Rheumatoid Arthritis

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Introduction

- Commonest inflammatory joint disease seen in clinical practice affecting approx 1% of population.
- Chronic multisystem disease of unknown cause.
- Characterized by persistent inflammatory synovitis lea ding to cartilage damage, bone erosions, joint deformit y and disability.

Causes

- Unknown → theories
- Genetic: HLA DR4+
- Infection: bacteria or a virus triggers RA in peo ple who have this genetic feature.
- In RA, the immune system's antibodies attack the synovium, which is the smooth lining of a j oint → Synovitis.

- Inflammation causes the synovium to thicken. Eventually, if left untreated, it can invade and destroy cartilage.
- The tendons and ligaments that hold the joint together can also weaken and stretch. The joi nt eventually loses its shape and configuration . The damage can be severe.

Onset

- Although Rheumatoid arthritis may present at any age, patients most c ommonly are first affected in the third to sixth decades.
- Female: male 3:1
- Initial pattern of joint involvement could be:-

1) Polyarticular : most common
2) Oligoarticular
3) Monoarticular

- Morning joint stiffness > 1 hour and improve with physical activity i s characteristic.
- Small joints of hand and feet are typically involved.

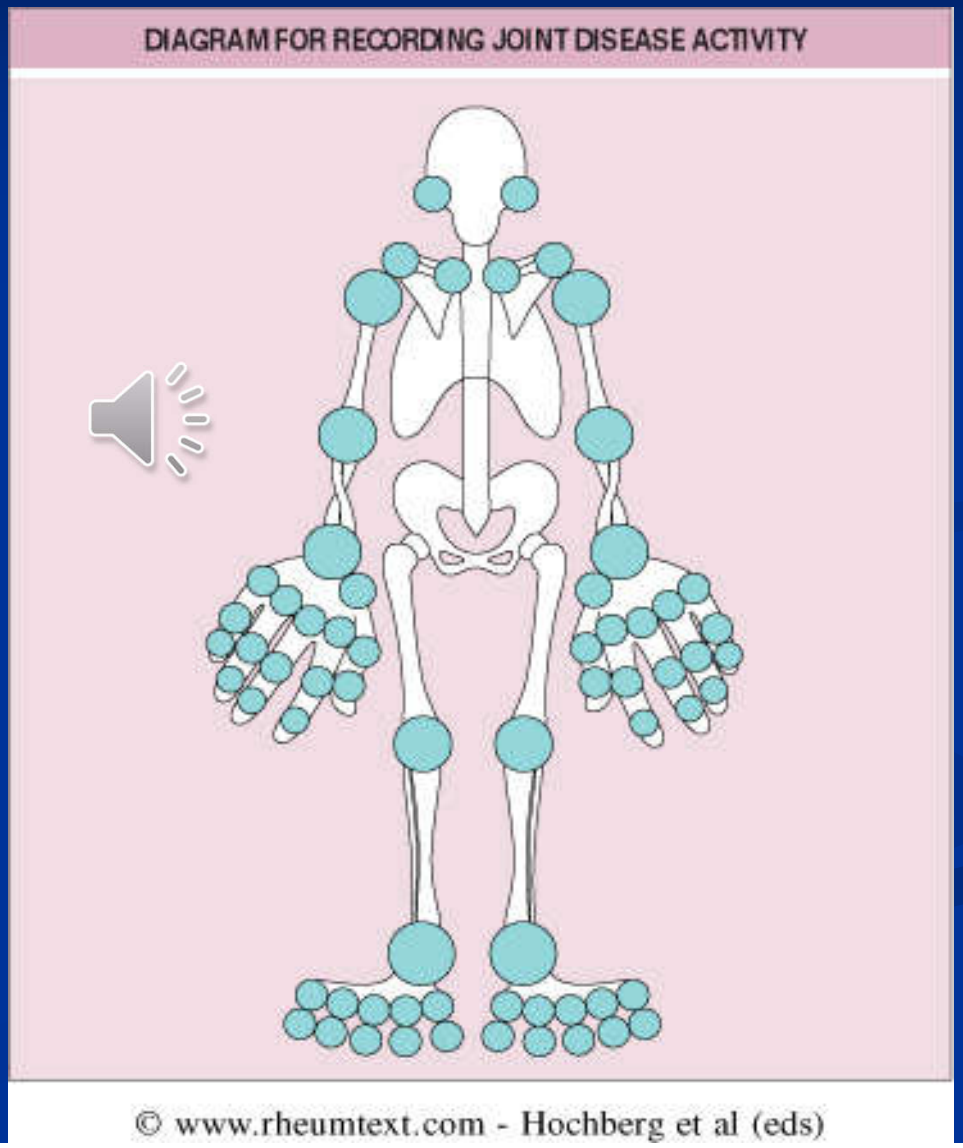
Clinical Manifestations

- Articular

- Extra-articular

Articular manifestation

- Pain in affected joint aggravated by movement is the most common symptom.
- Morning stiffness ≥1 hr
- Joints involved -→



Relative incidence of joint involvement in RA

- MCP and PIP joints of hands & MTP of feet 90%
- Knees, ankles & wrists- 80%
- Shoulders- 60%
- Elbows- 50%
- TM, Acromio - clavicular & SC joints- 30%

