Rheumatoid Arthritis- PART 1

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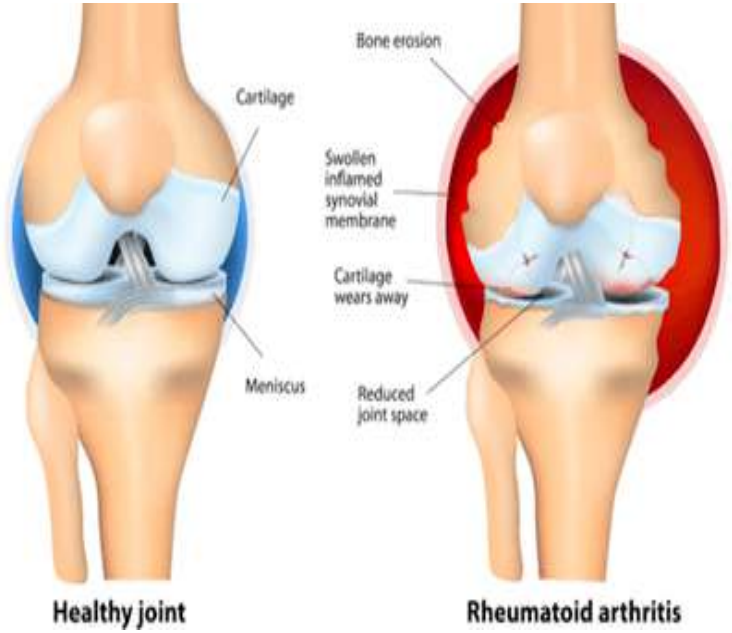
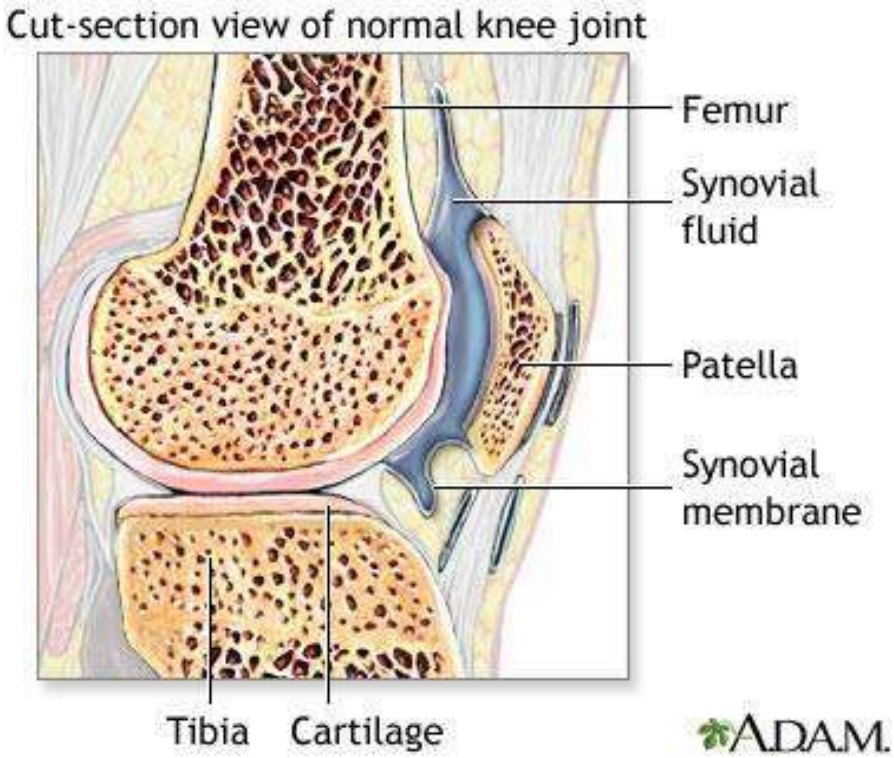
Rheumatoid Arthritis

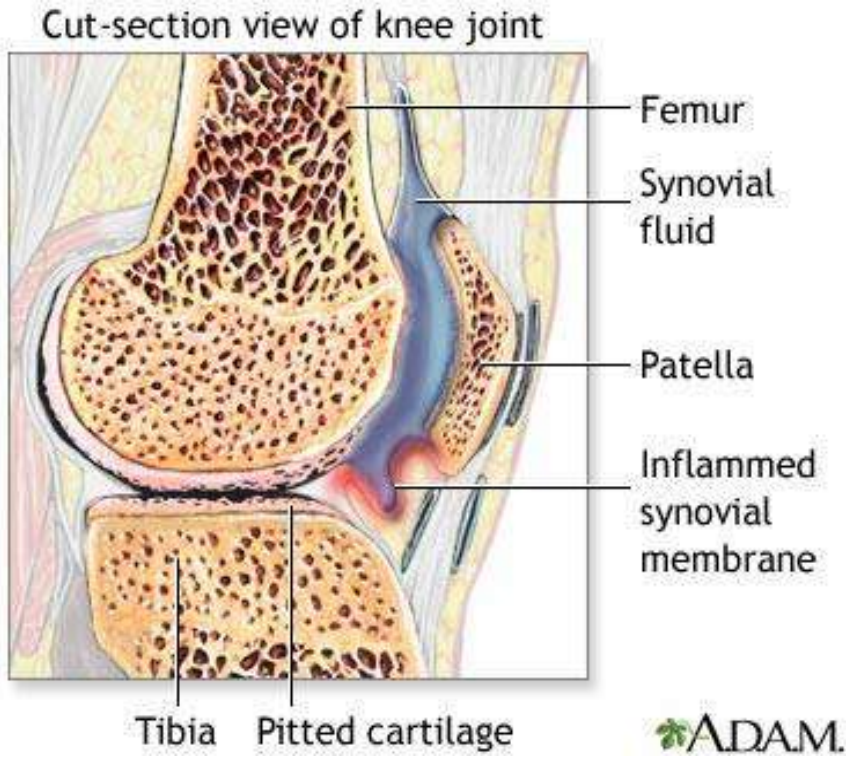
- Autoimmune inflammatory disease primarily characterized by synovitis (persistent inflammatory synovitis leading to cartilage damage---- bone erosions----joint deformity-(Joint destruction progresses rapidly after onset, resulting in irreversible physical dysfunction and deformation of the affected joints.)---Disability.

- Accompaniedby extra-articular organ involvement, such as interstitial pneumonia, in addition to clinical symptoms including pain, swelling, stiffness of multiple joints, fever, and malaise.
- Commonly affects women in their 30s to 50s, with an incidence of 1 in 150.



Anatomy of the Joint





Articular/hyaline cartilage
-acts as a shock absorber
- allows for friction-free movement
- not innervated!

Synovial membrane/synovium
-secretes synovial fluid
-nourishes cartilage
-cushions the bones

Overview

- Age: Any age, commonly 3rd to 6th decade
- Female: male 3:1
- pattern of joint involvement could be:-

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

- Morning joint stiffness > 1 hour and easing with physical activity is characteristic. (Patients often complain of stiffness from the onset of the disease and experience difficulty in moving fingers on awakening, which is often described as having difficulty in forming a fist).
- Small joints of hand and feet are typically involved.

The pathobiology of RA involves a complex interaction of three different scientific domains:

1) A complex genetic predisposition to the disease plus some environmental stimulus,

2) A self-perpetuating, self-amplifying, intra-synovial immune response;

3) Tissue injury mediated by pro-inflammatory cells, inflammatory effector molecules, and degradative enzymes.

Histo-Pathology

1. SYNOVIAL LINING ---Early on in the process, the synovial lining, which includes both Type A (macrophage-like) and Type B (mesenchymal or fibroblast-like) cells, becomes proliferative.

The synovial lining increases in cell number and mass.

INTERSTITIUM--- A diffuse and nodular inflammatory cell infiltrate is observed in the interstitium.

It includes CD4+ and CD8+ lymphocytes, dendritic cells, and other antigen presenting cells.

The histologic appearance showing focal aggregation of both T- and B-cells, as well as the presence of germinal centers similar to that which is seen in lymphoid tissues.

