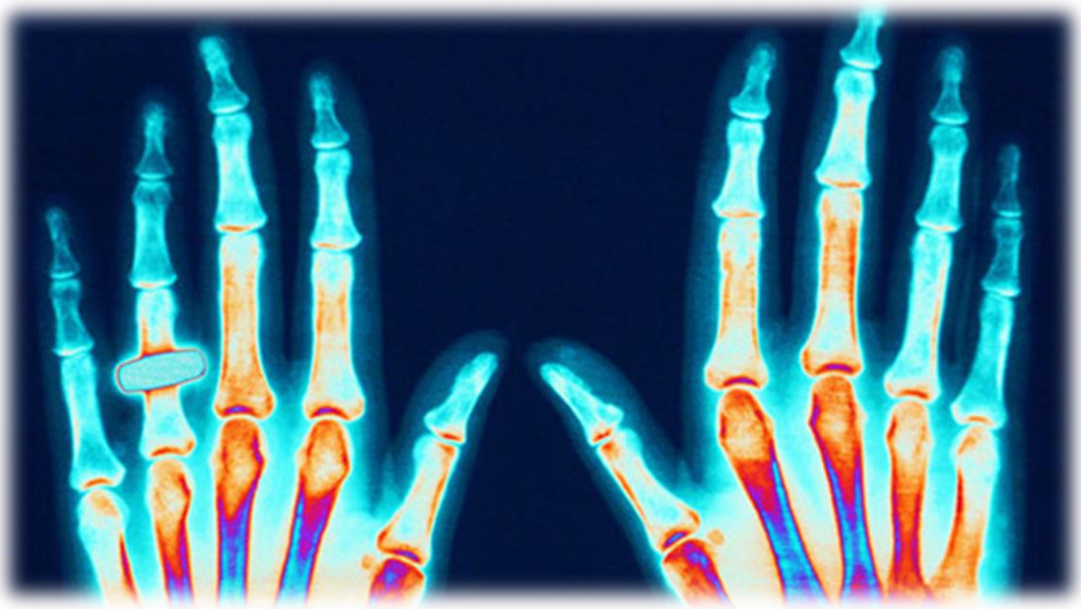


PATHOLOGY
TEAM 433

Introduction

Joints:
Joints are subject to a wide variety of disorders, including degeneration (e.g. osteoarthritis), immune-mediated injury (e.g. rheumatoid arthritis), and metabolism derangements (e.g. gout).

1st: Osteoarthritis. (Degenerative Joint Disease)

- It is the most common joint disorder and it is an important cause of physical disability in persons older than 65 years of age.
- Characterized by "***progressive erosion of articular cartilage in weight bearing joints***".
- Pain usually comes after doing any exercise "***The more he moves, the more he gets pain***".
- Women are more common than men in Osteoarthritis.

- ***Two main features:***
  Degeneration of articular cartilage. (Most important)
  Structural changes in the underlying bone. (Not always)

Types	Morphology	Clinical Course
1) Primary: - Appears insidiously (بشكل مفاجئ) with aging (50-60). - Usually is *Oligoarticualr* (affecting a few joints) such as Hands, Knees, Hips and Spines. - No predicted way to prevent the progression of primary osteoarthritis. **2) Secondary:** - Less than 5%. - caused by trauma, developmental deformity or underlying systemic disease such as Ochronosis, Hemochromatosis or **Marked Obesity.** - Could affect youngsters.	1- Alterations in the composition and structure of the matrix. 2- Vertical and horizontal fibrillation[1] and cracking of the matrix. 3- Chondromalacia; A soft granular-appearing articular cartilage surface. 4- Bone Eburnation. 5- Joint mice; small fractures can dislodge pieces of cartilage and subchondral bone into the joint, forming loose bodies. 6-Subchondral cyst; the fracture gaps allow synovial fluid to be forced into the subchondral regions to form fibrous walled cysts. 7- **Osteophytes;** mushroom-shaped (bony outgrowths) develop at the margins of the articular surface. 8- In severe disease, a fibrous synovial **pannus** covers the peripheral portions of the articular surface.	- Slow progression. - Most of the time, peaks at ages 50's – 60's. **Signs and Symptoms:** 1- Pain, rise by use. 2- Morning stiffness. 3- Joints crepitus (فرقعة). 4- Limitation in range of movement. 5- Hips, knees, lower lumbar and cervical vertebrae, proximal and distal interphalangeal joints of the fingers, first carpometacarpal joints, and first tarsometatarsal joints of the feet are commonly involved. **NOTES:** - **Osteophyte** impingement on **spinal foramina** can cause nerve root compression with radicular pain, muscle spasms, muscle atrophy, and neurologic deficits/