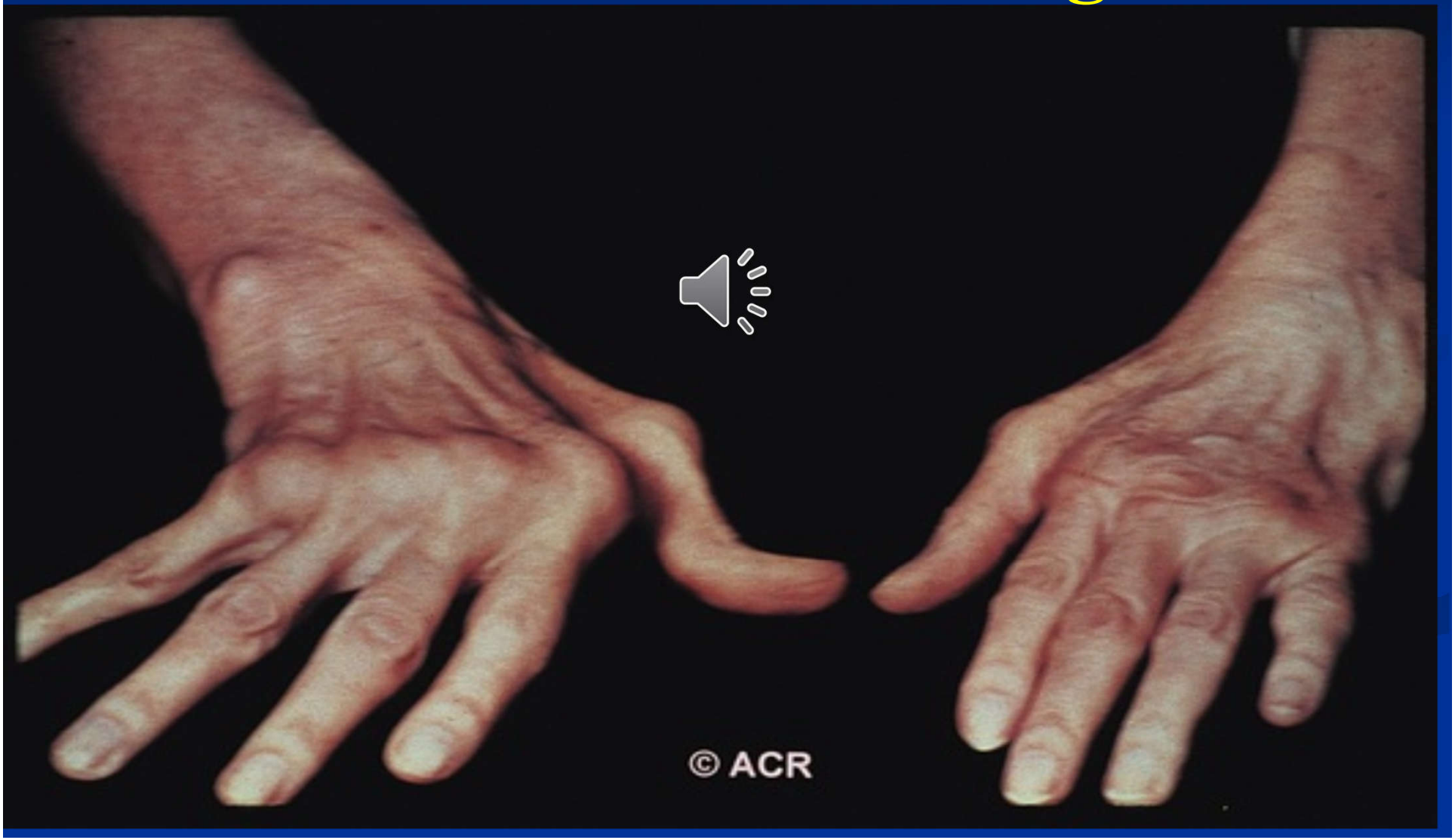
Joints involved in RA

- Don’t forget the **cervical spine**!!
  Instability at cervical spine can lead to impinge ment of the spinal cord.

- Thoracolumbar, sacroiliac, and distal interphal angeal joints (DIP)of the hand are **NOT** involv ed.

