Immunopathology

Dr. Methaq Mueen

Lec.3

Q: Is the Allergic dermatitis is the same to contact dermatitis?

Waiting your answers next lecture

Atopic dermatitis and **contact dermatitis**

are both very common types of eczema: (a skin condition that can cause itchy, scaly, inflammatory rashes).

Atopic dermatitis:

Often dry and scaly

Appears on flexural areas(such as the folds of the elbows (antecubital fossa), behind the knees (popliteal fossa), the front of the neck, folds of the wrists, ankles, behind the ears and in the face of babies.

Most common in children under 5years old

Genetic susceptibility

Common in those with allergies and asthma(Type I hypersensitivity)

Contact dermatitis

Often blisters and oozing

Can appear anywhere on the body exposed to chemicals

Most common in adults

Topical exposure to offending substance

Delayed hypersensitivity response

In some cases, the difference between the two is quite obvious; in other cases, it is not.

Some patients can even have both atopic and contact dermatitis at the same time, making assessment more difficult

Systemic Lupus Erythematosus(SLE):

Lupus : Latin: wolf

The disease was so named in 13th century as the rash was thought to appear like bite of the wolf

It is a multisystem autoimmune disease.

may involve any organ in the body; mainly the skin, kidneys, serosal membranes, joints, and heart.

-caused by autoantibodies produced against numerous self-antigens and the formation of immune complexes.

-Clinically: it is an unpredictable, remitting and relapsing often febrile illness of acute or insidious onset.

Epidemiology:

Age: Onset typically is in the **second or third** decade of life, but it may manifest **at any age**, including early childhood.

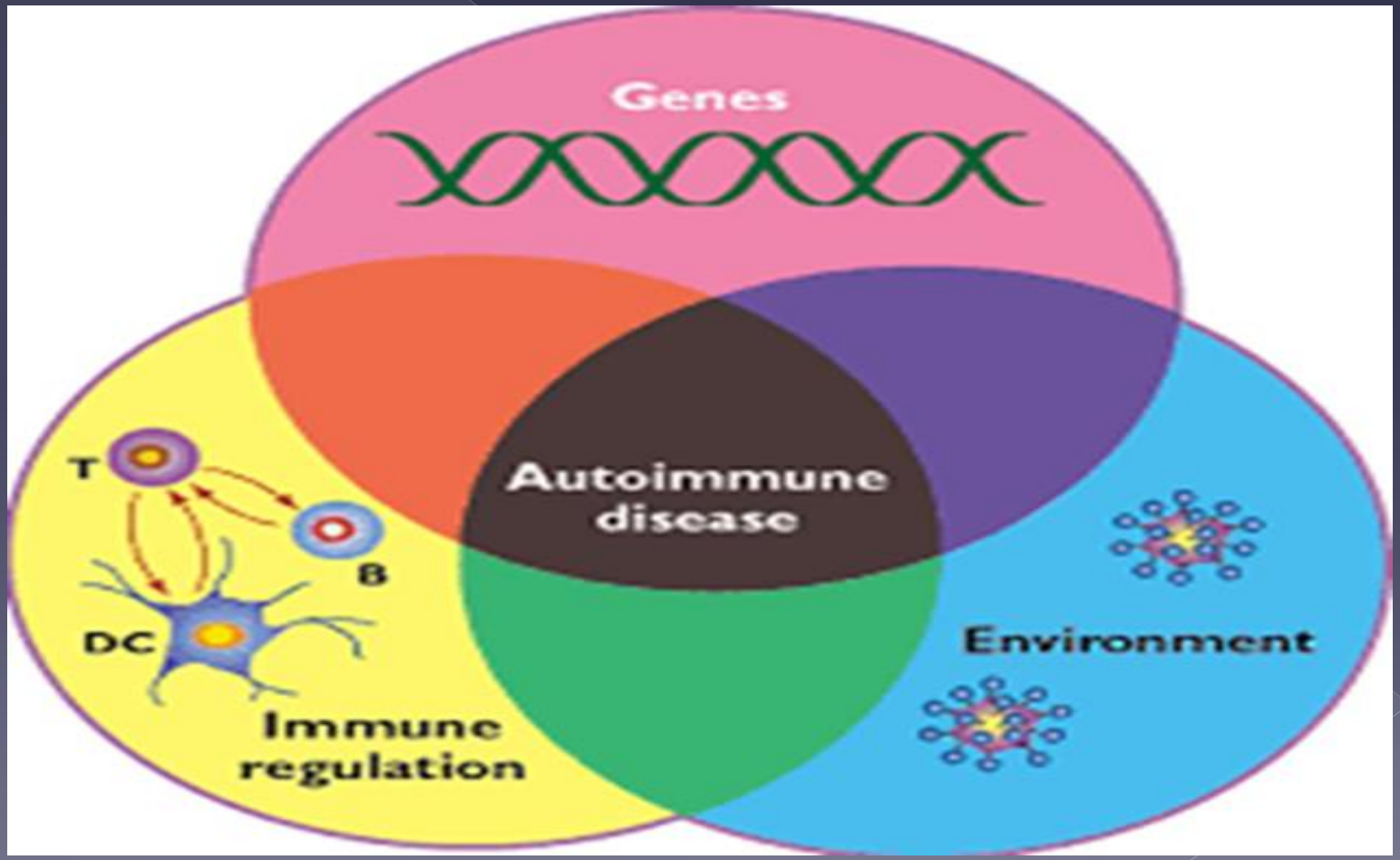
Gender: SLE predominantly affects **women**, with a female-to-male ratio of **9 : 1** for the reproductive age group of 17 to 55 years.

By comparison, the female-to-male ratio is only 2 : 1 for disease developing during childhood or after 65 years

Pathogenesis of SLE:

- The fundamental defect in SLE is a **failure of the mechanisms that maintain self-tolerance**.
- Although what causes this failure of self-tolerance **remains unknown**
- as general role for pathogensis of most autoimmune diseases, both genetic and environmental factors play a role

The pathogenesis of SLE involves a combination of genetic and environmental factors and immunologic factors .



1.Genetic Factors:

- **Familial association. If** Family members have the disease , there is an increased risk for the development of SLE.
- **HLA association:**

  HLA-DR2 , HLA-DR3
- **Other genes:**

Genetic **deficiencies** of classical pathway complement proteins, especially **C1q, C2, or C4,** are seen in about 10% of patients with SLE.

Lack of complement may impair removal of circulating immune complexes by the mononuclear phagocyte system, thus favoring tissue deposition

2.Environmental Factors.

- 1- **Ultraviolet (UV) radiation (sun exposure) exacerbates the lesions of SLE.**
- **2-Cigarette smoking**
- **3-Sex hormones : There is a strong female preponderance (female :male is 9 : 1)**

It has been suggested that factors other than hormones may account for the increased risk of this disease in women like certain genes on the X chromosome, independent of hormone effects.

- **4-Drugs: such as procainamide and hydralazine can induce an SLE- like disease.**

- 3. Immunologic factors:
- 1-Defective central tolerance in elimination of self-reactive B cells in bone marrow, and ineffective peripheral tolerance mechanisms are most important.
- 2-CD4+ helper T cells specific for nucleosomal antigens also escape tolerance and contribute to the production of high-affinity pathogenic autoantibodies

Based on these clues, a model for the pathogenesis of SLE has been proposed:

- The fundamental defect in SLE is a failure to maintain self tolerance.
- Cell injury (e.g., UV and other environmental insults) leads to apoptosis and an increased burden of nuclear antigens(due to defective clearance of nuclear antigens) .

Defective B and T-cell tolerance leads to autoantibodies directed against the nuclear antigens, with the resulting immune complexes, being ingested by B cells and dendritic cells; then further cellular activation, cytokine production, and augmented autoantibody synthesis, which causes more apoptosis in a self amplifying loop.

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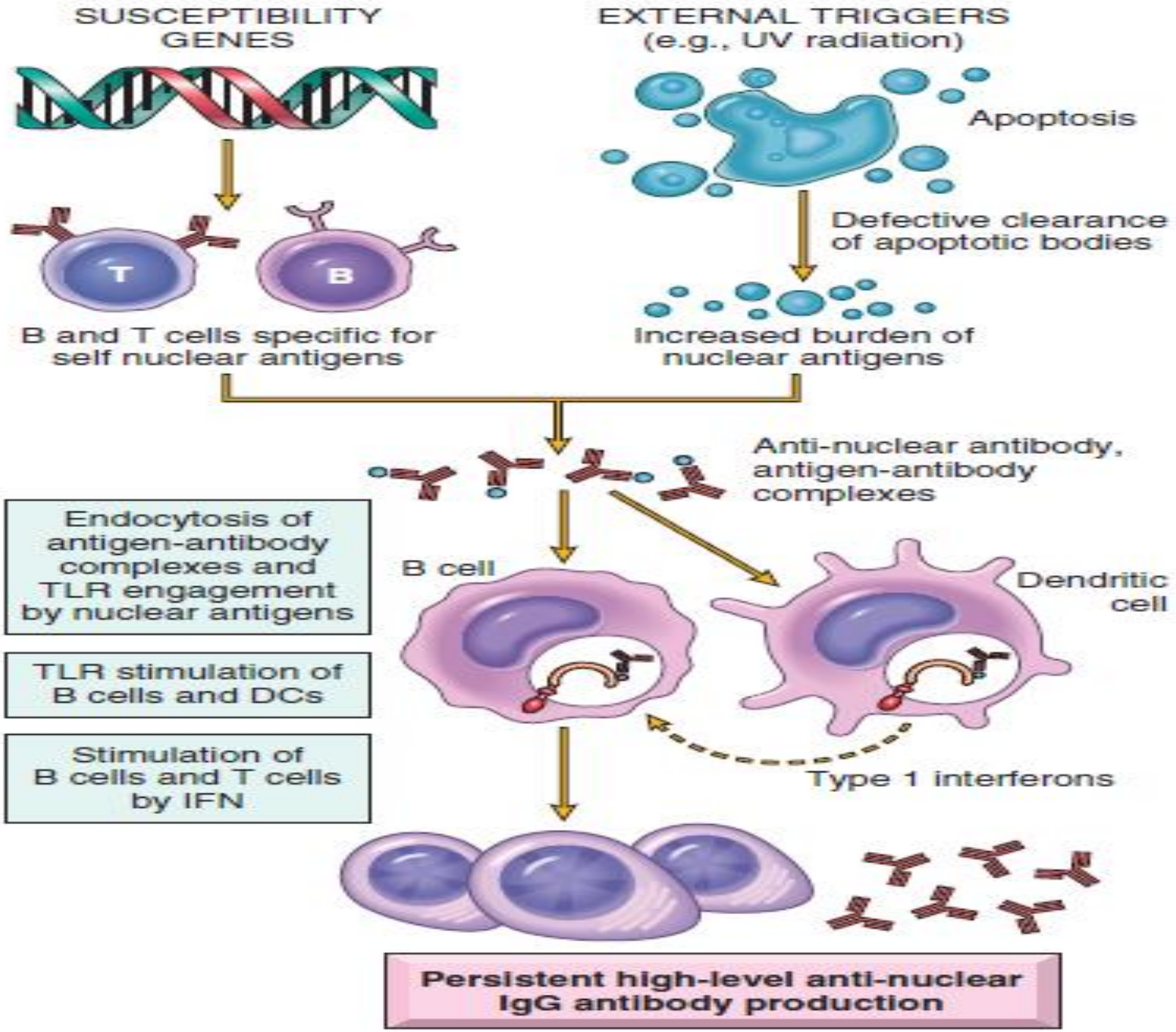

SUSCEPTIBILITY GENES
EXTERNAL TRIGGERS (e.g., UV radiation)
Apoptosis
Defective clearance of apoptotic bodies
T
B
B and T cells specific for self nuclear antigens
Increased burden of nuclear antigens
Anti-nuclear antibody, antigen-antibody complexes
Endocytosis of antigen-antibody complexes and TLR engagement by nuclear antigens
B cell
Dendritic cell
TLR stimulation of B cells and DCs
Stimulation of B cells and T cells by IFN
Type 1 interferons
Persistent high-level anti-nuclear IgG antibody production

Spectrum of Autoantibodies in SLE

A. Antinuclear antibodies(ANA):

ANAs are directed against several nuclear antigens and can be grouped into :

(1)antibodies to double stranded DNA.