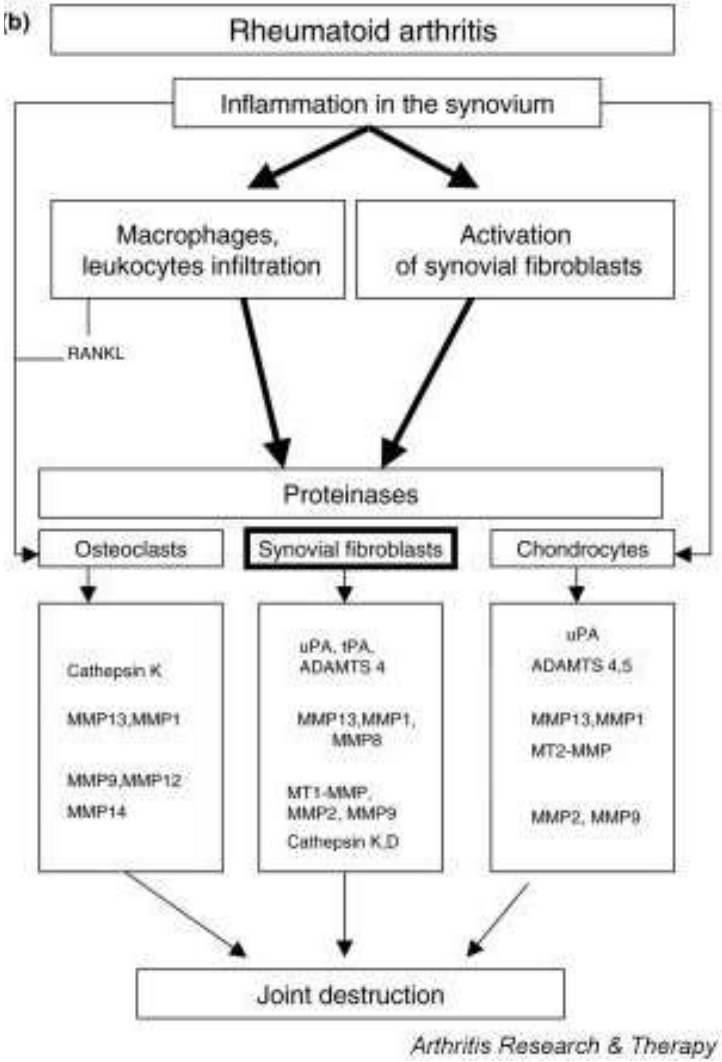
The **Microvasculature** initially reveals endothelial cell activation. As the process matures, plasma cells and multinucleated giant cells appear, and the vascular supply becomes exuberant.

Finally, the growing synovium appears as granulation tissue as it advances to the hyaline cartilage at the margin of the joint

- A local effect of degradative Enzymes and activated Osteoclasts produces the classic erosion at the bone and cartilage margin also to tendons, ligaments, and other musculoskeletal structures.
- Erosions are produced by bone and matrix protein resorbing osteoclasts, which may be induced and activated by cytokines released into the inflammatory milieu.

ROLE OF ENZYMES IN RA

1. Direct mechanism involves the production of MMPs and cathepsins by the RA synovium .
2. Indirectly induces cartilage remodelling by deregulation of chondrocyte function through the release of cytokines and other mediators from the synovium .
3. As part of the inflammatory process in RA, macrophages are recruited to the joints, where they release inflammatory cytokines such as IL-1β, TNF-α and IL-6.
4. These cytokines induce expression of proteinases in synovial fibroblasts and chondrocytes



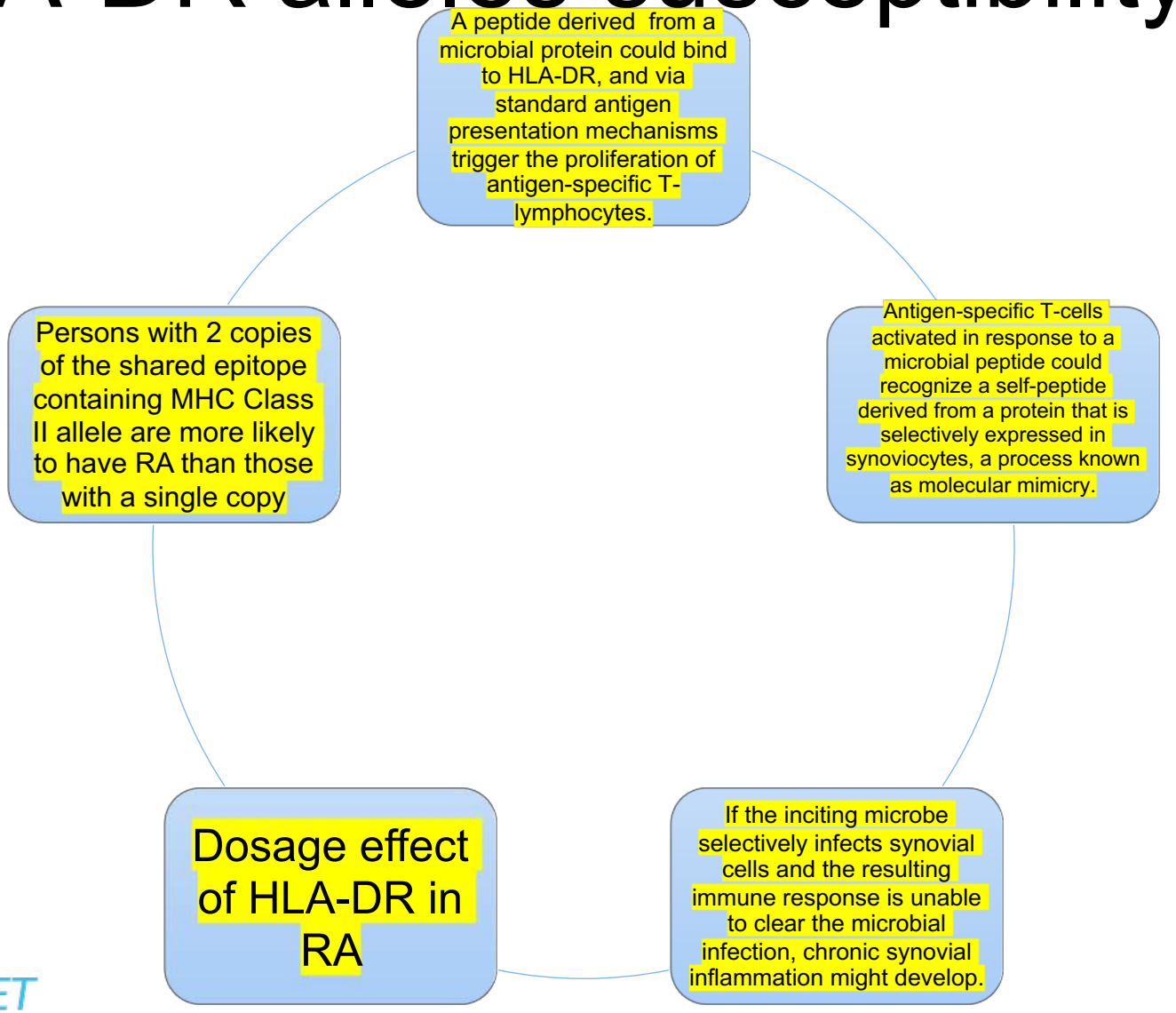
1. Synovial cells stimulated by TNF-α or IL-1β increase the transcription of cathepsin B .
2. Accumulation of active cathepsin B in the synovial fluid of RA patients is probably related to destruction of subchondral bone.
3. Cathepsin B, along with MMP-1 and cathepsin L, responsibel for joint destruction.
4. High levels of MMP

- synovial tissue exhibits high constitutive expression of MMP-2, MMP-11 and MMP-19
- MMP-1, MMP-3, MMP-8 and MMP-9 --- RA patients
- MMP-3 ...Cartilage erosion
-

Genetics and Environmental Stimulus

- Families of patients with RA suggest that monozygotic twins have a concordance rate for RA of between 15%-30%.
- Certain genes within the major histocompatibility complex (MHC), located on the short end of chromosome 6 (6p21. 3).
- Shared epitope hypothesis, ie, a 5-amino acid sequence found on several HLA-DR4 alleles defines a structural domain that confers susceptibility to RA
- Genome-wide analyses of single nucleotide polymorphisms in patients with rheumatoid arthritis have identified the human leukocyte antigen D-related B1 gene (HLA-DRB1).

HLA-DR alleles susceptibility to



Other disease-susceptible genes.

