Rheumatoid Arthritis

Objectives:

- By the end of the lecture student should know:
  - Pathology
  - Clinical features
  - Laboratory and radiologic changes
  - Line of management

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Resources: 435 team + Davidson + kumar + Recall questions step up to medicine.

- Editing file
- Feedback

★General characteristic of RA:

35 Female with multiple systemic joint pain, what is your differential diagnosis?

-Osteoarthritis

-Rheumatoid arthritis

-SLE

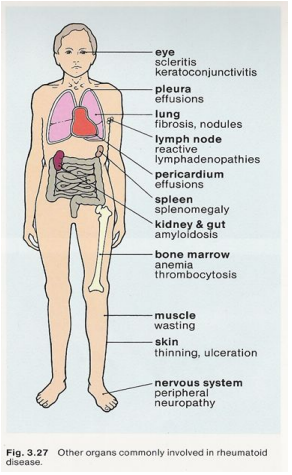


Fig. 3.27 Other organs commonly involved in rheumatoid disease.

What is it:

- RA is Systemic chronic inflammatory disease Mainly affects synovial joints and has many extra-articular manifestations.
- Variable expression, the severity and limitations caused by RA is variable.

Epidemiology:

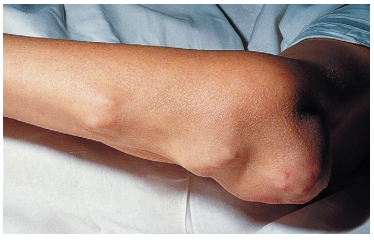
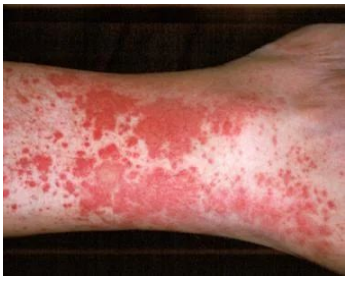
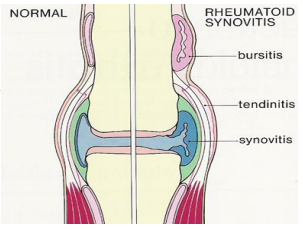
- Worldwide distribution: Prevalence about 3%
- Female:male ratio, 3:1
- Peak age of onset: 25-50 years. it can happen to anyone ,There's a juvenile type that occurs in children.

Etiology:

- Unknown etiology, we know that it's autoimmune but we don't know what triggers this response: Factors like genetics, environmental such as smoking and possible infectious component (most likely viral) play a role but, genetic predisposition is necessary 'associated with HLA-DR4'
- Autoimmune disorder.

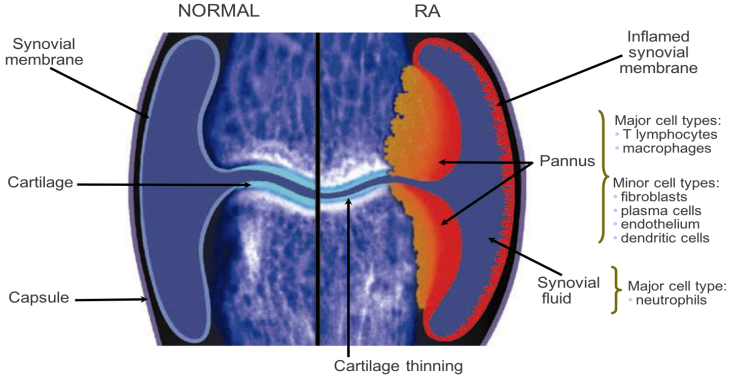
★Pathophysiology of RA:

The Pathology of RA (RA Can Cause):

1-Nodules	2-Vasculitis	3-Synovitis
		*enlarged bursae. *hypertrophy of synovium (thickened)=pannus. *inflammation of the tendon sheath is called tenosynovitis  3 major sites of rheumatoid synovitis: (Joints_Tendon sheaths_Bursae)

Comparison between healthy joint and Rheumatoid Arthritis:

-RA Is Characterized by Synovitis leading to the formation of (PANNUS), **pannus tissue** adheres to articular cartilage, and the cells within the **pannus** produce proteinases that can destroy cartilage.



