Genetic Factors

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LEC.2

There is much evidence supporting the genetic predisposition for SLE:

1- There is a higher rate of concordance in monozygotic twins (25%) than in dizygotic twins (l%-3%).

2- Family members have an increased risk of developing SLE & up to 20% of clinically unaffected first-degree relatives may have autoantibodies.

3- There is a positive association between SLE & class II HLA genes.

4- About 6% of SLE patients have inherited deficiencies of complement components.

Lack of complement may impair removal of immune complexes from the circulation & favor tissue deposition, resulting in tissue injury.

Nongenetic factors:

1. The clearest example of environmental factors in initiating SLE is the occurrence of a lupus-like syndrome in patients receiving certain drugs, including procainamide & hydralazine.

Thus, most patients treated with procainamide for more than 6 months develop ANAs, with clinical features of SLE appearing in 15%-20% of them.

2. Sex hormones; the female predominance of SLE, reflects the important influence of sex hormones in the development of the disease, due to the helpful effects of estrogens on antibody synthesis.

3. Exposure to ultraviolet light exacerbates the disease in many individuals.

Ultraviolet light may damage DNA & promote cell injury that will release cellular contents & augment the formation of DNA/antiDNA immune complexes.

Mechanism of tissue injury:

Most of the visceral lesions are caused by immune complexes (type III hypersensitivity). For example, DNA/anti-DNA complexes can be detected in the glomeruli. In addition, autoantibodies against red cells, white cells & platelets causing effect by type II hypersensitivity.

The denaturated nucleus of an injured cell will be engulfed by a neutrophil or macrophage producing the LE cell. LE cell test is positive in about 70% of patients with SLE.

Clinical manifestations:

The clinical presentation of SLE is so variable & with similarities to other autoimmune connective tissue diseases (rheumatoid arthritis, polymyositis & others) so that it has been necessary to develop diagnostic criteria.

If a patient has four or more of the criteria, serially or simultaneously, during any interval of observation, the diagnosis of SLE is established.

The range of features that can occur in SLE is shown by the **American Rheumatism Association List of Diagnostic Criteria for SLE:**

1. Discoid skin rash.
2. Malar rash.
3. Photosensitivity.
4. Oral ulcers.
5. Arthritis .
6. Serositis.
7. Renal disorder.
8. Neurologic disorder.
9. Hematologic disorder.
10. Immunologic disorder.
11. Presence of antinuclear antibody.

Skin rashes of various types occur in about 80% of all patients with SLE.

One of the most common tissues affected in SLE is the skin.

The most common patterns of skin rash are:-

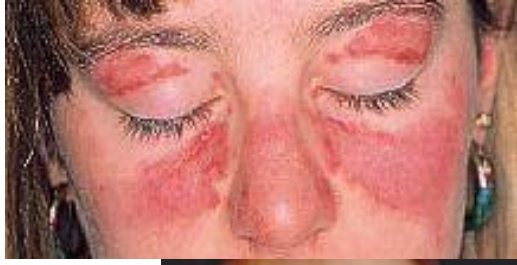
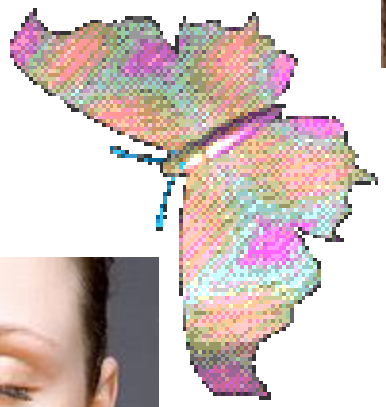
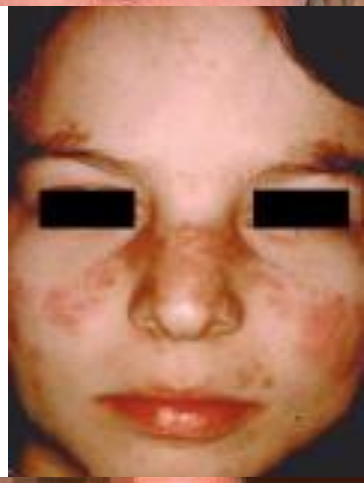
1. Chronic discoid LE: round (discoid), red scaly telangiectatic plaques, usually on the face & scalp.
2. Malar skin rash: a symmetrical, slightly raised red erythematous rash on the cheeks & across the bridge of the nose (butterfly rash). This is seen in 50% of the patients.