I.Protein tyrosine phosphatase non-receptor type 22 (PTPN22), a gene that encodes a tyrosine kinase involved in inhibition of T-cell activation

II.cytotoxic T-lymphocyte antigen-4 (CTLA4),

III.Signal transducer and activator of transcription 4 (STAT4)

IV.TNF alphainduced protein 3 (TNFAIP3)

V.C-C motif chemokine ligand

VI.21 (CCL 21)

VII. Peptidyl arginine deiminase 4 (PADI4) genes.

FACTORS

- In Japanese individuals, two haplotypes of the PADI4 gene have been identified that are disease-susceptible and non-susceptible, and the messenger RNA transcribed from the disease-susceptible gene is reported to be stable.

- Typical environmental factors, including smoking, gingivitis, and intestinal bacterial flora, can cause modulation of the epigenome and the demethylation of histones and DNA, inducing the transcription of proinflammatory cytokines.

Female Sex.

- RA is more common in women than in men, with a ratio of about 3:1.

1. Genetic factors involved in the presence or absence of the Y chromosome, or genetic factors in the random inactivation of one X chromosome.
2. Microbial flora (both pathogenic and commensurate) to which persons are differentially exposed.

AUTOIMMUNE AS A CAUSE

In rheumatoid arthritis, although no specific autoantigen has been identified, ...interaction between genetic and environmental factors and the citrullination of extracellular matrix molecules, such as filaggrin and fibrinogen, causes epigenetic modifications, breaking immune tolerance to antigens and inducing autoimmunity

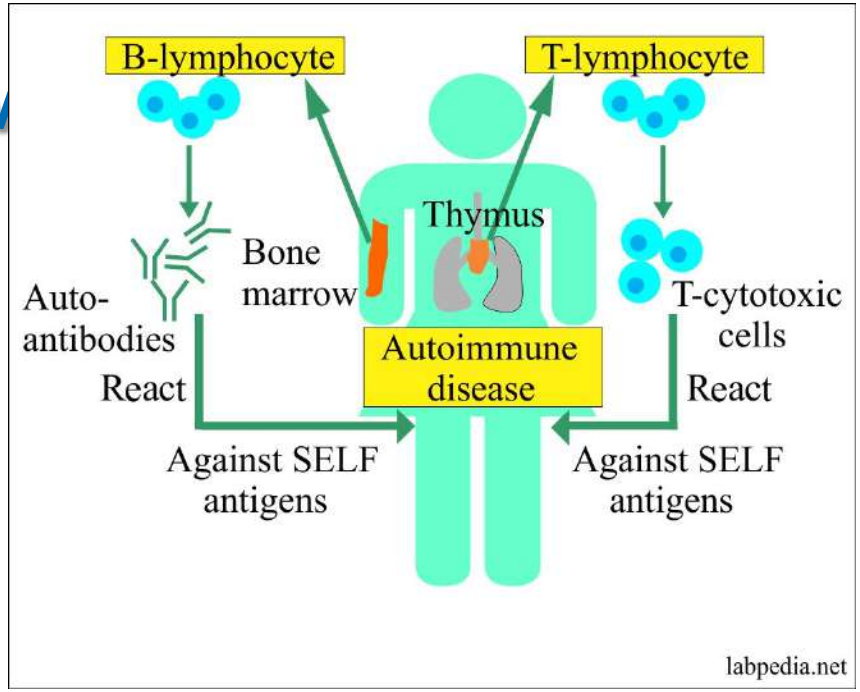
Note: **the specific antigen responsible for the induction of autoimmunity (eg, type II collagen in collagen-induced arthritis) and the MHC molecules that bind the peptide antigen, as well as the T-cell receptors.**

AUTO-IMM

1. Autoreactive T cells and B cells accumulate in the synovial tissues of patients with rheumatoid arthritis.

2. T cells are immunologically tolerant to autoantigens; BUT when self-tolerance is broken, autoreactive T cells are activated, and they stimulate B cells to induce the production of autoantibodies.

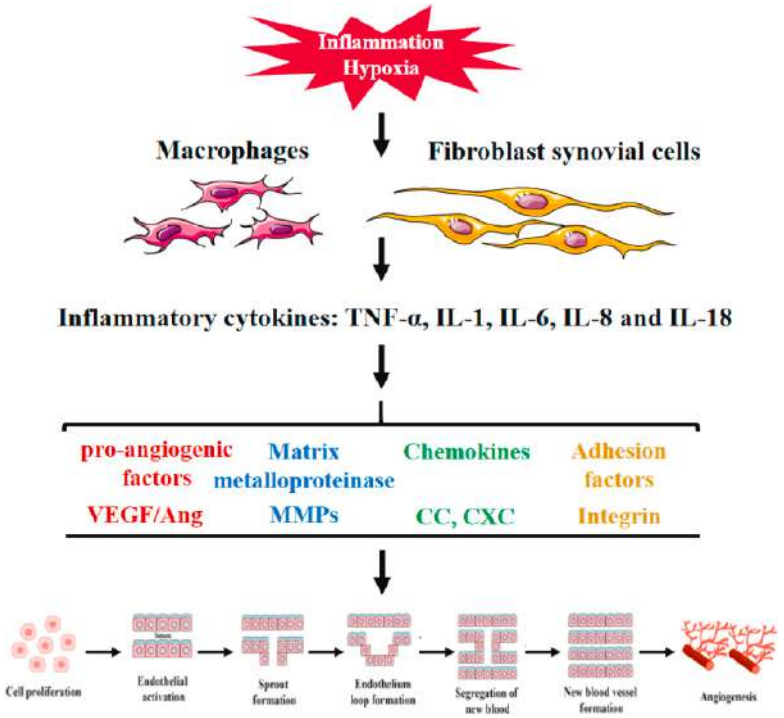
3. Autoantibodies form immune complexes with antigens, which are deposited in tissues and activate complements to cause histological damage (type III allergy).



- Tissues with synovitis are characterized by angiogenesis or vasodilation, proliferation of synoviocytes, and accumulation of lymphocytes.

- In tissues with diffuse inflammation, the accumulation of memory T cells and B cells can result in the formation of lymphoid follicle-like and germinal center-like structures.

- Co-stimulators and proinflammatory cytokines are highly expressed, and close cellular interactions are observed in these structures.



Intrasynovial Immune Response

The presence of activated T-cells, increased concentrations of pro-inflammatory mediators, and endothelial activation within the synovium appear to implicate an aberrant self-perpetuating and self-amplifying immune response central to the initiation and sustenance of rheumatoid synovitis

Both CD4+ and CD8+ T-cells can contribute to the initiation and propagation of autoimmune disease i

Activated macrophages found in synovial tissues are a major source of cytokines such as tumor necrosis factoralpha (TNF-_x0001_)

Fibroblasts, mast cells and B-cells

Effector Molecules and Cartilage Damage

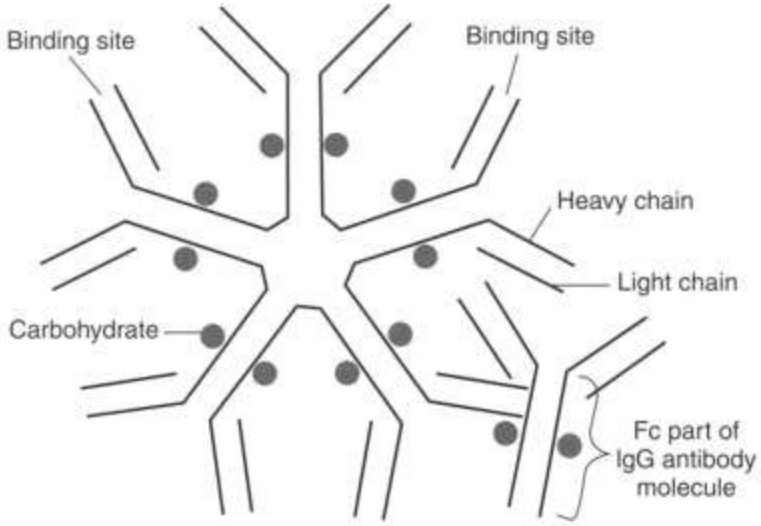
Once this biologic inflammatory process has matured, it appears to be regulated and amplified by inflammatory cells and their regulatory proteins, the most notable of which include the pro-inflammatory cytokines

T-cells and antigen presenting cells directly (by cell to cell contact) and indirectly (by other signals) stimulate macrophages to secrete interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-alpha), among other inflammatory mediators.