Pathogenesis of RA 'at a cellular level'

highly recommended video (RA Osmosis)

numerous cellular interaction dive the RA process

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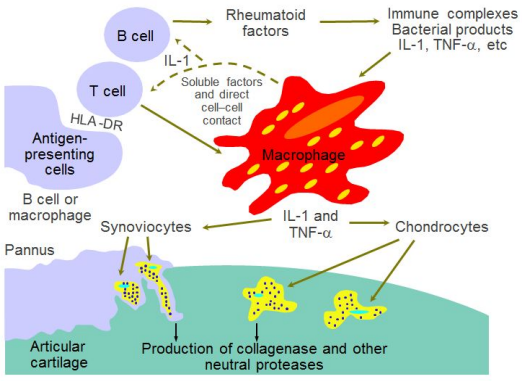
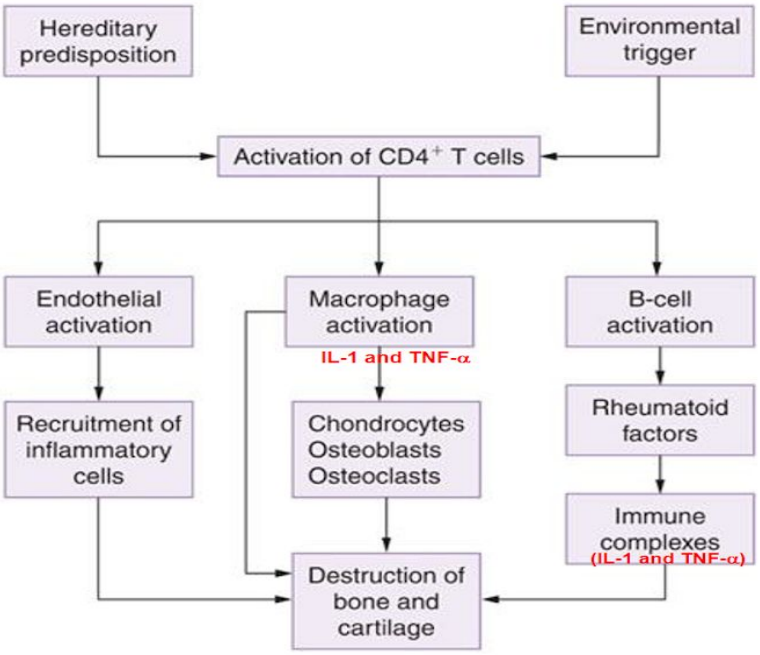
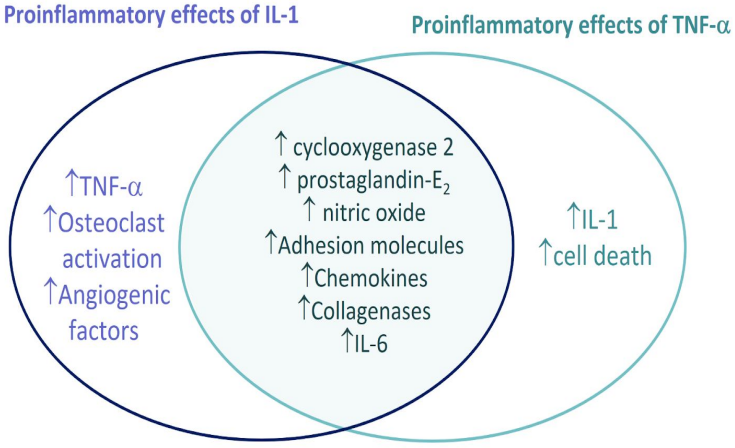
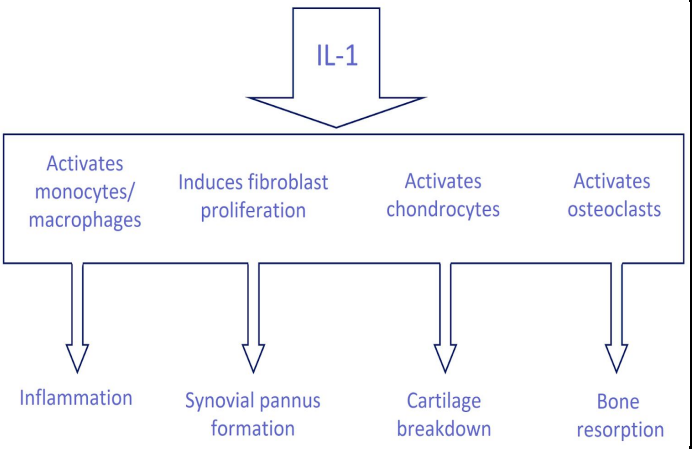




