RHEUMATOID ARTHRITIS

435 medicine teamwork

[Important | Notes | Extra | Editing file]

lecture objectives:

- ⇨ Modes of presentation of Rheumatoid Arthritis
- ⇨ Pathology of Rheumatoid Arthritis
- ⇨ Investigations and management
- ⇨ Differential Diagnosis for pt with polyarthritis

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References: Doctors' Slides+Davidson+step up to medicine

Rheumatoid Arthritis(RA)

General Characteristic of RA:

scenario :35 female with multiple symmetrical small joint pain: first think about RA then SLE

What is it:

- RA is Systemic chronic inflammatory disease Mainly affects synovial joints,It is a systemic disease that has many extra-articular manifestations.
- Variable expression:Disease severity is variable some patients have moderate restrictions and are capable of performing activities of daily living, whereas others are confined to a wheelchair or bed.

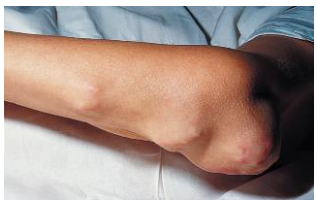
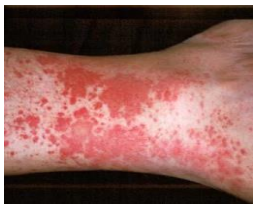
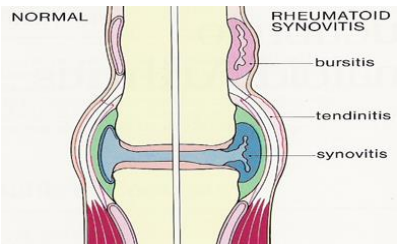
Epidemiology:

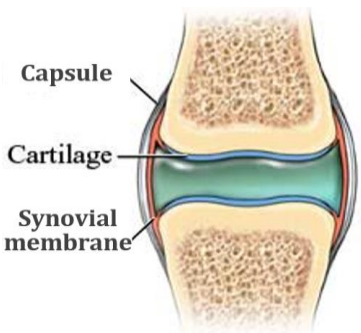
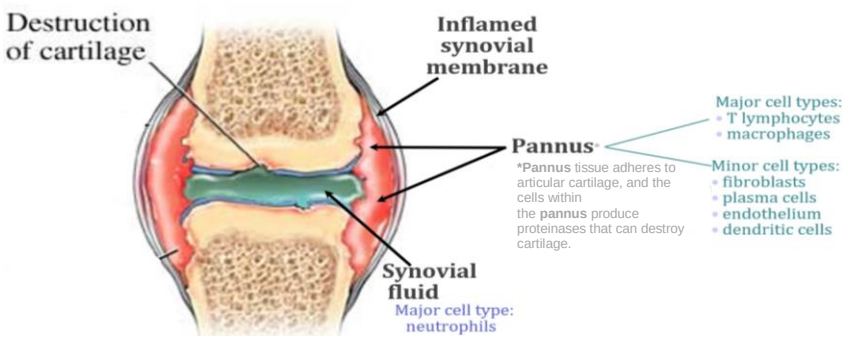
- Worldwide distribution:Prevalence about 3%
- Female:male ratio 3:1
- Peak age of onset: 25-50 years, it can happen to anyone ,There is a juvenile type that occurs in children.

Etiology:

- Etiology is uncertain(What we know for sure is that it's autoimmune): It may be caused by an infection or a series of infections(most likely viral), or environmental factor like smoking but genetic predisposition is necessary 'associated with HLA-DR4'.

Pathophysiology of RA:

The Pathology of RA (RA Can Cause):		
Nodules	Vasculitis	Synovitis
		 3 major sites of rheumatoid synovitis: (Joints_Tendon sheaths_Bursae)