IL-1 and TNF- alpha or their mRNA cause induction by synoviocytes of matrix metalloproteinases as well as the inhibition of tissue inhibitors of metalloproteinases (TIMPs)

Chondrocytes, enter a catabolic phase when exposedto these cytokines, leading to an increase in collagenase production and a decrease in matrix protein synthesis.
TNF alpha also induces adhesion molecules, eg, the intracellular adhesion molecule 1 (ICAM-1), which may in turn affect the homing and trafficking of inflammatory cells into the synovium.

RHEMATOID F



- Rheumatoid factors are autoreactive antibodies that bind to the Fc portion of IgG molecules. RF is not specific for rheumatoid arthritis.

- RF is present in approximately 75%-85% of people with RA.
- 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 seropositive.

- PROGNISTIC VALUE- Patients with high titres of RF, in general, tend to have POOR PROGNOSIS, MORE EXTRA ARTICULAR MANIFESTATION.

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- (cyclic citrullinated peptide

- A variety of other autoantibodies have been reported to be associated with RA, including antikeratin antibodies, antiperinuclear
- factor, and antifilaggrin antibody.
- Antigen recognized in common by these antibodies is citrullinated protein.
- Citrulline is a nonstandard amino acid created by the de-amination of arginine residues in proteins by the enzyme peptidyl arginine deiminase (PADI).
- Tests for anti-CCP (cyclic citrullinated peptide) antibodies are as sensitive as RF for the diagnosis of RA and are more specific.
- High titers of anti-CCP antibodies define patients with a more aggressive disease phenotype.
- Sensitivity (65%) & Specificity (95%)
- **Both diagnostic & prognostic value**
- Predictive of Erosive Disease
  - Disease severity
  - Radiologic progression
  - Poor functional outcomes

Typical Feature of RA

1. A symmetrical Polyarthritis & Tenosynovitis
2. Morning Stiffness
3. Elevation of ESR
4. Appearance of auto antibodies that targets Ig in serum.

- Patients often complain of stiffness from the onset of the disease and experience difficulty in moving fingers on awakening, which is often described as having difficulty in forming a fist.
- Arthralgia is often associated with swelling and limited mobility.

CAUSES

1. GENETIC SUSCEPTIBILITY
2. AN IMMUNOLOGICAL REACTION, INVOLVING A FOREIGN ANTIGEN , FOCUS ON SYNOVIAL TISSUE
3. AN INFLAMMATORY REACTION IN JOINTS & TENDON SHEATH
4. APP OF Rheamatoid factor IN BLOOD & SERUM
5. PERPETUATION OF INFLAMMTAORY PROCESS
6. ARTICULAR CARTILAGE DESTRUCTION

Clinical Presentation--

- Early feature (synovitis)

i. Most commonly affect MCPJ & PIPJ, wrist tendon sheath around joints sheath,

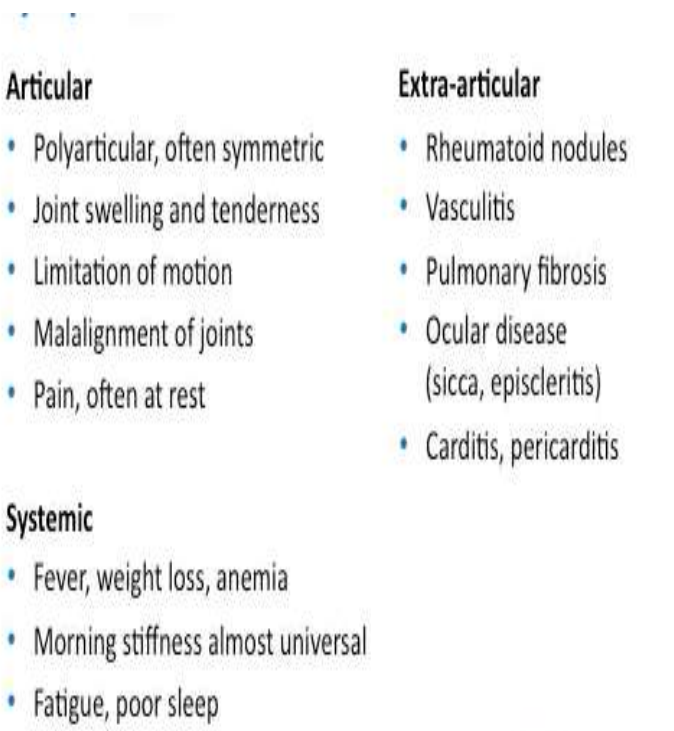
ii. B/L Symmetrical Polysynovitis

iii. Pain, fusiform swelling, stiffness, loss of mobility

iv. Constitutional Symptoms

❖ Loss of appetite, loss of weight, malaise, low grade fever

❖ Tenosynovitis



Articular

- Polyarticular, often symmetric
- Joint swelling and tenderness
- Limitation of motion
- Malalignment of joints
- Pain, often at rest

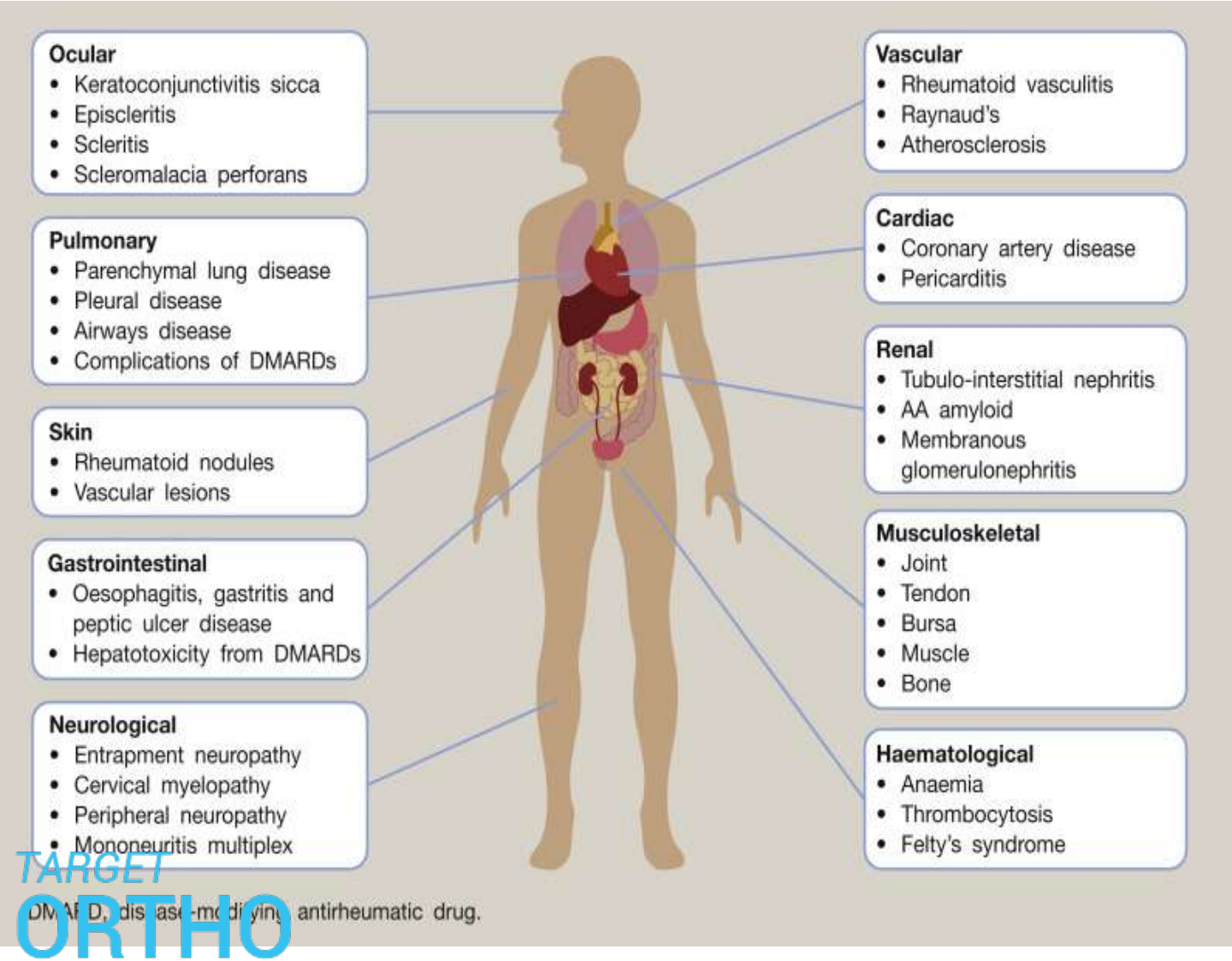
Extra-articular

- Rheumatoid nodules
- Vasculitis
- Pulmonary fibrosis
- Ocular disease (sicca, episcleritis)
- Carditis, pericarditis

