RHEUMATOID ARTHRITIS

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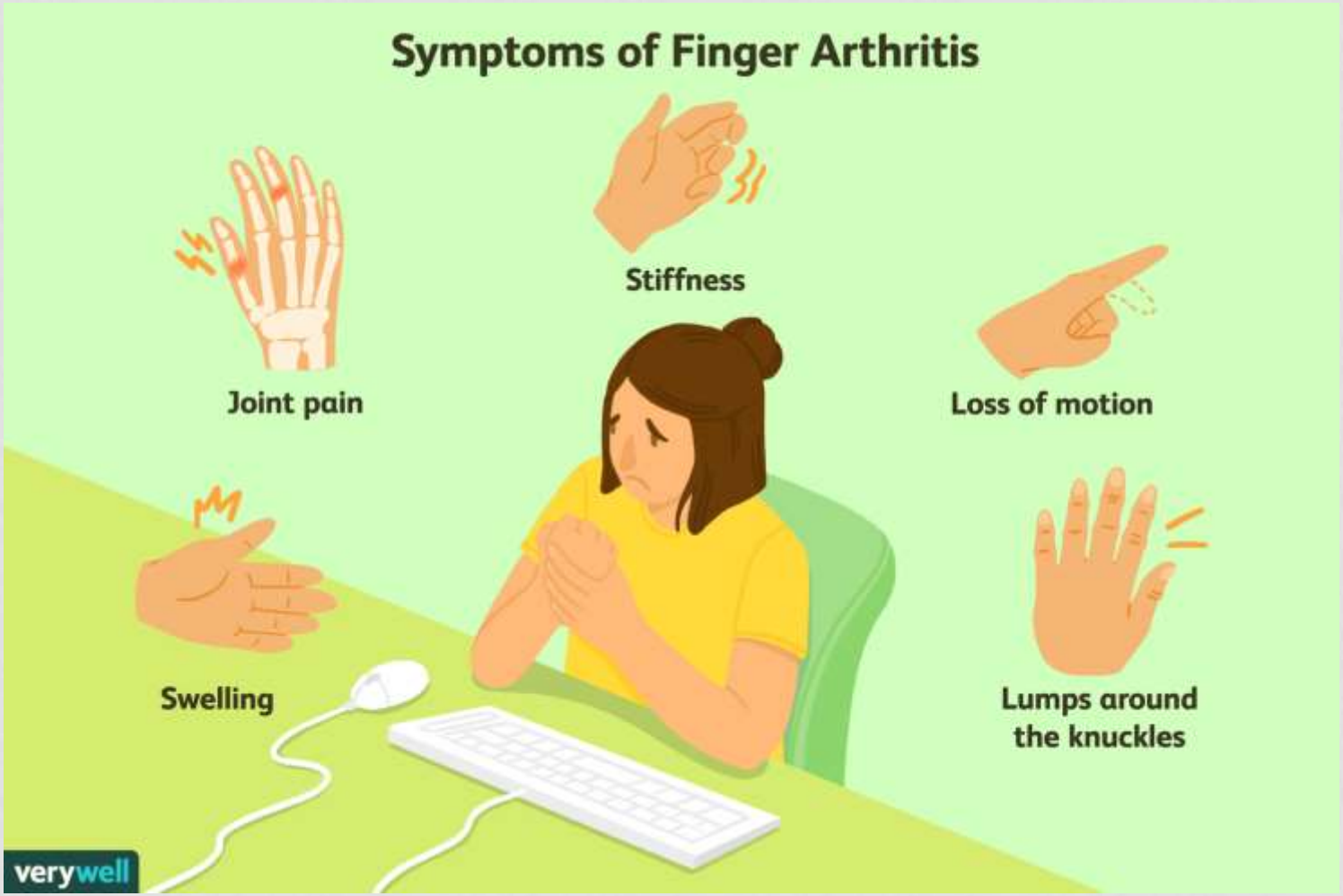
RHEUMATOID ARTHRITIS

IS A CHRONIC SYSTEMIC INFLAMMATORY ARTHRITIS . CHARACTERIZED BY REMISSION AND EXACERBATION , WITH EXTRA ARTICULAR MANIFESTATIONS

- Occurring throughout the world in all ethnic groups .
- Female : male ratio is 3:1.
- Can effect any age but the peak incidence occur within 4^{th} and 5^{th} decades of life.



ETIOLOGY :

GENETICS AND ENVIRONMENTAL FACTORS IMPLICATED CLEARLY IN THE ETIOLOGY AND PATHOGENESIS OF RA.

GENETIC FACTORS:

- concordance in monozygotic twins is 12-15% in compare with 3% in diazygotic twins.

  - increased frequency in 1st –degree relative of patients.

  - in up to 50% of genetic susceptibility is due genes in HLA region.

  HLA DR4 in(50-70%) in Caucasian patients compare to 20-25% in normal population.

  HLA DR4 also associated with progressive and severe disease.

NON GENETIC RISK FACTORS:

-**Sex hormones:**Two to three times are likely to occur in females than males.

- **Tobacco smoking** is strong risk factor for etiology and severity and reduce responsivness to DMARDs and biological treatment .

- susceptibility increase in **post partum** and **breast feeding** period.

- Although it is thought that RA is triggered by **infectious agent** in a genetically susceptible host , a specific pathogen has not been identified.

Pathology:

* swelling and congestion of synovial membrane
- Cellular infiltration of synovium
- CD4 Tcells and Th17 cells play important role in pathogenesis.
* Effusion of synovial fluid

Hypertrophy of synovial membrane

Lymphoid follicles formed in synovial tissue .B cell to produce cytokines and autoantibodies RF and ACPA

Synovial macrophages produce pro inflammatory cytokines(TNF, IL-1,IL-6 and IL15) these stimulating fibroblast to cause swelling and more soft tissue and cartilage damage

--Activation of osteoclast and chondrocyte and more bone and cartilage destruction. .
--Lymph node are often hyperrperplastic with production of RF and ACPA by plasma cells.

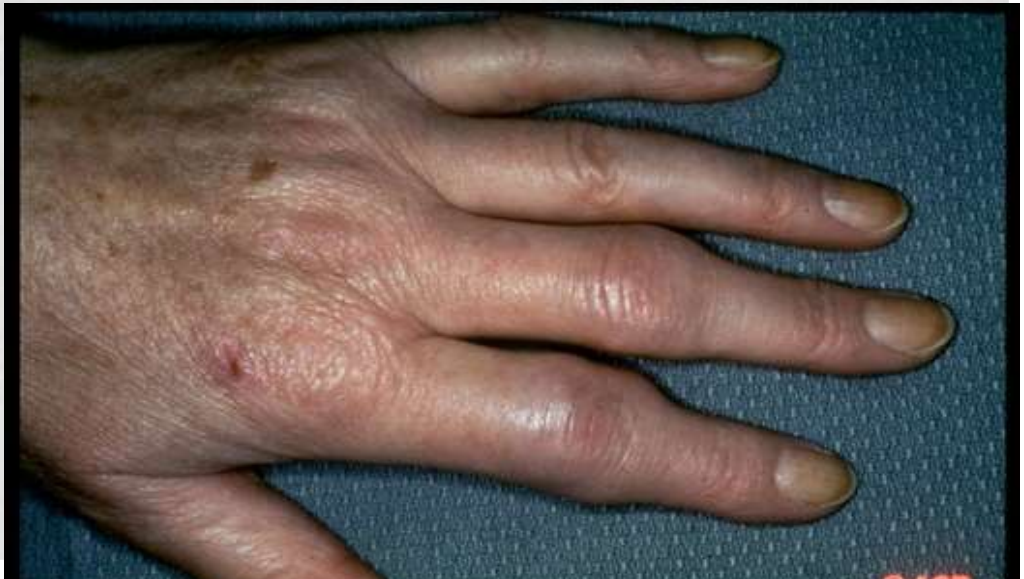
--Inflammatory granulomatous tissue (panus) extend under and over articular cartilage leading to cartilage and bone erosion.