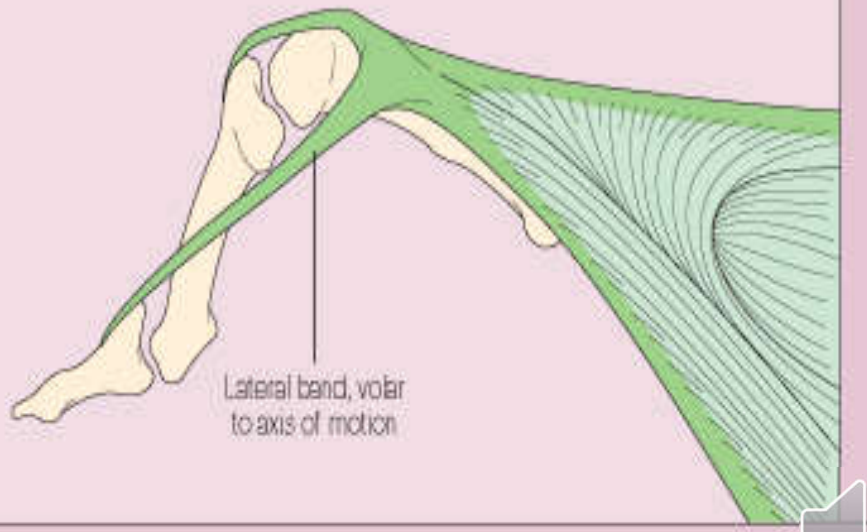
PIP Swelling

Ulnar Deviation, MCP Swelling, Left Wrist Swelling

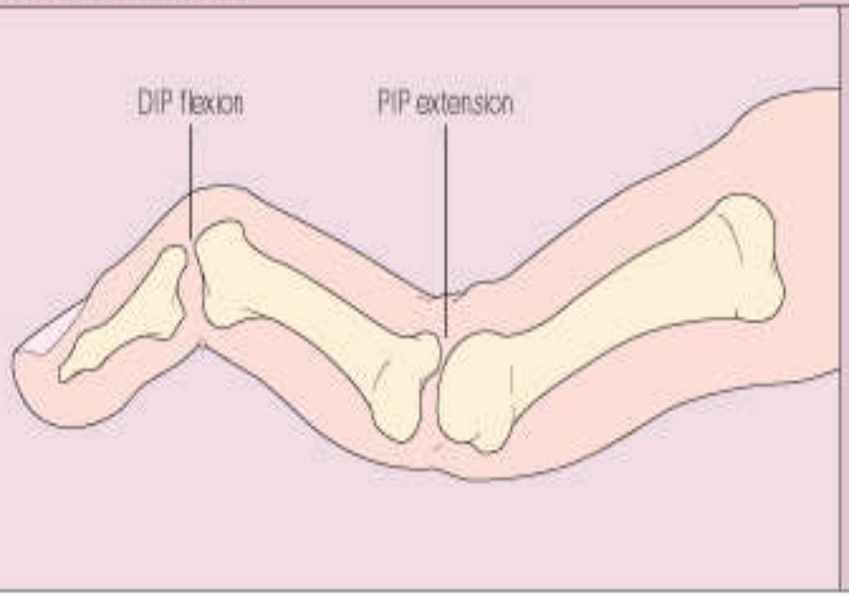


BOUTONNIERE AND SWAN-NECK DEFORMITIES

Boutonnière deformity



Swan-neck deformity



Extra-articular manifestations

- Present in 30-40%
- May occur prior to arthritis
- Patients that are more likely to get are:
  - High titres of RF/ anti-CCP
  - HLA DR4+
  - Male
  - Early onset disability
  - History of smoking

Extraarticular Involvement

- **Constitutional symptoms** (most common)
- **Rheumatoid nodules**(30%)
- **Hematological**-
  - normocytic normochromic anemia
  - leucocytosis /leucopenia
  - thrombocytosis
- ***Felty's syndrome-***
  - Chronic nodular Rheumatoid Arthritis
  - Spleenomegaly
  - Neutropenia

- **Respiratory**- pleural effusion, pneumonitis , pleuro -pulmonary nodules, ILD
- **CVS**-asymptomatic pericarditis , pericardial effusio n, cardiomyopathy
- **Rheumatoid vasculitis**- mononeuritis multiplex, c utaneous ulceration, digital gangrene, visceral infarc tion
- **CNS**- peripheral neuropathy, cord-compression fro m atlantoaxial/midcervical spine subluxation, entra pment neuropathies
- **EYE**- kerato cunjunctivitis sicca, episcleritis, scleriti s