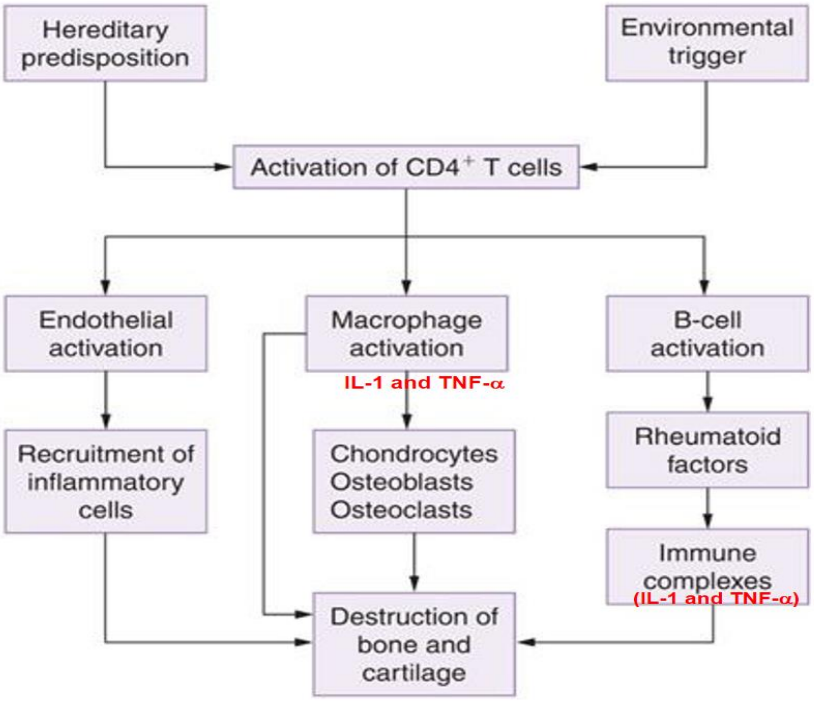
Comparison between healthy joint and Rheumatoid Arthritis:	
	
healthy joint	RA Is Characterized by Synovitis leading to formation of (PANNUS) Thickened synovium, called pannus and this will invade the cartilage, it will be seen on radiology as erosion (invasion of cartilage and bone)

Pathogenesis of RA 'at cellular level'

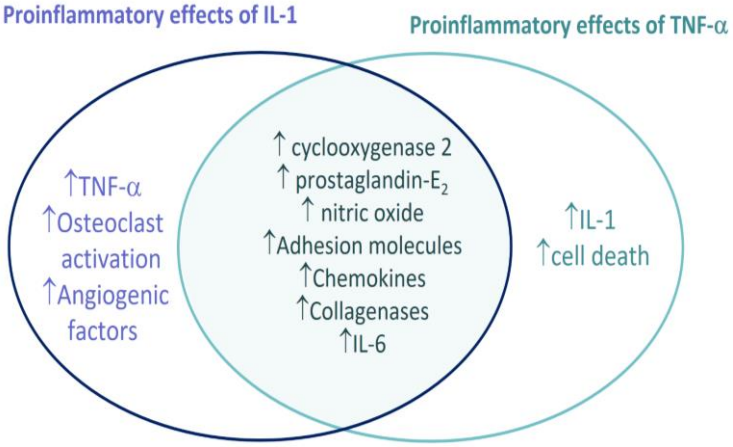
highly recommended video(3 min)

Invasion of inflammatory cells, T cells, B cells, &plasma cells are present in the synovium and in the fluid. The fluid will be mostly composed of neutrophils.

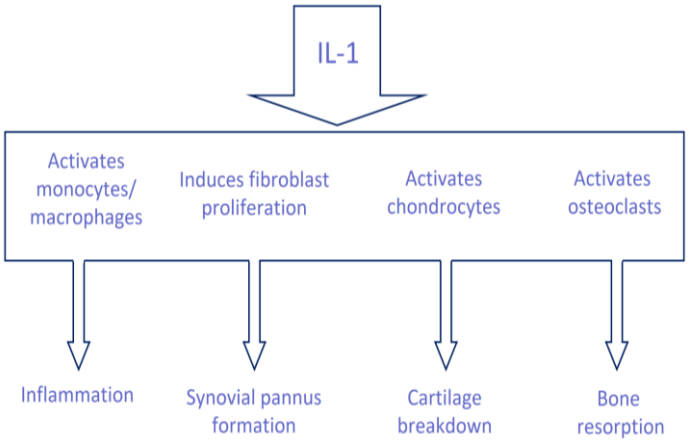
Activation of B cells, T cells, production of autoantibodies (Rheumatoid factor), cytokines, interleukins, TNF -> production of destructive enzymes -> more inflammation