--Later fibrous or even bony ankylosis may occur.
--Muscles atrophy

CLINICAL FEATURES:

-After a period of prodromal symptoms

- pain and joint swelling of small joints of hands ,wrist and feet (usually sparing the DIP joints) usually in symmetrical fashion **with morning stiffness** more than one hour. The inflamed joints are tender on pressure with painful restriction of movements. Large joints involvement and extra articular manifestations may occur.



ONSET:

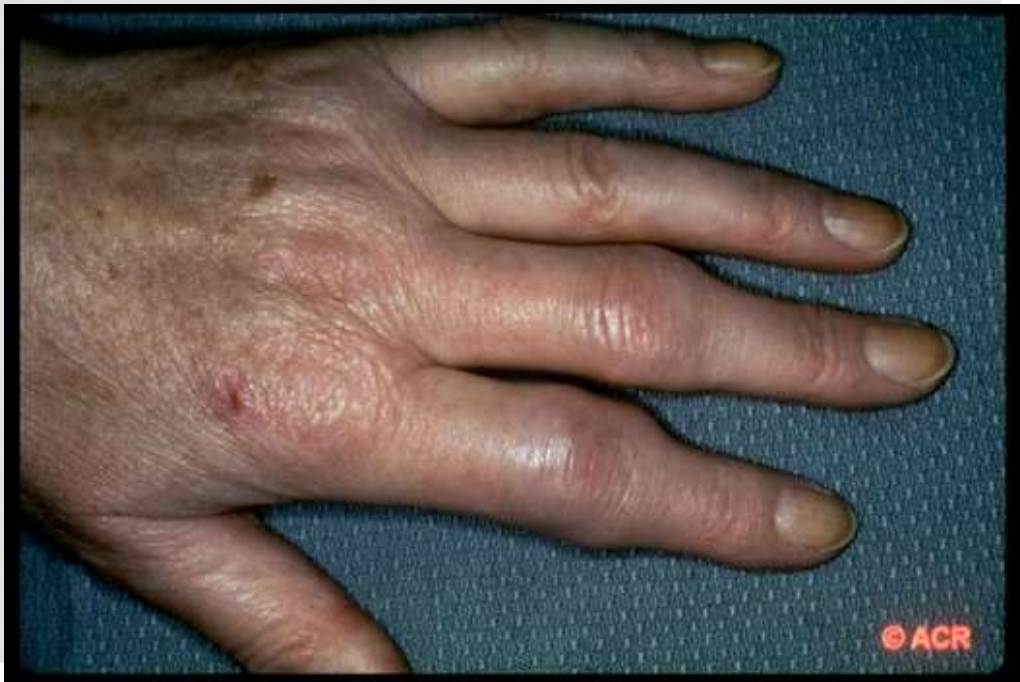
-INSIDIOUS
-ACUTE
-MIMIC POLYMALAGIA RHEUMATICA
-PALINDROMIC RHEUMATISM

If the disease is not halted early by disease modifying anti rheumatic drugs (DMARD) resulting in bone erosions , articular destruction , ligament and tendon laxity or contractures causing characteristic deformity.

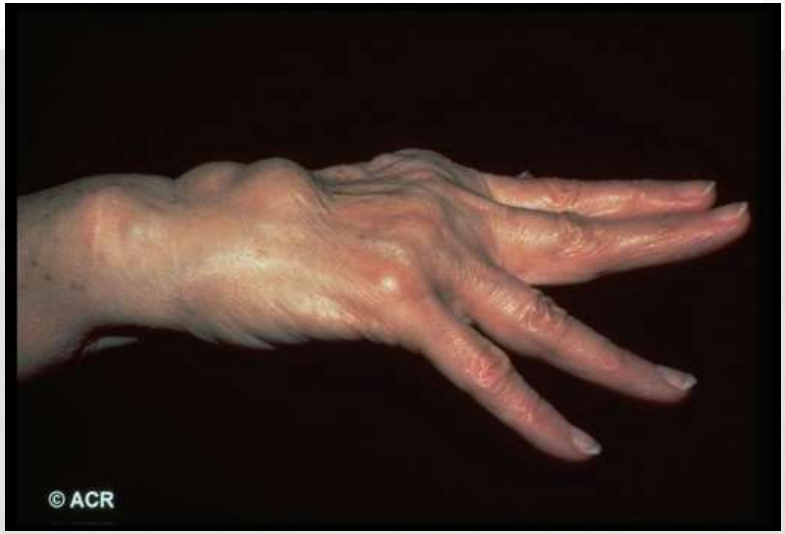
HAND JOINTS

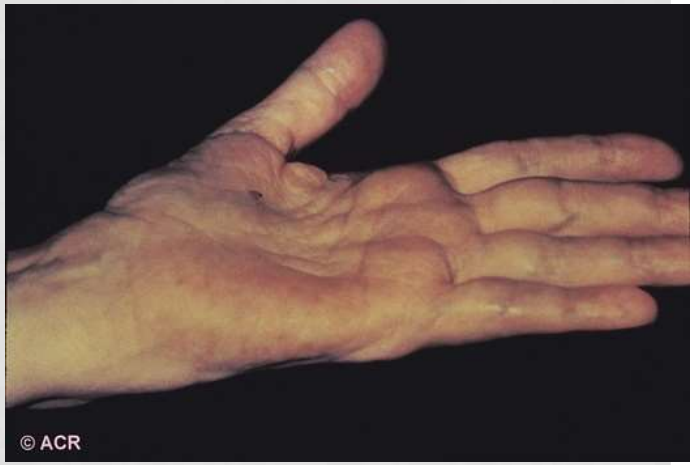
Swelling of proximal interphalangeal(fusiform)
and metacarpophalangeal
joints.

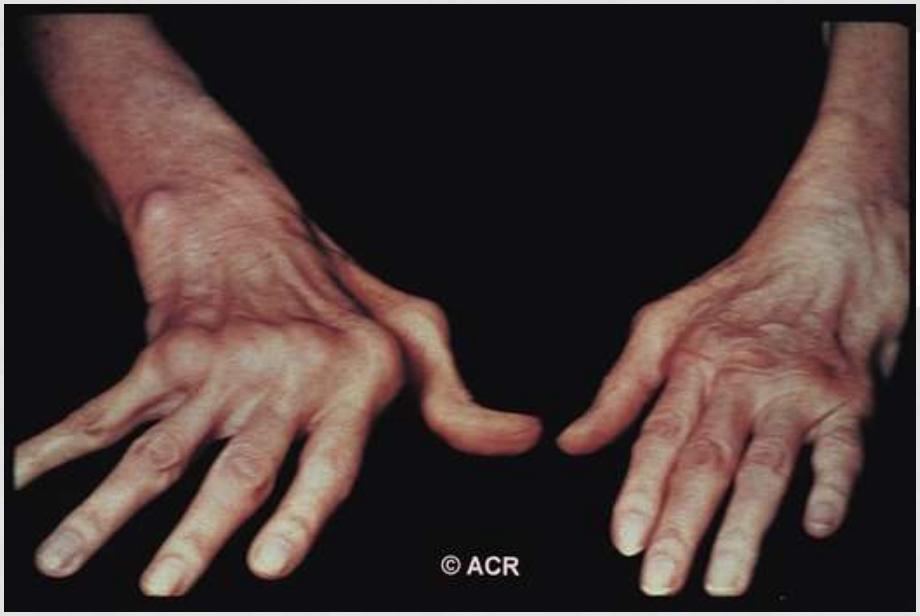
The distal interphalangeal joints are rarely involved
"usually spared".