IL-1 and TNF-a Have a Number of Overlapping Proinflammatory Effects:



IL-1 Plays a Pivotal(crucial) Role in Inflammatory and Destructive Processes of RA



Explanation: IL will lead to the accumulation of different components of the immune system, activation of monocytes will lead to inflammation, fibroblast proliferation will lead to synovial pannus formation (further thickening) chondrocytes will lead to cartilage destruction, and osteoclasts will lead to bone resorption (destruction)

★ Signs and Symptoms:

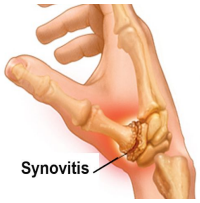
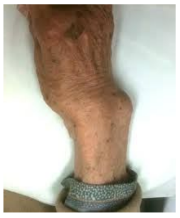
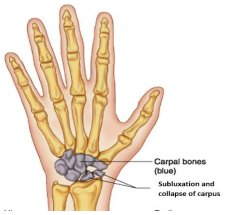
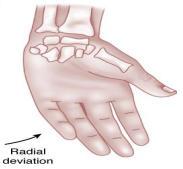
1. Joint inflammation:
   - Warm swollen and tender joints (Joint swelling is the most common sign)
   - Symmetrical pattern (both side equally).
2. Pain and *morning stiffness of joints (major symptom not specific for RA. but, in RA it will be prolonged ~1-2 hours).
3. Symptoms in other parts of the body. (Subcutaneous nodules, anemia, fatigue, fever, malaise)

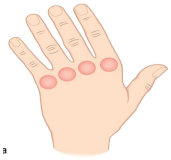
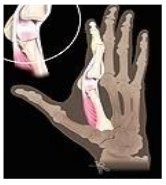
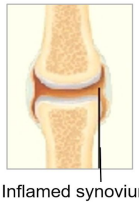
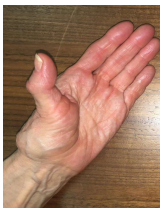
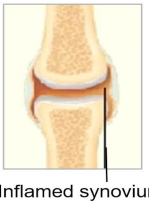
Joint Involvement On Presentation Of RA:

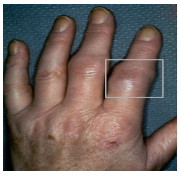
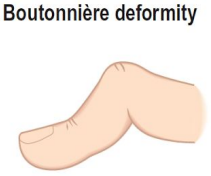
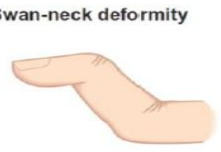
- **25%** of cases presented with monoarticular (one joint involved): 50% of them have Knee involvement only. The other 50% have: shoulder, wrist, hip, ankle, or elbow involvement.
- **75%** (dominant) of cases presented with Polyarticular (more than one joint involved): %60 of them have only small joints of hand & feet involved, while 30% have only large joints involvement, and 10% have BOTH small & large joint involvement.