Rheumatoid nodule

Laboratory investigations in RA

- CBC: Thrombocytosis, Leukocytosis
- Acute phase reactants, ESR, CRP
- Rheumatoid Factor (RF)
- Anti- CCP antibodies

Rheumatoid Factor (RF)

- Antibodies that recognize Fc portion of IgG
- Can be IgM , IgG , IgA
- 85% of patients with RA over the first 2 years become RF+
- A negative RF may be repeated 4-6 monthly for the first two year of disease, since some patients may take 18-24 months to become serop ositive.
- **PROGNISTIC VALUE-** Patients with high titres of RF, in general, tend to have POOR PROGNOSIS, MORE EXTRA ARTICULAR M ANIFESTATION.

Causes of positive test for RF

- Rheumatoid arthritis
- Sjogrens syndrome
- Vasculitis such as polyarteritis nodosa
- Sarcoidosis
- Systemic lupus erythematosus
- Cryoglobulinemia
- Chronic liver disease
- Infections- tuberculosis , bacterial endocarditis, infectious mononucleosis, leprosy, syphilis, leishmaniasis.
- Malignancies
- Old age(5% women aged above 60)

Anti-CCP

- IgG against synovial membrane peptides damaged via inflammation
- Sensitivity (65%) & Specificity (95%)
- **Both diagnostic & prognostic value**
- Predictive of Erosive Disease
  - Disease severity
  - Radiologic progression
  - Poor functional outcomes