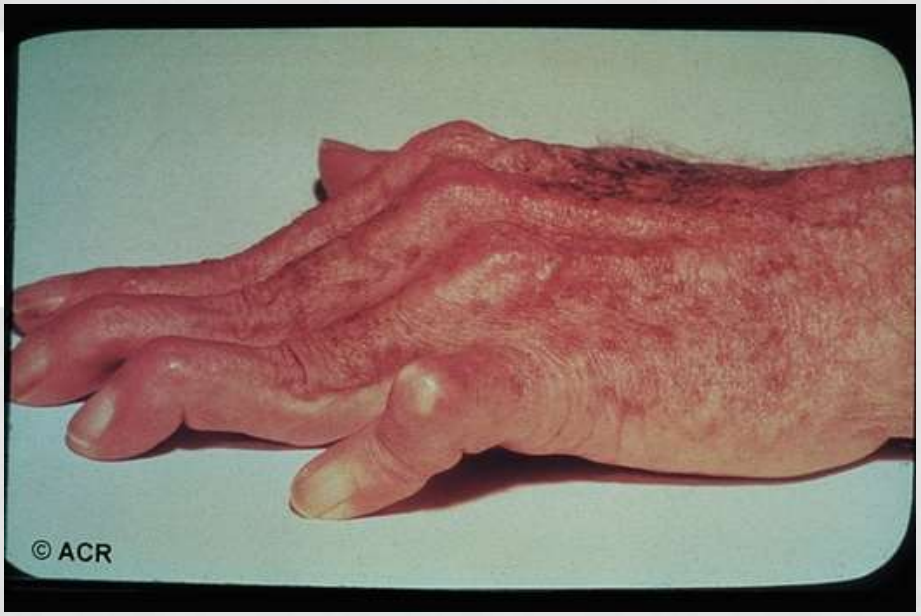


Synovitis of the wrist usually uniform feature of RA, may lead to limitation of movement, Dorsal subluxation of ulnar styloid is common and may contribute to rupture of the 4th and 5th extensor tendon. Median nerve entrapment can be occur.





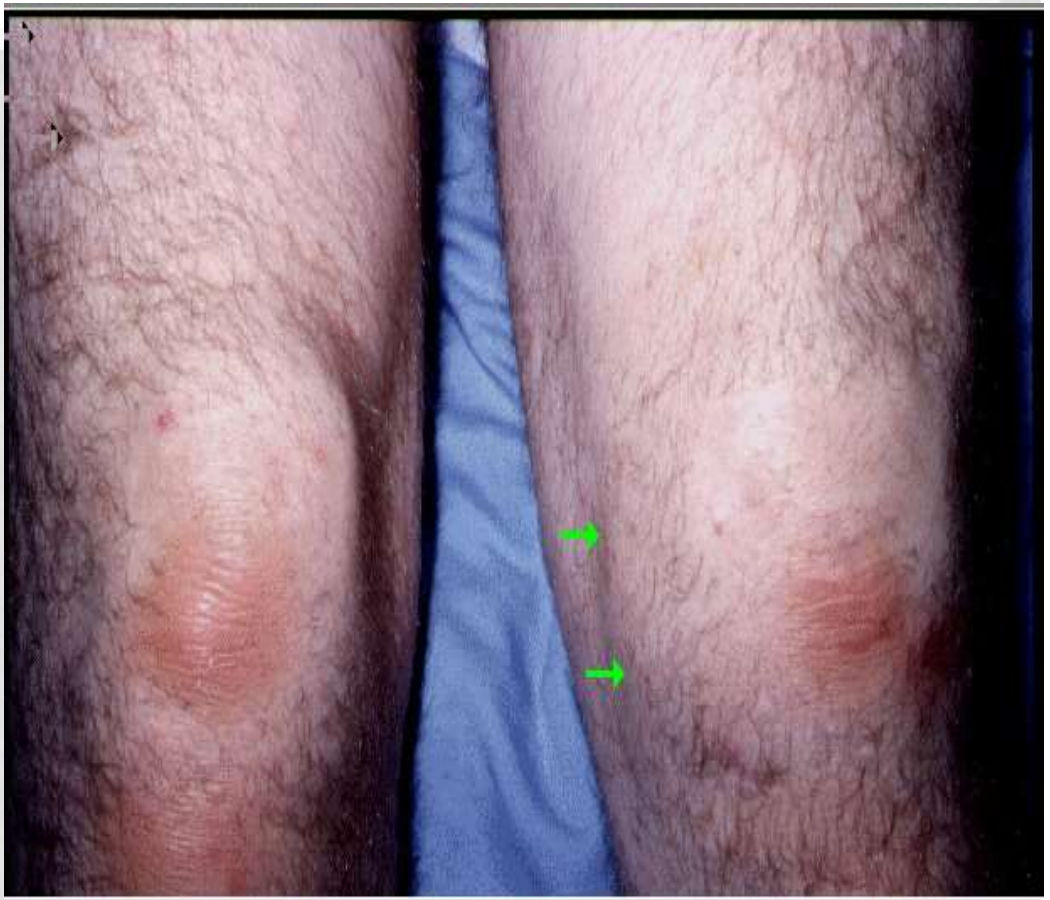




* Radial deviation at the wrist. Ulnar deviation of MCP joints.
* Swan neck deformity.
* Boutonniere deformity.
* (Z) deformity of the thumb.
* Triggering of finger may occur due to nodules formation in flexor tendon sheath.

Knee joint

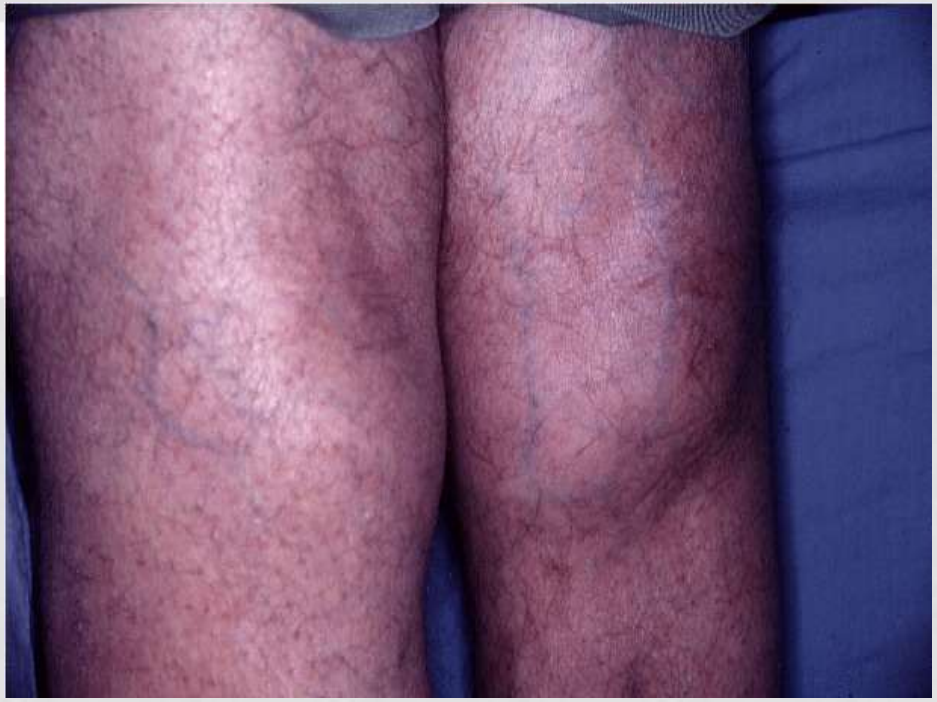
Is commonly involved with synovial hypertrophy, chronic effusion

