



- Synovium:

- It is the 1-3 cells thickness synovial membrane which forms the internal lining of the fibrous capsule of synovial joints and covering all structures except the articular hyaline cartilage.
- It contains synovial fluid -which is an ultrafiltrate of plasma- secreted by synovial cells and preventing friction of the joint.

- Rheumatoid arthritis:

- **Definition:** systemic, chronic, inflammatory, connective tissue, autoimmune disorder seen especially in joints.
- **It is characterized by:** symmetrical polyarthritis which involves synovial joints bilaterally with many extra-skeletal manifestations.
- **Etiology:** autoimmunity with genetic predisposition (familial tendency/ HLA-DR4). This genetic predisposition needs an appropriate antigenic stimuli (such as EBV infection) so the disease can be initiated and becomes self-perpetuating
- **Risk factors:**
  - ✓ Synovial joints:
    - ❖ Metacarpophalangeal and proximal interphalangeal joints.
    - ❖ Elbows.
    - ❖ Shoulders.
    - ❖ Knees.
    - ❖ Ankles.
    - ❖ Spine.
  - ✓ Gender: females.
  - ✓ Age: any age but typically 3<sup>rd</sup>-5<sup>th</sup> decade.
- **Pathogenesis:**
  - ✓ Genetic predisposition: familial tendency and association with MHC class-II gene (HLA-DR4).
  - ✓ Cellular immunity: infiltration of T-lymphocytes in the synovium affected with Rheumatoid Arthritis.
  - ✓ Humoral immunity: 80% of Rheumatoid Arthritis patients are sero-positive for Rheumatoid Factor (RF). RF is an IgM antibody –or can belong to any other Ig class- directed against the Fc portion of IgG leading to the formation of immune complexes which will activate macrophages and other inflammatory cells. Rheumatoid factor:
    - ❖ If the patient is sero-negative for RF but has the clinical features → RF might be detected in the synovial fluid.
    - ❖ RF is not specific for Rheumatoid Arthritis. It appears in many other conditions such as: SLE, Sjogren 's syndrome, chronic infections and elderly women.
    - ❖ Stimulus for RF production:
      - Extensive prophylactic immunization (although it is normal for RF to appear temporarily following vaccination).
      - Repeated blood transfusions.
      - Chronic infection as mentioned above (tuberculosis, hepatitis, kala-azar).
  - ✓ Tissue culture of synovial cells from RA patients shows:
    - ❖ Decreased response to glucocorticoids.
    - ❖ Increased production of hyaluronic acid.
    - ❖ Release of connective tissue activating peptide which influence the function of other pathways → production of increased amounts of E2I



- ✓ Hypothetical scenario of RA pathogenesis:
  - ❖ Both genetic as well as environmental factors are implicated in the pathophysiology of the disease. **The genetic association is with HLA-DR4.**
  - ❖ The negative feedback mechanisms that normally maintain tolerance of self are overtaken by aberrant positive feedback mechanisms for certain antigens such as the **Fc portion of IgG (bound by Rheumatoid Factor).**
  - ❖ Once the abnormal immune response has become established (which may take several years before any symptoms occur), **plasma cells derived from B-lymphocytes produce Rheumatoid Factors (RFs)** -which are IgM directed against the Fc portion of IgG- in large quantities.
  - ❖ These immune complexes will **activate macrophages** through Fc receptor and complement binding.
  - ❖ This contributes to **inflammation in the synovium**, in terms of edema, vasodilation and **infiltration by activated T-cells** (mainly CD4 in nodular aggregates and CD8 in diffuse infiltrates).
  - ❖ Synovial macrophages and dendritic cells further function as antigen presenting cells by expressing MHC class-II molecules leading to an established local immune reaction in the tissue.
  - ❖ The disease progresses with **formation of granulation tissue at the edges of the synovial lining (pannus)** with extensive angiogenesis and production of enzymes that cause tissue damage.
  - ❖ The synovium thickens, the cartilage and the underlying bone begin to disintegrate and evidence of **joint destruction occurs.**

- **Manifestations:**

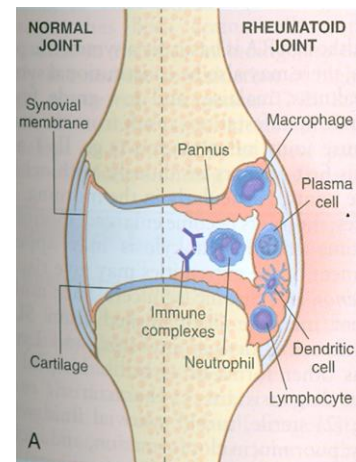
- ✓ Articular manifestations:

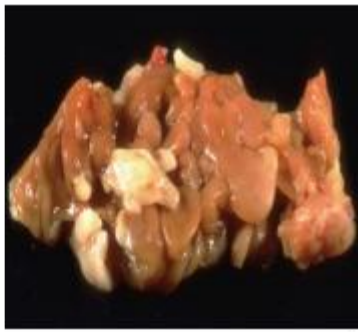
- ❖ **Synovial membrane changes:**

- ✚ Edema and increased vascularity.
- ✚ Accumulation of neutrophils (during acute exacerbation), macrophages, lymphocytes (T-lymphocytes: mainly CD4) and plasma cells.
- ✚ Exudation (perfusion) of fibrin in the joint space.
- ✚ Hyperplasia of synovial lining from 3 to 10 cell thickness.
- ✚ Hypertrophy of synovium manifested as papillary folding covered with fibrin and filling the joint space.
- ✚ Pannus formation: synovial hyperplasia and hypertrophy growing over the surface of articular cartilage in the joint in the form of pannus. This will interfere with nutrition of the cartilage causing degradation of its matrix and destruction. Pannus erodes **الغضروف الكartilاجي** articular cartilage and adjacent bone through action of collagenase produced by the pannus itself. Spread of the pannus to subchondral bone gives rise to radiological “erosion”. Eventually, pannus spreads to both sides of the bone leading to joint destruction, fibrous ankylosis and bony ankylosis.

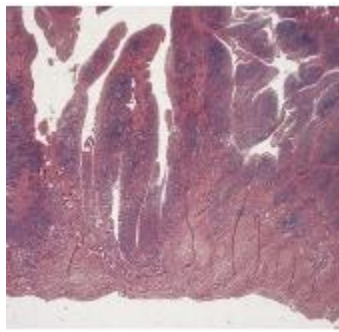
- ❖ **Synovial fluid changes:**

- ✚ Many neutrophils are present in the early stage and in exacerbation.
- ✚ Increase in volume and turbidity.
- ✚ Increased protein contents and decreased viscosity.
- ✚ Bacterial culture.

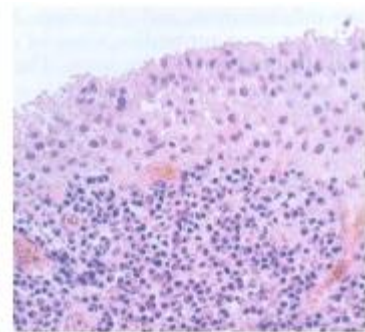




(Red): hemosiderin due to hemorrhage, (white): fibrin



Hyperplasia + villi (formation of folds)



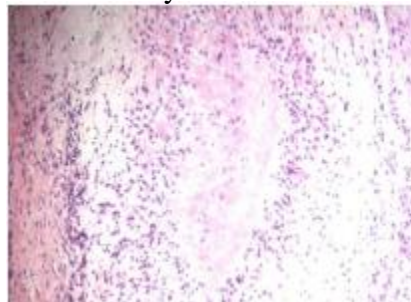
Hyperplasia with dilated blood vessels and inflammatory cells



✓ Extra-articular manifestations:

❖ Rheumatoid nodules:

- ✚ In 20-35% of patients.
- ✚ In subcutaneous tissue over olecranon and legs.
- ✚ Recur after surgical removal.
- ✚ Central area of fibrinoid necrosis surrounded by macrophages and fibrous tissue containing chronic inflammatory cells.



❖ Vasculitis/ acute necrotizing arteritis:

- ✚ Occurs in patients with severe RA.
- ✚ Damage is caused by: immune-complex deposition and complement activation.
- ✚ Affecting any organ: heart-MI, cerebrovascular occlusion, renal failure, mesenteric infarction and gangrene of digits.

❖ Cardiac disease:

- ✚ Rheumatoid nodule involving the conduction system and causing arrhythmia.
- ✚ Involvement of coronary arteries in acute necrotizing arteritis will lead to myocardial infarction.

❖ Pulmonary disease: pulmonary fibrosis.

❖ Serosal inflammation: pericarditis and pleurisy.

❖ Amyloidosis.

❖ Anemia: microcytic hypochromic anemia (anemia of chronic disease).

❖ Felty's syndrome: splenomegaly with hypersplenism and granulocytopenia making a person susceptible to infections.

❖ Eye involvement: keratoconjunctivitis and scleritis.