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



IL-1 Plays a Pivotal(crucial) Role in the 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)

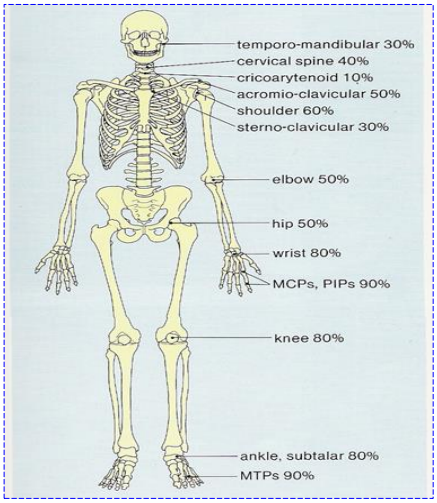
Signs and Symptoms:

Joint inflammation:

- on symmetrical pattern(both side equally).

- **Signs & symptoms:**'signs of inflammation' warm swollen joints(joint swelling is the most common sign) ,Tender, Pain and *morning stiffness*(morning stiffness prolonged in RA more than one hour while in osteoarthritis less than half hour

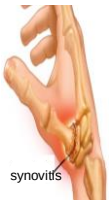
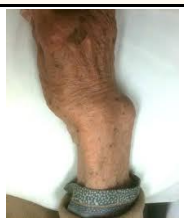
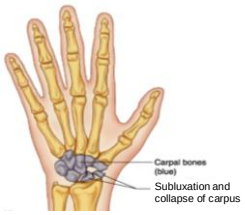
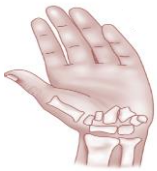
- **Joint Involvement On Presentation Of Ra:**
  - 25% of cases presented with monoarticular(one joint involved): 50% of them have Knee involvement only, while other 50% have shoulder ,wrist ,hip, ankle ,or elbow involvement.
  - 75% of cases presented with Polyarticular(more than one joint involved):%60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



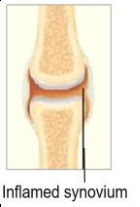
Joint involvement in RA **Classically: symmetrical polyarthritis** (many joints) but can present with one or two joints and any joint can be involved EXCEPT DIP.
*Examine all the joints, temporal, sternoclavicular, any other joint can be involved

Articular features seen in the Rheumatoid Hand

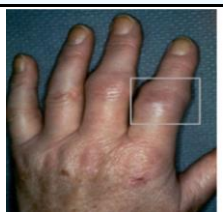
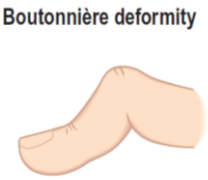
Wrist

Synovitis	Prominent ulnar styloid	Subluxation[1] and collapse of carpus	Radial deviation
 synovitis		 Carpal bones (blue) Subluxation and collapse of carpus	 Pulling of the tendon leads to radial deviation

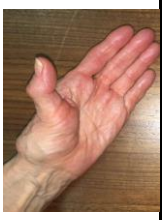
Metacarpophalangeal Joints

Ulnar Deviation	Subluxation	Synovitis
 Ulnar one at the metacarpophalangeal joints		 Inflamed synovium

Proximal Interphalangeal Joints

Synovitis	Fixed flexion(boutonniere deformity)	Fixed extension(Swan neck)
  Inflamed synovium inflammation of PIP joint result in swollen,spindle like finger localized in RA unlike seronegative spondyloarthritis the whole digit is swollen	 Boutonnière deformity	 Swan-neck deformity

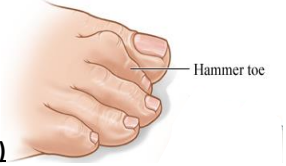
Thumbs

Z deformity	Synovitis
	 Inflamed synovium

Read them just in case:

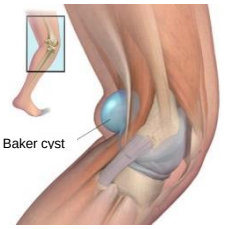
Articular features seen in Rheumatoid foot:

Hammertoe is a contracture **(bending)** deformity of one or both joints of the second, third, fourth or fifth (little) toes.
The foot becomes broader and a **hammer-toe deformity(cock-up toe)**



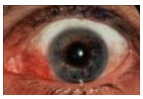
Articular features seen In Knee & popliteal:

Popliteal ('Baker's') cysts may occur in combination with knee synovitis.
A **Baker's cyst** is caused when excess joint fluid is pushed into one of the small sacs of tissue behind the knee.
Quick assessment of the possibility of DVT may be required where a Baker's cyst has compressed vascular structures, as this sets up conditions for a DVT to develop.
In patients with Baker's cyst, ultrasound may be required to establish the diagnosis, since DVT and Baker's cyst may coexist



[1] partial dislocation

Extra-articular manifestations:

General	- occasional fever, weight loss, fatigue,malaise - Anemia(anemia of chronic diseases result in normocytic normochromic anemia), - 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, vasculitis
Ocular (rare)	- The most common symptom is dry eyes (keratoconjunctivitis **sicca**)due to Sjögren's syndrome. - episcleritis/scleritis - scleromalacia perforans (Thin sclera, perforation and bulge of eye contents. There may be nodules in the retina as well)  - choroid and retinal nodules 
Cardiac	pericarditis, myocarditis, coronary vasculitis, nodules on valves,they're on high risk of IHD
Neuromuscular	- entrapment neuropathy(eg:carpal tunnel syndrome), - peripheral neuropathy - mononeuritis multiplex(Affection of nerve trunk due to vasculitis vasa nervosum, the vessel that supplies the nerve trunk, may be affected by vasculitis)
Hematologic	- large granular lymphocyte syndrome, lymphomas, - Thrombocytosis - Felty's syndrome: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(specially if pt on steroids)ulceration. - Secondary Sjögren's syndrome(characterized by Dry eye & mouth), - Amyloidosis is a rare complication of prolonged active disease and usually presents with nephrotic syndrome(MCQ).(any chronic inflammation may complicated by amyloidosis). **MCQ:** - RA by itself won't cause nephrotic syndrome BUT if it complicated by amyloidosis it usually presents with nephrotic syndrome in form of proteinuria. - RA by itself won't cause glomerulonephritis , while SLE can cause glomerulonephritis.

investigations:

To Establish Diagnosis:

1- Start with CBC: usually normocytic normochromic anemia with thrombocytosis is present in active disease, or sometime 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):

- **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 & extraarticular manifestations,Positivity is more with age, majority of people over 65 will have + RF. (Helpful in determining prognosis. High titers more severe disease)

- **Anti CCP:** like RF positive in 80% of patients, but more specific to RA.

4-Clinical criteria.

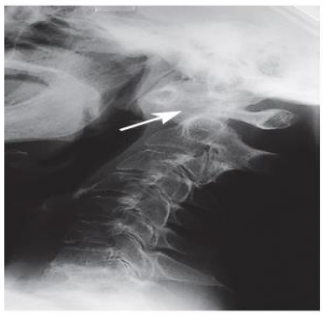
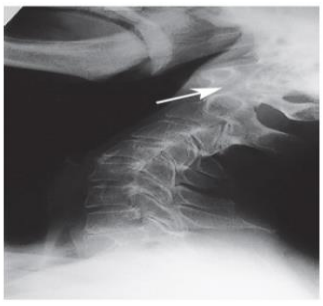
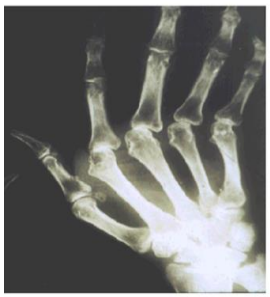
***NOTE:Ultrasound examination and MRI are not routinely required in patients with obvious clinical Signs.**
***NOTE:Abnormal x-ray is not necessary to confirm diagnosis of RA.**

To Monitor Drug Safety:

LFT and Renal profile (u should do them before starting treatment)

To Monitor Disease Damage:

Radiographic: Joints , Spines(To look for subluxation) ,Chest (Chest radiography for pleural effusion and lung fibrosis).

