Examples of autoimmune diseases

1-Systemic Lupus Erythematosus (SLE)

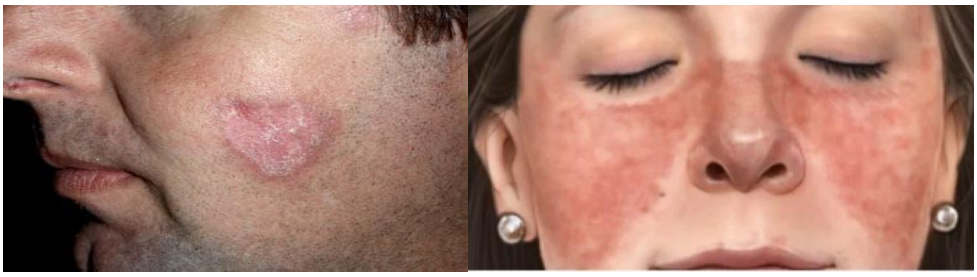
is a multisystem autoimmune disease . Caused by auotoantibodies produced against self antigens lead to formation of immune complexes .

- It affects principally skin, joints, kidney, serosal membranes , and heart , but every organ in the body may be affected .

- SLE presents when a person is in the twenties or thirties, it may occur in any age , even in early childhood .

- Predominantly affects women , female-to-male ratio of 9 :1 for the reproductive age group and only 2: 1 during childhood or after 65 years of age .

- Disease manifestations include nephritis , skin lesions like **"butterfly" rash** on the face ,**discoid rash** on the skin and arthritis (caused by the deposition of immune complexes), and hematologic and neurologic abnormalities .



Etiology

the disease is caused by a large number of **autoantibodies** that can damage tissues either directly or in the form of immune complex deposits .

Some of the Autoantibodies in SLE are directed against a host of nuclear and cytoplasmic components of the cell . while others are directed against cell surface antigens of blood cells , plate lets, and lymphocytes. Other called **Anti-phospholipid antibodies** are directed against the proteins that are in complex with phospholipids .

Anti-Nuclear Antibodies ANAs can be grouped into four categories: (1) antibodies to DNA, (2) antibodies to histones, and (3) antibodies to nucleolar antigens .

-**Anti- double stranded DNA** and **smith antigen antibodies** are specific for SLE .

Pathogenesis

both genetic and environmental factors play a role .

Genetic Factors

- Familial association Family members have an increased risk for the development of SLE, and up to 20% of unaffected first-degree relatives have autoantibodies . SLE is a higher in monozygotic twins than in dizygotic twins .

- HLA association HLA-DR2 or HLA-DR3.

- Other genes. Genetic deficiencies of complement proteins , especially C1q, C2, or C4

Environmental Factors

- UV irradiation (sun exposure) may induce apoptosis and also may alter DNA and make it immunogenic

- cigarrete smoking

- sex hormones

- Drugs such as hydralazine, and procainamide can induce an SLE-like disorder **.**

Mechanisms of Tissue Injury

- Immune complexes (type III hypersensitivity). DNA/anti-DNA complexes can be detected in the glomeruli and small blood vessels .

- Anti body mediated (type II hypersensitivity) autoantibodies against red cells, white cells, and platelets opsonize these cells and lead to their phagocytosis result in cytopnia .

- Antiphospholipid antibodies Patients with antiphospholipid antibodies may develop venous and arterial thrombosis , which may be associated with recurrent spontaneous abortion and focal cerebral or ocular ischemia . These clinical features, in association with lupus , is referred to as the secondary antiphospholipid antibody syndrome .

- The neuropsychiatric manifestations of SLE antibodies that cross the blood-brain barrier and react with neurons .

MORPHOLOGY

Although any organ can be involved , The most characteristic organs are blood vessels , kidneys , connective tissue , and skin .

Blood Vessels. acute vasculitis , The arteritis leads to fibrinoid necrosis of the vessel walls .

Kidney. Renal involvement is the most important clinical feature in SLE, mostly is **lupus nephritis** .

Skin. Characteristic malar erythema affects the face along the bridge of the nose and cheeks (the butterfly rash) , Exposure to sunlight incites the erythema (so called photosensitivity).

Joints. Joint involvement is typicall synovitis .

Central Nervous System involvement as neuropsychiatric manifestations of SLE .

Spleen (splenomegaly) , **lungs** (pleural effusion), and **heart** (endocarditis) as libman endocarditis -thrombotic deposits on valve.