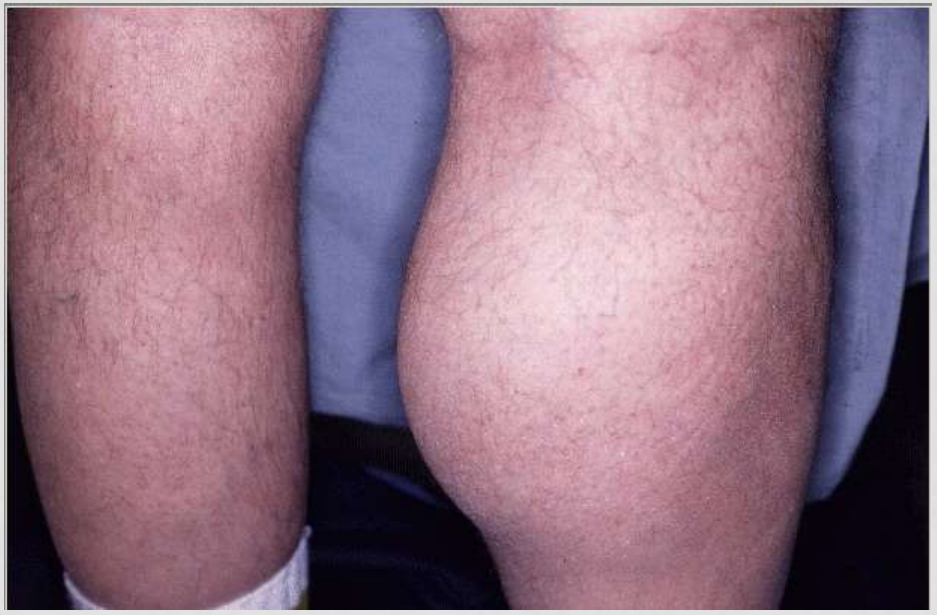


- Popliteal (Baker's) cyst ,with knee synovitis and the synovial fluid communicating to cyst in valve- like mechanism preventing the fluid to return back to joint cavity. Rupture of cyst

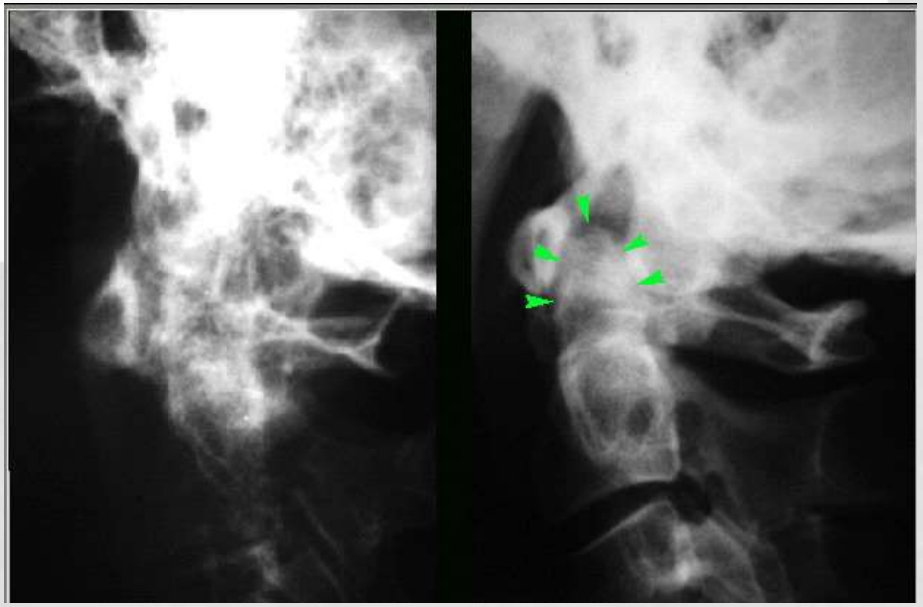
producing picture similar to DVT

- ***Characteristic pre-existing history of joint problem. Doppler ultrasound study is required to establish the diagnosis.***



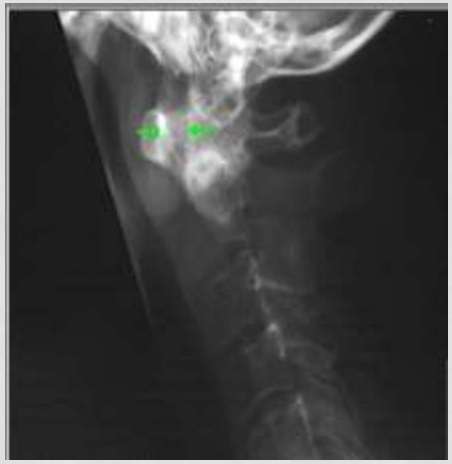


Cervical spine:



*Atlanto-axial subluxation

*Spinal cord compression



Foot & Ankle

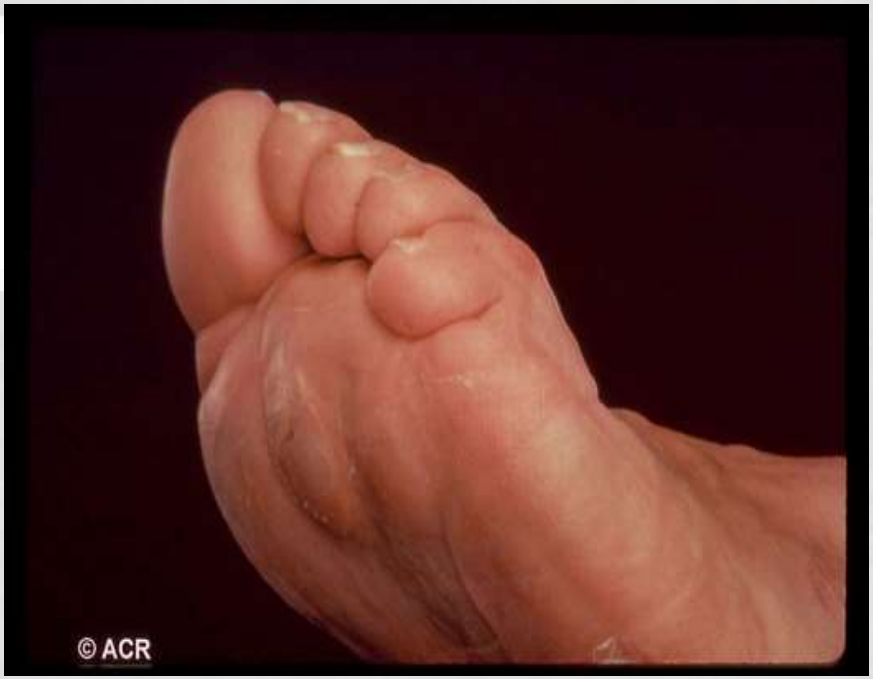
Eversion.