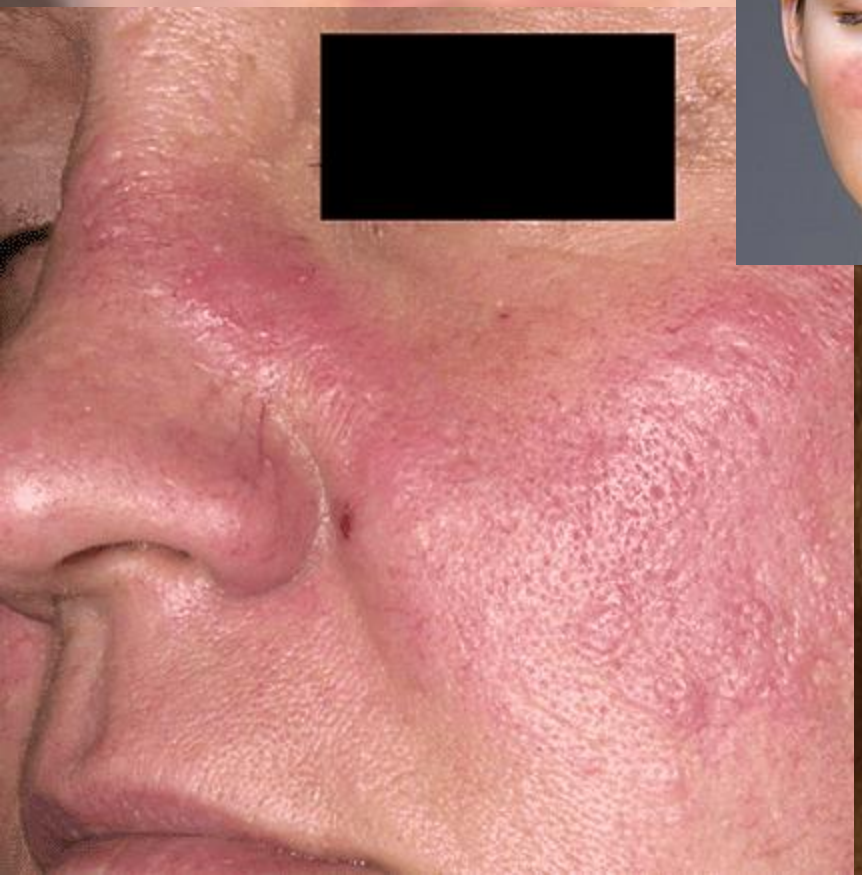
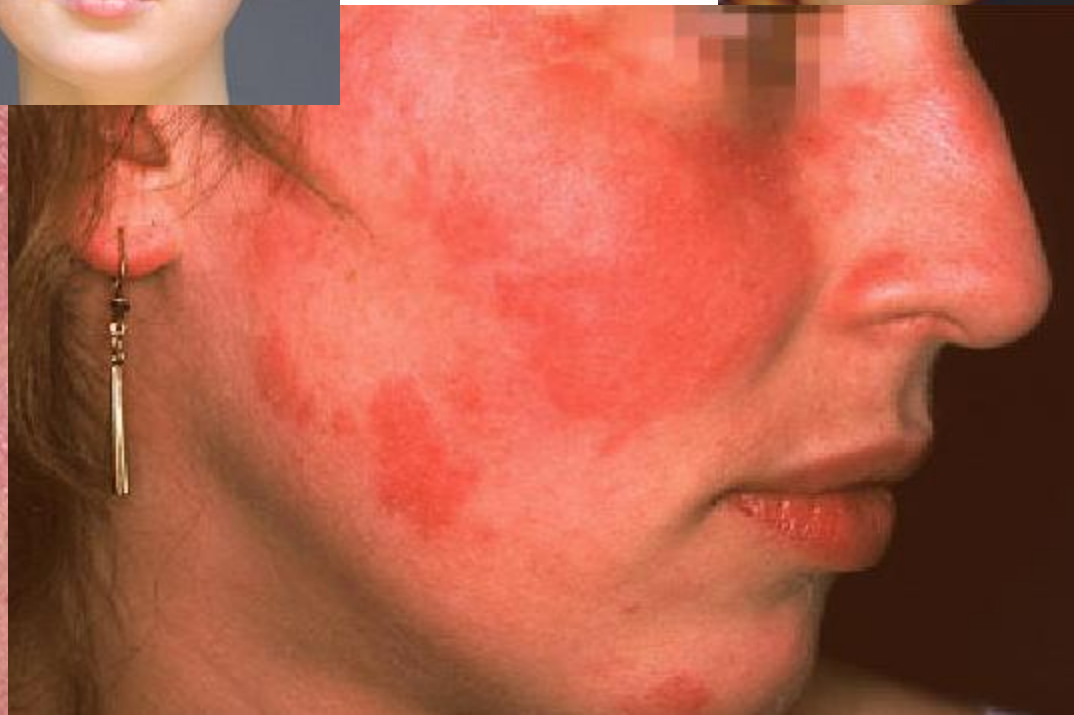
3. Photosensitivity reactions: exposure to sunlight (ultraviolet light) exacerbates the erythema & the rash will be seen on the face & sun-exposed areas mainly.

Direct immunofluorescence microscopy reveals deposition of immunoglobulins (IgG, IgM) & complement at the dermo- epidermal junction.

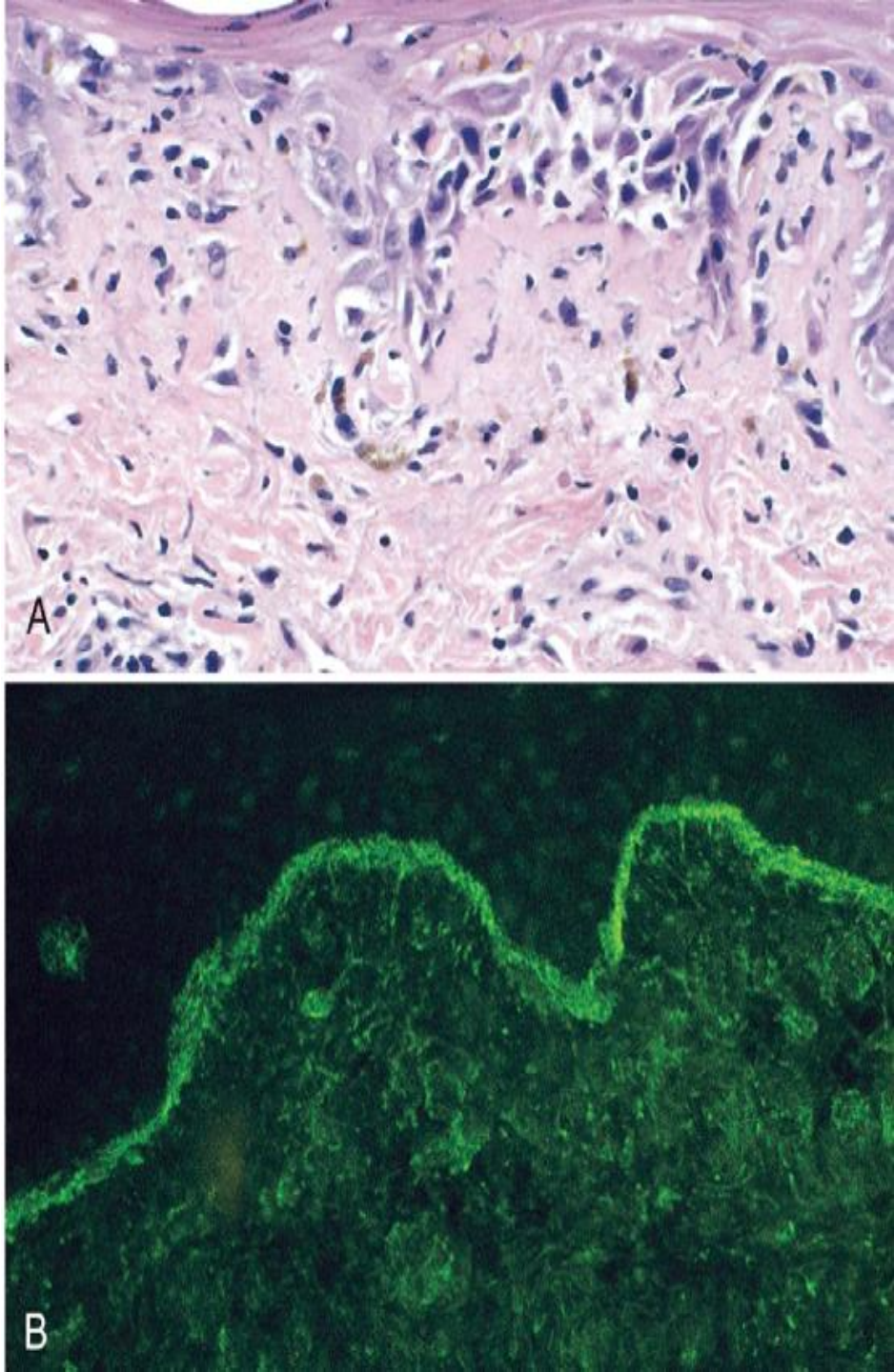
Histologically:

There is characteristic liquefactive degeneration of the basal layer of epidermis, edema at the dermo-epidermal junction & mononuclear infiltrates around blood vessels & skin appendages.

A, An H&E-stained section shows liquefactive degeneration of the basal layer of the epidermis and edema at the dermoepidermal junction. B, An immunofluorescence micrograph stained for IgG reveals deposits of Ig along the dermoepidermal junction.



4. Oral mucosal lesions in SLE produce superficial erosions & ulcers.

5. Musculoskeletal symptoms may be the earliest presenting feature of SLE. Joint pain and swelling occurs in about 90% of patients.

6. Serositis: the pericardium & pleura are usually affected. In the acute phase they may lead to serous effusion.

7. Renal disorder: kidney involvement in SLE is common & is an important cause of morbidity & mortality.

The severity of involvement can vary from minor abnormalities (such as asymptomatic albuminuria) to sever glomerular disease leading to renal failure. The basis of the glomerular damage is the deposition of immune complexes within glomeruli.

8. Neurological & psychiatric disorders are common in SLE.

9. Hematological abnormalities are common in SLE, some having an unknown cause & others having an autoimmune mechanism:-

a. Normocytic, hypochromic anemia.

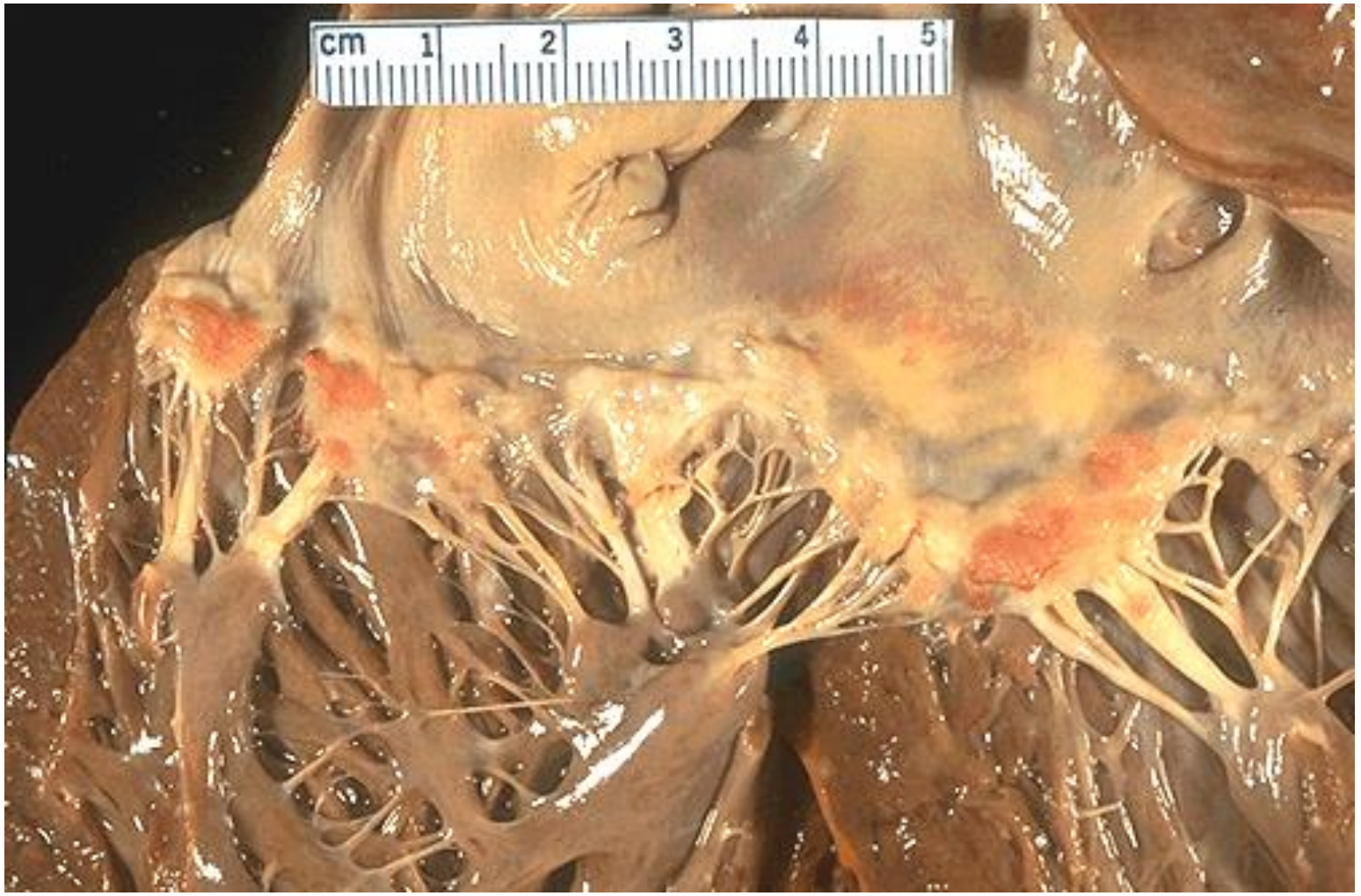
b. Autoimmune hemolytic anemia.

c. Leucopenia usually due to disproportionate reduction of lymphocytes (lymphopenia).

d. Thrombocytopenia.