(2) antibodies to histones.

(3) antibodies to nonhistone proteins bound to RNA (smith Ag, SS-A, SS-D).

(4) antibodies to nucleolar antigens.

-ANAs also occur in other autoimmune disorders, and in 5-15% of normal individuals .

- anti-double-stranded DNA and anti-Smith antigen antibodies strongly suggest SLE.

B. Other autoantibodies:

-Some directed against blood elements (i.e., red blood cells, platelets, leukocytes).

opsonize these cells and promote their phagocytosis and lysis.

Mechanisms of Tissue Injury :

1.type III hypersensitivity

Most organ damage in SLE is caused by immune complex deposition.

2. type II hypersensitivity.

Autoantibodies against red cells, white cells, and platelets opsonize these cells and lead to their phagocytosis, resulting in cytopenias (autoimmune haemolytic anaemia, immune thrombocytopenia)

MORPHOLOGY:

Although any organ can be involved, the most characteristic tissues affected are skin, blood vessels, kidneys and connective tissue.

-Classically, there is a type III hypersensitivity response with acute necrotizing vasculitis and fibrinoid deposits involving small arteries and arterioles.

Immune complexes can be found in vessel walls.

1. Kidneys. Kidney involvement is one of the most important clinical features of SLE.

Mostly it is glomerular pathology (lupus nephritis), although interstitial and tubular lesions are also seen in SLE.

2. Skin: Malar erythema is the classic lesion (butterfly rash) , Exposure to sunlight (UV light) exacerbates the erythema (so-called photosensitivity)

3. Joints: There is synovitis.

4. CNS. Central nervous system (CNS) involvement

5. Spleen , Lungs , heart

Cardiac pathology of SLE:

- * Pericarditis (most common).
- * Endocarditis (Libman-Sacks).
- * Non specific myocarditis.
- * Accelerated coronary atherosclerosis

Table 6-9 1997 Revised Criteria for Classification of Systemic Lupus Erythematosus*

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	Pleuritis—convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion, or Pericarditis—documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal disorder	Persistent proteinuria >0.5 g/dL or >3 if quantitation not performed or Cellular casts—may be red blood cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	Seizures—in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance), or Psychosis—in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance)
9. Hematologic disorder	Hemolytic anemia—with reticulocytosis, or Leukopenia—$<4.0 \times 10^9$ cells/L (4000 cells/mm^3) total on two or more occasions, or Lymphopenia—$<1.5 \times 10^9$ cells/L (1500 cells/mm^3) on two or more occasions, or Thrombocytopenia—$<100 \times 10^9$ cells/L (100×10^3 cells/mm^3) in the absence of offending drugs
10. Immunologic disorder	Anti-DNA antibody to native DNA in abnormal titer, or Anti-Sm—presence of antibody to Sm nuclear antigen, or Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, (2) a positive test for lupus anticoagulant using a standard test, or (3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by negative *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus syndrome

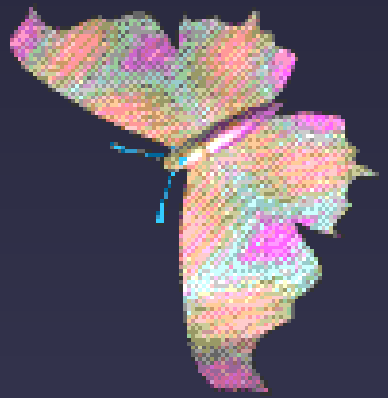
*This classification, based on 11 criteria, was proposed for the purpose of identifying patients in clinical studies. A person is said to have SLE if any four or more of the 11 criteria are present, serially or simultaneously, during any period of observation.

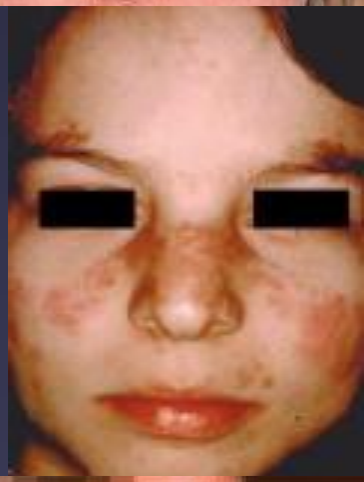
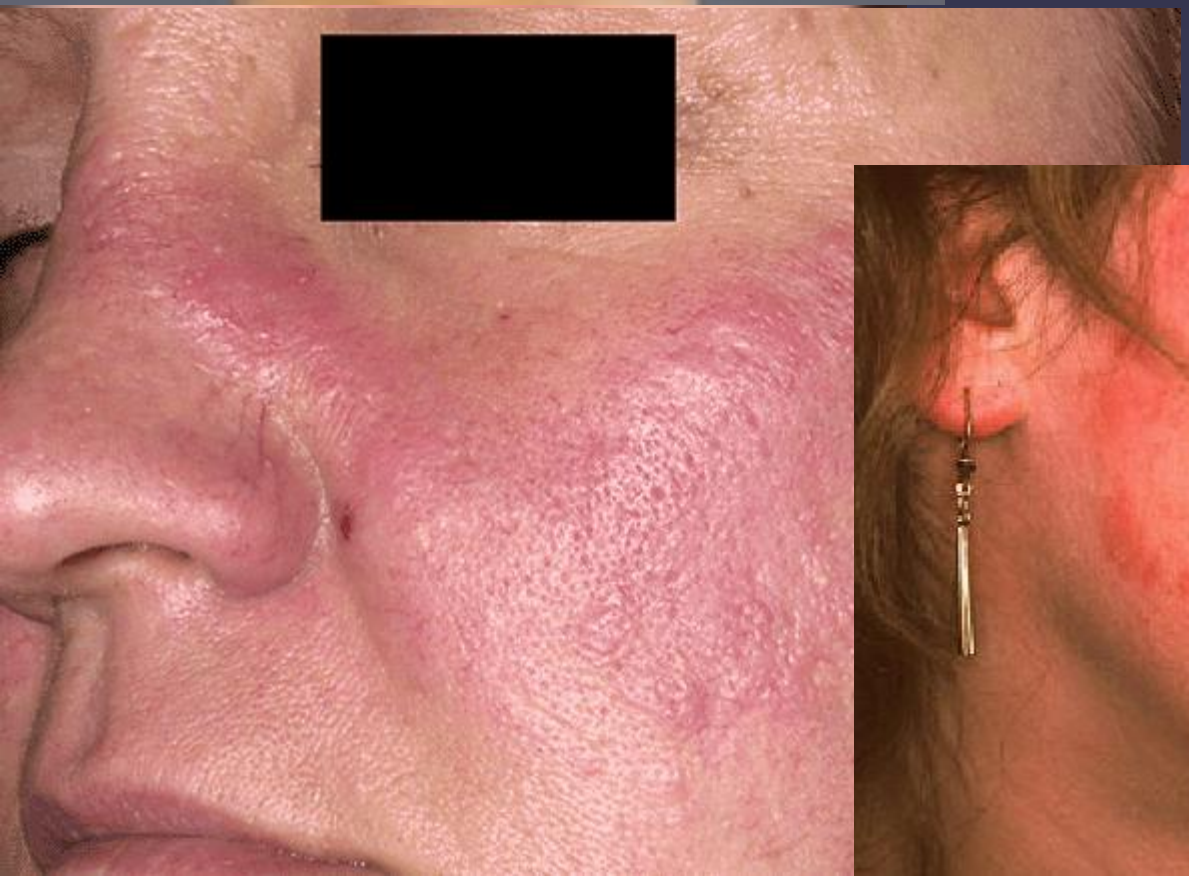
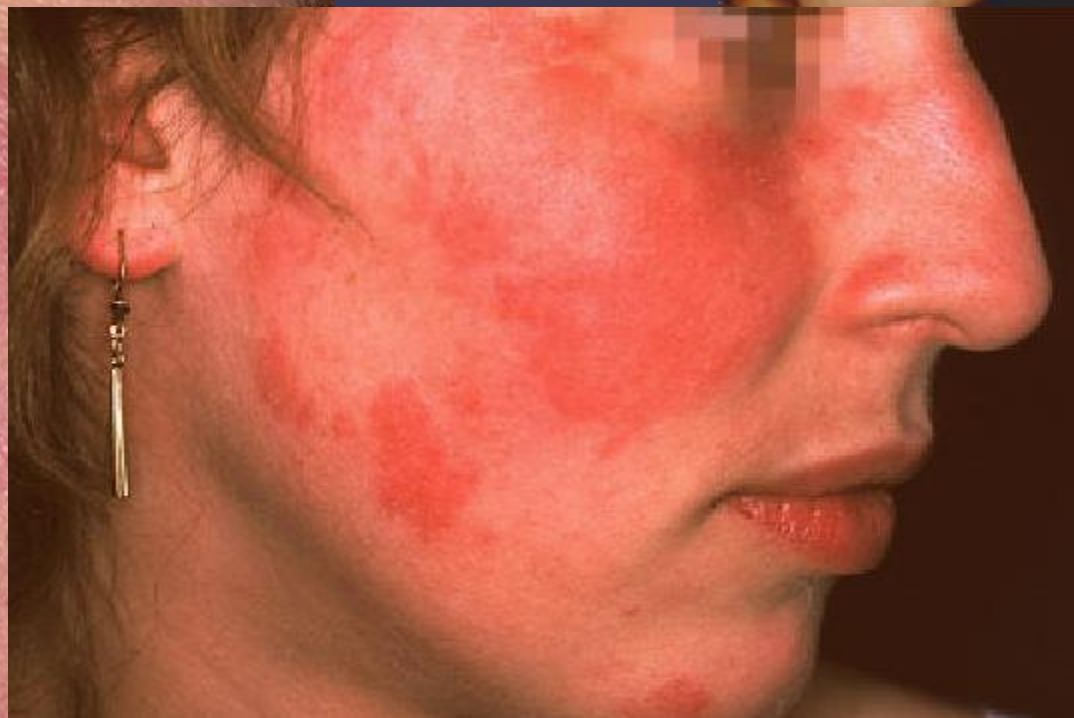
From Tan EM, et al: The revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271; and Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.