Radiographic (joint destruction)		
 Subluxation of cervical spine. Flexion, showing widening of the Atlantoaxial space(Normal shouldn't be more than 3mm)	 Subluxation of cervical spine Extension, showing reduction in this space. (Sub axial subluxation more in children)	 Subluxation of Metacarpophalangeal periarticular osteopenia and joint erosion
#معلومه: مهم مهم لأي مريض RA قبل يسوي اي عمليه انك تسويله spine cervical X ray: to detect possible instability in vertebrae is essential prior to the hyperextension of the neck with endotracheal intubation,لوكان عنده انستيبلتي وانت مانتبهت لها وسويلته هايبراكستنشن مع الانتيوبيشن ممكن يصير له شلل رباعي		

25.54 Criteria for diagnosis of rheumatoid arthritis*

Criterion	Score
Joints affected	
1 large joint	0
2–10 large joints	1
1–3 small joints	2
4–10 small joints	5
Serology	
Negative RF and ACPA	0
Low positive RF or ACPA	2
High positive RF or ACPA	3
Duration of symptoms	
< 6 wks	0
> 6 wks	1
Acute phase reactants	
Normal CRP and ESR	0
Abnormal CRP or ESR	1
Patients with a score ≥ 6 are considered to have definite RA.	

*European League Against Rheumatism/American College of Rheumatology 2010 Criteria.
(ACPA = anti-citrullinated peptide antibodies; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor)

لا تحفظونها!!
We can use it on any patient with at least one joint arthritis (pain & swelling) that isn't explained by any other condition (e.g. septic arthritis, you cannot apply this criteria)
احنا بالروماتولوجى مانعتمد على الكرايتيريا للتشخص وهي غالبا تستخدم للأبحاث
we may use it as a guide not diagnostic

Treatment and management:

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(Less than 10 yrs If u treat early u may prevent bone destruction)
- Destruction is **irreversible**
- 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 modification like smoke cessation, rest with gradual physiotherapy (Rest shouldn't be prolonged to prevent atrophy and contractures), meds and surgery sometimes.
Education is a very important part of treatment, the patient should know what is the nature of the disease.

Treatment approaches:

<table>
<tr><th colspan="3">Medications:</th></tr>
<tr><td>Disease Modifying Antirheumatic Drugs (DMARDs)</td><td><u>Methotrexate:</u>
- Best initial,'gold standard' drug in RA. MOA Inhibits DNA synthesis and cell division,
- Main side effects:idiosyncratic interstitial pneumonitis, which may lead to pulmonary fibrosis so avoid them in lung fibrosis. has teratogenic effect so It should not be used in pregnancy. Conception should be delayed for 3–6 months off the drug for either partner.
- monitoring requirement:(CBC:For any bone marrow suppression, LFTs)

<u>Alternatives to Methotrexate:</u>
- Hydroxychloroquine:use with mild disease,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: Used if there is lung involvement (e.g. lung fibrosis),monitoring requirement(CBC, LFTs)</td><td><u>Uses:</u>
- 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)
- Effects generally not seen until a few weeks to months</td></tr>
<tr><td>NSAIDs</td><td><u>Traditional NSAIDs:</u>
- Aspirin
- Ibuprofen
- Ketoprofen
- Naproxen

<u>COX-2 Inhibitors:</u> selective = less adverse effects on GI
- Celecoxib
- Etericoxib</td><td><u>Uses:</u>
- To relieve pain and inflammation
- Use in combination with a DMARD
*Note that NSAIDs and Glucocorticoids only relief the symptoms of RA. DMARDs, on the other hand, arrest the progression of the disease.

