**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 disease of acute or insidious onset that may involve virtually any organ in the body; mainly the skin, kidneys, serosal membranes, joints, and heart.

**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 a general role for pathogenesis 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.**

• **Ultraviolet (UV) radiation** (sun exposure) exacerbates the lesions of SLE.

• **Cigarette smoking**

• **Sex hormones :** There is a strong **female preponderance (approximately 9 : 1)**(female :male)

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.

• **Drugs:** such as procainamide and hydralazine can induce an SLE- like disease,

**3. Immunologic factors:** several components of the innate and adaptive

immune system are involved in the pathogenesis of SLE.

1- **Defective central tolerance in elimination of self-reactive B cells,** 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.

**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 involvementis 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:**

1- Pericarditis (most common). 2- Endocarditis (Libman-Sacks).

3- Non specific myocarditis. 4- Accelerated coronary atherosclerosis

**Four out of 11 clinical or laboratory criteria must be prese 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.

-**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 : renal failure, intercurrent infections, and cardiovascular disease.**

**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
* 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
* **Skin.** Rheumatoid **subcutaneous nodules** are the most common cutaneous lesions. They occur in approximately 25% of affected individuals, usually those with severe disease, and 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

**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.

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

Therapies include : corticosteroids, synthetic and biologic disease-modifying drugs such as methotrexate, 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.

However, anti TNF agents are not curative, and patients must be maintained on TNF antagonists to avoid disease flares.

**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

**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.

• 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 and even perforation of the nasal septum.

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

**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

**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

**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 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.**

***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 cytokinesthat 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-Scl70**), 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 **anticentromereantibody***,* 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**.