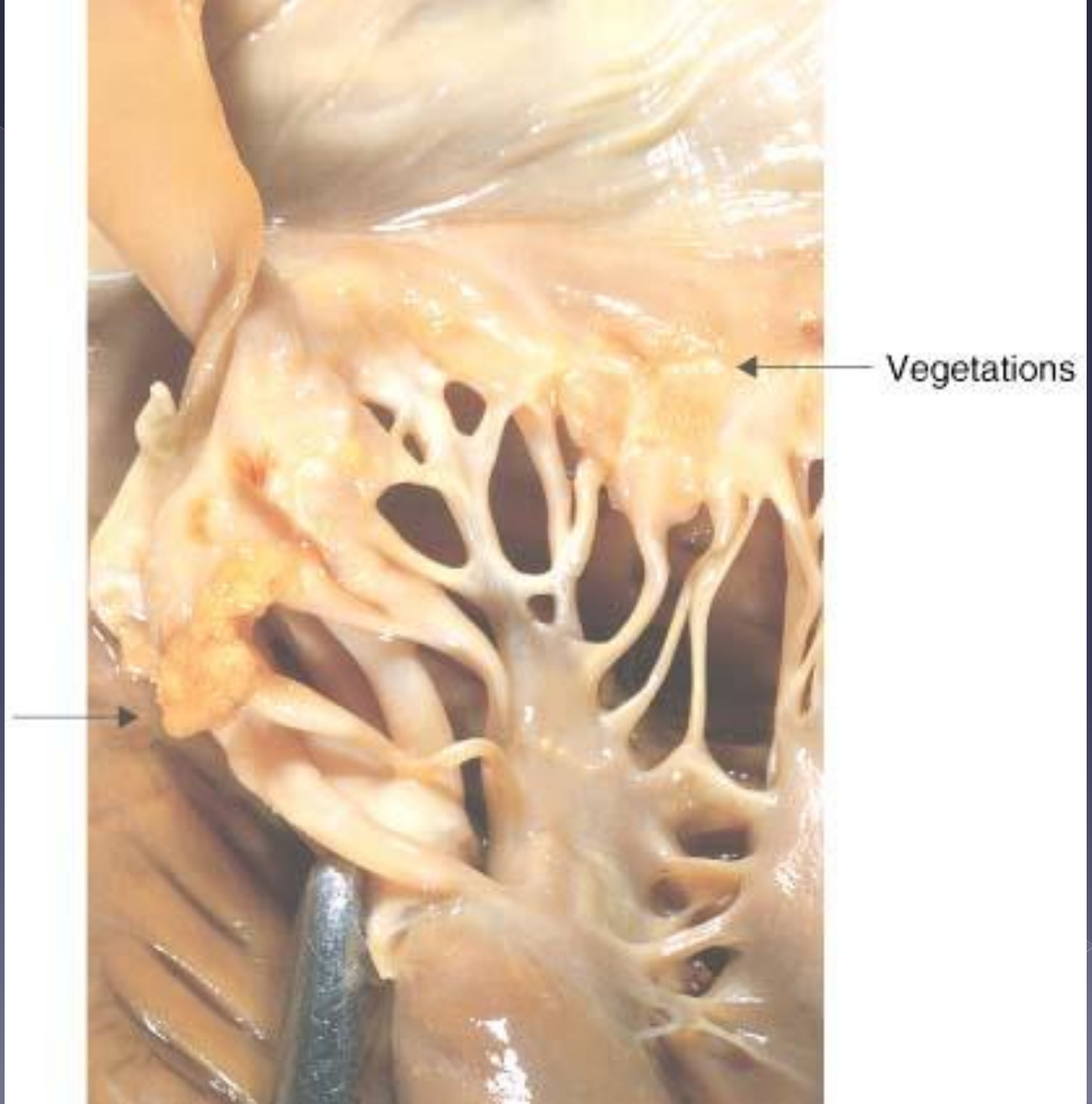
Systemic Lupus Erythromatosus

Four out of 11 clinical or laboratory criteria must be present for diagnosis of SLE:

(1) Malar rash.
(2) Discoid rash.
(3) Photosensitivity.
(4) Oral ulcers.
(5) Arthritis.
(6) Serositis.
(7) Renal disorders.
(8) Neurological disorders (seizures, psychosis).
(9) Hematological disorders (cytopenia, hemolytic anemia).
(10) Immunological disorder (Ab to DNA or anti-Sm, antiphospholipid Ab).
(11) Antinuclear Ab.


Vegetations

Disease manifestations

-It typically presents insidiously as a systemic, chronic, recurrent, febrile illness with symptoms referable to virtually any tissue but especially joints, skin, kidneys, and serosal membranes(pleural and pericardial effusion).

-Autoantibodies to hematologic components may induce

thrombocytopenia, leukopenia, anemia.

-neurologic abnormalities with focal neurologic deficits and/or neuropsychiatric symptoms

-

The most common causes of death are :

1-renal failure.

2- intercurrent infections.

3-cardiovascular disease.

Rheumatoid arthritis

Rheumatoid arthritis (RA)

is a chronic inflammatory disorder of autoimmune origin that may affect many tissues and organs (blood vessels, skin, heart, lungs, and muscles) ,

but principally attacks the joints especially small joints (digits before wrist, ankles, elbows, and knees) in a bilaterally symmetric pattern, producing a NON Suppurative proliferative and inflammatory synovitis.

The prevalence in the United States is approximately 1%.

Age: The disease peaks in the second to fourth decades

Gender: it is three times more common in women than men.

Pathogenesis.

As in other autoimmune diseases,

genetic predisposition (Specific **HLA-DRB 1** alleles are linked to rheumatoid arthritis and **PTPN22 gene**) and

environmental factors (e.g. infection , smoking) contribute to the development, progression, and chronicity of the disease.

The pathologic changes are mediated by **antibodies** against self-antigens and **cytokine**-mediated inflammation, predominantly secreted by CD4+ T-cells

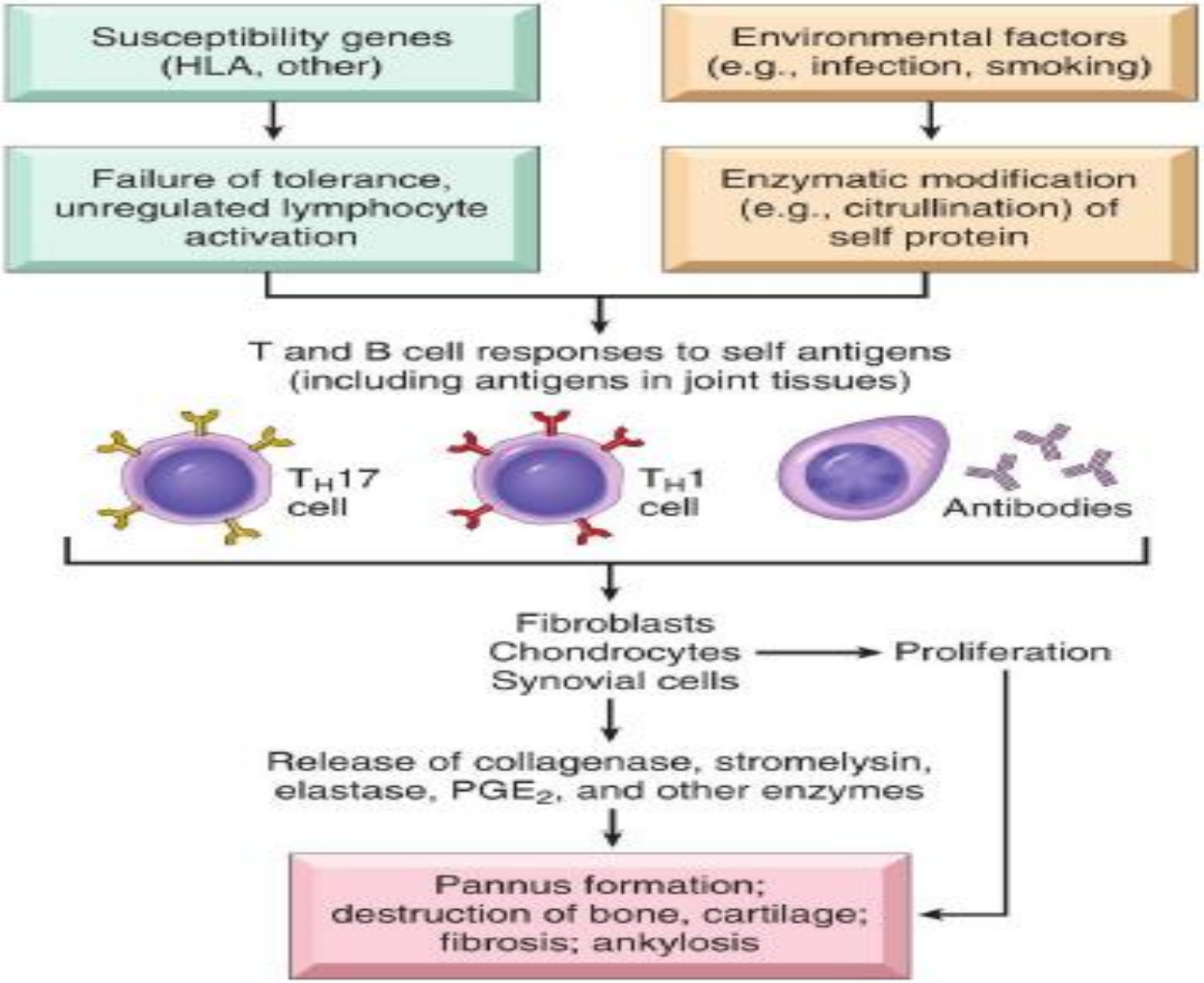


Figure 26-42 Major processes involved in the pathogenesis of rheumatoid arthritis.

- RA is caused by an autoimmune response against an unknown self-antigen(s),
- which leads to **T cell reactions** in the joint with production of cytokines that activate phagocytes that damage tissues and stimulate **proliferation of synovial cells (synovitis).**

The cytokine (TNF) plays a central role, & antagonists against TNF are of great benefit.

Antibodies also contribute to the disease.

Antibodies:

1-About 80% of patients have **rheumatoid factor**: serum immunoglobulin M (IgM) (and, less frequently, IgA) autoantibodies that bind to the Fc portions of their own (self) IgG.

They may form immune complexes with self-IgG that deposit in joints and other tissues, leading to inflammation and tissue damage.

2-Anti citrullinated peptides (**anti-CCPs**) are diagnostic markers and may mediate joint injury.