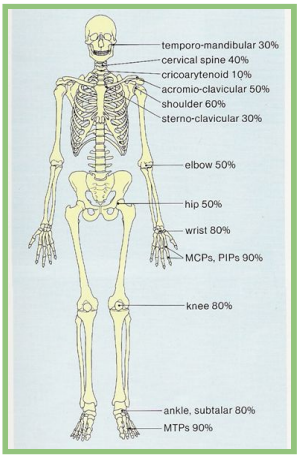
It might start as monoarthritis>oligo>poly arthritis (not common)

★ Articular features seen in the Rheumatoid Hand

Wrist			
Synovitis	Prominent ulnar styloid	Subluxation[1] and collapse of carpus	Radial deviation
			 Pulling of the tendon leads to radial deviation at the level of wrist

Metacarpophalangeal Joints			Thumbs	
Ulnar Deviation	Subluxation	Synovitis	"Z" deformity	Synovitis
at the level of Metacarpals 				

Proximal Interphalangeal Joints		
Synovitis	Fixed flexion (boutonniere deformity)	Fixed extension (Swan neck)
 		
spindle shaped swelling, unlike other forms e.g; psoriatic arthritis >the whole finger will be swollen. DIP (Distal Interphalangeal joint) is spared in RA.		Hyperextension of PIP (Proximal InterPhalangeal joint).



*The picture will remind you what joint should be examined and if you suspect RA, look for muscle wasting.

★ Extra-articular manifestations:

General	- Occasional fever, weight loss, fatigue, malaise - Anemia (Anemia of chronic disease result in normocytic normochromic anemia). - Thrombocytosis: indicates active inflammation. - Lymphadenopathy (Patients with persistent lymphadenopathy should be biopsied since there is an increased risk of lymphoma in patients with longstanding RA)
Dermatologic	Palmar erythema, nodules over the bony prominence, vasculitis (it can affect any vessel but mainly small ones)
Ocular (rare)	- The most common symptom is dry eyes (keratoconjunctivitis **sicca**) due to *Sjögren's syndrome. - Episcleritis/scleritis "red eyes" - Scleromalacia perforans (perforation of the globe of the eye) - Choroid and retinal nodules (nodules can occur anywhere). - (You can also have thinning of the sclera)

[1] partial dislocation
*Sjogren's syndrome secondary to RA

Cardiac	Pericarditis, myocarditis, coronary vasculitis, nodules on valves. RA is a risk for IHD.
Neuromuscular	- Entrapment neuropathy (carpal tunnel syndrome) - Peripheral neuropathy - Mononeuritis multiplex it affects nerve trunk so patient may present with foot drop or wrist drop. vasa nervorum, the vessel that supplies the nerve trunk, may be affected by vasculitis
Hematologic	- Large granular lymphocyte syndrome - Lymphomas - Felty's syndrome. It's a triad of RA + Neutropenia + Splenomegaly
Pulmonary	- Pleuritis, nodules, interstitial lung disease, bronchiolitis obliterans, arteritis, pleural effusions (very common), lung fibrosis.
Others	- Muscle wasting - Skin thinning - Secondary Sjögren's syndrome - Amyloidosis, It's a rare complication of prolonged active disease and usually presents with nephrotic syndrome (MCQ). Any patient presenting with arthritis and peripheral edema and proteinuria (kidney involvement) it could be glomerulonephritis caused by SLE , or RA causing amyloidosis.. How to differentiate? GN has RBC Casts.

★ Investigations:

hematology	**CBC, ESR**
biochemistry	**LFT, Renal profile** (Important before prescribing medications to know the patients baseline)
serology	**RF, Anti-CCP** (if the patient has +ve ACCP but does not have the disease they may get it at some point in their lifetime)
radiography	**Joints, Spines, Chest**

To Establish a Diagnosis: **we don't have 100% diagnostic test. not like cancer and infections.**

1- Start with CBC. sometimes Microcytic anemia can occur due to iron deficiency resulting from NSAID-induced GI blood loss.
2- ESR and CRP: are usually raised but normal results do not exclude the diagnosis.
3- Rheumatoid factor(RF) and anti-citrullinated peptide antibodies(ACPA):
- (Helpful in determining prognosis. High titers more severe disease)3-Rheumatoid factor(RF) and anti-citrullinated peptide antibodies(ACPA):
- RF: Immunoglobulin (could be IgG or IgM, routinely they check IgM). Autoantibody, IgM against the patient's IgG.
  *If +ve : not specific, supports the diagnosis, but not diagnostic, in 80% of patients it's +ve.
  *If the levels were elevated, it means that the patient is more prone to have complications & extra articular manifestations, Positivity is more with age, majority of people over 65 will have + RF.
- Anti CCP: Positive in 80% of patients, but more specific to RA. (Anti-cyclic citrullinated peptide, IgM against pt IgG)

4-Clinical criteria. it is not diagnostic we may use it as a guide but it's used more as a classification criteria for scientific purposes.