Systemic

- Fever, weight loss, anemia
- Morning stiffness almost universal
- Fatigue, poor sleep

SUMMARY OF CLINICAL MANIFESTATION OF RA

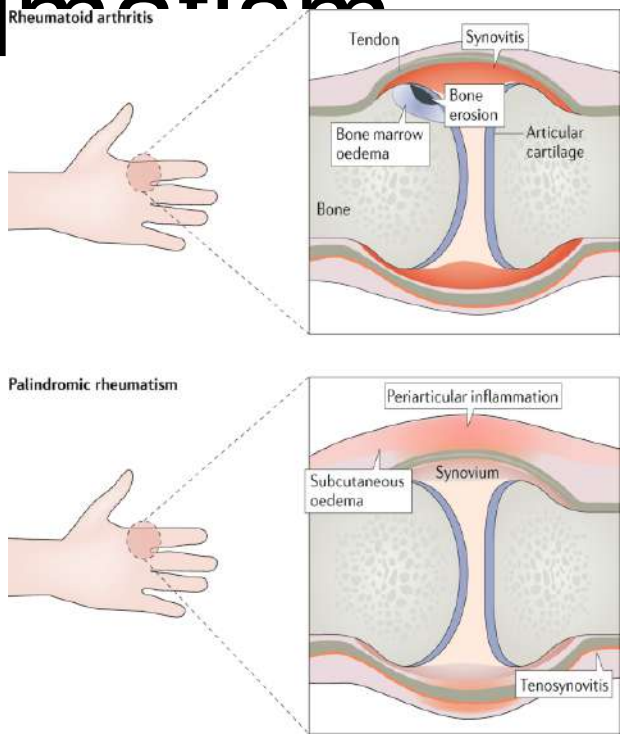


antirheumatic drug.

Palindromic Rheumatism

- Palindromic rheumatism (PR) is a type of recurrent arthritis characterized by episodes or ""attacks"" of joint inflammation, sequentially affecting one to several joint areas for hours to days.
- Attack often occurs suddenly without any obvious triggers or warning symptoms.
- Any joint(s) may be affected, but finger joints, wrists, and knees are most commonly affected.
- Symptoms during episodes may include pain, swelling, stiffness, and redness in and around the joints.
- Between episodes... no symptoms.
- Length of an attack is extremely variable from few hours to days.
- Unlike RA palindromic rheumatism affects men and women equally.

- Palindromic rheumatism is frequently the presentation for Whipple disease which is caused by the infectious agent Tropheryma whipplei (formerly T. whippelii),



Proposed classification by Guerne and Weismann in 1992

1. A 6-month history of brief sudden-onset and recurrent episodes of monoarthritis or rarely polyarthritis or of soft tissue inflammation.
2. Direct observation of one attack by a physician.
3. Three or more joints involved in different attacks.
4. No radiologic evidence of bone or joint erosion.
5. Exclusion of other arthritides, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or gout

DIAGNOSTIC CRITERIA

1987 American College of Rheumatology (ACR)Criteria for the Classification of Rheumatoid Arthritis*

- 1. Morning stiffness in and around the joints lasting at least 1 hour before maximal improvement
- 2. At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are: right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
- 3. At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint
- 4. Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)
- 5. Subcutaneous nodules over bony prominences, extensor surfaces, or in juxta-articular regions, observed by a physician
- 6. Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in less than 5% of normal control subjects
- 7. Radiographic changes typical of rheumatoid arthritis o posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

- **A person shall be said to have rheumatoid arthritis if he or she has satisfied 4 of 7 criteria, with criteria 1-4 present for at least 6 weeks.**

1991 American College of Rheumatology Revised Criteria for Classification of Functional Status in Rheumatoid Arthritis*

- Class I Completely able to perform usual activities of daily living (self-care, vocational, and avocational)
- Class II Able to perform usual self-care and vocational activities, but limited in avocational activities
- Class III Able to perform usual self-care activities, but limited in vocational andavocational activities
- Class IV Limited in ability to perform usual self-care, vocational, and avocational activities

*Usual self-care activities include dressing, feeding, bathing, grooming, and toileting. Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age- and sex-specific.

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

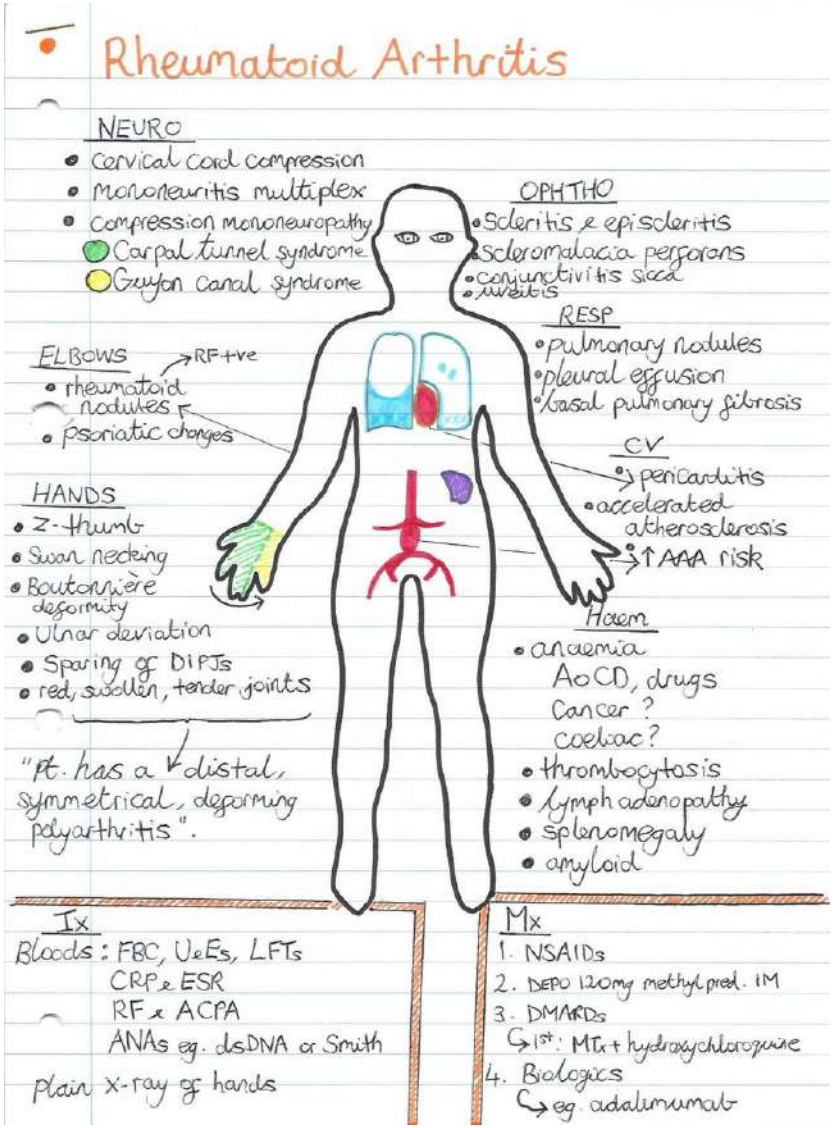
- **B. Serology** (at least 1 test result is needed for classification)
- Negative RF *and negative ACPA* *0*
- Low-positive RF *or low-positive ACPA* *2*
- High-positive RF *or high-positive ACP* *3*