<u>Main side effect:</u>
- GI side effects:Ulceration and bleeding in addition to liver and renal we need to watch them.</td></tr>
<tr><td>Corticosteroids</td><td colspan="2">(low dose)use these if NSAIDs do not provide adequate pain relief.
Short-term treatment may be appropriate but avoid long-term use(not maintenance)
Long standing with high dose causes complications like compression fracture of the spine</td></tr>
<tr><td>If no better – use: Biologic Response Modifiers</td><td colspan="2">3rd line or 2nd if severe disease and very high inflammatory parameters
- <u>TNF Inhib:</u> etanercept,infliximab,Adalimumab
- <u>IL6 receptor inhib:</u>tocilizumab
- <u>T Cell costimulation modulator:</u> abatacept

Other meds:
- IL1 inhibitor: anakinra
- Anti-CD20 (B cell): rituximab "very effective"</td></tr>
<tr><th colspan="2">Physiotherapy:</th><th>Occupational Therapy:</th></tr>
<tr><td colspan="2">- Effective in maintaining the range of motion
- Strengthening of muscles
- Prevent contractures
- Prevent deformities
- Maintain activities of daily living</td><td>- Education of patients in the use of daily living activities
- Prevention of joint contractures and deformities
  </td></tr>
<tr><td colspan="3">Surgery: (Joint replacement for severe pain unresponsive to conservative measures)</td></tr>
</table>

MCQs

1) Patient with 10--year history of rheumatoid arthritis came with melena, before sending him to upper GI endoscopy. Which one of the following you should order?

A. CT of the brain
B. CT of the chest
C. X-ray of cervical spine
D. X-ray of the hand

2) A 38 year old women with rheumatoid arthritis presented with fatigue and Low white cell count (WBC 2500ml). She has no active joint symptoms and her RA is controlled with low dose methotrexate and NSAIDS . On examination she has chronic joint deformity of her hands and a palpable spleen .
Which of the following is the most likely diagnosis

A. Methotrexate therapy
B. rheumatoid nodules disrupting bone marrow architecture
C. felty's syndrome
D. myelofibrosis

3)A 67 years old man has a long history of symmetrical small joint arthritis with deformities. He now develops shortness of breath on exertion with a dry cough, but no sputum or chest discomfort. His heart sounds have a loud P2, and the lungs have fine bibasilar crackles.
Which one of the following is the most likely diagnosis:

A. pericarditis
B. caviating lung lesions.
C. Pneumonia
D. Interstitial fibrosis

4)Which one of the following is most helpful to differentiate rheumatoid arthritis from systemic lupus erythematosis:

A. positive rheumatoid factor
B. microcystic anemia
C. erosion of ulnar styloid
D. symmetrical arthritis

5)A 45 y\o lady complaining of bilateral hand pain for last 6 months. On examination she had 10 swollen joints.Labatory tests are positive for RF and ACCP.There're no erosion in X ray.She was diagnosed to have RA. Which one of the following drugs is the best option in this moment?

a. Etanercept
b. Hydroxychloroquine
c. Sulfasalazine
d. Methotrexate

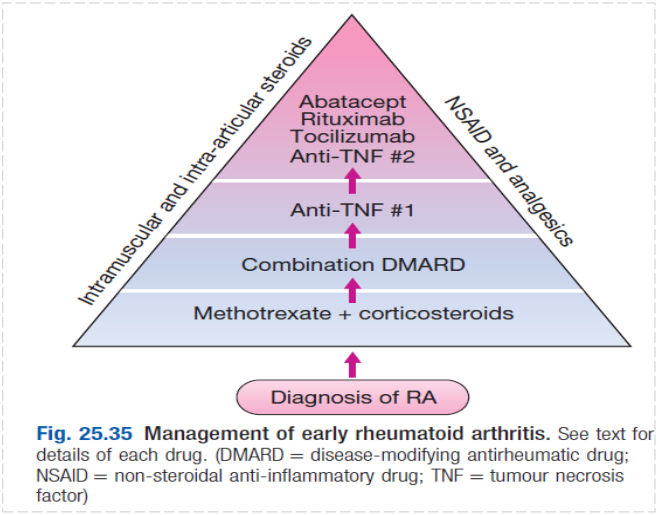


Fig. 25.35 Management of early rheumatoid arthritis. See text for details of each drug. (DMARD = disease-modifying antirheumatic drug; NSAID = non-steroidal anti-inflammatory drug; TNF = tumour necrosis factor)

Answer key:

1 (C) | 2 (C)| 3(D) | 4 (C) | 5 (D)