*NOTE: Ultrasound examination and MRI are not routinely required in patients with obvious clinical Signs.
*NOTE: Abnormal x-ray is not necessary to confirm the diagnosis of RA.

To Monitor Drug Safety:

LFT and Renal profile. Before and after starting the treatment because the medications have side effects.

To Monitor Disease Damage:

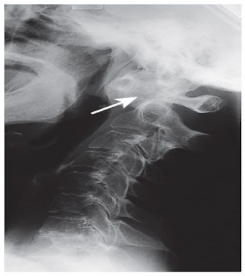
Radiographic: Joints, Spine To look for subluxation, Chest it's a routine test Chest radiography for pleural effusion and lung fibrosis.

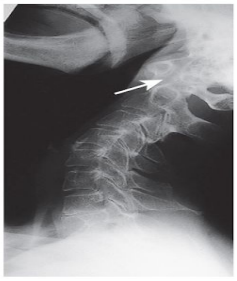
Radiographic (joint destruction)

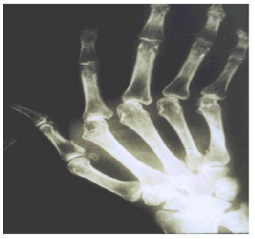
معلومة مهمه لكل مريض عنده ريماتويد وبيسوي عملية لازم يسوي

X-Ray OF CERVICAL SPINE Prior to ANY SURGERY to detect possible instability in vertebrae. It's essential because the endotracheal intubation could cause hyperextension of the neck subluxation of the atlantoaxial joint compressing the cord

لو كان عنده مشكله انت ماتدري عنها وسويت له انتيوبيشن ممكن تضغط على الحبل الشوكي وتسوي له شلل رباعي







- Subluxation of Metacarpophalangeal.
- periarticular osteopenia (the dark area).

The 2010 ACR/EULAR classification criteria for rheumatoid arthritis: *الدكتور قال مو لازم تحفظون الكرايتيريا

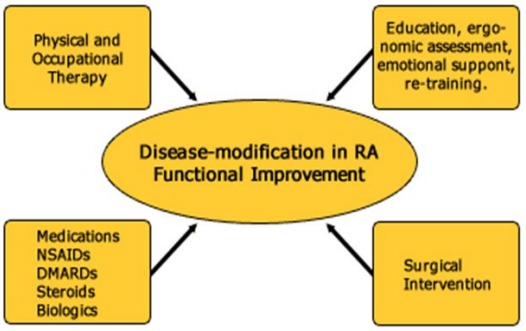
target population (who should be tested?) Patients:

1- who have at least 1 joint with definite clinical synovitis (Swelling)

2- with the synovitis not better explained by another disease.

In the old criteria erosion was included but in new one its not because its very late manifestation of RA.

Add **A–D**; a score of 6/10 is needed to classify patient as having definite RA	
A. Joint involvement	
1 large joint.	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
3-10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF *and negative ACPA*	*0*
Low-positive RF *or low-positive ACPA*	*2*
High-positive RF *or high-positive ACPA*	*3*
C. Acute-phase reactants (1 test result is needed for classification)	
Normal CRP *and normal ESR*	*0*
Abnormal CRP *or abnormal ESR*	*1*
D. Duration of symptoms	
6 weeks	0
>6 weeks	1



★ Treatment and Management: First we have to do lifestyle modifications to improve quality of life and the physical therapy will make the muscles stronger

Treatment Goals:

- Relieve pain
- Reduce inflammation
- Prevent/slow joint damage
- Improve functioning and quality of life

Rationale for the Early Treatment of RA:

- Erosions develop **early** in the disease course
- Destruction is **irreversible.** so try to act early to prevent disabilities
- Disease **activity** is strongly associated with joint destruction later in the disease course.
- Early treatment can slow down radiographic progress
- Disease activity must be suppressed maximally in its **early** stages to prevent destruction and preserve function.
- There is no curative agent available for RA but drugs are now available that prevent disease deterioration.

