Lec 2

(2)Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE), is the most common type of lupus. SLE is an autoimmune disease in which the immune system attacks its own tissues, causing **widespread inflammation and tissue damage in the affected organs.** It can affect the joints, skin, brain, lungs, kidneys, and blood vessels. There is no cure for lupus, but medical interventions and lifestyle changes can help control it.

In this disease, the immune system targets **intracellular particles** that contain both nucleic acids (DNA&RNA)and nucleic acid binding proteins.

Approximately, **all components of the immune system** have been implicated in SLE, with:

1. B-cell hyperactivity (**فرط نشاط الخلايا البائية**)
2. Antigen- Presenting Cell activation (APCs)
3. T-cell dysfunction (**خلل في الخلايا التائية**)
4. Altered cytokine profiles documented.

Epidemiology

1- The prevalence of SLE in USA have reported rates of disease ranging between 14.6 and 50.8 per 100,000.

2- This disease **occurs in women more than in men** especially in childbearing age (**سن الانجاب**) with a ratio of 10:1. The reason for this may be due to hormonal factors in the pathogenesis of the disease.

3- Different races (**اختلاف الاعراق**) lead to an increased the incidence of disease, for example, African American women have an increased relative risk of disease compared with Caucasian women.

Etiology

Multiple factors are associated with the development of SLE, including: genetic, racial, hormonal, and environmental factors.

1- Genetic factors: HLA-DRB1 were significantly associated with SLE susceptibility.

2- Hormonal Effects: Several factors indicate that **sex hormones play** a role in the modulation of the disease including:

a. The large female predominance (9:1 female: male ratio)

b. The influence of puberty and pregnancies at the onset of the disease.

c. Estrogens and prolactin administered to animals promote anti-DNA antibody synthesis.

3- Environmental Factors

Several environmental factors have been related to the onset or relapse of SLE including:

a. Sunlight exposure: This could be related to the fact that the Langerhans cells of the skin and keratinocytes release significant amounts of interleukin-1 upon exposure to UV light, and could thus represent the initial stimulus tipping(**منبه**) off a precarious balance of the immune system.

b. Infections: normal immune response to bacterial and viral infections may spin-off into a state of B-cell hyperactivity, triggering a relapse. Infection, can initiate an autoimmune response. Also, various infections may suppress the autoimmune response and in their absence autoimmune manifestations may occur at increased rates.

c. Drugs: particularly those with DNA binding ability, such as hydantoin(**هايدينتون**), isoniazide**(ايزونيازايد)**, and hydralazine, can cause a drug-induced lupus-like syndrome. Patients with drug-induced SLE usually have a milder disease, without significant vital organ involvement.

Pathophysiology:

❖ One proposed mechanism for the development of autoantibodies involves a defect in apoptosis or clearance of apoptotic cells, leading to a disturbance in immune tolerance.

❖ The redistribution of cellular antigens during apoptosis leads to a display of **cytoplasmic** and **nuclear antigens** on the cell surface, enhancing immune reactivity to antigens, which are normally protected intracellularly.