Morphology

Joint: symmetric arthritis principally affecting the **small joints** of the **hand and feet.** **The synovium** becomes grossly edematous, thickened, and hyperplastic,

transforming its smooth contour to one covered by delicate and bulbous **villi.**

The characteristic histologic features include

(I) synovial cell hyperplasia and proliferation;

(2) dense inflammatory infiltrates (frequently forming lymphoid follicles) of CD4+ helper T cells, B cells, plasma cells, dendritic cells, and macrophages

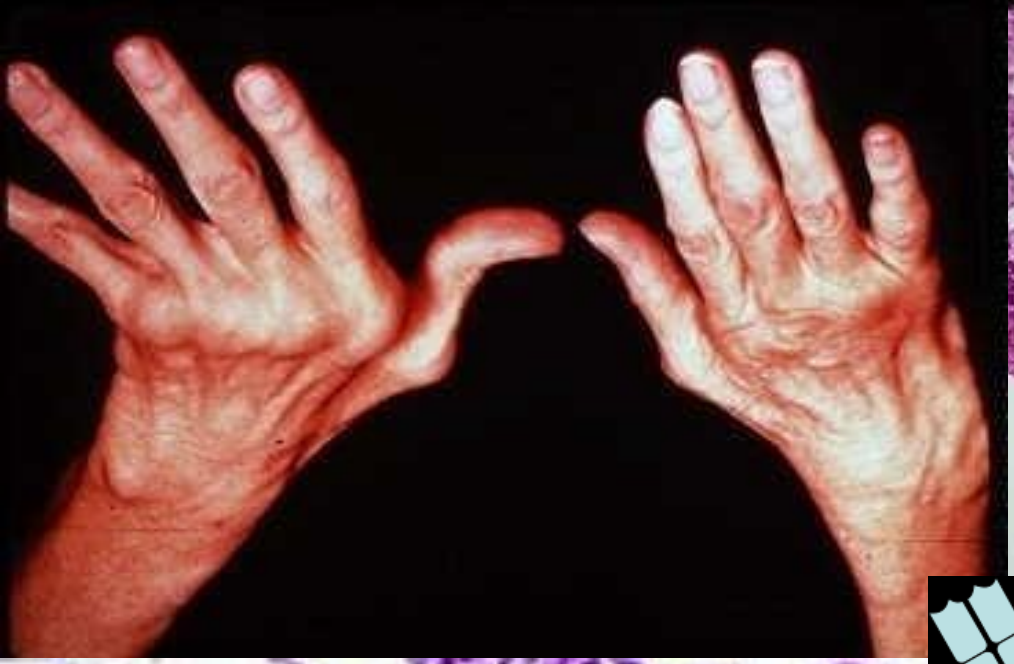
(3) increased vascularity due to angiogenesis;

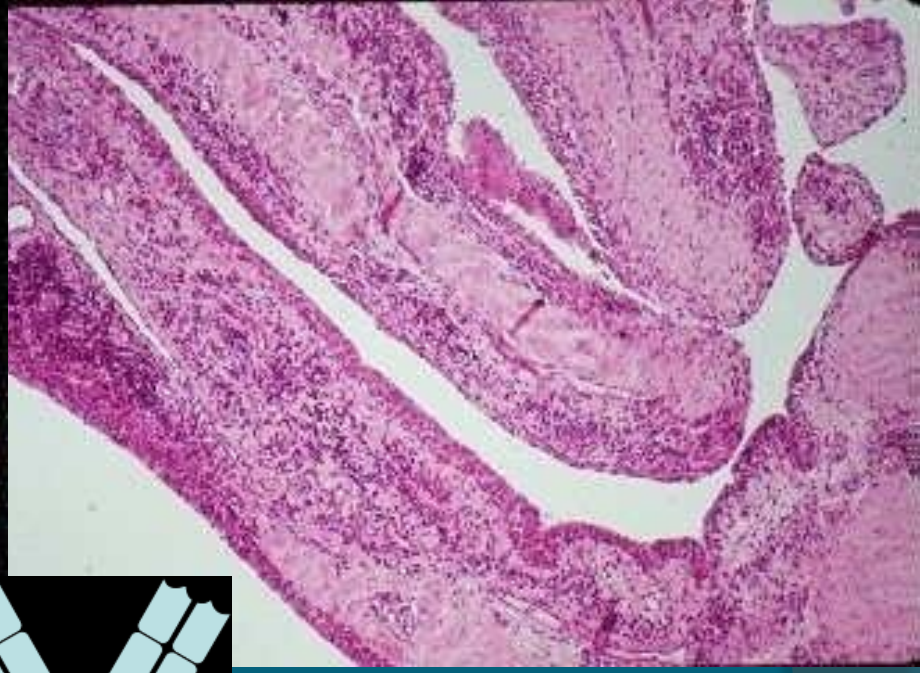
(4) osteoclastic activity in underlying bone, allowing the synovium to penetrate into the bone and cause periarticular erosions and subchondral cysts.

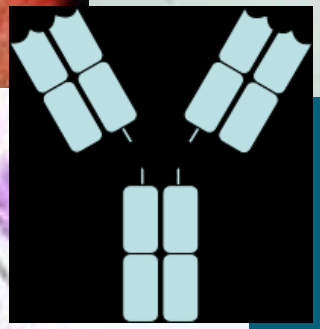
the above changes produce a **pannus:**

a mass of edematous synovium, inflammatory cells, granulation tissue, and fibroblasts that grows over the articular cartilage and causes its erosion.

With time, after the cartilage has been destroyed, the pannus bridges the apposing bones to form a fibrous ankylosis, which eventually ossifies and results in fusion of the bones, called bony ankylosis







Destructive Rheumatoid Synovitis

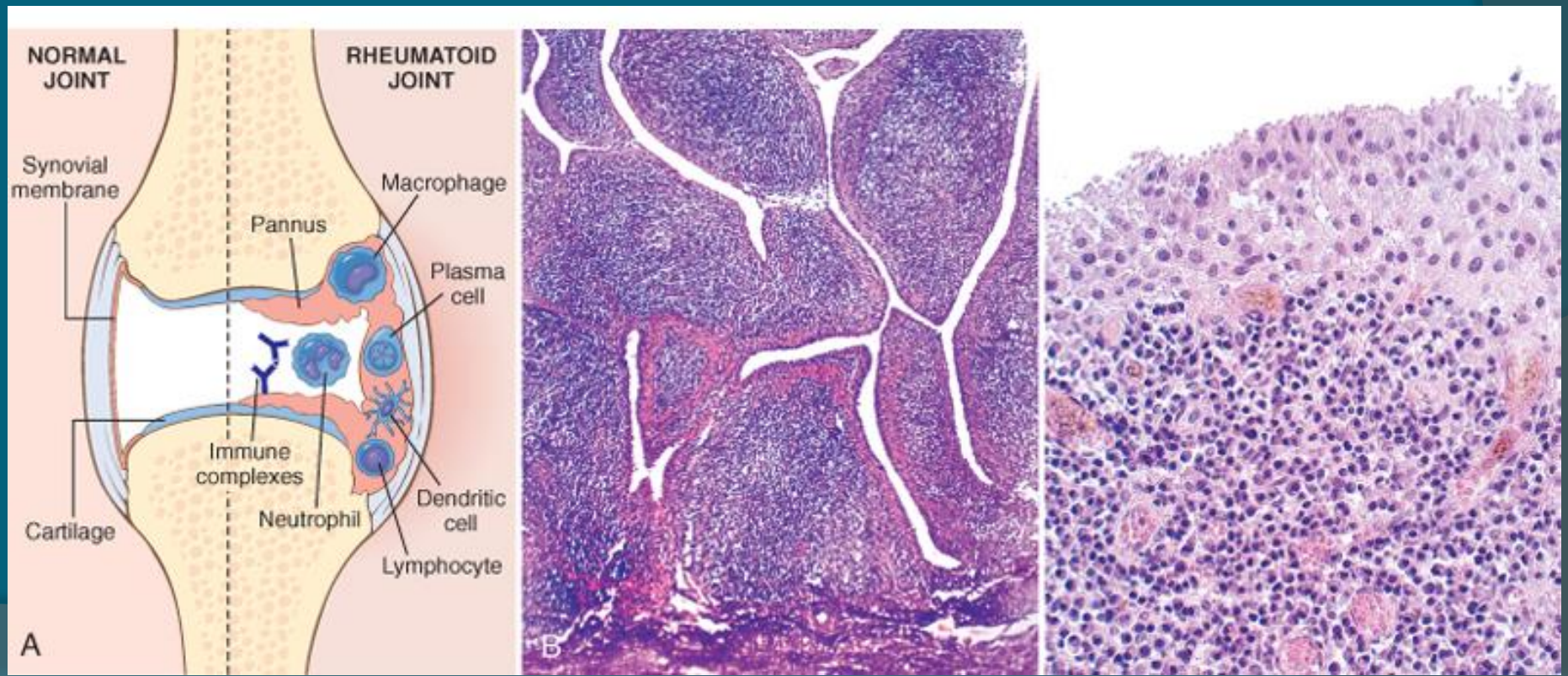
←**NORMAL** Bi-Layered Synovium

.Rheumatoid arthritis

.A joint lesion ,A

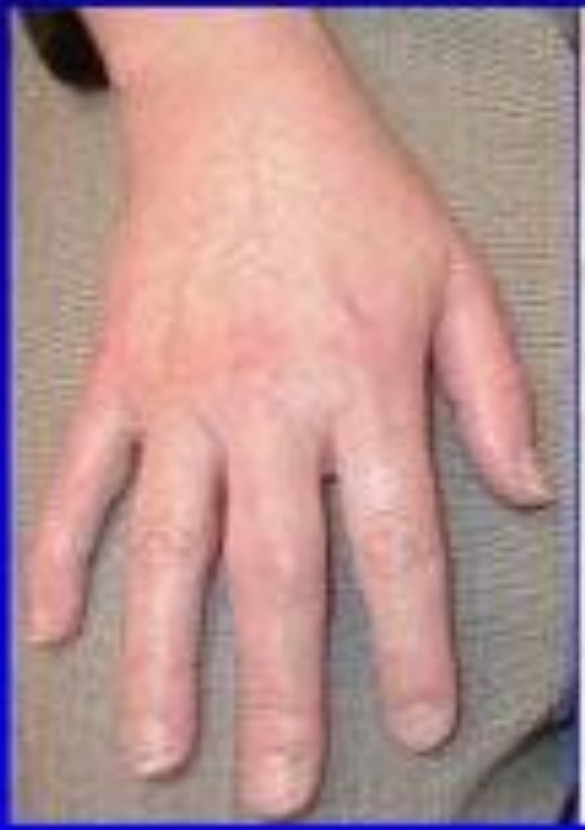
.Low magnification reveals marked synovial hypertrophy with formation of villi ,B dense lymphoid aggregates are seen in the synovium , may contains germinal centers with secondary follicles and abundant plasma cells which produce antibodies, some of which are against