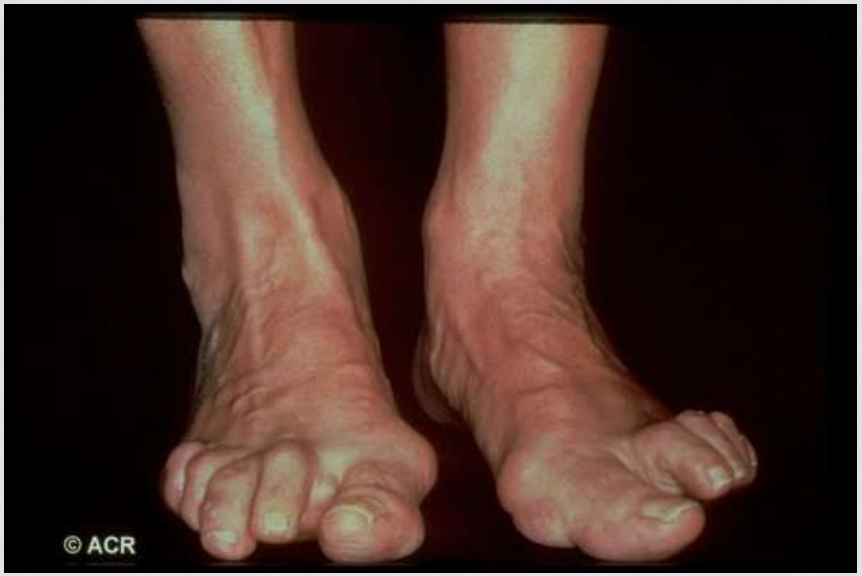
Dorsal sub luxation of MTP joint may result in Cock-up toe deformity.

Painful burse and Callosities.

Flat foot due to rupture of the tibialis post.tendon.

Hallux valgus.





EXTRA ARTICULAR MANIFESTATIONS:

OCCUR MAINLY IN LONG-STANDING SEROPOSITIVE EROSIVE DISEASE.

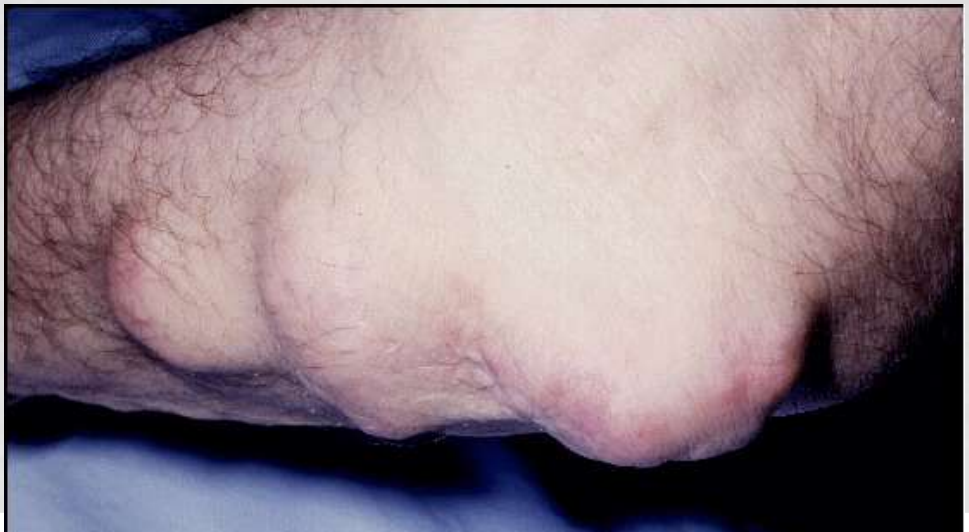
- WEIGHT LOSS, ANOREXIA, GENERALIZED OSTEOPOROSIS, WASTING OF MUSCLES DUE TO SYSTEMIC INFLAMMATION.

CUTANEOUS AND VASCULAR FEATURES:

RHEUMATOID NODULES:

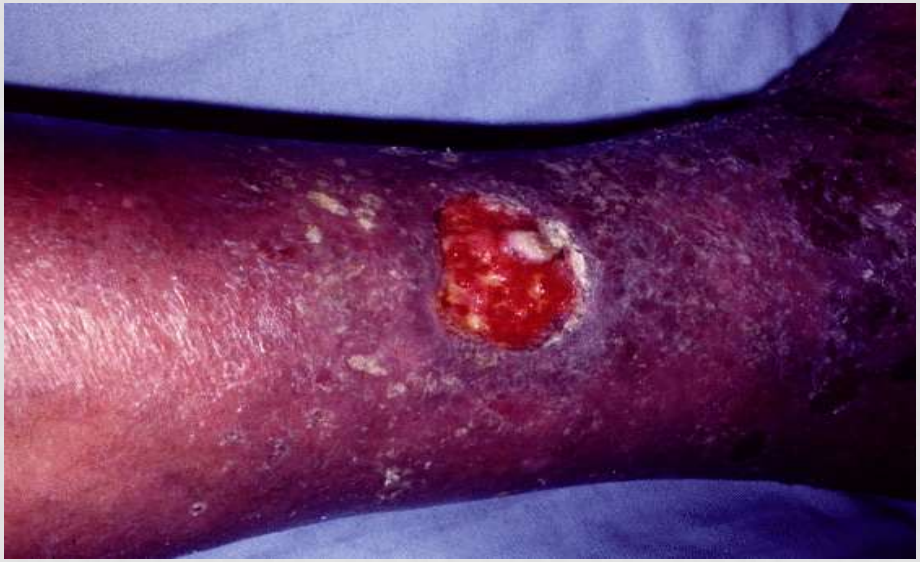
USUALLY OCCUR AT PRESSURE SITE SUCH AS EXTENSOR SURFACE OF FOREARM , SACRUM, ACHILLES TENDON.

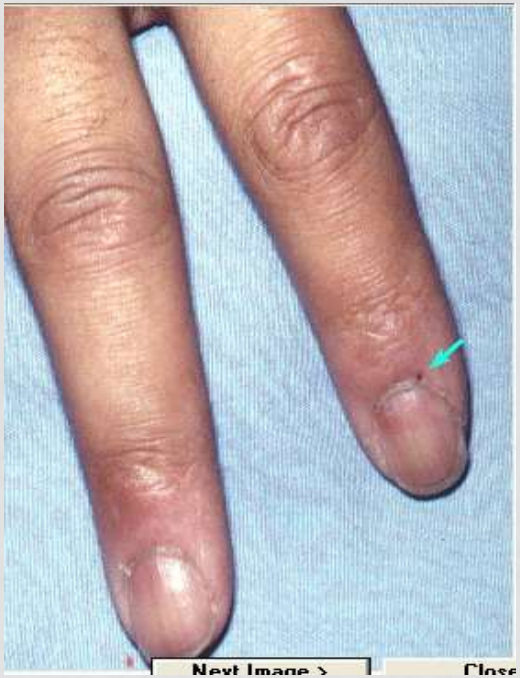
THE NODULES ARE FIRM NON TENDER . IT ALMOST EXCLUSIVELY OCCUR IN SEROPOSITIVE DISEASE.



- Rheumatoid vasculitis:

  occur in seropositive patients. vasculitis ranging from benign nail-fold infarct to wide spread ulceration and skin necrosis.
  Vasculitis of medium size artery can lead to mesentric, renal, and coronory occlusion.