Osteophytes formation in **Distal** interphalangeal joint known as Hebderden's Nodes.
Osteophytes formation in **Proximal** interphalangeal joint known as Bouchard's Nodes
1- Fibrillation: the initial degenerative changes in osteoarthritis, marked by erosion and fragmentation of the cartilage.
Heberden nodes are more common in women than men.
Advanced cases of osteoarthritis, elderly sufferers may become confined to wheelchairs.
Eburnation = إعوجاج Joint Mice = بمعنى أنها تتحرك في السائل كالفأرة

Osteoarthritis Pathogenesis:

Articular cartilage endures the most of the degenerative changes in osteoarthritis.

- Proteoglycan and Type II collagen (which are secreted by Chondrocyte) maintain the functions of articular cartilage.

- Chondrocyte's normal function is critical to maintain cartilage synthesis and degradation; any ***imbalance*** *can lead to osteoarthritis.*

- The very first change seen in osteoarthritis is proliferation of osteoblast.

Pathogenesis:

1. *Fibrillation*
2. *Portions of the cartilage flake off.*
3. *Full-thickness loss of the cartilage Exposure of the underlying bone.*
4. *Development of polished ivory appearance (Eburnation).*
5. *Loss of the articular cartilage stimulates thickening of the subchondral plate and the adjacent cancellous[1] bone.*
6. *Impairing the movement ability of the joint.*
7. *Increased damage to the residual cartilage.*
8. *Penetration of the synovial fluid to the subchondral area.*
9. *Formation of subchondral pesudocytes.*
10. *Fragments of cartilage and bone fall into the joint space forming loose bodies (Joint mice).*
11. *Bone Outgrowth (Osteophytes).*

NOTES:

- Genetic factors, *including polymorphisms and mutations in genes encoding components of the matrix and signaling molecules, contribute to osteoarthritis.*

- Increasing in ***bone density*** *» Increases the risk of osteoarthritis.*

- Decreasing in ***estrogen level*** *» Increases the risk of osteoarthritis.*

1- Cancellous bone also know as tubercle bone or spongy bone.

2nd: Rheumatoid Arthritis. (RA)

- Autoimmune mediated disease which cause noninfectious arthritis.
- It affects the joints and many other systems "***Systemic disease***"
- Most cases of Rheumatoid Arthritis occur in people between the ages 20 - 50.
- Not as common as Osteoarthritis.
- The pathology of Rheumatoid Arthritis is in the articular cartilage, in the synovial membrane (synovium).
- Autoimmunity will create a very severe inflammatory reaction in the synovium, and the synovium becomes inflamed and infiltrated by lymphocyte and plasma cells. This inflammation will cause the symptoms.

Diagnosis and Symptoms:

- Patients usually complain of pain in the joints early in the morning when they wake up "***Pain occurs from rest***". Usually the presentation is with pain which occur at rest, unlike osteoarthritis which occurs following movement.
- Swelling in the joints.
- May be associated with systemic symptoms like, **Myalgia** (muscle pain) increasing weakness, and mild fever.

So, when a patient comes with pain that occurs at rest associated with myalgia, reduction in the movement and ankylosis, and there is a swelling in the joints, then he/she might have Rheumatoid Arthritis.

For diagnosis serological tests are made. Some of serological tests are not specific, for example:

1- ESR (any inflammation can cause increased ESR) so ESR is sensitive.

2- C-reactive protein can be increased.

3- **Rheumatoid factor is usually positive** in patients with Rheumatoid Arthritis, but some people have rheumatoid factor though they do not have Rheumatoid Arthritis so it is sensitive.

Pathogenesis[1]

Autoimmune reaction leading to the formation of immune complexes, which will accumulate inside the joints creating inflammatory reaction. The inflammatory reaction will attract neutrophils that will release lysosomal enzymes "*Lysosomal enzymes can cause damage to the joints*".
There is a lot of inflammation in the synovium, swelling, edema and vascular granulation tissue formation inside the joint.
- Vascular granulation tissue is formed of fibrin, inflammatory cells, blood vessels and chronic inflammatory cells. The vascular granulation tissue formation in Rheumatoid Arthritis is called pannus formation.
- With time the inflammation starts to subside a little bit and the pannus is replaced by fibrosis, then the fibrosis forms adhesions in the joint. "*These adhesion are called ankylosis*".
- Ankylosis are adhesions inside the joints that are affected by Rheumatoid Arthritis when there is fibrosis in the pannus.
- As a result of ankylosis, the patient will find it very difficult to move his joints, and usually painful.