- The spleen may be moderately enlarged.
- Involvement of the heart showing mainly pericarditis, myocarditis & vascular lesions called Libman-Sacks endocarditis, which represent a nonbacterial verrucous endocarditis.

Libman-Sacks endocarditis



Flat, pale tan, spreading vegetations over the mitral valve surface and even on the chordae tendineae. This patient has systemic lupus erythematosus (consistent with Libman-Sacks endocarditis).

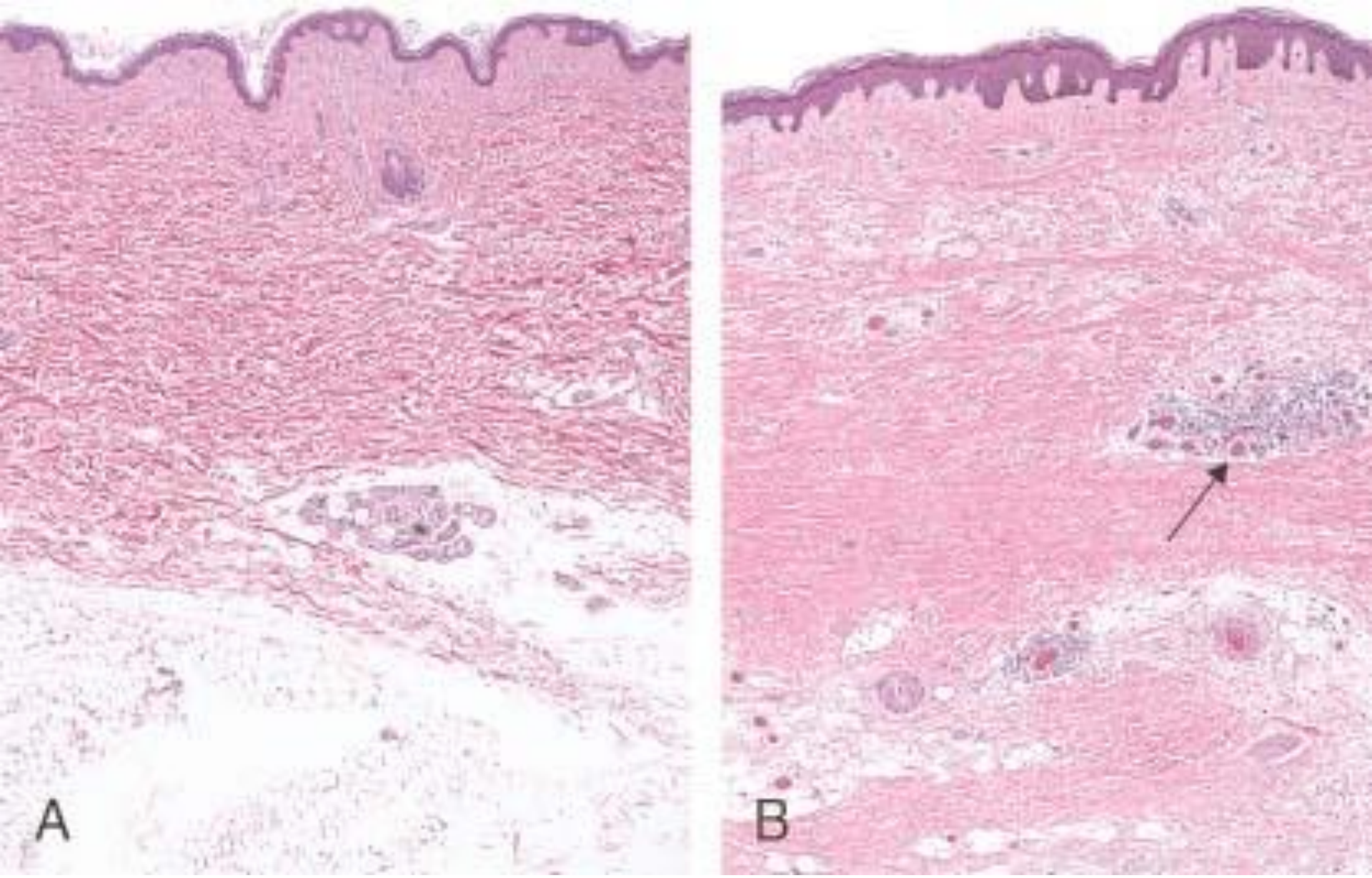
Systemic sclerosis (SS):

It is one of the connective tissue diseases & affects many systems & organs. It is three times more common in women than in men & occurs mainly in middle-aged or elderly individuals. The main abnormality is an excess formation of fibrous tissue, which leads to rigidity of the affected organ. Vessel wall thickening & perivascular fibrosis are characteristic features in SS & are responsible for slowly progressive ischemic damage in a wide range of tissues.

The skin is the most commonly affected organ (scleroderma), but the alimentary tract, lung, kidney & heart may also be involved.