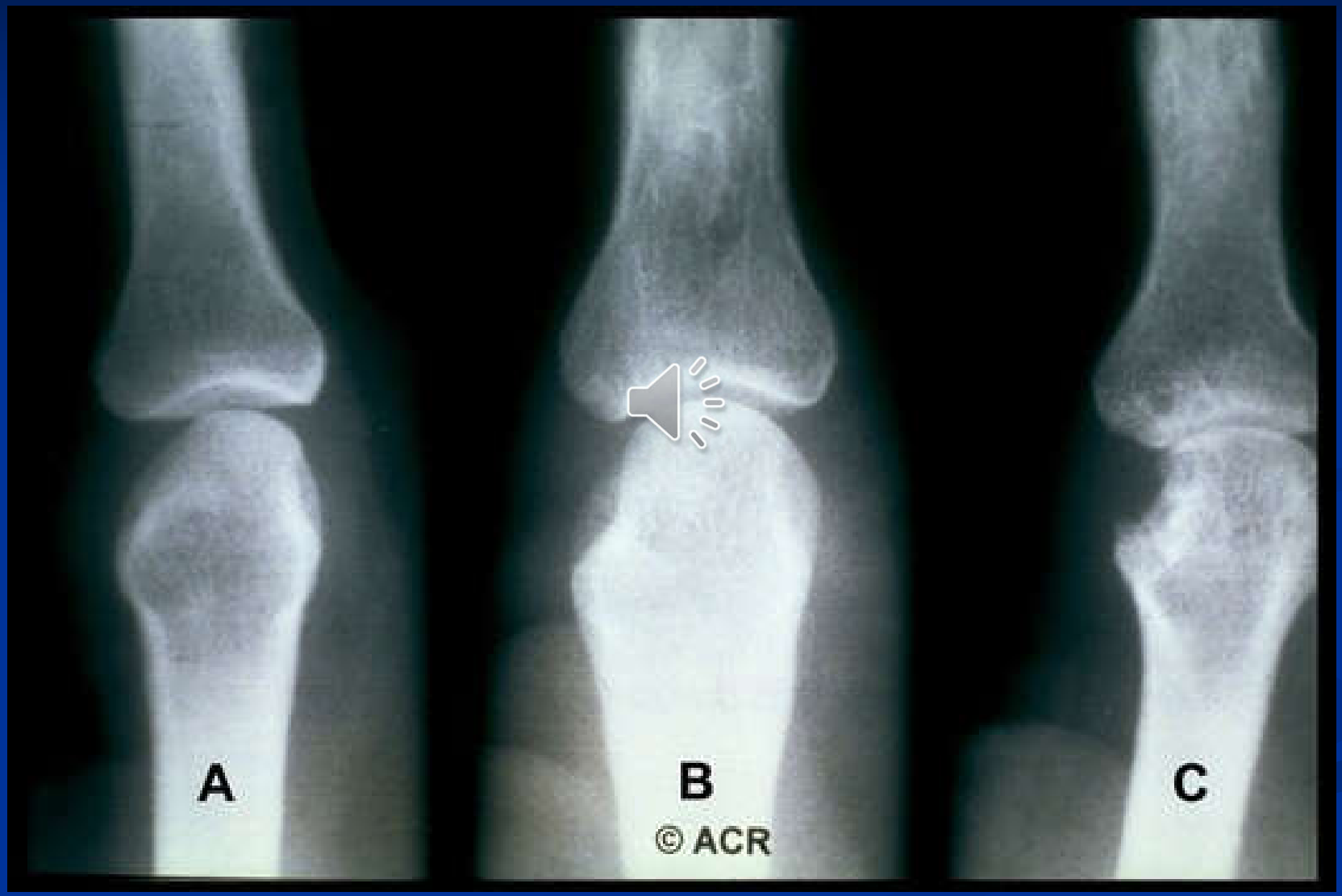
Other Lab Abnormalities

- ANA
  - 30-40%
- Inflammatory synovial fluid
- Hypoalbuminemia

Radiographic Features

- Peri-articular osteopenia
- Uniform symmetric joint space narrowing
- Marginal subchondral erosions
- Joint Subluxations
- Joint destruction
- Collapse