NOTES:
- Antibodies to **CCP**, type II collagen, α-enolase, and vimentin *are the most important* and may form immune complexes that deposit in the joints. These antibodies are a diagnostic marker for the disease and may be involved in tissue injury.
- Genetic factors: It is estimated that 50% of the risk of developing RA is related to genetic factors. Susceptibility to rheumatoid arthritis is linked to the **HLA-DRB1 locus.**
- Environmental factors: Many candidate infectious agents whose antigens may activate T or B cells. In at least 70% of patients the blood contains anti-CCP antibody, which may be produced during inflammation.

Morphology

1. synovial cell hyperplasia and proliferation
2. dense perivascular inflammatory cell infiltrates (frequently forming lymphoid follicles) in the synovium composed of CD4+ T cells, plasma cells, and macrophages
3. increased vascularity due to angiogenesis
4. neutrophils and aggregates of organizing fibrin on the synovial surface (edema)
5. increased osteoclast activity in the underlying bone ➔ bone erosion.
6. **Pannus**
   formed by proliferating synovial-lining cells admixed with inflammatory cells, granulation tissue, and fibrous connective tissue
   Eventually the pannus fills the joint space, and subsequent **fibrosis and calcification** may cause permanent **ankylosis.**
7. Small detached fragments fall into the joint space and are called **Rice Bodies**

NOTES:
- Destruction of tendons, ligaments, and joint capsules produces the characteristic deformities:
A) Radial deviation of the wrist.
B) Ulnar deviation of the fingers.
C) Flexion-hyperextension abnormalities of the distal interphalangeal joint (swan-neck deformity).
D) Felxion abnormalities of proximal interphalangeal joint (boutonniere deformity)
- **Rheumatoid subcutaneous nodules** develop in about one fourth of patients, occurring along the extensor surface of the forearm or other areas subjected to mechanical pressure; rarely, they can form in the lungs, spleen, heart, aorta, and other viscera. Rheumatoid nodules are firm, nontender, oval or rounded masses as large as 2 cm in diameter.

Clinical Features

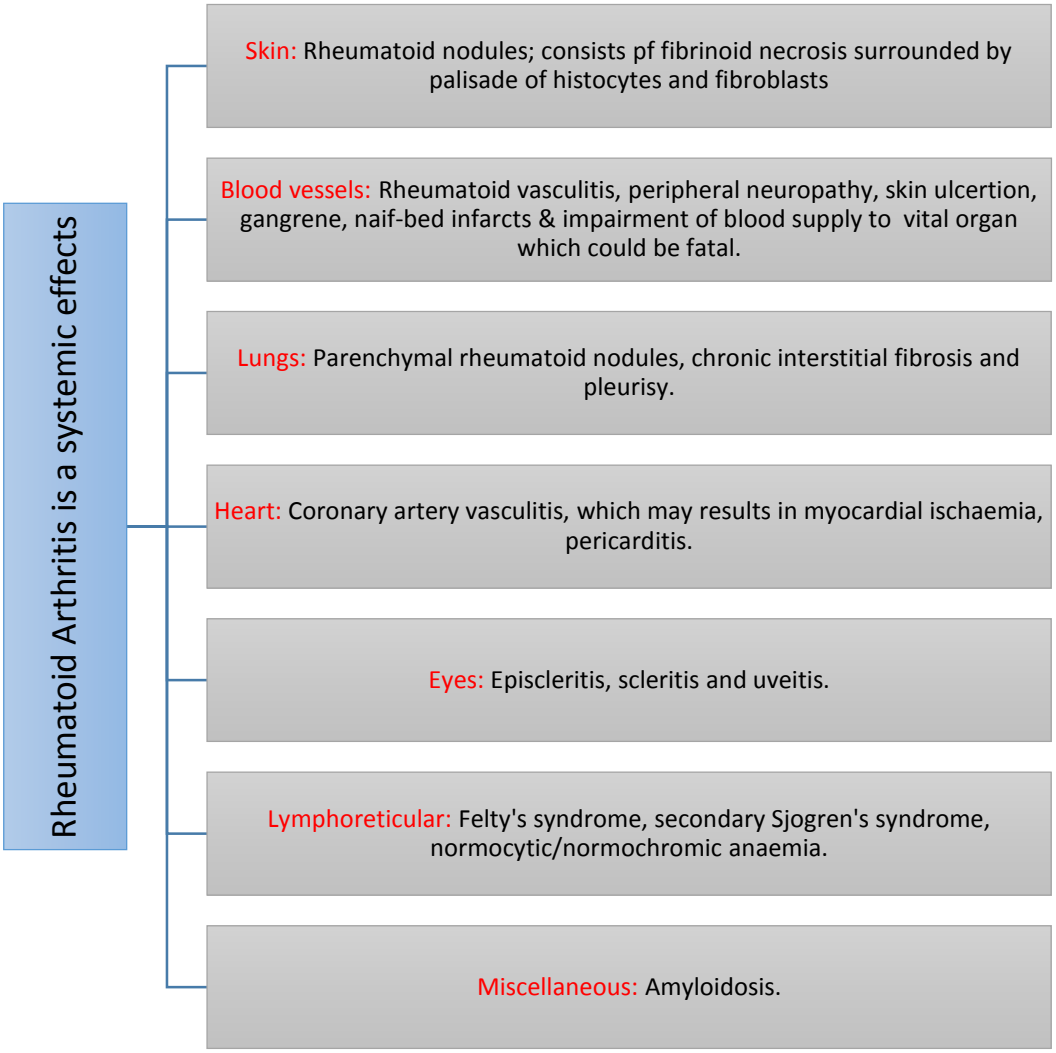
Symptoms:
1- Weakness.
2- Malaise.
3- Low-grade fever.
4- Pain, stiffness of the joints, especially in the morning.
5- Myalgia
In advanced situations:
1- The joints become enlarged.
2- Motion is limited.
3- Chronic leg ulcer.