higher magnification, ,C

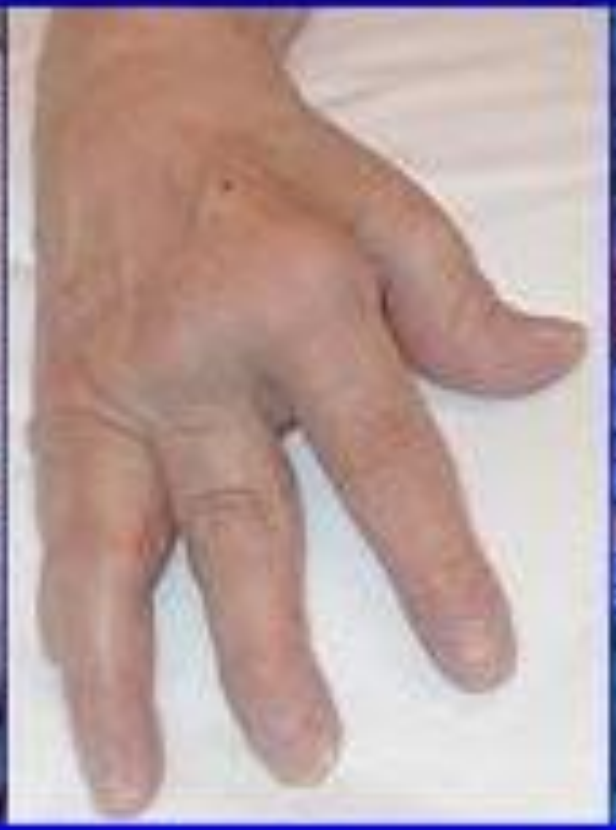


Stages of RA

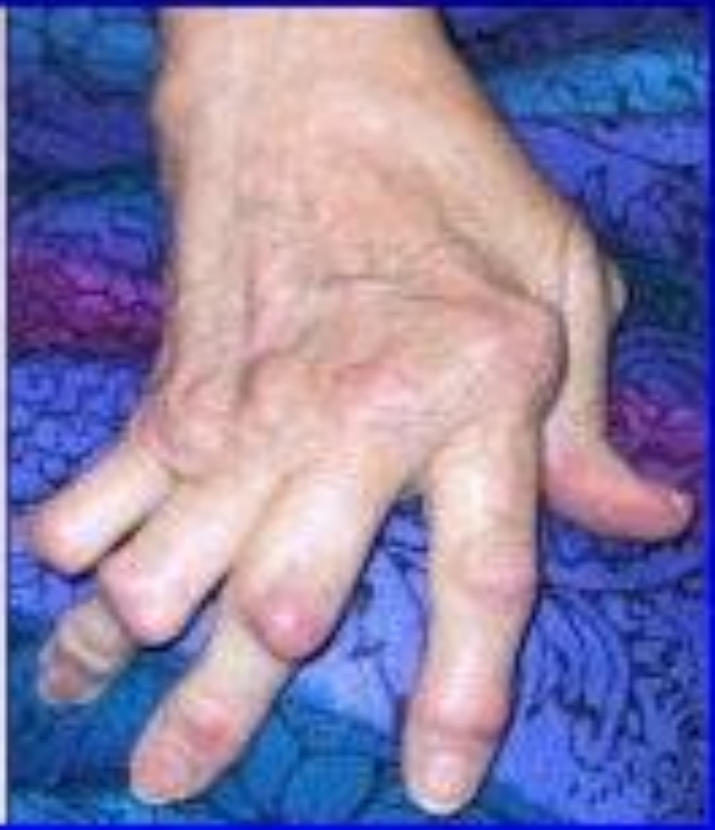
Early RA

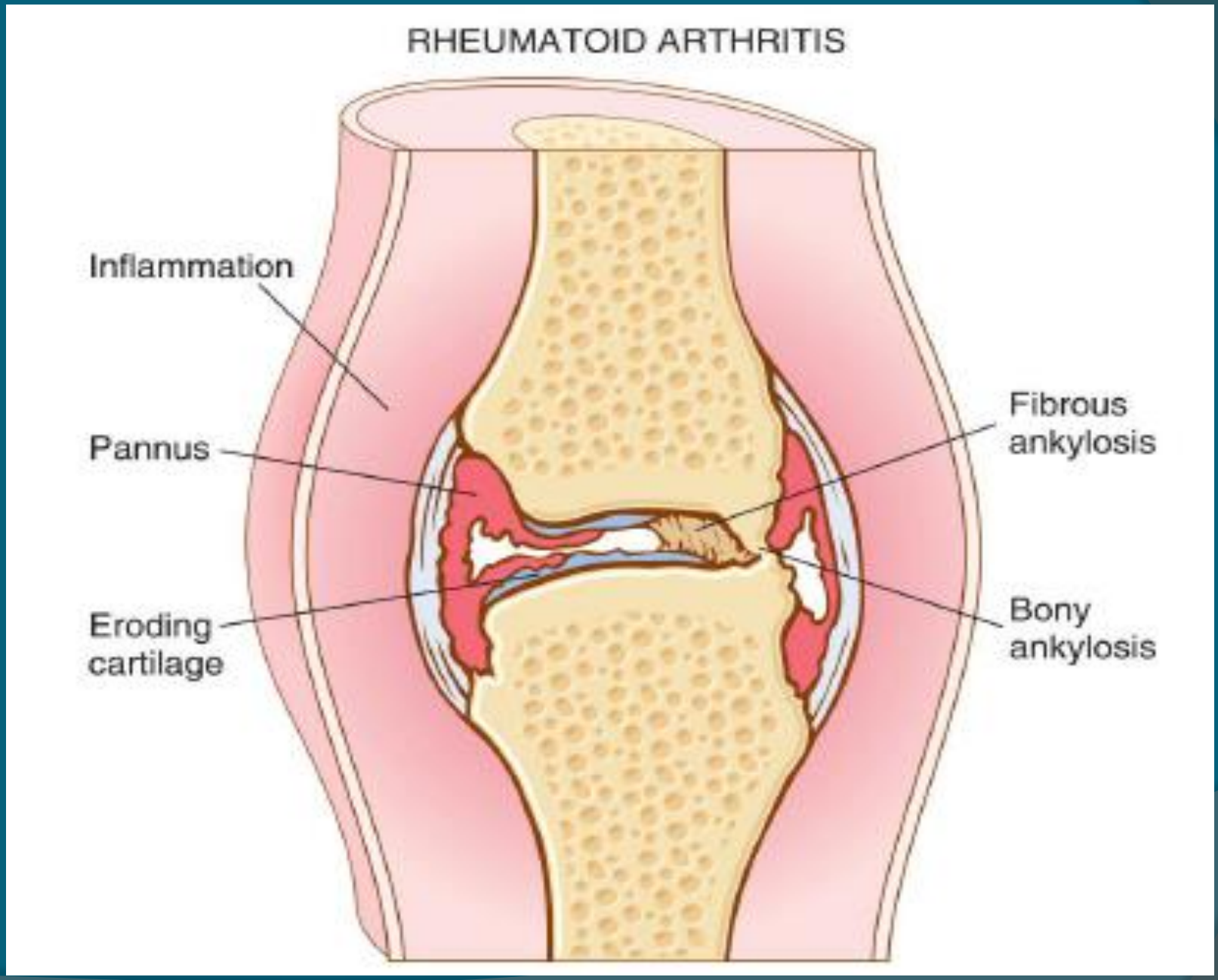


Intermediate RA



Late RA




RHEUMATOID ARTHRITIS
Inflammation
Pannus
Eroding cartilage
Fibrous ankylosis
Bony ankylosis

Skin. Rheumatoid subcutaneous nodules

are the most common cutaneous lesions.

They occur in approximately 25% of affected individuals, usually those with severe disease,

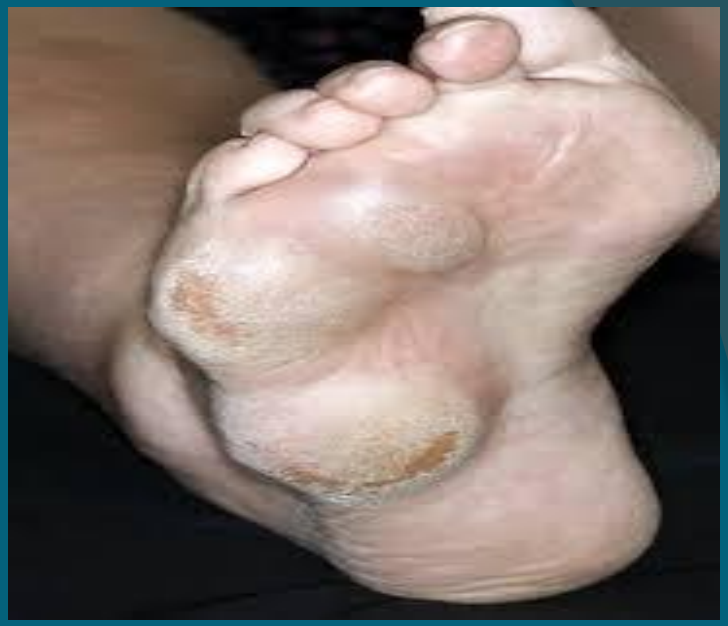
arise in regions of the skin that are subjected to pressure,

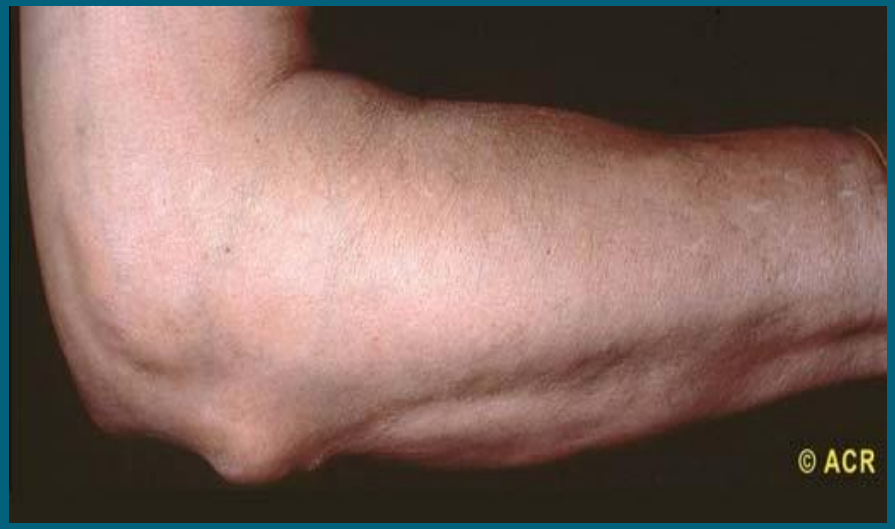
including the ulnar aspect of the forearm, elbows, occiput, and lumbosacral area.

Less commonly they form in the lungs, spleen, pericardium, myocardium, heart valves, aorta, and other viscera.

Rheumatoid nodules are firm, non tender, and round to oval, and in the skin arise in the subcutaneous tissue.