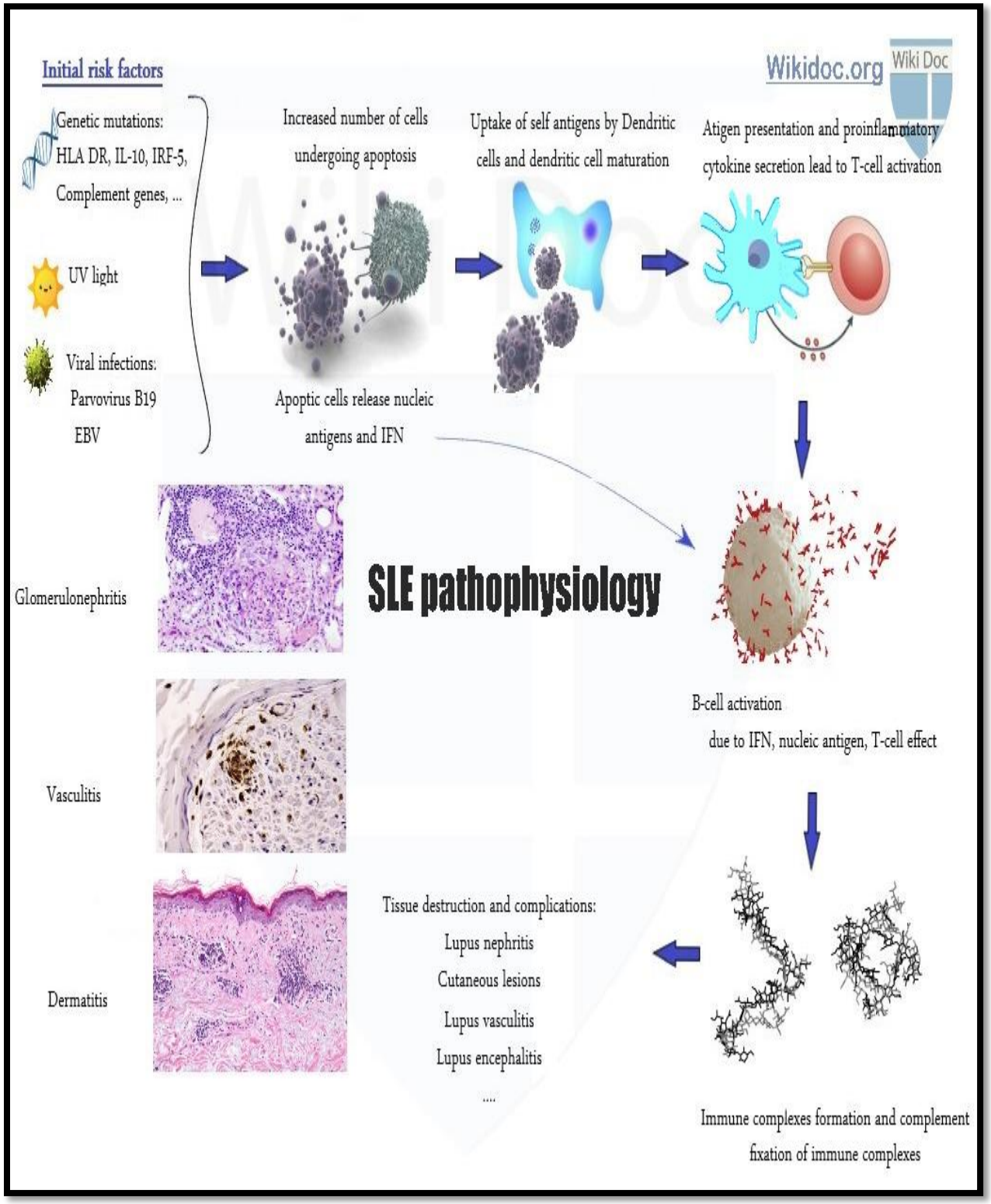
❖ Activation of antigen-presenting cells (APC) by IFN-α might promote presentation of auto antigens to self-reactive T cells.

❖ Immune complexes form in the microvasculature, leading to **complement activation and inflammation.**

❖ Antibody–antigen complexes deposit on the basement membranes of skin and kidneys.

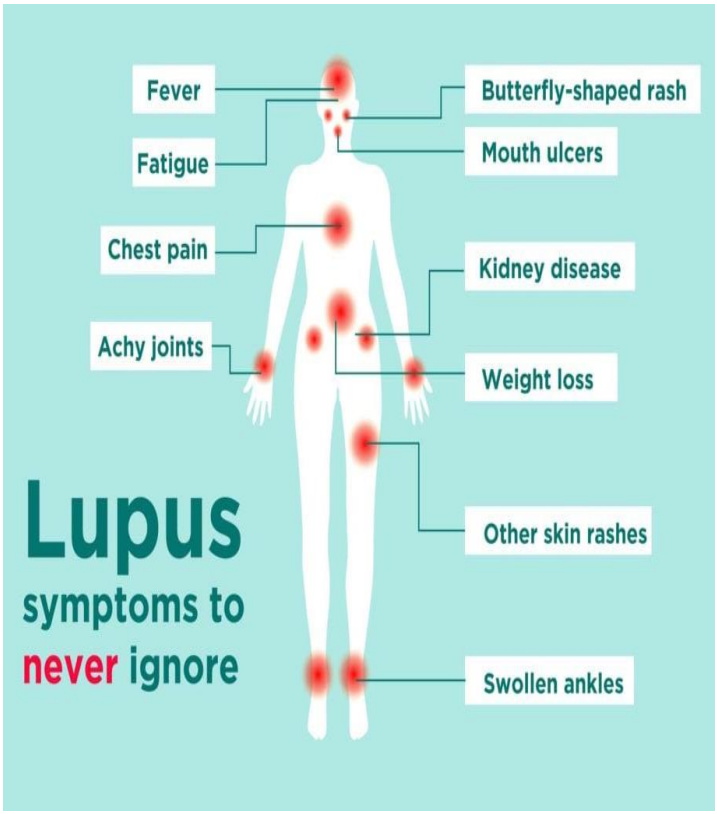
❖ In active SLE, this process has been confirmed based on the presence of complexes of nuclear antigens such as **DNA**, **immunoglobulins**, and **complement proteins** at these sites.