- The small joints are affected before the large joints.

Rheumatoid factor is an IgM that acts against the IgG of the same person, it is an IgM against the Fc fragment (portion) of the IgG (Fc fragment is a part of the immunoglobulin molecule). In recent studies it is found that 30-40% of normal population have rheumatoid factor.
The test, which is very specific, is CCP (cyclic citrullinated proteins), CCP are metabolites of arginine. Anti-CCP antibodies are increased in ***Rheumatoid Arthritis***. It is positive in more than 70% of case of ***Rheumatoid Arthritis***.

Extra Information:
1. The pathogenesis is not well understood yet.
- CCPs: derived from proteins in which arginine residues are converted to citrulline residues posttranslationally.
- An x-ray of a patient with severe Rheumatoid Arthritis:
1- Loss of articular cartilage leading to narrowing of the joint space.
2- Joint effusion.
3- Localized osteoporosis.
4- Erosion.
- Swollen knee joint, aspirating it and sometimes injecting it with drugs like steroid relieve symptoms.

Rheumatoid Arthritis is a **systemic effects**, which **may cause** the following:



3rd: Gouty Arthritis (GA):

- Gout affects about 1% of the population, especially men.
- It is caused by *excessive amounts of uric acid, an end product of purine metabolism, within tissues and body fluids.*
- Monosodium urate crystals precipitate and induce an acute inflammatory reaction.
- *Gout is marked* by recurrent episodes of acute arthritis, sometimes accompanied by the formation of large crystalline aggregates called *tophi*, and eventual permanent joint deformity.
- Not all hyperuricemia cause gout.

***Pathogenesis* (Could be in two pathways):**

First pathway

1. Accumulation of urate crystals (derived from uric acid) in the joints.
2. Inflammatory reaction "*activated by the complements (Chemotaxic complements)*".
3. Accumulation of neutrophil.
4. Release of lysosomal enzymes.
5. Damage to tissues of joints.

Second pathway

1. Urate crystals engulfed by microphages.
2. Secretion of lymphokines (TNF, IL1, IL6).
3. Damage to tissues of joints.
4. Inflammatory reaction.