Microscopically they resemble necrotizing granulomas with a central zone of fibrinoid necrosis surrounded by a prominent rim activated macrophages and numerous lymphocytes and plasma cells





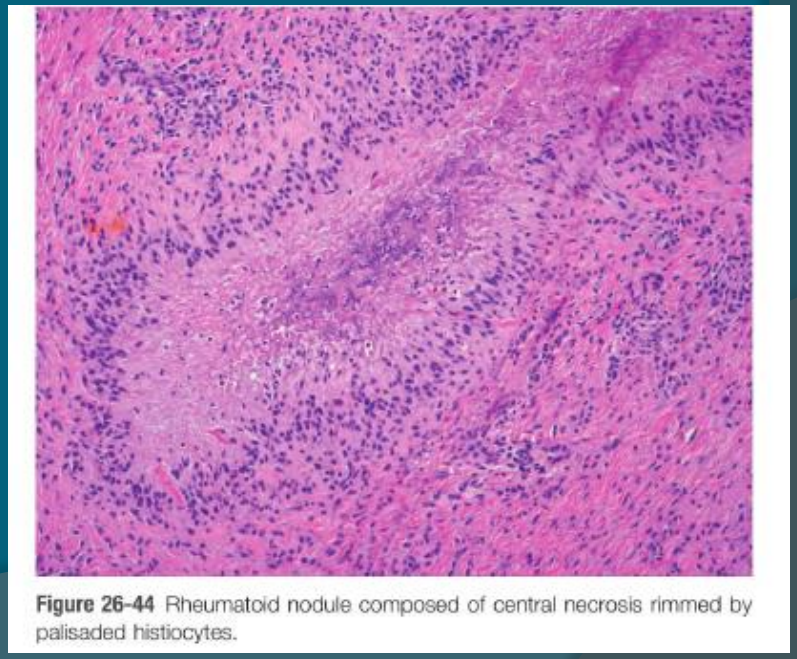


Figure 26-44 Rheumatoid nodule composed of central necrosis rimmed by palisaded histiocytes.

Blood Vessels.

acute necrotizing vasculitis involves small and large arteries.

It may involve the pleura, pericardium or lung evolving into chronic fibrosing processes, ulcers,and gangrene.

Clinical features:

In about half of patients, RA may begin slowly and insidiously with malaise, fatigue, and generalized musculoskeletal pain, likely mediated by IL-l and TNF.

After several weeks to months the joints become involved.

Pattern of joint involvement: **symmetrical** and the **small joints** are affected before the larger ones. Symptoms usually develop in the **hands** (metacarpophalangeal and proximal interphalangeal joints) and **feet**, followed by the wrists, ankles, elbows and knees.

Involved joints are **swollen, warm, painful**, and particularly **stiff** when rising in the morning or following inactivity.

The typical patient has progressive joint enlargement, decreased range of motion evolving to complete **ankylosis**, with the greatest damage occurring in the first 4 or 5 years.

Approximately 20% of affected individuals enjoy periods of partial or complete remission, but the symptoms inevitably return and involve previously unaffected joints.

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The treatment

of rheumatoid arthritis is aimed at relieving the pain and inflammation, and slowing or arresting the joint destruction.

Therapies include :

1-corticosteroids,

2- methotrexate,

3-antagonists of TNF.

Such drugs prevent or slow joint destruction, which is the greatest source of disability, and have altered the natural history of the disease for the better.

.

Long-term complications :

1-Inflammation in the tendons, ligaments, and occasionally the adjacent skeletal muscle frequently accompanies the arthritis and produces the characteristic radial deviation of the wrist, ulnar deviation of the fingers and flexion hyperextension of the fingers (swan-neck deformity).

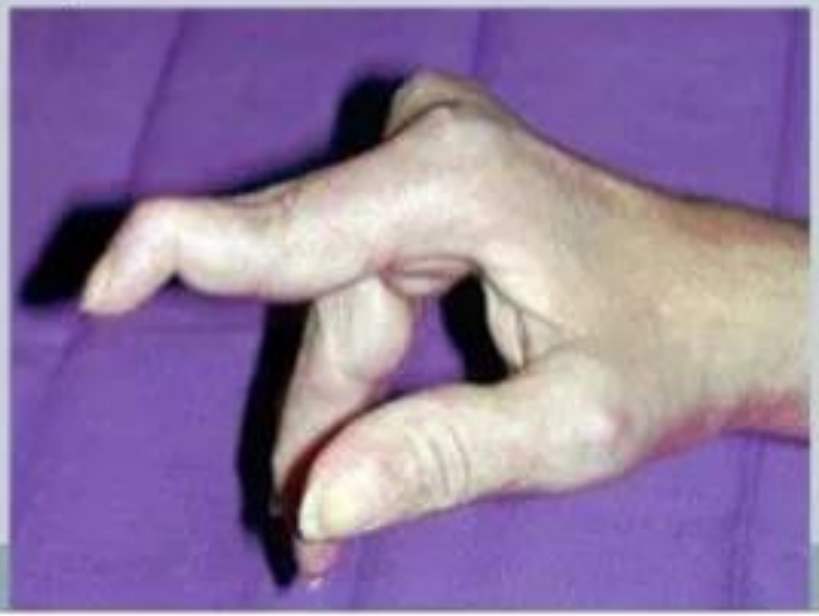
2-The end result is a joint that has no stability and minimal or no range of motion.

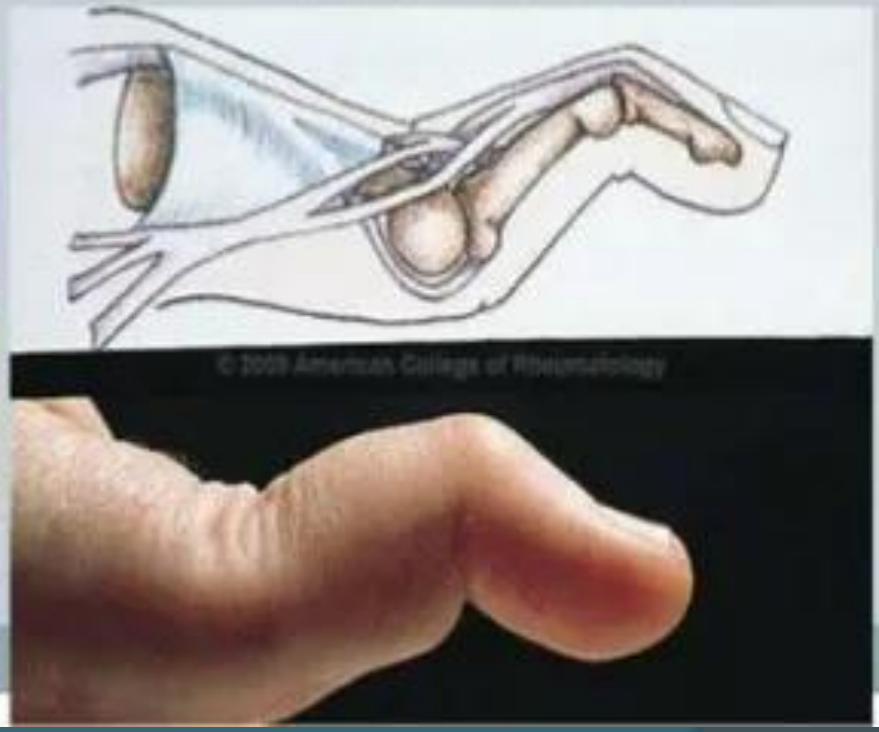
3- systemic amyloidosis: in 5% to 10% of patients

4- infection with opportunistic organisms in patients who receive long-term anti-TNF or other immunosuppressive agents

Swan-Neck Deformity

- Result of contracture of the intrinsic muscles
- Often seen after trauma or in patients with RA
- Flexion of the MCP & DIP joints & extension of the PIP joint





Sjogren syndrome

Sjogren syndrome

It is systemic autoimmune disease, the lacrimal and salivary gland are the major targets.

- mainly characterized by:

1-dry eyes (*keratoconjunctivitis sicca*): due to lack of lacrimation

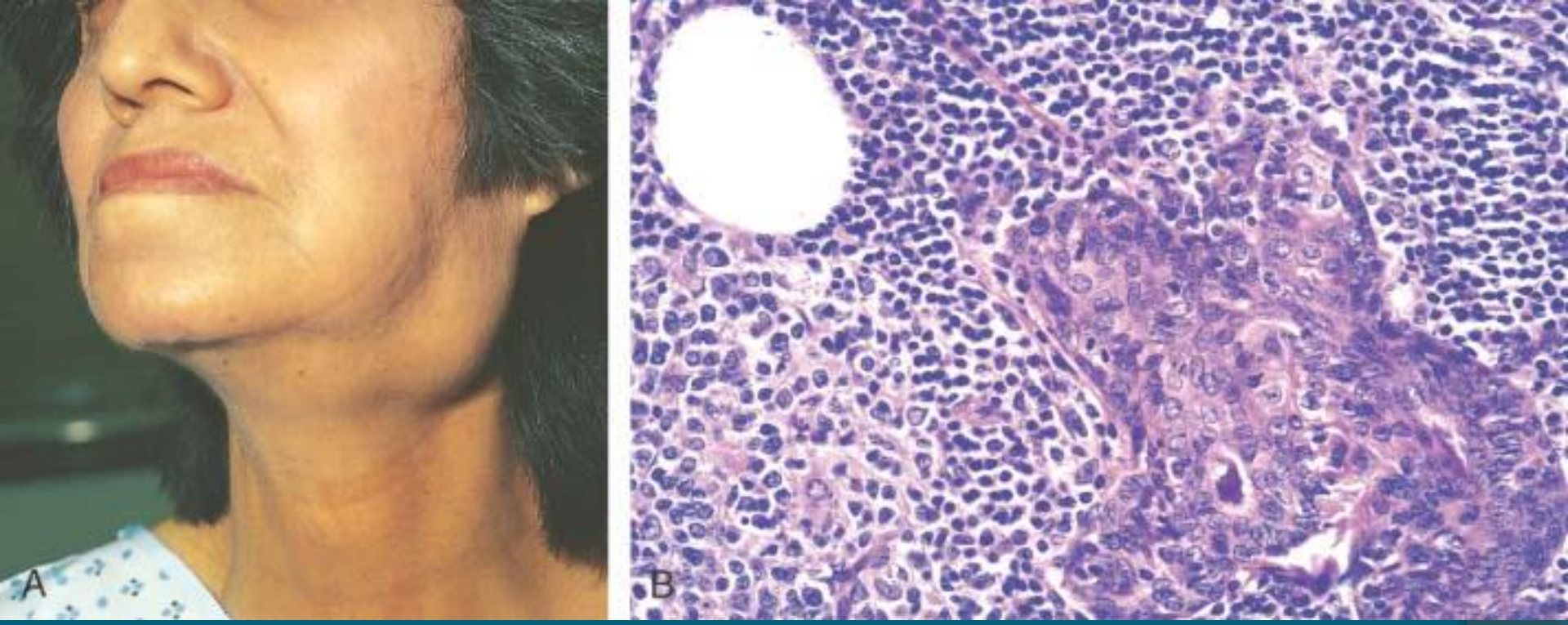
2- dry mouth (*xerostomia*):due to lack of saliva

resulting from immune-mediated destruction mainly affect the **lacrimal** and **salivary glands, other exocrine glands, including those lining the respiratory and GIT and the vagina, may also be involved .**