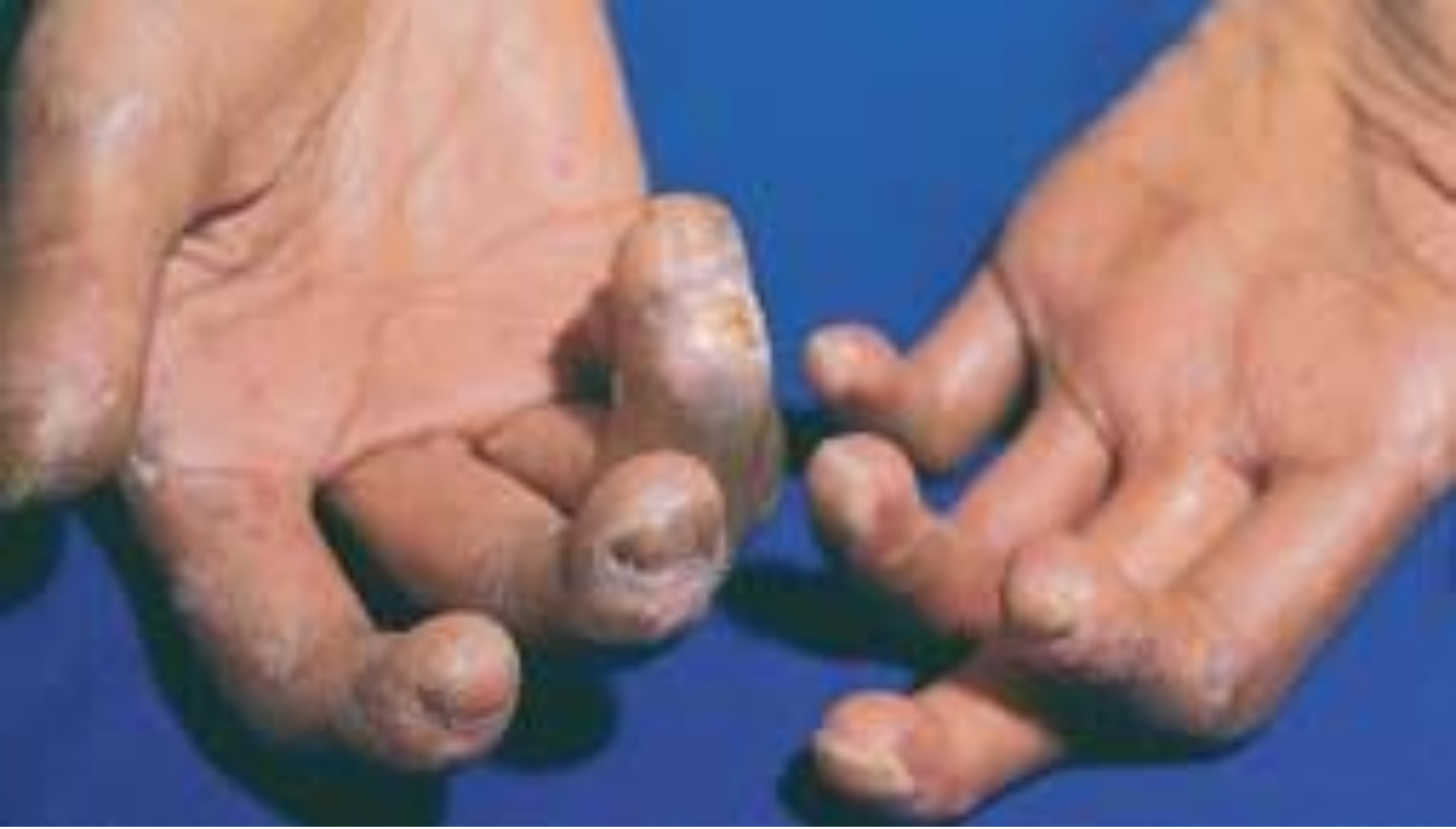
There is usually affection of the skin of the fingers & distal regions of the upper extremities. Extending to the upper arms, shoulders, neck & face may occur.

There *is* dermal thickening *due* to fibrous replacement of the normal dermal structures.



SCLERODERMA

(SYSTEMIC SCLEROSIS)



SYSTEMIC SCLEROSIS

(SCLERODERMA)

Rheumatoid disease (rheumatoid arthritis) (RA)

RA is a multi-system connective tissue disease in which the dominant effects are on the joints.

It is characterized by the presence of a circulating autoantibody, ***"rheumatoid factors"*** **(**seropositive arthritis).

RA is a very common condition, with a prevalence of about 1%.

It is three to five times more common in women than in men & the usual age of onset is between 35 to 45 years.

The disease is not limited to joints but also affects, among others, the skin, lungs, blood vessels, eyes & the hemopoietic system.

Pathologic changes:

RA typically presents as symmetric polyarthritis, mainly affecting the small joints of the hands & feet.

However, larger joints may also be involved e.g. ankles, knees, wrists, elbows & shoulders. Classically, the proximal interphalangeal & metacarpophalangeal joints are affected. The affected joints become swollen, painful & warm, often with redness of the overlying skin.

There are three main pathological changes

1. In the early stage there will be rheumatoid synovitis.

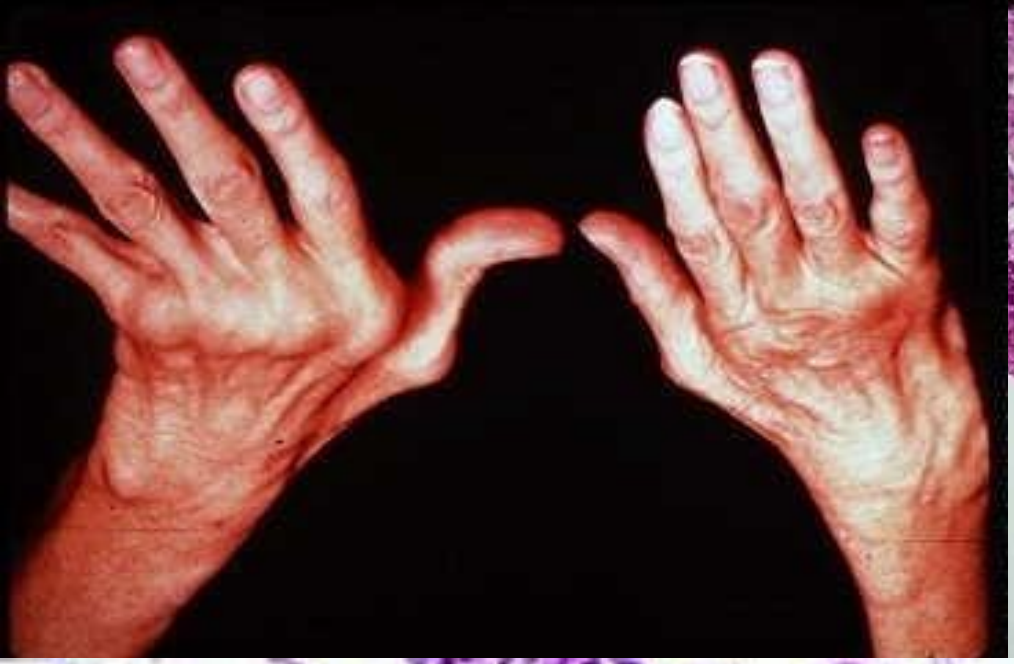
The synovium is swollen with prominent villous pattern.