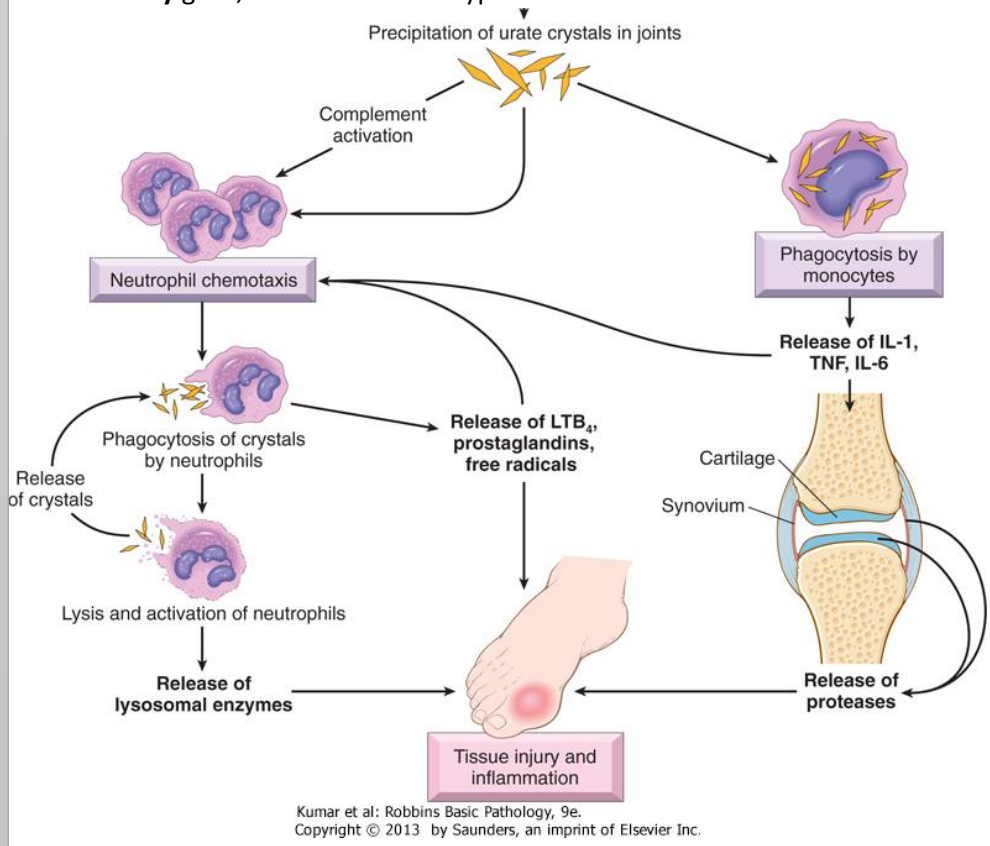
Features:

- G.A. can affect any joint but it prefers big toes "***Common in big toes***"
- For diagnosis, we do uric acid test in serum.
- Gouty Arthritis could be ***primary*** for people with familial tendency, or it may be ***secondary*** to another conditions like cancers (e.g. lymphoma or leukemia).

- Causes of hyperuricemia :

1- Lesch-Nyhan syndrome.
2- Food.
3- Some Drugs.
4- Idiopathic (80 – 90% of the cases).
5- Overproductions of uric acid due to increase purine turnover (e.g. due to leukemia) or an enzyme defect.
6- Decrease excretion of uric acid (e.g. chronic renal failure, **thiazide** diuretics).
7- High dietary purine intake.

- Gout traditionally is divided into ***primary*** and ***secondary*** forms.
- **Primary** gout designates cases in which the basic cause is **unknown** (idiopathic) or in which the disorder is due to an inborn metabolic defect **that causes hyperuricemia**.
- **Secondary** gout, the cause of the hyperuricemia **is known**.



- *Overall rule of Gouty Arthritis:*

Uric acid » Urate crystals » Accumulation in joints » Inflammation.

- **Patients appear with:** Redness, Swelling and Pain
- Note: Uric acid the the end product of purine metabolism and is excreted by the kidney. Purines can either be derived from the breakdown of nucleic acid or synthesized de novo.

The major morphologic manifestations of gout

Acute arthritis	chronic tophaceous arthritis	Tophi pathogenmonic for gout	Gouty nephropathy
Characterized by 1-dense neutrophilic infiltrate permeating the synovium and synovil fluid 2-long slender needle shaped monosodium urate crystals. 3- the synovium is edematous and congested and contains scattered mononuclear inflammatory cells 4- found in the cytoplasm of neutrophils and small clusters in the synovium.	Evolves from repetitive precipitation of urate crystals during acute attack. The urates can heavily encrust the articular surfaces and form visible deposits in the synovium. The synovium becomes hyperplastic, fibrotic and thickened by inflammatory cells , forming a pannus that destroys the underlying cartilage	They are formed by large aggregations of urate crystals surrounded by intense inflamatroy reactions of lymphocytes macrophages and foreing -Body giant cells attempting to engulf the masses of crystals. Tophi can apper in the articular cartilage of joint and in the periarticular ligaments tendons and soft tissue (including the ear lobes, nasal carilage and skin of the fingertips). the superficial tophi can lead to ulceration of the overlying skin	this refers to renal complications associated with urate deposition, variously forming medullary tophi, intratubular precipitation, or free uric acid crystals and renal calcuil, resulting in acute uric acid nephropathy, chronic renal disease or uric acid stones causing renal colic. Secondary complications such as pyelonephritis can occur especially when there is urinary abstructions