- Ultrasound detects early soft tissue lesions.
- MRI has greatest sensitivity to detect synoviti s and marrow changes.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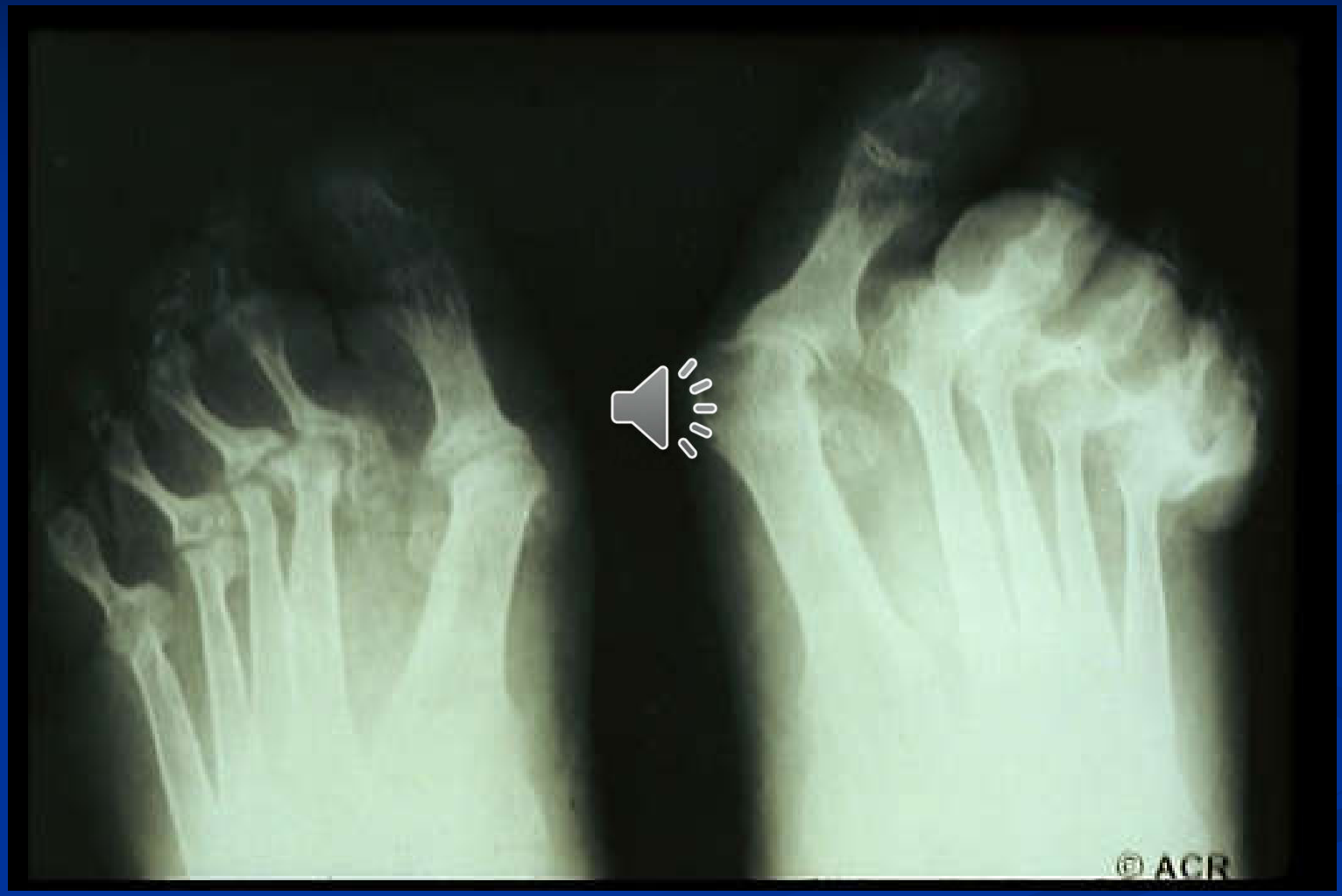
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Diagnostic Criterias

ACR Criteria (1987)

- 1.Morning Stiffness ≥1 hour
- 2.Arthritis of ≥ 3 joints observed by physician simulteneously-Rt/L t-PIP, MCP,wrist, elbow, knee, ankle, MTP
- 3.Arthritis of hand joints-PIP,MCP,wrist
- 4. Symmetric arthritis
- 5. Rheumatoid nodules
- 6. Positive Rheumatoid Factor
- 7. Radiographic Erosions or periarticular osteopenia in hand or wrist joints

- Criteria 1-4 must be present for ≥6 wks
- Must have ≥4 criteria to meet diagnosis of RA

2010 ACR/EULAR Classification Criteria

- a score of ≥6/10 is needed for classification of a patient as having definite RA
- **A. Joint involvement** **SCORE**
- 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
- >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 ACP* *3*

- **C. Acute-phase reactants** (at least 1 test result is needed for classification)
- Normal CRP *and normal ESR* *0*
- Abnormal CRP *or ESR* *1*