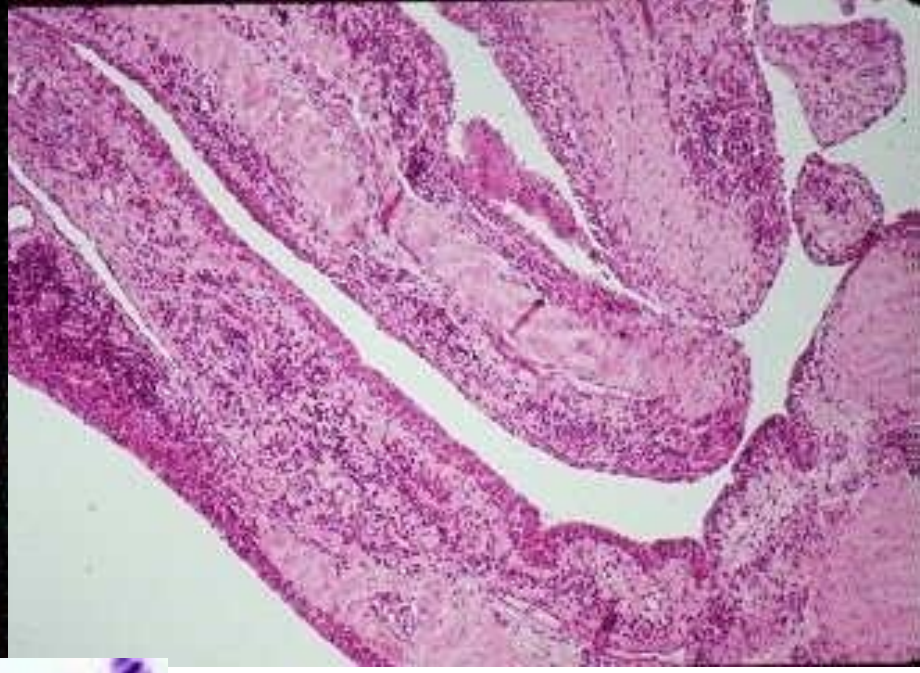
There is a great increase in chronic inflammatory cells mainly lymphocytes, plasma cells & macrophages with formation of lymphoid follicles. There is marked synovial hypertrophy & hyperplasia, often with increased vascularity due to angiogenesis. There is often fibrinous effusion in the joint space; the fibrin gets deposited on the synovial surfaces.

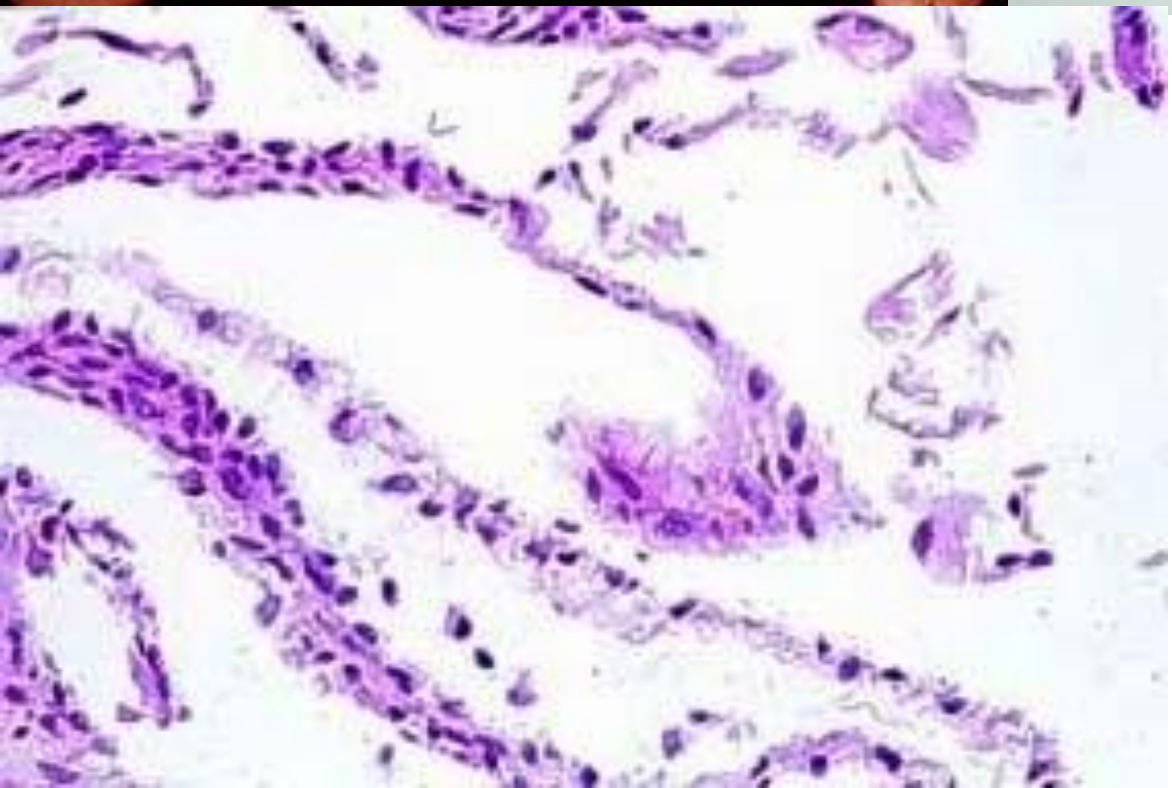
2. With time there is articular cartilage destruction with replacement by vascular granulation tissue (pannus). The latter grows across the surface of the articular cartilage from the edge of the joint.
3. The inflammatory pannus causes focal destruction of the subjacent bone; this is manifested as "erosions" on radiographs. Following destruction of the articular cartilage & erosion of the subarticular bone, the pannus fills the joints space. Subsequent fibrosis & calcification may cause permanent ankylosis of the affected joint.

The loss of articualr cartilage can lead to secondary osteoarthritis (a degenerative joint disease), especially in the weight-bearing joints such as the knee.