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

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

Clinical Manifestations

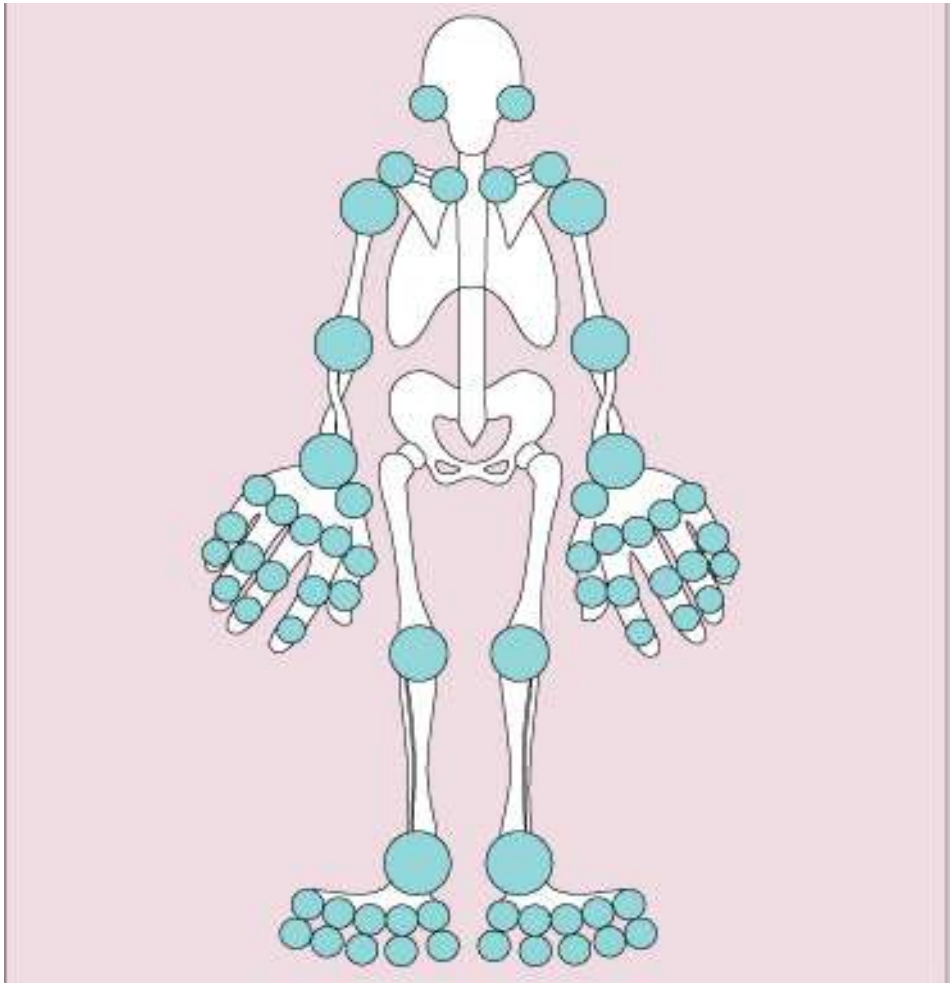
- Articular
- Extra-articular



Articular manifestation

- Pain and swelling in affected joint aggravated by movement is the most common symptom.

- Morning stiffness ≥1 hr
- Joints involved -→



Relative incidence of joint involvement in RA

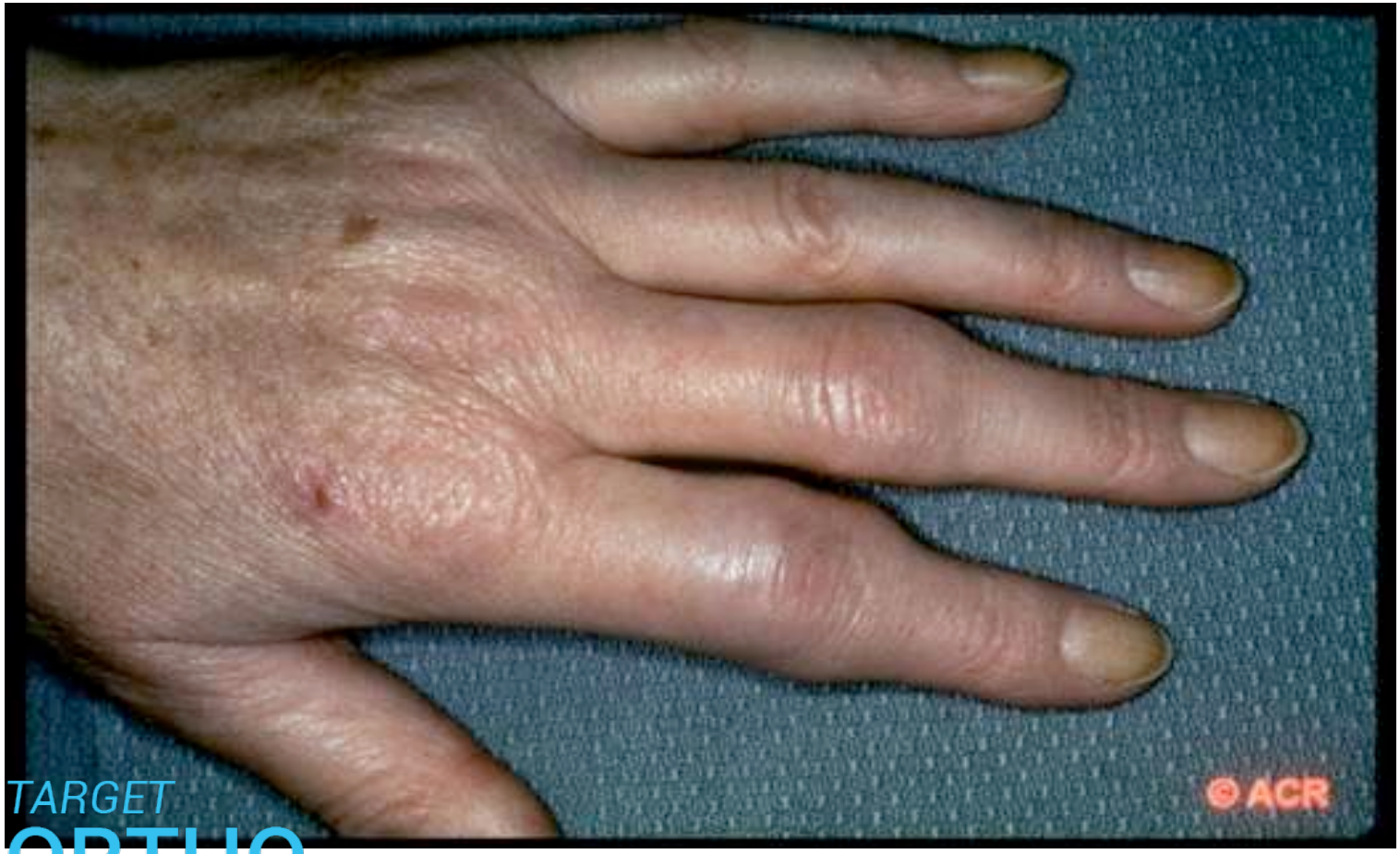
- MCP and PIP joints of hands & MTP of feet 90%
- Knees, ankles & wrists- 80%
- Shoulders- 60%
- Elbows- 50%
- TM, Acromio - clavicular & SC joints- 30%

Joints involved in RA

- Don't forget the **cervical spine**!! Instability at cervical spine can lead to impingement of the spinal cord.

- Thoracolumbar, sacroiliac, and distal interphalangeal joints (DIP)of the hand are **NOT** involved.