2-Rheumatoid Arthritis (RA)

is a chronic autoimmune inflammatory disease that affects mainly the joints, especially small joints (digits, wrist , ankles, elbow , and knees) in bilateral symmetric and produce a synovitis that progresses to destroy articular cartilage . in addition to joint It can affect multiple tissues as the skin, heart, blood vessels, muscles , and lungs .

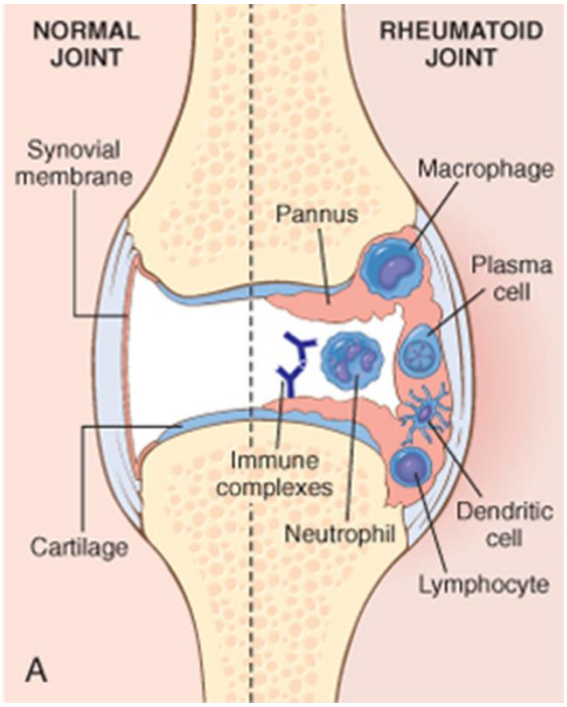
-The disease is caused by an autoimmune response against self-antigen , which leads to T-cell activation in the joint with production of cytokines that

1- Activate phagocytes in the joint space , releasing degradative enzymes and other factors that perpetuate inflammation of joint (synovitis) .

2- Activate B cells, resulting in the production of antibodies , some of which are directed against self-antigens in the joint .

The cytokine TNF plays a central role .

Antibodies may contribute to the disease (IgM) ,and less frequently IgA autoantibodies that bind to self IgG . these autoantibodies called **rheumatoid factors**



3- Sjogren syndrome

- Is a chronic disease characterized by dry eyes and dry mouth resulting from immune- mediated destruction of the lacrimal and salivary glands .

- It occurs as an isolated disorder (primary form), also known as **the sicca syndrome**, or more often in association with another autoimmune disease (secondary form) .

- Its caused by CD4+ helper T cells reaction against unknown self antigens expressed in these gland or antigens of virus that infect the tissue .

4- Systemic sclerosis (Scleroderma)

is an immunologic disorder characterized by **excessive fibrosis** in multiple tissues , obliterative vascular disease, and evidence of autoimmunity, mainly the production of multiple autoantibodies.

Although the term scleroderma is ingrained in clinical medicine but the name systemic sclerosis is preferred because excessive fibrosis is seen in multiple organs .

Cutaneous involvement appears in approximately 95% of cases, but it is the visceral involvement (gastrointestinal tract, lungs, kidneys, heart, and skeletal muscles) that is responsible for most of the morbidity and mortality .

Systemic sclerosis is classified into two groups on the basis of its course:-

• **Diffuse systemic sclerosis**, characterized by initial widespread skin involvement, with rapid progression and early visceral involvement .

• **Limited systemic sclerosis**, with mild skin involvement, confined to the fingers and face . visceral involvement occurs late , This presentation also is called CREST syndrome because of its frequent features of Calcinosis , Raynaud phenomenon, Esophageal dysmotility , Sclerodactyly, and Telangiectasia .

IV-IMMUNE DEFICIENCY DISEASES

Immune deficiencies can be divided into

- Primary (or congenital) immunodeficiency caused by **inherited defects** affecting immune system development and manifest between 6 months and 2 years of life .

- Secondary (or acquired) immunodeficiencies, which may arise as complications of cancers , infections, malnutrition, immunosuppression , irradiation , or chemotherapy or autoimmunity .

Clinically, patients with immune deficiency present with increased susceptibility to infections as well as to certain forms of cancer .

The type of infections in patient depends largely on the component of the immune system that is affected. Patients with defects in Immunoglobulins , complement, or phagocytic cells typically suffer from recurrent infections with pyogenic bacteria . Patients with defects in cell-mediated immunity are prone to infections by viruses, fungi, and intracellular bacteria .