❖ Immune complexes containing nucleic acids also play an important role in lupus pathogenesis based on their capacity to stimulate **toll-like receptors** and amplify production of **IFN-α. Gene targets** of IFN-α include pro-inflammatory mediators, chemokines, and cytokines, and activation of those mediators can result in recruitment of inflammatory cells to target tissue, resulting in target organ damage.


Initial risk factors
Wikidoc.org
Wiki Doc
Genetic mutations:
HLA DR, IL-10, IRF-5,
Complement genes, ...
UV light
Viral infections:
Parvovirus B19
EBV
Increased number of cells undergoing apoptosis
Apoptic cells release nucleic antigens and IFN
Uptake of self antigens by Dendritic cells and dendritic cell maturation
Atigen presentation and proinflammatory cytokine secretion lead to T-cell activation
SLE pathophysiology
Glomerulonephritis
Vasculitis
Dermatitis
B-cell activation
due to IFN, nucleic antigen, T-cell effect
Immune complexes formation and complement fixation of immune complexes
Tissue destruction and complications:
Lupus nephritis
Cutaneous lesions
Lupus vasculitis
Lupus encephalitis
....

Clinical features (Symptoms): Constitutional symptoms include:

1. General (Fatigue, fever, and arthralgiaالم مفصلي).
2. Skin (Butterfly- shaped rash, malar rash, erythematous rash over cheeks and nasal bridge, **discoid lesions).**
3. Kidney diseases (inflammations and failure)
4. Joints and muscles (Swollen joints arthritis)
5. Blood (blood clot, anemia, immune complexes).
6. Heart (Other organ systems that may be involved in SLE include the cardiopulmonary system, with episodes of pleuritis and pericarditis.



Laboratory diagnosis:

A. Complement:

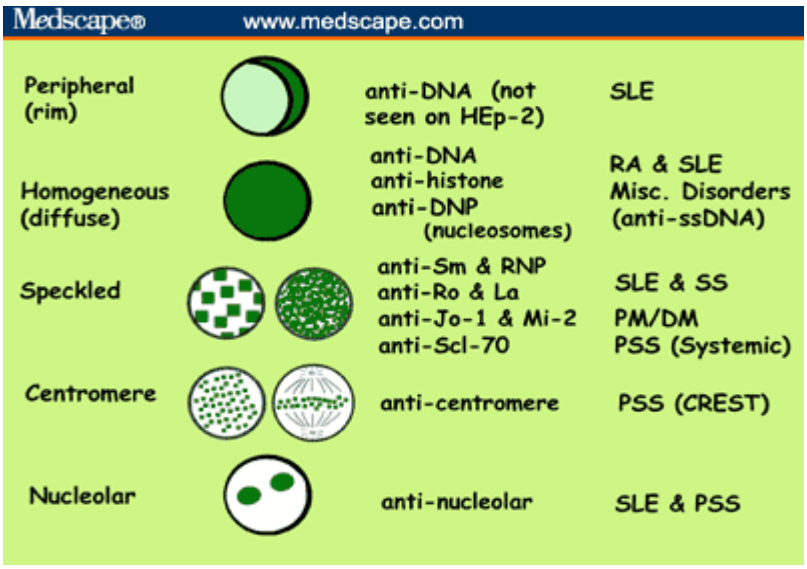
Serum complement is frequently reduced in active SLE because of increased use by immune complexes together with reduced liver synthesis of complement components including C3 & C4.