- **D. Duration of symptoms**
- <6 weeks 0
- ≥6 weeks 1

Management

Goals of management

- Relieving pain
- Preventing damage/disability
- Patient education about the disease
- Physical Therapy for stretching and range of motion e xercises
- Occupational Therapy for splints and adaptive device s
- Treatment should be started early and should be individ ualised .
- ***EARLY AGGRESSIVE TREATEMNT***

Treatment modalities for RA

- NSAIDS
- Steroids
- DMARDs
- Immunosuppressive therapy
- Biological therapies
- Surgery

NSAIDS

Non-Steroidal anti-inflammatories (NSAIDS) / Coxibs for symptom control

1) Reduce pain and swelling by inhibiting COX
2) Do not alter course of the disease.
3) Chronic use should be minimised.
4) Most common side effect related to GI tract.

Corticosteroids in RA

- Corticosteroids , both systemic and intra-articular are i mportant adjuncts in management of RA.
- Indications for systemic steroids are:-
  1. For treatment of rheumatoid flares.
  2. For extra-articular RA like rheumatoid vasculitis and inters titial lung disease.
  3. As ***bridge therapy*** for 6-8 weeks before the action of DM ARDs begin.
  4. Maintainence dose of 10mg or less of predinisolone daily i n patients with active RA.
  5. Sometimes in pregnancy when other DMARDs cannot be used.

Disease Modifying Anti-rheumatic Drugs

- Drugs that actually alter the disease course .
- Should be used as soon as diagnosis is made.
- Appearance of benefit delayed for weeks to mon ths.
- NSAIDS must be continued with them until true remission is achieved .

DMARDs

Commonly used	Less commonly used
Methotrexate	Chloroquine
Hydroxychloroquine	Gold(parenteral &oral)
Sulphasalazine	CyclosporineA
Leflunomide	D-penicillamine/bucillamine
	Minocycline/Doxycycline Levamisole
	Azathioprine,cyclophosphamide, chlorambucil

When to start DMARDs?

- DMARDs are indicated in all patients with RA who continue to have active disease even after 3 months of NSAIDS use.
- The period of 3 months is arbitary & has been chose n since a small percentage of patients may go in spon taneous remission.
- The vast majority , however , need DMARDs and m any rheumatologists start DMARDs from ***Day 1.***

How to select DMARDs?

- There are no strict guidelines about which DMARDs t o start first in an individual.
- Methotrexate has rapid onset of action than other DM ARD.
- Taking in account patient tolerance, cost consideratio ns and ease of once weekly oral administration ***MET HOTREXATE* is the** DMARD of choice, most wid ely prescribed in the world.

Should DMARDs be used singly or i n combination?

- Since single DMARD therapy (in conjunction with NSAI DS) is often only modestly effective , combination therap y has an inherent appeal.

- DMARD combination is specially effective if they include ***methotrexate*** as an anchor drug.

- **Combination of methotrexate with leflunamide** are sy nergestic since there mode of action is different.

Limitations of conventional DMARDs

1) The onset of action takes several months.
2) The remission induced in many cases is partial.
3) There may be substantial toxicity which require s careful monitoring.
4) DMARDs have a tendency to lose effectiveness with time-(slip out).

- These drawbacks have made researchers look f or alternative treatment strategies for RA- **The Biologic Response Modifiers.**

BIOLOGICS IN RA

- Cytokines such as TNF-α ,IL-1,IL-10 etc. are key mediators of immune function in RA and have be en major targets of therapeutic manipulations in R A.
- Of the various cytokines TNF-α has attaracted ma ximum attention.
- Various biologicals approved in RA are:-

1) Anti TNF agents : Infliximab Etanercept Adalimumab
2) IL-1 receptor antagonist : Anakinra
3) IL-6 receptor antagonist : Tocilizumab
4) Anti CD20 antibody : Rituximab
5) T cell costimulatory inhibitor : Abatacept

Immunosuppresive therapy

Agent	Usual dose/route	Side effects
Azathioprine	50-150 mg orally	GI side effects , myelosuppression, infection,
Cyclosporin A	3-5 mg/kg/day	Nephrotoxic , hypertension , hyperkalemia
Cyclophosphamide	50 -150 mg orally	Myelosuppression , gonadal toxicity ,hemorrhagic cystitis , bladder cancer

How to monitor Tt in RA?