Treatment approaches:

(lifestyle modifications, Rest (but not too much), physical and occupational therapy, medication & surgery)

Medications:

Disease-Modifying Antirheumatic Drugs (DMARDs) 2nd line

Methotrexate:

- Best initial, gold standard drug in RA. MOA Inhibits DNA synthesis and cell division, most commonly used, very effective.
- monitoring requirement: (CBC, LFTs)

Alternatives to Methotrexate:

- **Hydroxychloroquine:** It requires eye examinations every 6 months because of the risk of visual loss due to retinopathy (although quite rare).
- **Sulfasalazine:** monitoring requirement (CBC, LFTs)
- **Leflunomide:** monitoring requirement (CBC, LFTs)
- **Azathioprine:** monitoring requirement (CBC, LFTs) you have to do CBC because it causes bone marrow suppression.

Uses:

- Control symptoms
- **No immediate** analgesic effects**, so begin treating RA With NSAID while waiting for DMARD to take effect**. Once the effect is evident, gradually taper and discontinue NSAIDs and continue the disease-modifying program.
- Can **delay progression of the disease** (prevent/slow joint and cartilage damage and destruction)
- Should be initiated early (at the time of diagnosis) it takes time to produce its action (6 weeks).
- Effects generally not seen until a few weeks to months

NSAIDs 1st line

Traditional NSAIDs: working on both cox1 and cox2

- Aspirin
- Ibuprofen
- Ketoprofen
- Naproxen

COX-2 Inhibitors: (inflammatory cox) selective>less side effects

- Celecoxib
- Etericoxib

Uses:

- To **relieve pain** and inflammation
- Use in combination with a DMARD

*Note that NSAIDs and Glucocorticoids only relieve the symptoms of RA. DMARDs, on the other hand, arrest the progression of the disease.

Main side effect:

- GI side effects mainly, patients should also be monitored for such side effects.

Corticosteroids

(low dose) use these if NSAIDs do not provide adequate **pain relief.** not for long-term maintenance (we give it for a short period until other medications produce their action)

Short-term treatment may be appropriate but avoid long-term use

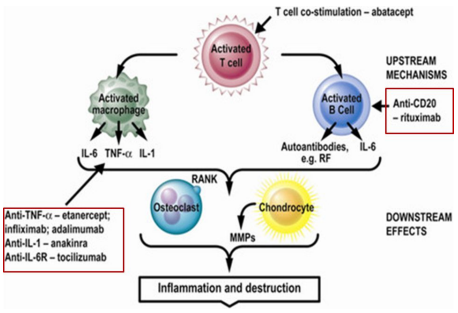
If not better, use: Biologic Response Modifiers

Before using any drug (specially TNF inhib) we have to exclude infections like latent TB >it will dissolve the granuloma >spread of infection.

- TNF Inhib: etanercept infliximab,Adalimumab
- IL6 receptor inhib: tocilizumab
- T Cell costimulation modulator: abatacept

Other meds:

- IL1 inhibitor: anakinra
- Anti-CD20 (B cell): rituximab "very effective"



Physiotherapy:

- Effective in maintaining the range of motion.
- Strengthening of muscles.
- Prevent contractures.
- Prevent deformities.
- Maintain activities of daily living.

Occupational Therapy:

- Education of patients in the use of daily living activities
- Prevention of joint contractures and deformities.

Surgery: (Joint replacement for severe pain unresponsive to conservative measures)

Summary

Rheumatoid Arthritis

- RA is Systemic chronic inflammatory disease Mainly affects synovial joints, It is a systemic disease that has many extra-articular manifestations.

Etiology

Unknown could be :

1. Genetic 2. infectious 3. environmental 4.Autoimmune

Pathophysiology

- Chronic synovitis leads to **pannus formation,** which damages all the structures surrounding the joint (bone, ligaments, tendons, and cartilage).
- IL-1 and TNF-a, IL6 have a number of overlapping proinflammatory effects
-

Clinical presentation

Joint inflammation:

- symmetrical.
- polyarticular.
- warm swollen joints.
- morning stiffness.