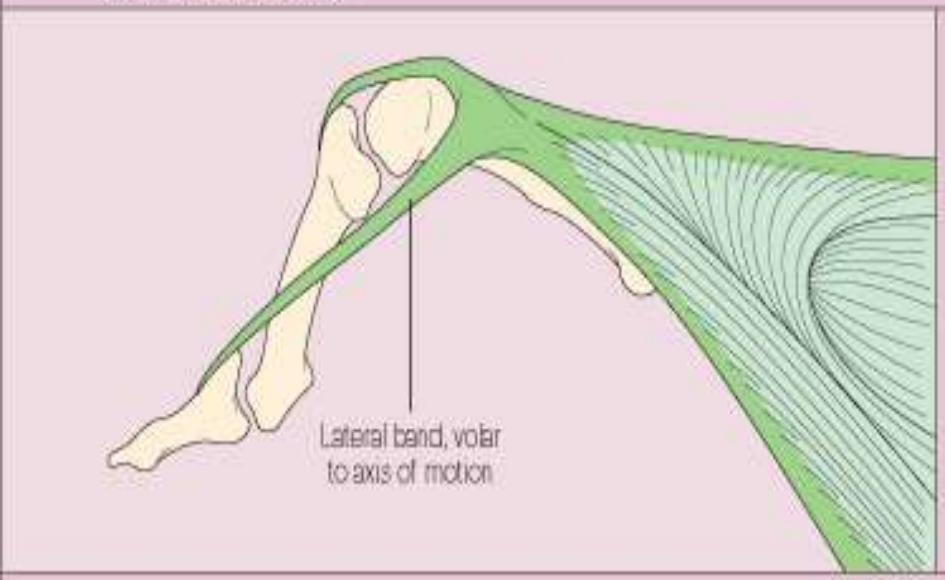
PIP Swelling



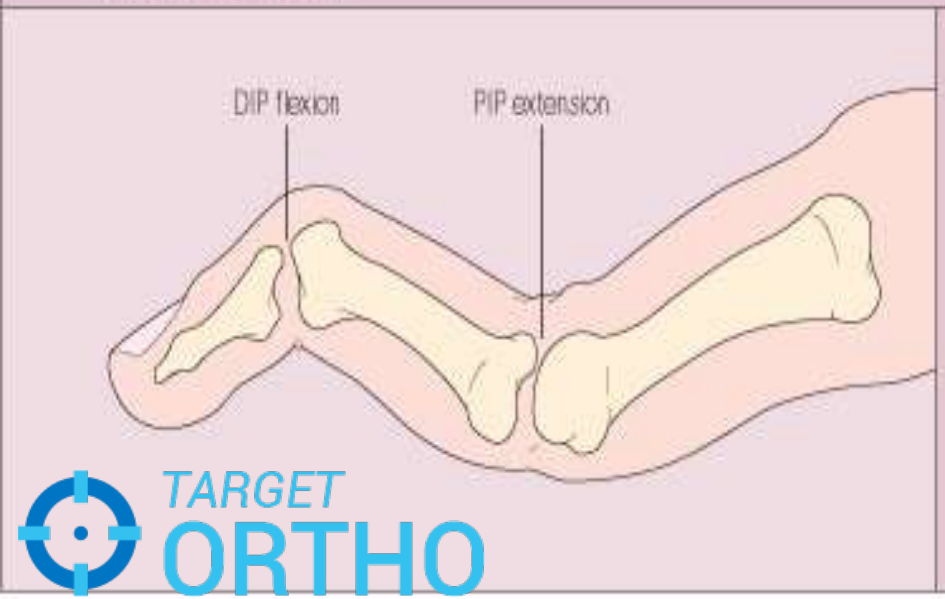
Ulnar Deviation, MCP Swelling, Left Wrist Swelling

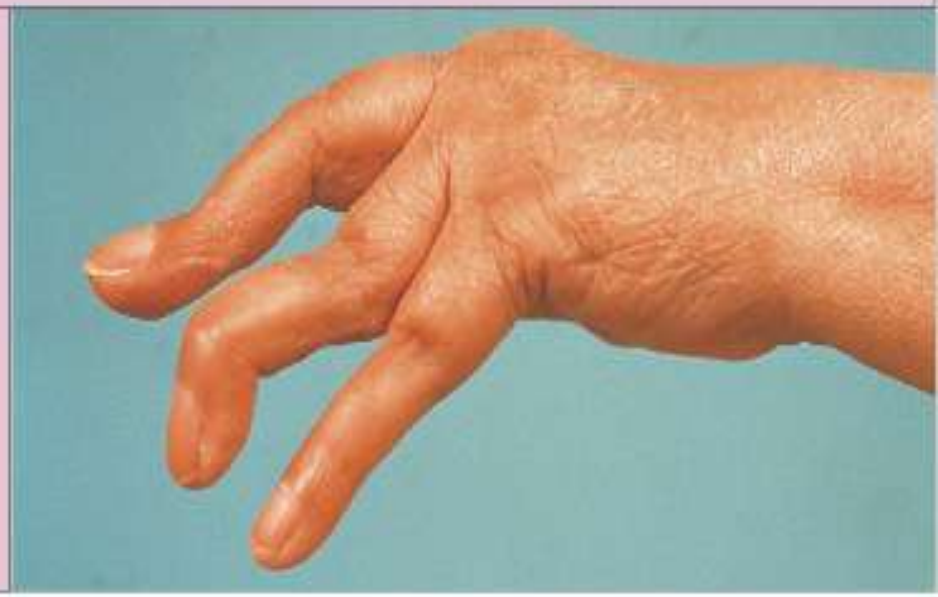
BOUTONNIERE AND SWAN-NECK DEFORMITIES

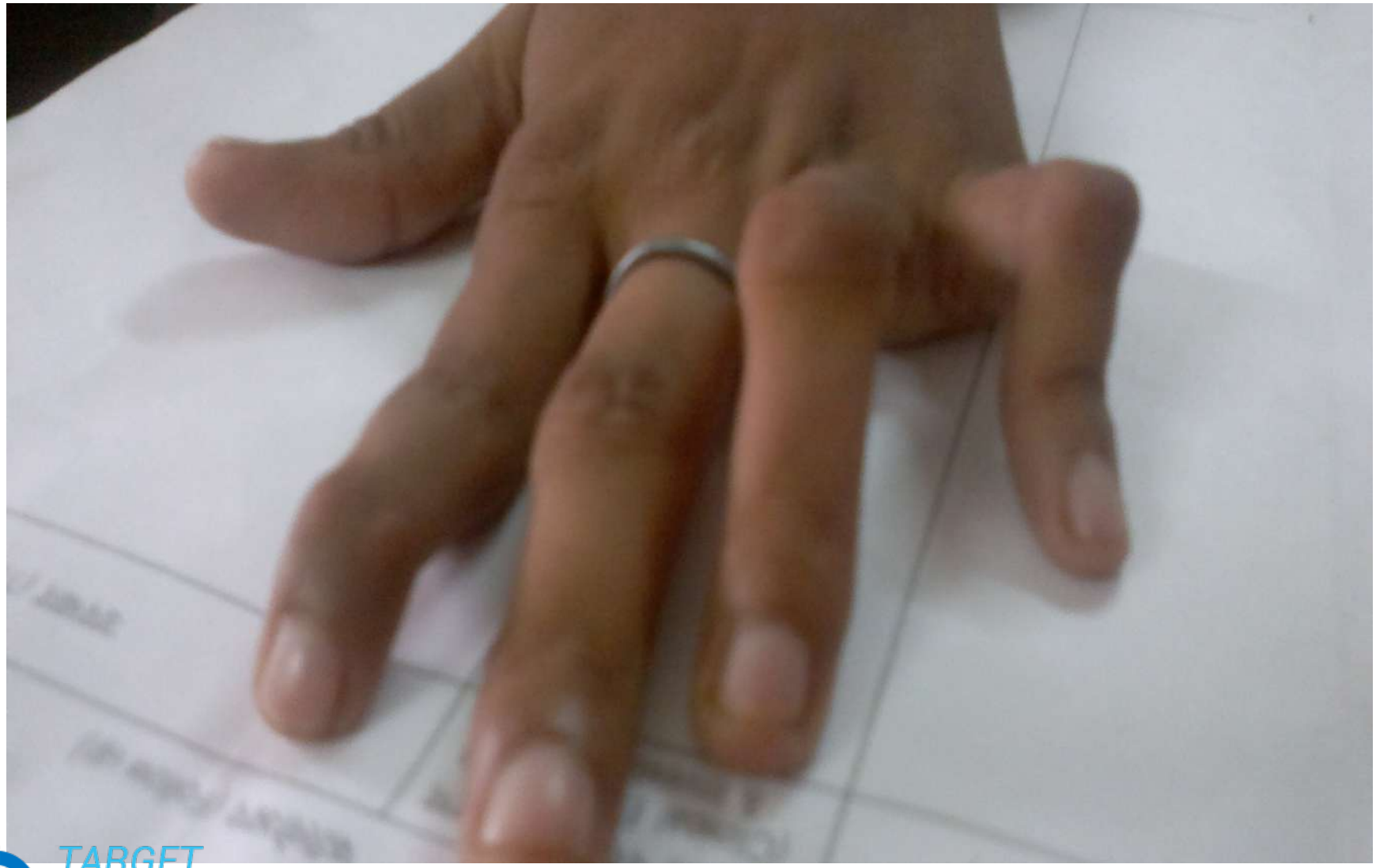
Boutonnière deformity



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

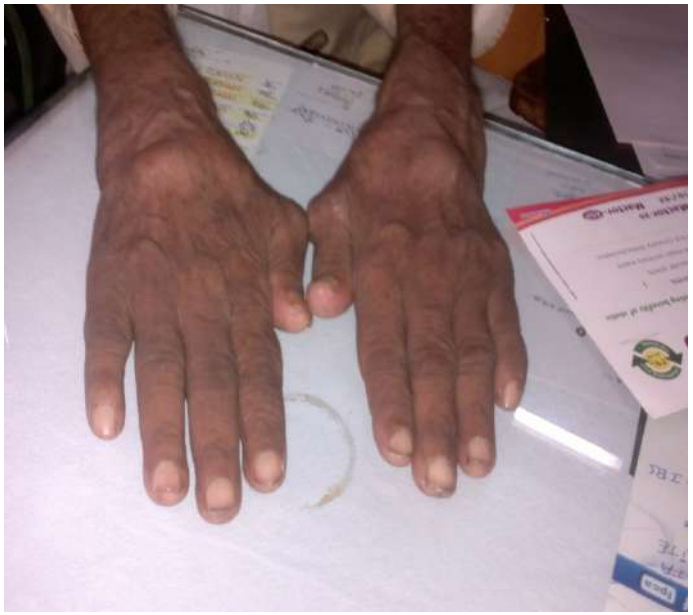
- **Constitutional symptoms** (most common)
- **Rheumatoid nodules**(30%)