- Disease activity is assesed by several parameters…

1. duration of morning stiffness
2. tender joint count
3. swollen joint count
4. visual analogue scale for pain
5. health assessment questionnaire
6. ESR.
7. NSAID pill count.

- Patient should be observed for 6 months before decl aring a DMARD ineffective.

How long should Tt. be continued?

- Once remission is achieved , maintenance dose for lon g period is recommended.
- DMARDs are discontinued by patients because of **tox icity** or **secondary failure** (common after 1-2 yrs) and such patients might have to shift over different DMA RDs over 5-10 yrs.
- Disease flare may require escalation of DMARD dose with short course of steroids.

Surgical Approaches

- Synovectomy is ordinarily not recommended for patients with rheumatoid arthritis, primarily because relief is only transient.
- However, an exception is synovectomy of the wrist, which is r ecommended if intense synovitis is persistent despite medical t reatment over 6 to 12 months. Persistent synovitis involving t he dorsal compartments of the wrist can lead to extensor tend on sheath rupture resulting in severe disability of hand functio n.
- Total joint arthroplasties , particularly of the knee, hip, wrist, a nd elbow, are highly successful.
- Other operations include release of nerve entrapments (e.g., c arpal tunnel syndrome), arthroscopic procedures, and, occasio nally, removal of a symptomatic rheumatoid nodule.

Thank you.

Clinical information about DMARDs

NAME	DOSE	SIDE EFFECTS	MONITORING	ONSET OF ACTION
1) Hydroxychloroquine	200mg twice daily x 3 months, then once daily	Skin pigmentation , retinopahy ,nausea, psychosis, myopathy	Fundoscopy& perimetry yearly	2-4 months
2) Methotrexate	7.5-25 mg once a week orally,s/c or i/m	GI upset, hepatotoxicity, Bone marrow suppression, pulmonary fibrosis	Blood counts,LFT 6-8 weekly,Chest x-ray annually, urea/creatinine 3 monthly; Liver biopsy	1-2 months

Clinical information about DMARDs contnd..

NAME	DOSE	SIDE EFFECTS	MONITORING	ONSET OF ACTION
3)Sulphasala-zine	2gm daily p.o	Rash, myelosuppression, may reduce sperm count	Blood counts ,LFT 6-8 weekly	1-2 months
4)Leflunomide	Loading 100 mg daily x 3 days, then 10-20 mg daily p.o	Nausea,diarrhoea,alopecia, hepatotoxicity	LFT 6-8 weekly	1-2 months

Agent	Usual dose/route	Side effects	Contraindications
Infliximab (Anti-TNF)	3 mg/kg i.v infusion at wks 0,2 and 6 followed by maintainence dosing every 8 wks Has to be combined with MTX.	Infusion reactions, increased risk of infection, reactivation of TB ,etc	Active infections,uncontrolled DM,surgery(with hold for 2 wks post op)
Etanercept (Anti-TNF)	25 mg s/c twice a wk May be given with MTX or as monotherapy.	Injection site reaction,URTI , reactivation of TB,development of ANA,exacerbation of demyelenating disease.	Active infections,uncontrolled DM,surgery(with hold for 2 wks post op)
Adalimumab (Anti-TNF)	40 mg s/c every 2 wks(fornightly) May be given with MTX or as monotherapy	Same as that of inflximab	Active infections

Agent	Usual dose/route	Side effects	Contraindications
Anakinra ***(Anti-IL-1)***	100 mg s/c once daily May be given with MTX or as monotherapy.	Injection site pain ,infections, neutropenia	Active infections
Abatacept (CTLA-4-IgG1 Fusion protien) Co-stimulation inhibitor	10 mg/ kg body wt. At 0, 2 , 4 wks & then 4wkly	Infections, infusion reactions	Active infection TB Concomittant with other anti-TNF-α
Rituximab (Anti CD20)	1000 mg iv at 0, 2, 24 wks	Infusion reactions Infections	Same as above
Tocilizumab **(** Anti IL-6)	4-8 mg/kg 8 mg/kg iv monthly	Infections, infusion reactions,dyslipidemia	Active infections