1- Primary Immune Deficiencies (Congenital) Immune Deficiency

Caused by mutations in genes involved in lymphocyte maturation or function, or in innate and humoral immunity . detected in fancy, the telltale sign is increased susceptibility to recurrent infections in early life between 6 months to 2 years .

Some of these disorders as

1- X-linked agammaglobulinemia (XLA), or Bruton disease,

characterized by the failure of pre–B cells to differentiate into mature B cells and, there is a resultant absence of antibodies (gamma globulin) in the blood . XLA does not become apparent until the infant reach 6^{th} month of age.

2- Severe Combined Immunodeficiency

Severe combined immunodeficiency (SCID) involve genetically distinct syndromes, all cause impaired development of mature T lymphocytes and/or B lymphocytes and defects in both humoral and cell- mediated immunity.

Affected infants present with thrush (oral candidiasis), severe diaper rash, and failure to thrive .

Children with SCID are extremely susceptible to recurrent, severe infections by a wide range of pathogens, including Candida albicans, Pseudomonas, cytomegalovirus, varicella.

3- Isolated IgA Deficiency

This is the most common primary immune deficiency disease.

Weakened mucosal defenses due to IgA deficiency predispose patients to recurrent sinopulmonary infections and diarrhea because IgA is the major immunoglobulin in mucosal secretions and is involved in defending the airways and the gastrointestinal tract .

2- Secondary Immune Deficiencies (Aquired Immunodeficiency Syndrome AIDS)

the secondary immune deficiencies are more common than primary immune deficiencies . It occurs in patients with malnutrition , infection , diabetes , renal disease , patients receiving chemotherapy or radiation therapy for treatment of cancer , or immunosuppressive drugs to prevent graft rejection or to treat autoimmune diseases .

The most important example of Secondary Immune Deficiencies is Acquired Immunodeficiency Syndrome (AIDS)

Acquired Immunodeficiency Syndrome (AIDS)

AIDS is a retroviral disease caused by the human immunodeficiency virus (HIV). It is characterized by profound immunosuppression leading to opportunistic infections , secondary neoplasms, and neurologic manifestations .

The major routes of HIV infection are :-

1- sexual contact is the dominant mode of infection worldwide, accounting for more than 75% of all cases of HIV transmission . Sexual transmission of HIV is enhanced by sexually transmitted diseases , especially those diseases cause genital ulceration .

2-parenteral inoculation occur in

- hemophiliacs who received contaminated factor VIII and factor IX concentrates , and other contaminated blood products .

- sharing of needles, syringes, and other instruments contaminated with HIV-containing blood .

3- passage of the virus from infected mothers to their newborns.

Infected mothers can transmit the infection to their offspring by three routes:

(A) in utero by transplacental spread

(B) during delivery through an infected birth canal .

(C) after birth by ingestion of breast milk .

Pathogenesis

While HIV can infect many tissues , the two major targets of HIV infection are the immune system and the central nervous system .

the hallmark of AIDS is affecting cell mediated immunity.

Life Cycle of HIV

Virus entry into cells :

HIV infects cells by use CD4 molecules which acts as a high-affinity receptor for the virus and cell surface chemokine receptors (co-receptors) . involves binding and fusion of virus with the cell . The main cellular targets are CD4+ helper T cells , macrophages and DCs .

Viral replication:

the RNA genome of the virus undergoes reverse transcription , leading to the synthesis of double stranded complementary DNA (proviral DNA)

provirus genome integrates into host cell DNA; After integration, the provirus may remain non transcribed for months or years, and the infection becomes latent . proviral DNA may be transcribed to form complete viral particles that bud from the cell membrane. extensive viral budding, lead to cell death .

Progression of infection:

Acute infection of mucosal T cells and DCs; **Chronic infection** is characterized by dissemination of the virus, viremia , and the development of host immune responses . latent infection of cells in lymphoid tissue; continuing viral replication and progressive loss of CD4+ T cells .

Mechanisms of immune deficiency:

Loss of CD4+ T cells is occur due to :

1- T-cell death during viral replication and budding .

2- Apoptosis as a result of chronic activation of uninfected cells by HIV or by other concurrent infectious microbes .

3- Decreased production of mature CD4+ T cells by direct infection of thymic progenitor cells .

4- Defective macrophage and DC functions .

5- Impaired immune responses result from Infection of various cells in lymphoid tissues may disrupt the normal architecture and function .

Clinical Features

The clinical manifestations of HIV infection range from a mild to severe disease. adult patient with AIDS presents with fever, weight loss , diarrhea, generalized lymphadenopathy, multiple opportunistic infections , neurologic disease , and secondary neoplasms .