Ocular features:

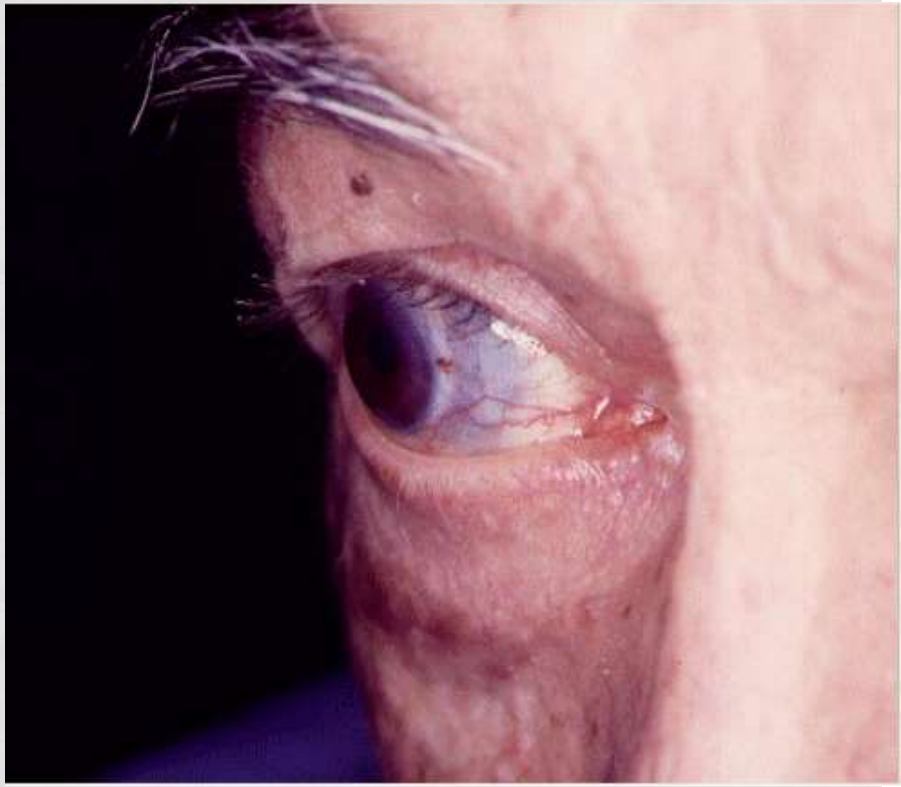
*Dry eye
Keratoconjuctivitis Sicca" secondary sjogren disease.

*Episcleritis (painless unimpaired sight).

*Scleritis (painful and more serious sight - threatining).

*Scleromalacia (bilateral thinning of the sclera).

*Corneal melting rare, serious, associated with vasculitis, if untreated , it can lead to perforation



Cardiac manifestations:

occur up to 30%usually asymptomatic.

Symptomatic pericardial effusion and constrictive pericarditis are rare.

Heart block, cardiomyopathy, coronary artery occlusion or aortic regurgitation can occur.

Accelerated atherosclerosis also occur. Patients with RA have an increased mortality when compared with age-matched controls, primarily due cardiovascular disease

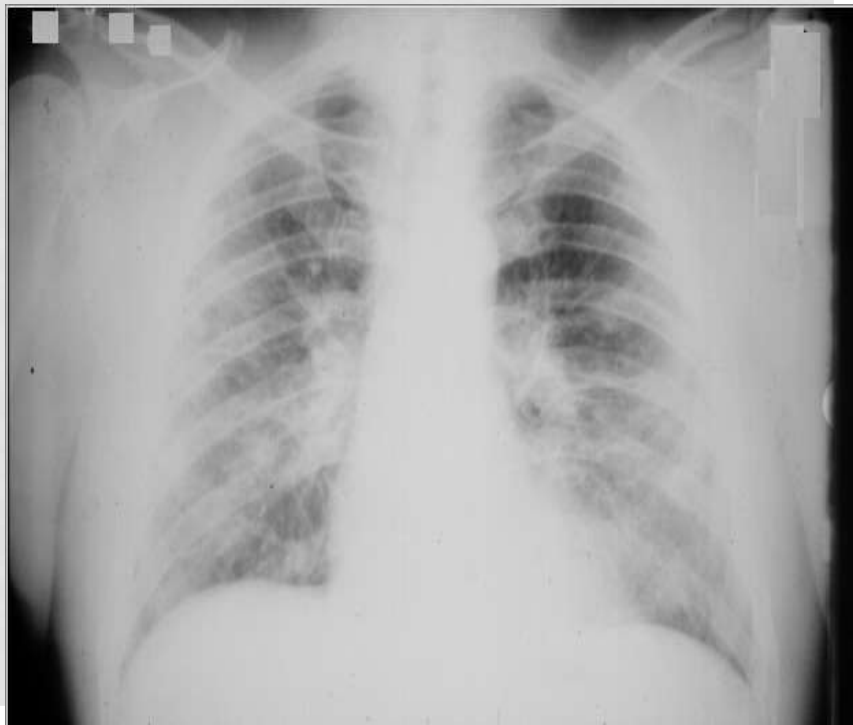
furthermore the nsaids and corticosteroid exacerbate cardiac diseases.

Pulmonary features [Rheumatoid lung]

- Pulmonary fibrosis • Pleural effusion.
- Rheumatoid nodule (pulmonary)

Bronchitis and bronchiectasis are common in RA..

- Rarely potentially fatal obliterative bronchiolitis may occur .
- Bacterial infection especially those on corticosteroid.
- Pulmonary fibrosis may caused by methotrexate.
- Anti TNF therapy associated with TB reactivation..



Neurological complications:

-entrapment neuropathy . compression of median nerve is common (carpal tunnel syndrome). Ulnar nerve compression and tarsal tunnel syndrome can also occur.

- Diffuse peripheral neuropathy and mononueritis multiplex (in rheumatoid vasculitis)

-cervical cord compression at atlanto-axial joint or sub axial level subluxation.

Hematological features:

-Microcytic iron deficiency anaemia (NSAID-induced GIT blood loss).

-Normochromic normocytic anaemia, thrombocytosis in active disease.

Felty's syndrome: constitute of:

RA , splenomegaly and neutropenia,

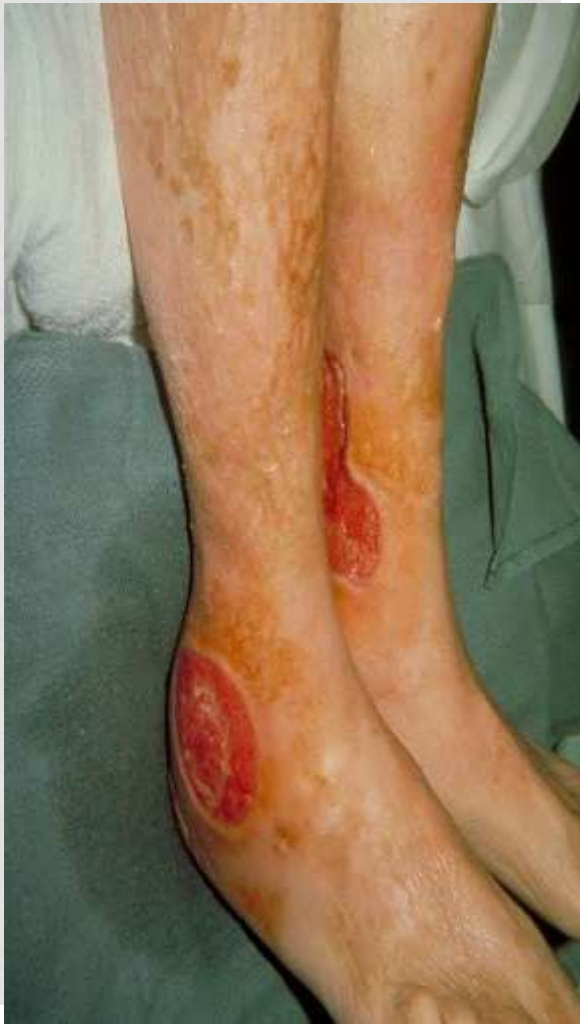
in long standing seropositive at age

between 50-70 ,female>male, ass.

with Sjogren disease, LAP,

thrombocytopenia, recurrent

infection, leg ulcer (vasculitis)



- Other complications:

-Amyloidosis (rare) presented as nephrotic syndrome

-Generalized or localized lymphadenopathy. In persistent lymphadenopathy biopsy indicated because there is risk of associated lymphoma in patient in long standing disease.