B. Autoantibodies:

1. Antinuclear Antibodies (ANA) there are five types of ANA autoantibodies:

a. **Homogenous** (diffuse or solid): due to **anti-histone Ab** expression which occurs in SLE or drug-induced SLE.

b. Peripheral (or rim pattern): due to the presence of **ds-DNA**. It is a characteristic of active SLE.



c. Speckled pattern: reflects the presence of **Abs directed against non-DNA nuclear materials.** Such as anti-ENA (Sm & RNP) which are a characteristic features of SLE & mixed connective tissue disease (MCTD**)** respectively.

d. Nucleolar: This pattern is caused by homogenous staining of nucleolus. It was suggested that this fashion **occurs due to ribosomal Abs** which associated with Scleroderma and polymyositis-dermatomyositis(التهاب الجلد والعضلات) **.**

e. The centromere pattern: is caused by **anti-centromere Ab** and it is typically seen in limited Scleroderma patients (مرضى تصلب الجلد).

2. Anti-DNA:

(a) ssDNA or denatured DNA (b)ds-DNA or (c) both. These Abs either IgG or IgM classes. **High titer of ds-DNA is a characteristic of SLE.** In contrast anti-ssDNA Ab are **not specific for SLE** and may found in other autoimmune diseases such as RA, & drug-induced lupus.

3. Anti-erythrocytes Abs.

These Abs of class IgG, IgA & IgM which detected by **direct Coombs' test**. These Abs usually associated with **hemolytic anemia** that occurs in 10-65% of SLE patients.

4. Circulating Anticoagulant, Antiphospholipds (APL) & Anti-platelete Abs

APL develop in 10-15% of patients. Antiplatelets are found in 80% of SLE patients and can induce **thrombocytopenia**.

5. Rheumatoid Factor (IgM autoantibodies)

Almost 30% of patients with SLE have positive RF test.

6. Anti-cytoplasmic Abs. (anti-mitochondrial, anti-ribosomal, anti-lysosomal**)**

It were reported in SLE patients. Anti-ribosomal Ab occurs in 25-50% of SLE patients.

7. Antibodies to the DNA–Histone Complex (present in 65% of patients with SLE)

8. Antibodies to Non-Histone Proteins that include:

a) Anti- Smith Ab: present about 35% of patients with SLE against Smith antigen (Sm-Ag). Sm antigen is a non-histone nuclear protein composed of several polypeptides of differing molecular weights. Sm-Ag are proteins that are resistant to ribonuclease.

b) Anti-U1-Ribonucleoprotein (Anti-U1-RNP): present in the majority of patients with SLE and mixed connective tissue disease.**U1** is small nuclear ribonucleoprotein.

c)Anti-Sjogren's syndrome-A/Ro(Anti-SS-A/Ro):these antibodies are present approximately 35% and 70% in patients with SLE and Sjogren's syndrome (SS) respectively. Ro are small cytoplasmic ribonucleoproteins.

d)Anti-Sjogren's syndrome-B/La (Anti-SS-B/La): Antibodies to **La antigen** are present in about 35% of patients with SLE and in approximately 50% of the patients

with SS. **La antigen** is Sjogren syndrome type B antigen (SS-B) also known as Lupus La protein.

9. Cardiolipin and Phospholipid Antibodies: frequently presents in patients with SLE.

C. Tissue Immunofluorescence:

1. Skin: About 90% of patients have Igs (Class IgG or IgM) and Complement deposition in the dermal-epidermal junction of sun-exposed skin that is not involved with an active lupus rash. However discoid lupus Erythematosus show deposition of Igs & Complement only in involved skin.

2. Kidney: Irregular or granular accumulation of Igs & Complement occurs along the glomerular basement membrane and in the mesangium in patients with lupus nephritis. On electron microscopy, these deposits are seen in the subepithelial, subendothelial and mesengial sites.

Differential Diagnosis

The diagnosis of SLE in patients with classic multiple system involvement and positive ANA test is not difficult. Poly arthritis is often similar to that in viral infection, infective endocarditis, mixed connective tissue diseases, rheumatoid arthritis and rheumatic fever. When Raynaud's phenomenon is predominant complaint, progressive systemic sclerosis should be considered. SLE can present withy a myositis similar to that of polymyositis-dermatomyositis. The clinical constellation of arthritis, alopecia and positive VDRL may denote secondary syphilis. Felty's syndrome (Thrombocytopenia, leucopenia, splenomegalyin patients with RA) can be simulate SLE. Takayasu's disease should be considered in young women with arthralagias, fever, and asymmetric pulses.