- **other organ that may involve: kidney, lung.**

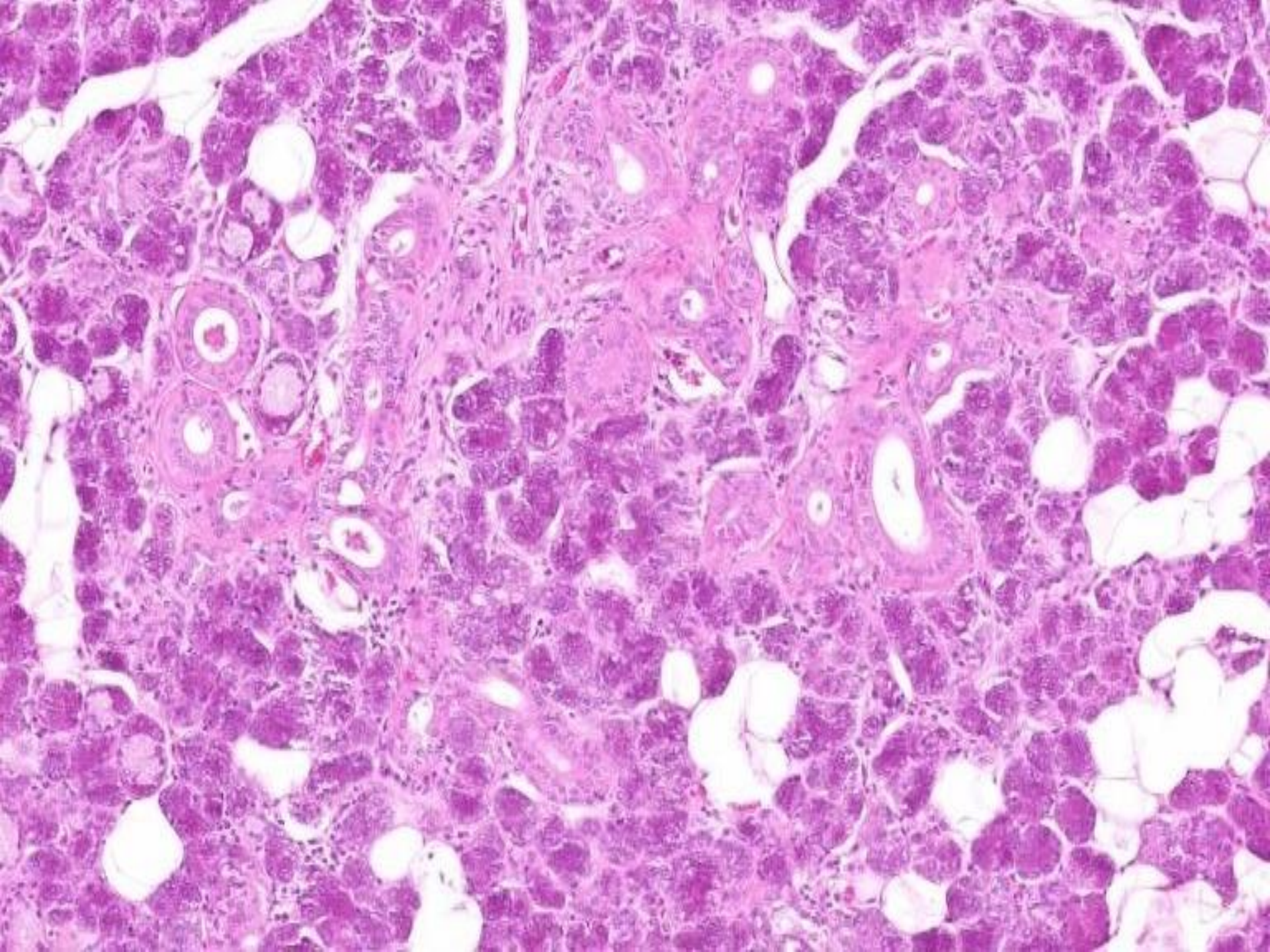
The characteristic decrease in tears and saliva is the result of **lymphocytic infiltration** and **fibrosis** of the lacrimal and salivary glands.

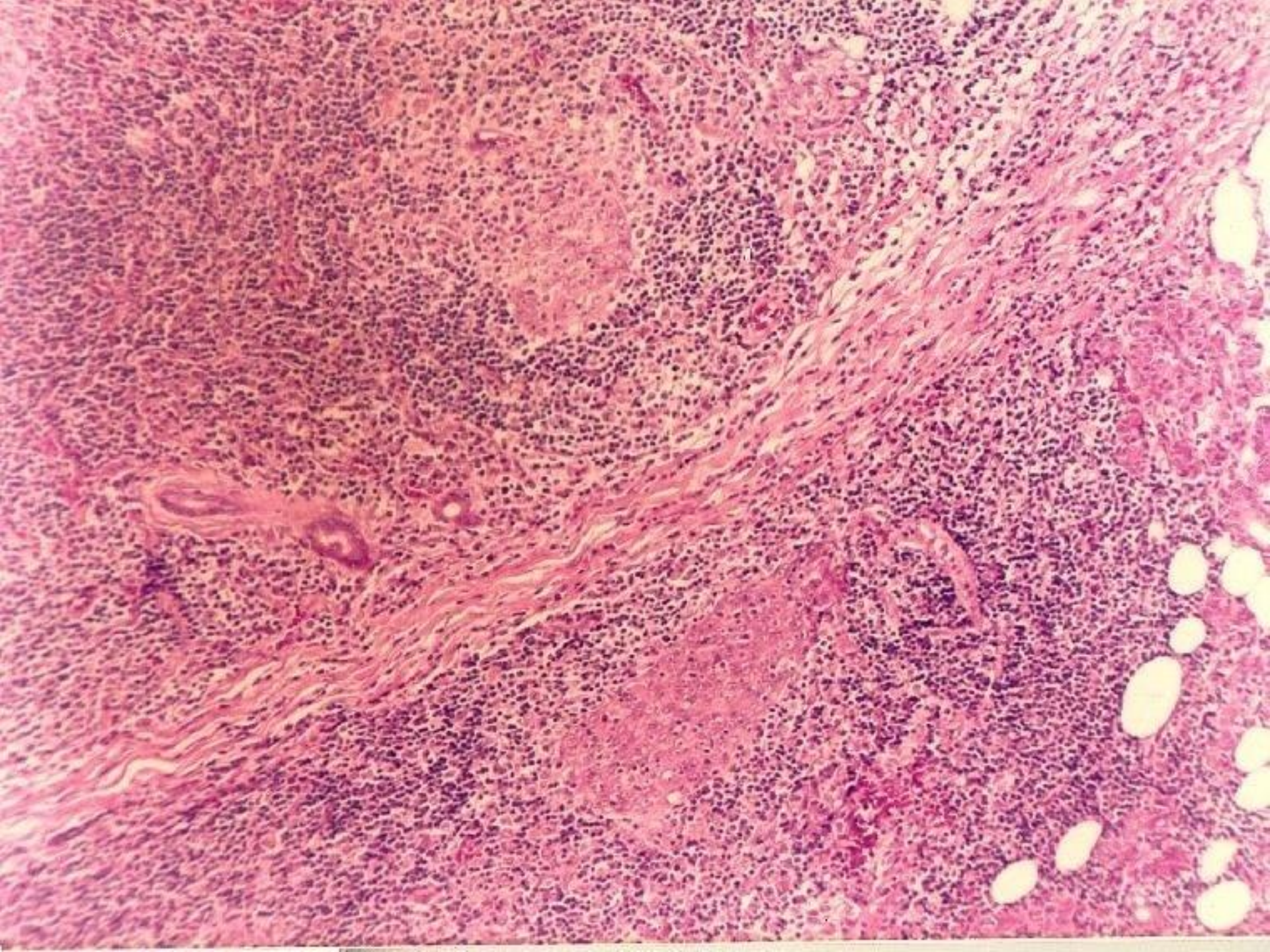
The infiltrate contains predominantly activated CD4+ helper T cells and some B cells, including plasma cells.



SJÖGREN SYNDROME

- A, Enlargement of the salivary gland. B, Intense lymphocytic and plasma cell infiltration with ductal epithelial hyperplasia in a salivary gland.





Most patients have rheumatoid factor without having rheumatoid arthritis;

ANAs against ribonucleoproteins SS-A (Ro) and **SS-B (La)** are especially common

The disease is believed to be caused by an autoimmune **T cell reaction** against one or more unknown self antigens expressed in these glands, or immune reactions against the antigens of a virus that infects the tissues.

Pathogenesis:

Although the pathogenesis of Sjogren syndrome remains obscure, aberrant T-cell and B-cell activation are both implicated.

The initiating trigger may be a **viral infection**

of the salivary glands, which causes local cell death and release of tissue self antigens.

In genetically susceptible individuals, **CD4+ T** cells and B cells specific for these self antigens may have **escaped tolerance** and are able to react.

The result is inflammation, tissue damage, and, eventually, fibrosis.

Clinical features

occurs most commonly in **women** between the ages of **50 and 60**.

The **keratoconjunctivitis** produces blurring of vision, burning, and itching.

xerostomia results in difficulty in swallowing solid foods, a decrease in the ability to taste, cracks and fissures in the mouth, and dryness of the buccal mucosa.

Parotid gland enlargement is present in half the patients.

Complications:

1-The **lack of tears** leads to drying of the corneal epithelium, which becomes inflamed, eroded, and ulcerated.

2-the **oral mucosa** may atrophy, with inflammatory fissuring and ulceration.

3- **dryness and crusting** of the **nose** may lead to ulcerations, epistaxix and even perforation of the nasal septum.

4-high risk for development of **B-cell lymphomas,**

Systemic Sclerosis (Scleroderma) (SS)

Systemic Sclerosis (Scleroderma) *(SS)*

It is an immunologic disorder characterized by:

1- excessive fibrosis in skin and multiple tissues.

2-obliterative vascular disease.

3-and evidence of autoimmunity, mainly the production of multiple autoantibodies.

- **female-to-male ratio of 3: 1**

with a peak incidence in the 50- to 60-year age group.

The distinctive feature of SS is the striking cutaneous involvement which **is the usual presenting manifestation and appears in 95% of cases.**

The visceral involvement of the GIT, lungs, kidneys, heart, and skeletal muscles—is responsible for most of the related morbidity and mortality.