-Osteoporosis

-Ante -date or accelerated atherosclerosis

- Infections

Investigations:

The diagnosis of RA usually done on clinical background.

The lab. Invest. is needed for confirmation of diagnosis or for monitoring of disease

--Acute phase response. ESR and CRP are elevated and may be not in isolated joint arthritis ..so normal values don't exclude the diagnosis.

--Rheumatoid factor (RF)and anti citrullinated peptide antibodies (APCA)are present in about .(٧٠%)
Rf has low diagnostic specificity. The principle use of RF is for prognosis since a high RF titer at presentation carry poor prognosis

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--Investigation to monitor drug safety:
urinalysis, liver enzyme, s. Urea and creatinine , full blood count , CXR.

Disease activity score :DAS-28

is frequently used to assess the disease activity and response to treatment and the need for biological therapy.

To calculate DAS- 28 :

count the number of tender and swollen joints **In upper limbs and knees**

- measure the ESR
- ask the patient to rate global activity of arthritis during the past week using visual analogue scale (VAS) from 0 (no symptoms) to 100 (very severe)
- enter data into calculator or work out using a SPECIAL FORMULA.

A DAS28 score of higher than 5.1 is indicative of high disease activity, whereas a DAS28 below 3.2 indicates low disease activity. A patient is considered to be in remission if they have a DAS28 lower than 2.6 .

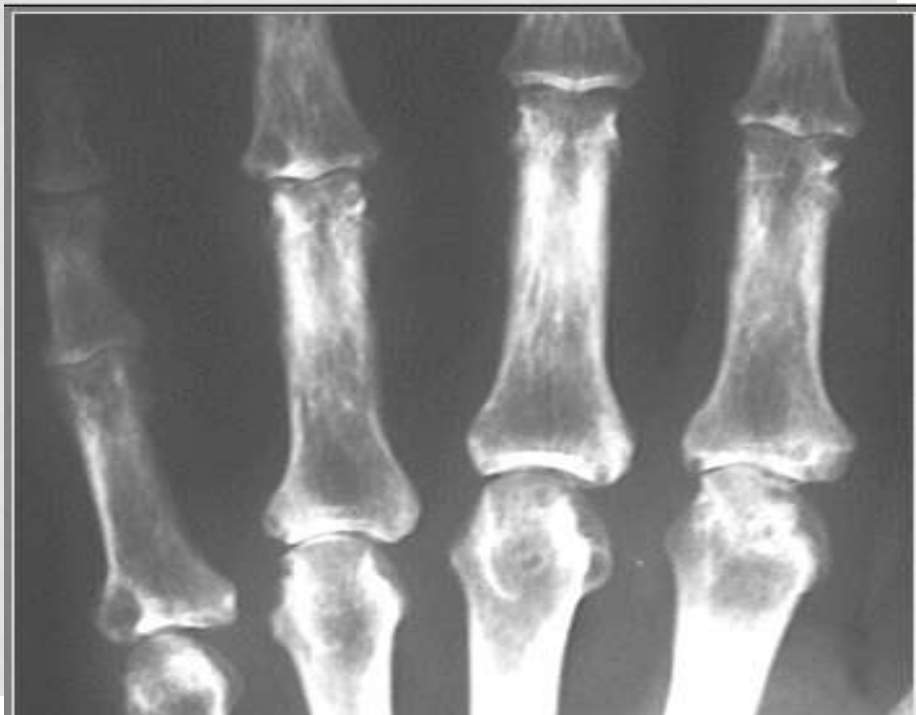
Synovial fluid examination :shows non specific inflammatory changes.

Radio graphical features:

Plain radiography: Can be normal in early stage of disease apart from soft tissue swelling

Periarticular osteopenia.

*marginal **non-proliferative** erosions and symmetrical joint narrowing. Plain x-ray also used to detect atlanto-axial or subaxial subluxation(in flexion and extension position) where as the degree of cord compression need MRI.*



-MRI and ultrasound are more sensitive in detecting early erosions and when uncertainty of synovitis .(not used routinely in clinical obvious cases).

-Ultrasound is indicated in rupture of baker cyst to confirm diagnosis and to exclude possibility of DVT as in some instances both can co exist.

- the American College of Rheumatology (ACR), in collaboration with European League Against Rheumatism (EULAR), released the updated classification criteria EULAR/ ACR

- which depend mainly on the number and distribution of involved joints, serology, acute phase reactants, and duration of disease ,

- with goal of distinguishing newly presenting patients with early undifferentiated arthritis who had a high probability of developing persistent or erosive RA.

The ACR/ EULAR criteria

Criterion	***Score***
Joint affect	
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	
Less than 6 weeks	0
More than 6 weeks	1
Acute phase reactant	
Normal CRP and ESR	0
Abnormal CRP or ESR	1

Patients with 6 or more are considered to have RA.

Management:

goal is disease control and induction of disease remission

- Patient education
- Multidisciplinary team
- Physical rest and passive exercises.
- Re assessment

Drug Therapy:

- Prompt and early introduction of small molecules DMARDs and corticosteroid play a central role in induction of remission.
- The patient should be informed that DMARDs will not improve symptoms immediately. But in longer term the symptoms will be under control and joint damaged will be prevented. If no or partial response to DMARD therapy this necessities increase the dose or combine with other DMARD, with progression to biological drugs if needed.

Some of dmards are contraindicated in pregnancy.

Regular monitoring is necessary to exclude side effect and toxicity (mainly hematological and liver toxicity) and to evaluate drug efficacy.

It not reverse the already present erosions but can stop or modify the disease progression .

*the most common DMARD of choice is methotrexate (MTX).

Disease Modifying Anti-Rheumatic Drugs(DMARDs):

Methotrexate(MTX):

It is considered the main drug of choice or the anchor of DMARD therapy .

The starting dose is 10-15 mg /week increasing by 2.5 mg every 2- 4 week until benefit or toxicity. The maximum dose is 25mg/week.

It can used alone or with other DMARD (combination) therapy.

benefit appear after 1- 4 months after initiation of drug.

Main early side effect are nausea , vomiting , malaise if persist patients can effectively treated by subcutaneous rout.

Patients should alarm about drug interaction with sulphonomides.

Also patient should avoid alcohol which may enhance hepatotoxicity.

Regular monitoring is essential for early detection of serious side effect (hepatic or bone marrow toxicity) .

pulmonary pneumonitis is rare serious side effect, if occur the drug should stopped immediately and patient treated with high dose of steroid.

Sulfasalazine:

- CAN Taken orally alone, but usually with MTX.
- GIT upset and nausea main side effect.
- Starting dose 500mg/day and increasing gradually to 2-4 gm /day
- Monitoring for hematological and hepatic toxicity

Hydroxychlorquine:

- Ususlly used with comnination with other DMARD(mainly MTX.sulfasalazine.)
- Given in dose of 400mg/d.
- Retinal damage may occur in long term treatment.
- Visual acuity should tested before treatment and repeated regularly as treatment is going on.

Leflunomide:

- Can be used alone or with other drug.
- Given in dose of 10- 20 mg/day.
- Usually well tolerated, low marrow toxicity, but may cause liver dysfunction.
- Require regular liver and hematological monitoring.

Gold, pencillamine, ciclosporine:

- these drugs are occasionally used for RA treatment due to availability of other drugs with a better risk-benefit profile.