Destruction of tendons, ligaments & joint capsules produces deformities of the joints; that of the hand are characteristic, which include radial deviation of the wrist, ulnar deviation of the fingers & flexion-hyperextension abnormalities of the fingers **(swan-neck deformity).**



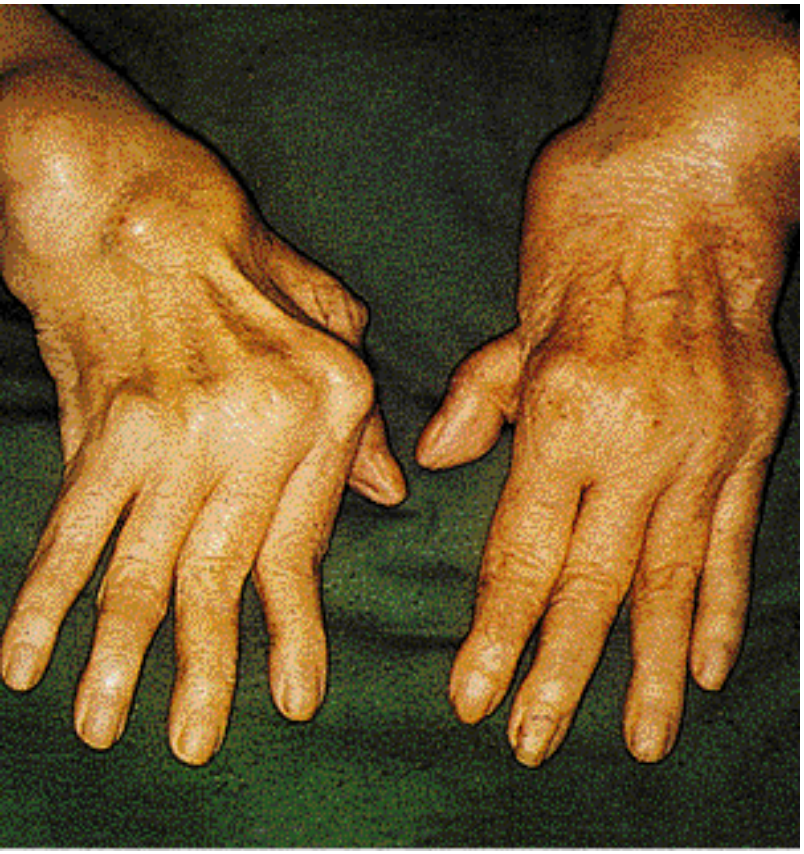


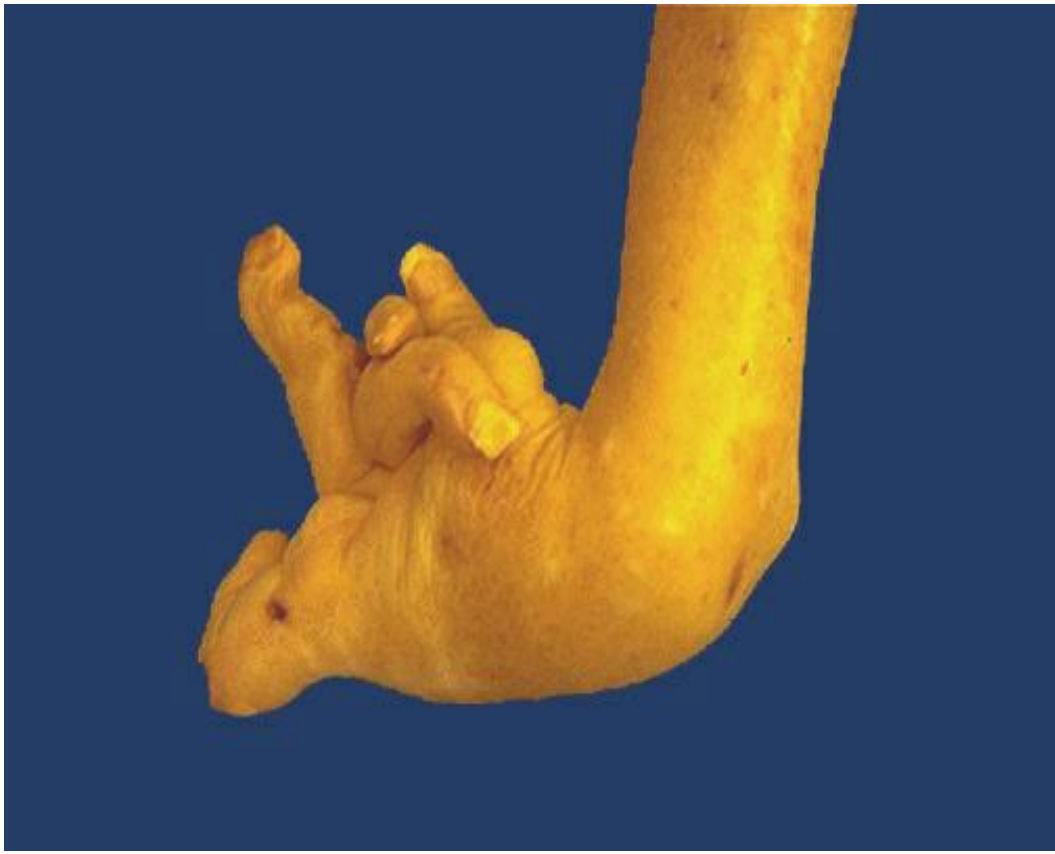


Destructive Rheumatoid Synovitis

←**NORMAL** Bi-Layered Synovium

Rheumatoid arthritis





This deformity of the hand is due to rheumatoid arthritis (RA). This autoimmune disease leads to synovial proliferation and joint destruction, typically in a symmetrical pattern involving small joints of hands and feet, followed by wrists, ankles, elbows, and knees. Rheumatoid factor can be identified serologically in most, but not all, RA patients.

Rheumatoid subcutaneous nodules

develop in about 25% of the patients.

They occur along the extensor surface of the forearm or other areas subjected to mechanical pressure.

Rheumatoid nodules are firm, nontender, oval or rounded masses up to 2 cm in diameter.

Microscopically there is central focus of fibrinoid necrosis surrounded by a palisade of macrophages which is rimmed by granulation tissue.

Pulmonary involvement in RA takes the form of interstitial pneumonitis & fibrosing alveolitis, which leads eventually to a pattern of interstitial fibrosis called "honeycomb lung". The latter is also caused by other diseases such as systemic sclerosis.

Anemia is very common in rheumatoid disease as is increased susceptibility to **infections** & **sepses,** which are important & common causes of death.

Pathogenesis of RA:

There is a genetic predisposition to RA which is suggested by:-

1. The increased frequency of this disease among first-degree relatives.

2. The strong association of the disease with HLA-DR4 &/or HLA-DR1.

About 80% of the patients have rheumatoid factors (RF) in their serum & synovial fluid.

RF represents an autoantibody mainly of IgM class directed against the Fc portion of IgG.