In some patients the disease seems to remain confined to the skin for many years(old name Scleroderma), but in the majority it progresses to visceral involvement with death from :

renal failure, cardiac failure, pulmonary insufficiency, or intestinal malabsorption

Almost all patients exhibit Raynaud phenomenon:

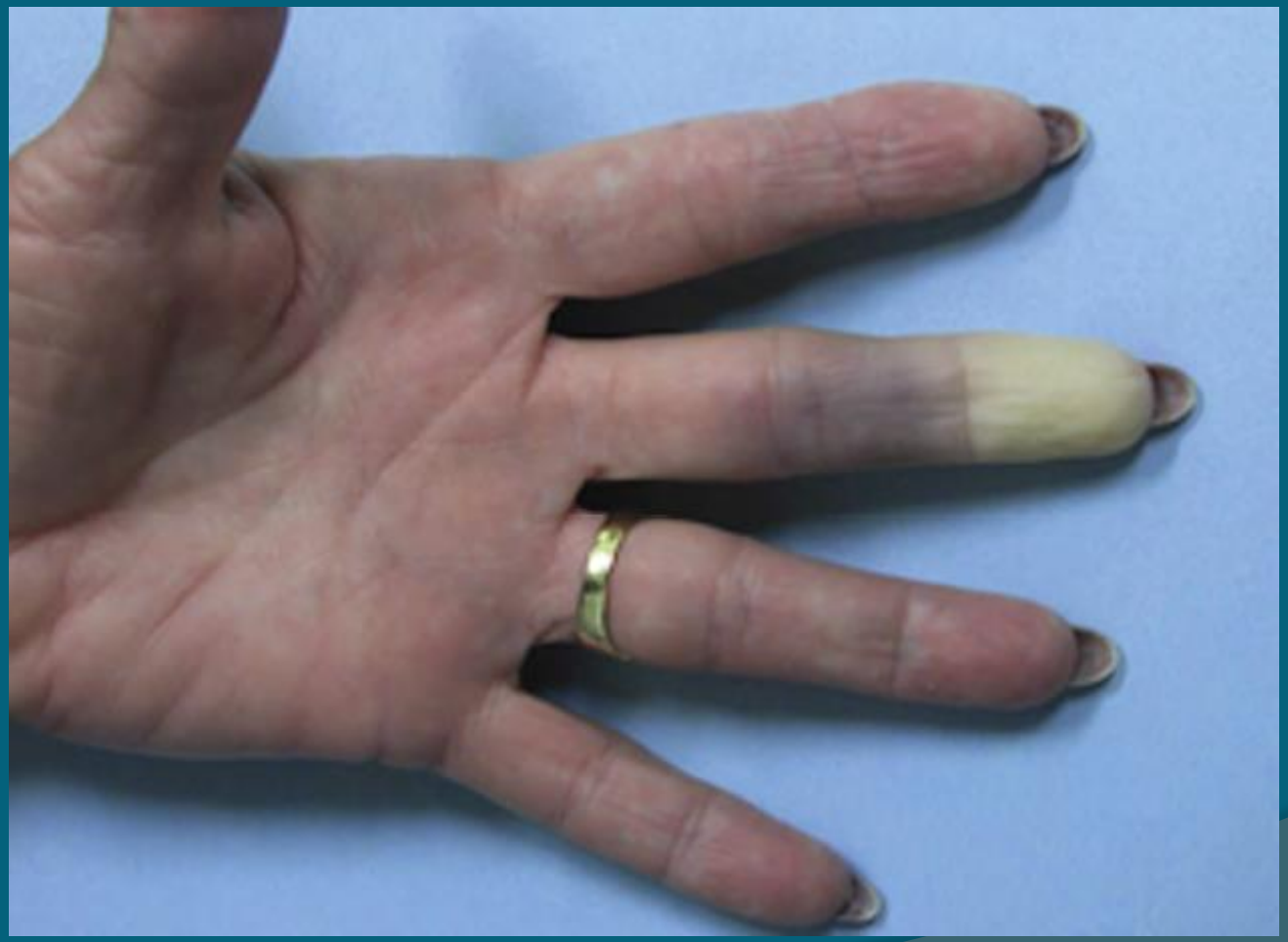
a vascular disorder characterized by reversible vasospasm of the arteries.

Typically the hands turn white on exposure to cold, reflecting vasospasm,

followed by change to blue as ischemia and cyanosis develop.

Finally, the color changes to red as reactive vasodilation occurs

Raynaud phenomenon



The extensive subcutaneous fibrosis has virtually immobilized the fingers, creating a clawlike flexion deformity. Loss of blood supply has led to cutaneous ulcerations and to atrophic changes in the terminal phalanges .Sometimes the tips of the fingers undergo autoamputation.

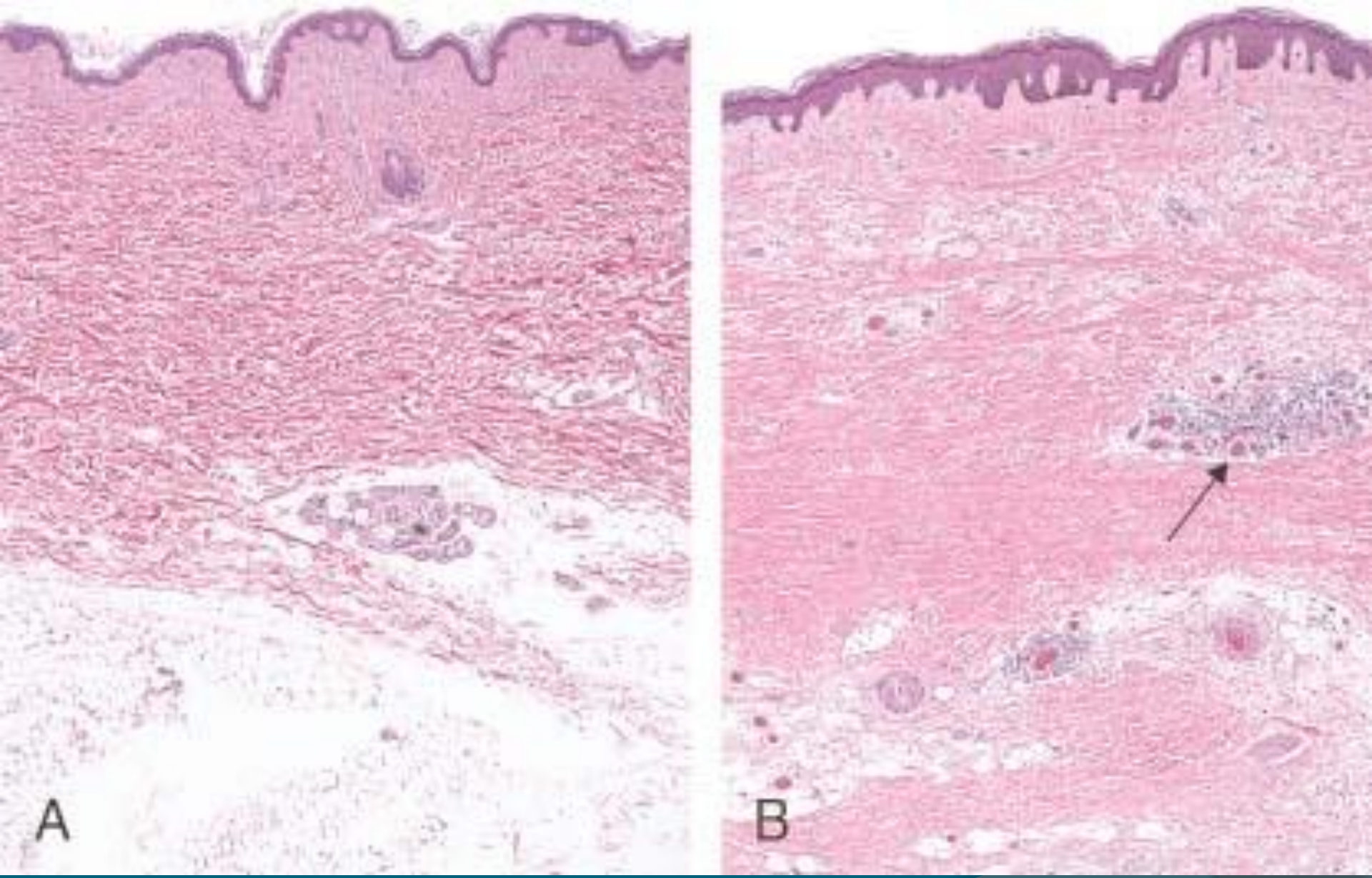
Histological changes in skin:

1-thinning of the epidermis.

2-There is marked increase of compact collagen in the dermis.

3-atrophy of the dermal appendages.

4- hyaline thickening of the walls of dermal arterioles and capillaries



A-Normal skin. B, Skin biopsy from a patient with systemic sclerosis. extensive deposition of dense collagen in the
dermis with virtual absence of appendages (e.g., hair follicles) and foci of inflammation (arrow).

SS can be classified into two groups on the basis of its clinical course:

-***1-Diffuse scleroderma,*** **characterized by initial widespread skin involvement, with rapid progression and early visceral involvement**

2- Limited scleroderma, **with relatively mild skin involvement, often confined to the fingers and face. Involvement of the viscera** occurs late.

Some patients with the limited disease also what is clled called “ CREST syndrome” because of its frequent features of:

Calcinosis(finger, knee, and elbow)

Raynaud phenomenon,

Esophageal dysmotility(collagen fibers leads to difficulties in swallowing(dysphagia)

Sclerodactyly(fingers appear “wooden”)

Telangiectasia.

Focal and sometimes diffuse subcutaneous calcifications may develop, especially in patients with the CREST syndrome

Scleroderma: purse-string pattern of skin folds
around the mouth(deepening of perioral facial folds ,radial furrowing, lip thinning and retraction, microstomia (small oral aperture) and a mask-like face(loss of facial expression), pinched nose,

Etiology and Pathogenesis

The cause of systemic sclerosis is not known, but the disease likely results from three interrelated processes :**autoimmune responses**, vascular damage, and **collagen deposition**

1-Autoimmunity: It is proposed that **CD4+ T cells** responding to unidentified antigen accumulate in the skin and release cytokines that activate inflammatory cells and fibroblasts.

There is also evidence for inappropriate activation of **humoral immunity**, and the presence of various autoantibodies mainly ANAs.

2-Vascular damage.

Microvascular disease is consistently present early in the course of systemic sclerosis and may be the initial lesion.

Intimal proliferation is evident in the digital arteries of patients with systemic sclerosis.

unknown cause….vascular injury …chronic inflammation…..fibrosis

widespread narrowing of the microvasculature leads to ischemic injury and scarring.

3- fibrosis: due to the previous causes : chronic inflammation and ischemic damage

Autoantibodies:

All patients have **ANA**

Two ANAs strongly associated with systemic sclerosis

One of these, directed against **DNA topoisomerase I (anti-Scl 70**), is highly specific.

It is present in 10% to 20% of patients with diffuse systemic sclerosis.

Patients who have this antibody are **more likely to have pulmonary fibrosis** and **peripheral vascular disease**.

The other, an **anticentromere antibody**, is found in 20% to 30% of patients, who tend to have the CREST syndrome.

Patients with this syndrome have relatively **limited involvement of skin**, often confined to fingers, forearms, and face, and calcification of the subcutaneous tissues.

Involvement of the viscera, including esophageal lesions, pulmonary hypertension, and biliary cirrhosis, **may not occur at all** or **occur late**.

Thank you