Constitutional symptoms:

- Low-grade fever.
- weight loss.
- Fatigue.

Articular feature :

Wrist :

synovitis , **radial deviation** , subluxation and collapse of carpus prominent ulnar styloid.

MCP:

synovitis , **ulnar deviation,** subluxation.

Thumbs:

synovitis, Z defotmiy.

PIP:

synovitis, swan neck , boutonniere deformity.

Extra-articular manifestations:

- palmar erythema.
- nodules.
- vasculitis.
- dry eyes (Sjögren's syndrome)
- pericarditis + IHD
- (carpal tunnel syndrome)
- peripheral neuropathy
- Felty's syndrome.its a triad ;RA +neutropenia +splenomegaly
- lymphoma
- Pleural effusions
- Muscle wasting, Skin thinning
- Amyloidosis

Investigation

1. **hematology:** CBC, ESR
2. **Biochemistry:** LFT, Renal profile
3. **Serology:** RF, Anti-CCP
4. **Radiology:** joints, spines, chest

Treatment

Treatment approaches:

(lifestyle modifications, rest, physical and occupational therapy, medication, surgery)

Medication:

1. **DMARDs: eg. methotrexate** (Best initial, gold standard' drug in RA)
2. **NSAIDS:** To **relieve pain** and inflammation, Use in combination with a DMARD.
3. **Corticosteroids:** only in active phase, avoid long-term use.
4. **Biologic Response Modifiers:** (used if the patient doesn't get better)
    a. TNF Inhib: etanercept, infliximab, Adalimumab
    b. IL6 receptor inhib: tocilizumab
    c. T Cell costimulation modulator: abatacept
    d. Anti-CD20 (B cell): rituximab "very effective"
    e. IL1 inhibitor: anakinra

Questions:

Q1: A 20 years old presented to the rheumatology clinic complaining of joints pain has been diagnosed with rheumatoid arthritis, what would you Initially prescribe to slow the progression of the disease?

A. NSAIDs
B. Methotrexate
C. Corticosteroids
D. sulfasalazine

Answer: B

Q2: Regarding the previous question , what would be the drug of choice to quickly control his symptoms?

A. Corticosteroids
B. Sulfasalazine
C. Methotrexate
D. NSAIDs

Answer: D

Q3: What is the gene that is highly linked to pathogenesis of rheumatoid arthritis?

A. HLA-DR4
B. HLA-b27
C. HLA-DR3
D. HLA-DR5

Answer: A

Q4: A 50 years old lady presented to your clinic and you are suspecting rheumatoid arthritis, upon hand inspection: all of the following can be present in metacarpophalangeal joints EXCEPT :

A. Ulnar deviation
B. z deformity
C. Subluxation
D. Sinovitis

Answer: B

Q5: If the NSAIDs could not control the pain of your patient, what would be the next step?

A. Switch to biological treatment
B. Switch to steroids
C. Refer him to physiotherapy
D. Do nothing and wait until the methotrexate starts working

Answer: B

Q6: A patient is having rheumatoid arthritis and is asking about the rationale of using methotrexate, what would be your response?

A. To reverse the Joint damage
B. Only to slow down the progression of joint destruction
C. It is mainly an analgesic
D. Only to control the extra articular manifestations)

Answer: B

Q7: A patient has been referred to a thoracic surgeon, upon inquiry about his past medical history he stated that he has rheumatoid arthritis but it is well controlled with no pain.
what would you do next?

A. Increase the dose of Methotrexate
B. Do nothing as the patient is stable right now
C. Order an X-ray of the cervical spine to avoid cord compression
D. Refuse to operate on him as he is not fit for that

Answer: C

Q8: Which of the following features supports the diagnosis of rheumatoid arthritis?

A. The pain increases with movement
B. Pain decreases with movement
C. Swollen achilles tendon
D. Patient presents with psoriasis followed by severe joint pain

Answer: B