NOTES:

- The Events, which lead to the deposition of urate crystals in the joint are uncertain, but possible triggers include alcohol, trauma, surgery and infections.
- Repeated attacks of acute gouty arthritis eventually lead to chronic taphaceous gouty arthritis, where the affected joint is damaged and impaired in function.
- Tophi occur in the joints and the soft tissues of people with persistent hyperuricemia and the common site is pinna of ear.

Calcium Pyrophosphate Crystal Deposition Disease:

This condition is due to the deposition of calcium pyrophosphate crystals in articular cartilage (Chondrocalcinosis) and in the synovium (Pseudogout).

- The pathway leading to crystal formation is not understood, they are likely to involve the overproduction or decrease breakdown of pyrophosphate, resulting in its accumulation and eventual crystallization with calcium in the matrix surrounding chondrocytes.
- It can occur in three main settings:
  1- Sporadic (more common in elderly)
  2- Hereditary (mutations in a transmembrane pyrophosphate transporter), which is rare.
  3- Secondary to other conditions, such as previous joint damage, hyperparathyroidism, hypothyroidism, hemochromatosis and diabetes.
- **Pathogenesis:**
  1- Developing of the crystals in the articular cartilage (chondrocalcinosis) which is usually asymptomatic.
  2- The crystals **may** shed into the joint cavity resulting in an acute arthritis, which *mimics gout* and therefore called pseudogout.
- Pseudogout can be differentiated from gout in three ways:
  1- The knee is most commonly affected.
  2- X-rays show the characteristic line of calcification of the articular cartilage.
  3- The crystals look different under polarizing microscopy, they are rhomboid in shape and exhibit positive birefringence with a red filter.

Q1: Female aged 61 years presents with swollen hands and fingers that are becoming severely deformed with the fingers curling inward and twisting. Her right hand is worse, but both hands suffer sharp pains and a burning sensation. They also have no strength and limited movement, her right hand she couldn't close. Which of the following conditions is she most likely to have?
A – Osteoporosis
B – Arthritis
C – Padget's Disease of Bone
D – Ricket's Disease

Q2: An 85-year-old man presents with several days of swelling and severe pain in both hands limiting his ability to use his walking frame. He has a history of gout but has not experienced these symptoms before. On examination, he has a temperature of 37.8°C (100.1°F). There is diffuse warmth, mild erythema, and pitting oedema over the dorsum of both hands. There is tenderness and limited hand grip bilaterally. There are multiple nodules around several of the proximal interphalangeal and distal interphalangeal joints, and effusion and tenderness in his left olecranon bursa with palpable nodules.
A – Reactive Arthritis
B – Rheumatoid Arthritis
C – Gout
D – Osteoporosis

Q3: A 54-year-old man complains of severe pain and swelling in his right first toe that developed overnight. He is limping because of the pain and states that this is the most severe pain he has ever had ('even covering my foot with the bed sheet hurts'). He has had no previous episodes. His only medication is hydrochlorothiazide for hypertension. He drinks 2 to 3 beers a day. On examination, he is obese. There is swelling, erythema, warmth, and tenderness of the right first toe. There is also tenderness and warmth with mild swelling over the mid foot.
A – Gout
B – Reactive Arthritis
C – Osteoporosis
D – Rheumatoid Arthritis

Q4: A 72-year-old man develops severe pain and swelling in both knees, shortly after undergoing an abdominal hernia repair surgery. Physical examination shows warmth and swelling of both knees with large effusions. Arthrocentesis of the right knee reveals the presence of intracellular and extracellular weakly positive birefringent crystals in the synovial fluid. Gram stain is negative. Which of the following is the most likely diagnosis?
A. Gout
B. Septic arthritis
C. Calcium oxalate deposition disease
D. Reactive arthritis
E. Pseudogout

Q5: A 36-year-old woman was seen by her physician due to pain in her hands, wrists, and knees. She is diagnosed with rheumatoid arthritis. Which of the following treatments will reduce joint inflammation and slow progression of the disease?
A. NSAIDs
B. Joint aspiration
C. Methotrexate
D. Systemic corticosteroids

1- B 2- C 3-A 4-F 5-C