Corticosteroid :

although it has disease modifying effect, but its main use are:

- ***Induction*** of remission in patients with RA who starting synthetic DMARD. And tapering till the effect of DMARD appear(***bridge therapy).***
- ***In flare up*** **of disease while patient already on DMARD therapy.**
- ***Flare up during pregnancy***
- ***Intraarticular*** ***injection of*** **corticosteroid when one or two joints with persistent synovitis in spite of generalized well being and other joints are remitted (in this situation possibility of infection should be excluded)**
- **Corticosteroid therapy carry many side effects mainly osteoporosis, which is also main complication of RA even in absence of steroid therapy.**
- **DEXA should considered in RA with anti osteoporotic measures especially for those on steroid of 7.5 mg/day for more than 3 months.**

Biological therapies

- Are reserved for the treatment of patients who have high disease activity despite having had an adequate trial of traditional DMARDs.
- More effective and cost more greater than synthetic DMARDs.
- In UK its used restricted to patient with active RA (das28 > 5.1);
- When an adequate trial of at least two other DMARDs (including methotrexate)

1-ANTI-TNF THERAPY:

ETANRECEPT

INFLIXIMAB

ADALIMUMAB

GOLIMUMAB

CERTOLIZUMAB

CAN BE USED AS MONOTHERAPY (ALTHOUGH A COMBINATION WITH MTX GIVE BETTER RESULTS) . MTX REDUCED NEUTRALIZING EFFECT OF ANTIBODIES FORMATION AGAINST ANTI-TNF THERAPY

The main side effects of anti TNF alpha therapy are increase risk of infection mainly reactivation of latent T.B and increase risk of malignancy mainly basal cell carcinoma of skin and increase progression of cancer in patients with prior tumor.

2- Anti B cell therapy: Rituximab

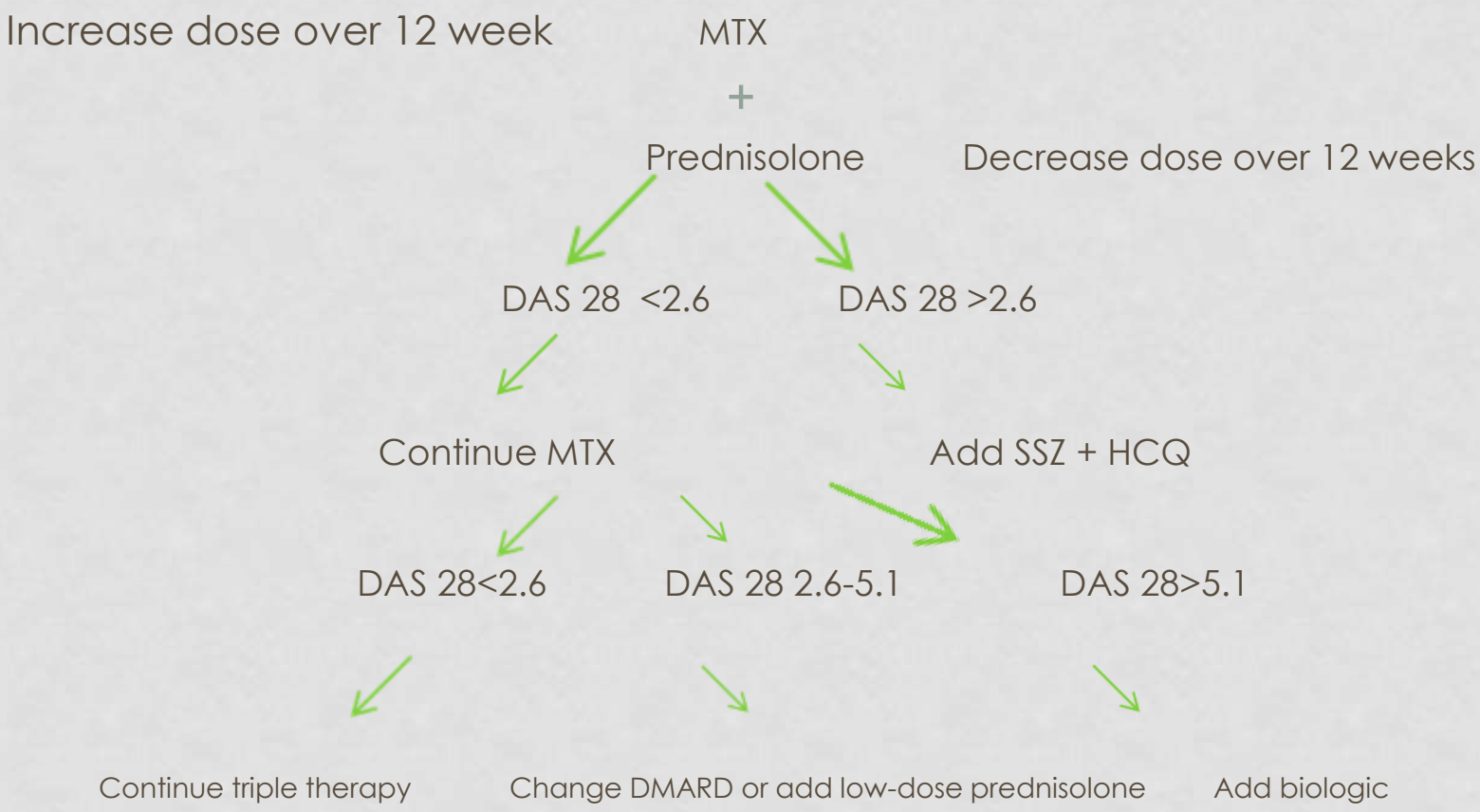
3- Inhibitor of T- cell activation: (Abatacept).

4- ANTI IL-6(Tocillizumab).

5- Anti IL-1(Anakinra).

now JAK (janus kinase inhibitor): tofacitinib and baricitinib.

New diagnosis of rheumatoid arthritis



Surgery:

in complicated conditions surgical interventions may required as: synovectomy, tendon repair, arthrodeses, arthroplasty.

General measures:

- Patient education about nature of disease, regular monitoring and periodic disease assessment.
- Physical rest, NSAIDs and analgesia.
- Joint protection , splinting, regular active and gentle passive exercise to preserve joint function prevent muscle atrophy and joint contracture.
- Hospitalization needed in multiple joint injection , splinting, joint injections.

*Prognosis:

the following factors at presentation are associated with poor prognosis:

1- higher base line disability.
2- insidious onset.
3- female gender.
4- positive Rheumatoid factor , anti-ccp(ACPA) and nodule formation, smoking
5- positive family history of severe RA.
6- involvement of MTP.
7- disease duration of over three months.
8- presence of extra-articular manifestations.

- RA during pregnancy: most patients with RA go into remission during pregnancy.
- methotrexate should be discontinued for at least 3 months and leflunomide discontinued for at least 24 months before trying to conceive.
- **Paracetamol**: the oral analgesic of choice during pregnancy.
- **Oral NSAIDs and selective COX-2 inhibitors**: can be used after implantation to 20 weeks' gestation.
-
- **Corticosteroids**: may be used to control disease flares; the following maternal risks as hypertension, glucose intolerance and osteoporosis should be considered.

DMARDs that may be used: sulfasalazine, hydroxychloroquine, azathioprine if required to control inflammation.

DMARDs that must be avoided: methotrexate, leflunomide, cyclophosphamide, mycophenolate ,gold .

Biological therapies: safety during pregnancy is currently unclear. Theoretical risk is immunosuppression of neonate.

Breastfeeding:

methotrexate, leflunomide, cyclophosphamide, are contraindicated.


ANY
QUESTIONS


Thank
You