RF & IgG form immune complex that fix complement, attract neutrophils & lead to injury by a type III hypersensitivity reaction.

It is proposed that the disease is initiated in a genetically predisposed individual, by activation of helper T-cells possibly by microbial agent, the activated CD_4+cells produce cytokines that will:-

1. Activate macrophages & other cells in joint space to release degrading (proteolytic) enzymes & other factors that initiate inflammation and cause tissue destruction.

2. Activate B-cells, which produce RF (autoantibody).

These will- form immune complexes with IgG that often get deposited on the synovial membrane with subsequent joint injury.

3. It has been found that activated T-cells will also induce osteoclast cell differentiation & activation that leads to bone resorption.

Juvenile rheumatoid arthritis (JRA):

It is a chronic idiopathic arthritis that occurs in children.

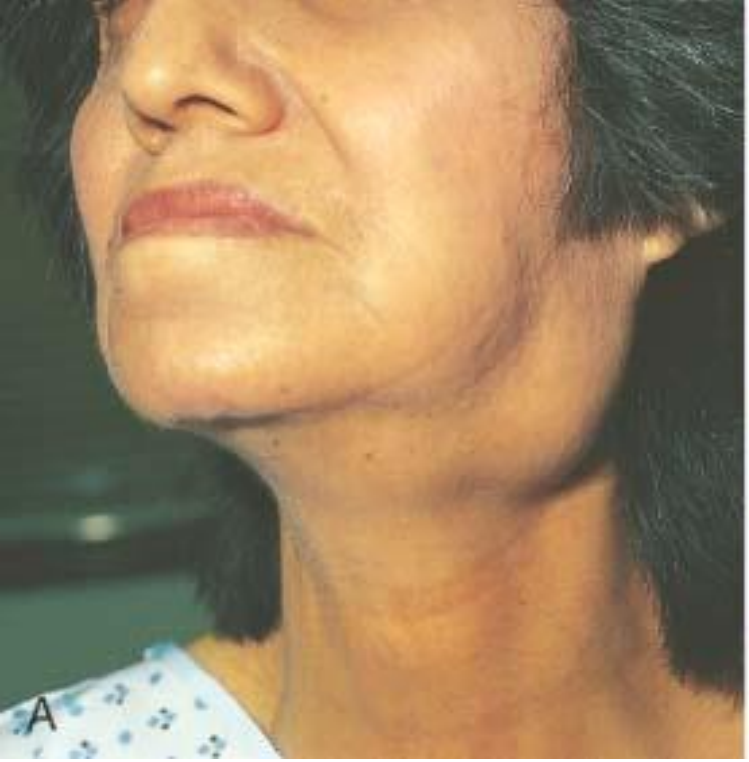
Like the adult form of (RA) it is a destructive arthritis but differs from it by the following points:-

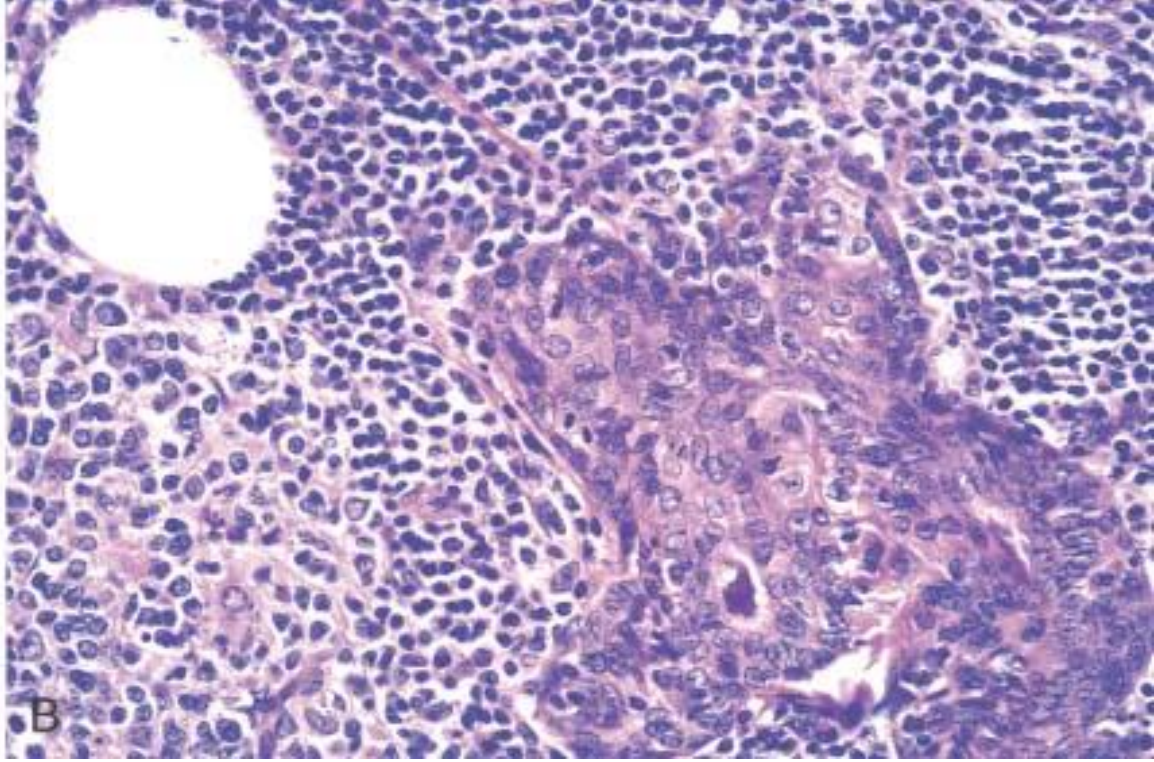
1. It affects large joints.
2. There is absence of RF.
3. There are no rheumatoid nodules.
4. Some cases of JRA are associated with HLA-B27.

SjOgren syndrome:

This autoimmune disease is characterized by dry eyes (keratoconjunctivitis sicca) & dry mouth (xerostomia) resulting from immune-mediated destruction of the lacrimal & salivary glands.

It occurs in two forms a primary form i.e. an isolated disorder, and as a secondary form associated with other autoimmune disorder such as RA, SLE, polymyositis, systemic sclerosis, vasculitis and thyroiditis.





SJÖGREN SYNDROME