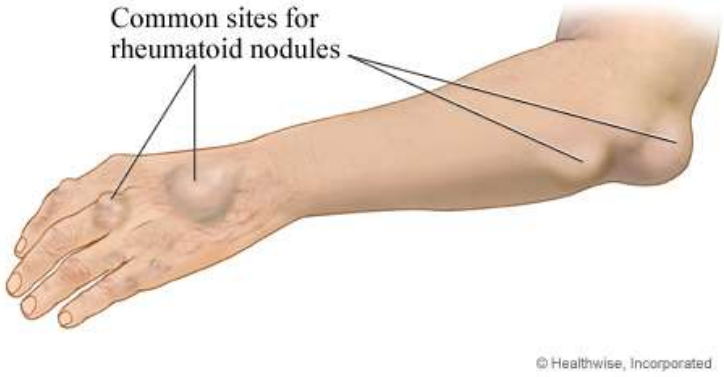
- **Hematological**-
  - Normocytic Normochromic anemia
  - Leucocytosis /leucopenia
  - Thrombocytosis
- ***Felty's syndrome-***
  - Chronic nodular Rheumatoid Arthritis
  - Spleenomegaly
  - Neutropenia

- **Respiratory**- Pleural effusion, Pneumonitis , Pleuro-pulmonary nodules, ILD
- **CVS**- Asymptomatic pericarditis , Pericardial effusion, Cardiomyopathy
- **Rheumatoid vasculitis**- Mononeuritis multiplex, Cutaneous ulceration, Digital gangrene, Visceral infarction
- **CNS**- Peripheral neuropathy, Cord-compression from atlantoaxial/midcervical spine subluxation, Entrapment neuropathies
- **EYE**- Kerato-conjunctivitis sicca, Episcleritis, Scleritis

Rheumatoid nodule

•Rheumatoid nodules are the most common extra-articular manifestation of rheumatoid arthritis (RA)
•Subcutaneous Rheumatoid nodules are firm, nontender and movable within the subcutaneous tissue; they could also be attached to underlying structures, such as the periosteum, fascia and tendons.
•Most common on pressure points (such as the olecranon process)
•They could also be attached to underlying structures, such as the periosteum, fascia and tendons





- 2 - 4 fold increase in mortality for patients with extra-articular manifestations, including rheumatoid nodules.
- Subcutaneous nodules:
- Mostly on extensor surfaces at sites of frequent trauma

✓ Proximal ulna,

✓ Olecranon process (where they must be differentiated from olecranon bursitis with enlargement of the synovial layer)

✓ Extensor tendons of the hand (metacarpophalangeal or the proximal interphalangeal joints)

✓ Back of the head and ears

✓ Back of the heels

✓ Ischial tuberosities

Pathophysiology

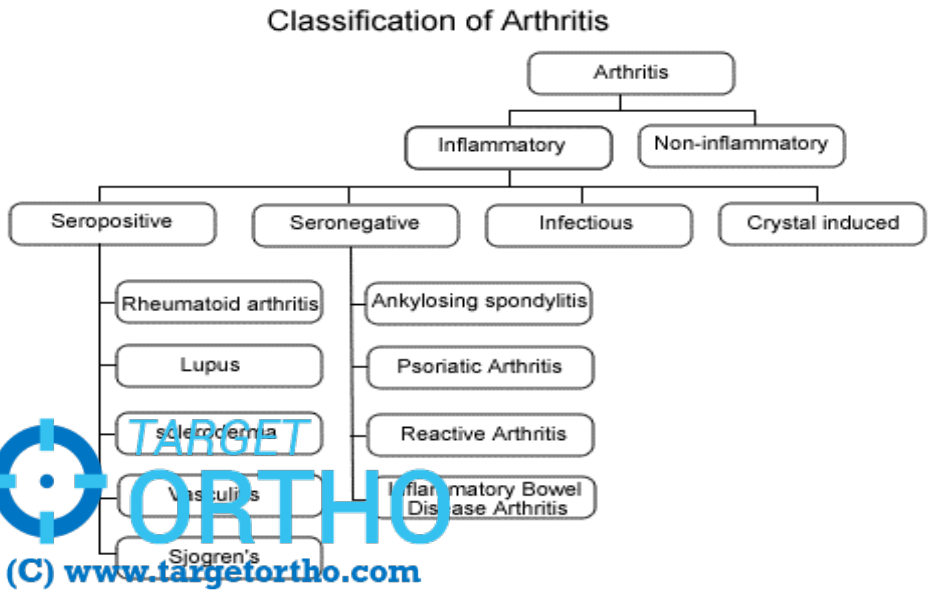
- Predominant infiltrating inflammatory cell in the rheumatoid nodule is the macrophage.
- TNF alpha, IL1 beta and IL1Ra mRNA, particularly in perivascular cells of the stroma and in the palisading layer.
- Cytokines, proteinases and other immune factors
- Tumor necrosis factor (TNF) alpha ,Interferon gamma, Interleukin (IL) 1 beta IL1 receptor antagonist, IL10, IL15, IL18 and IL12, Adhesion molecules, including E-selectin, Intracellular adhesion molecule (ICAM) 1, Platelet endothelial cell adhesion molecule (PECAM), Vascular cell adhesion molecule (VCAM)
- Peptidyl arginine deiminases 2, 3 and 4 and myeloperoxidase

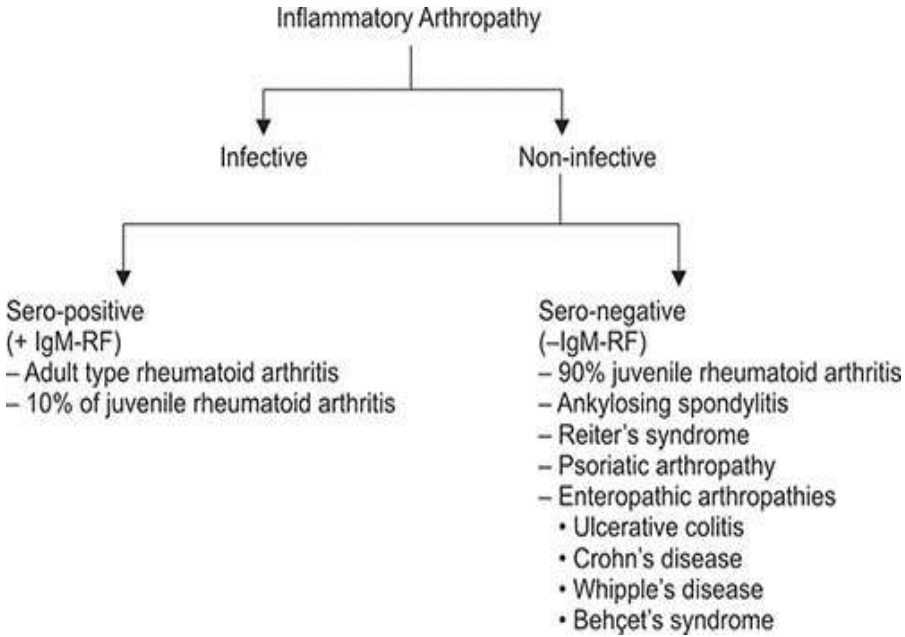
SERO POSITIVE

- Blood tests positive for the presence of protein called rheumatoid factor (RF) OR autoantibodies it indicates that your body may be producing an immune reaction to your normal tissues.
- Hvae a common sequence of amino acids, also known as the shared epitope, encoded in the HLA genetic site.

SERO NEGATIVE

- Test negative for the presence of antibodies or RF in the blood are referred to as seronegative.
- But they can still have RA.
- RF negative are likely to have a milder form of RA than those who test positive.





Thank you.

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