**Lecture 11 General pathology Dr. Ali H. Murad**

***Diseases of the Immune System***

**I. Hypersensitivity reaction (Allergy)**

**II. Transplantation immunopathology:**

Transplantation of solid organs (e.g., liver, kidney, heart) and bone marrow become nearly routine with the greater understanding of humoral and cellular immune response, the development of immunosuppressive drugs such as cyclosporine, and understanding of the role of the major histocompatibility complex (MHC) antigens (human leukocyte antigen =HLA) which is cell surface antigens that determine whether transplanted tissue is recognized as foreign or not.

Transplanted tissue can be categorized as:

1- Allogeneic if the donor and recipient are related or unrelated but share similar HLA types.

2- Syngeneic if the donor and recipient are identical twins.

3- Autologous if donor and recipient are the same person.

**III. Autoimmune disorders**

They are caused by a breakdown in the ability of the immune system to differentiate between self and nonself antigens. Normally, there is a high degree of immunologic tolerance to self-antigens, which prevents the immune system from destroying the host. Autoimmune diseases can affect almost any cell or tissue in the body. Some autoimmune disorders are tissue specific; others affect multiple organs and systems.



***Examples of autoimmune diseases:***

**1- Systemic Lupus Erythematosus**

SLE is caused by autoantibodies, some of which are directed against nuclear antigens and the formation of circulating immune complexes. Other autoantibodies directed against erythrocytes, platelets, and various complexes of phospholipids with proteins.

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

**2- Rheumatoid Arthritis**

RA is a chronic inflammatory disease 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 plays a central role; antibodies may also contribute to the disease.

**3-Sjögren Syndrome**

Sjögren syndrome is an autoimmune disease in which there are autoantibodies against the ductal epithelial cells of the exocrine gland, characterized by dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia), resulting from immune-mediated destruction of the lacrimal and salivary glands.

It occurs as:

1-Isolated disorder (primary form), also known as the sicca syndrome.

2- In association with another autoimmune disease (secondary form, RA is the most common, but some patients have SLE, polymyositis, systemic sclerosis, vasculitis, or thyroiditis).

**Morphology**

1- Lacrimal and salivary glands are the primary targets, but other secretory glands, including those in the nasopharynx, upper airway, and vagina, may

also be involved.

2- Involved tissues show an intense lymphocyte (primarily activated CD4+ T cells) and plasma-cell infiltrate, occasionally forming lymphoid follicles

with germinal centers. There is associated destruction of the native architecture.

3- Lacrimal gland destruction results in a lack of tears, leading to drying of the corneal epithelium, with subsequent inflammation, erosion, and ulceration (keratoconjunctivitis).

4- Similar changes may occur in the oral mucosa as a result of loss of salivary gland output, giving rise to mucosal atrophy, with inflammatory fissuring and ulceration (xerostomia).

5-Dryness and crusting of the nose may lead to ulcerations and even perforation of the nasal septum.

6- When the respiratory passages are involved, secondary laryngitis, bronchitis, and pneumonitis may appear.

**Clinical features:**

Dry mouth, Lack of tears, Salivary glands enlargement as a result of lymphocytic infiltrates. Extra glandular manifestations include synovitis, pulmonary fibrosis, and peripheral neuropathy.

**IV- Immune deficiency diseases**

Caused by inherited defects affecting immune system development, or they may result from secondary effects of other diseases (e.g., infection, malnutrition, aging, immunosuppression, autoimmunity, or chemotherapy). Clinically, patients present with increased susceptibility to infections as well as to certain forms of cancer.

We have two type of immune deficiency diseases:

1- Primary immune deficiencies.

2- Secondary immune deficiency. (AIDS) (Acquired immunodeficiency syndrome)

**Primary (Congenital) Immune Deficiency Diseases:**

Caused by mutations in genes involved in lymphocyte maturation or function, or in innate immunity. They have increased susceptibility to infections in early life

**Secondary Immune Deficiencies**

Immune deficiencies secondary to other diseases or therapies are much more common than the primary (inherited) disorders. It occurs in patients with malnutrition, infection, cancer, renal disease, or sarcoidosis. However, the most common cases of immune deficiency are therapy-induced suppression of the bone marrow and of lymphocyte function.

The most important is Acquired Immunodeficiency Syndrome (AIDS).

**Acquired Immunodeficiency Syndrome**

AIDS is a retroviral disease caused by the human immunodeficiency virus (HIV), characterized by infection and depletion of CD4+ T lymphocytes, and by immunosuppression leading to opportunistic infections, secondary neoplasms, and neurologic manifestations.

**The major routes of HIV infection are:**

1- Sexual contact.

2- Intravenous drug abusers.

3- Hemophiliacs receiving factor VIII or IX concentrates.

4- Random recipients of blood transfusion.

5- Passage of the virus from infected mothers to their newborns.

**Pathogenesis:**

The two major targets of HIV infection are the immune system and the CNS.

**Virus entry into cells:** Requires CD4 and co-receptors, which are receptors for chemokines; involves binding and fusion of the virus with the cell; main cellular targets are CD4+ helper T cells, macrophages, and DCs.

**Viral replication:** Provirus genome integrates into host cell DNA; viral gene expression is triggered by stimuli that activate infected cells (e.g., infectious microbes, cytokines produced during normal immune responses)

**Progression of infection:** Acute infection of mucosal T cells and DCs; viremia with dissemination of virus; 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 occurs due to :

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

2- Apoptosis as a result of chronic stimulation.

3- Decreased thymic output.

4- Defects in macrophage and DC functions

5- Destruction of architecture of lymphoid tissues (late).

**Clinical Features**

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

**Amyloidosis:**

It is systemic disease that may involve components of the immune system. It is characterized by the extracellular deposits of misfolded proteins that aggregate to form insoluble fibrils.

Amyloid deposits cause tissue injury and impair normal function by causing pressure on cells and tissues. They do not evoke an inflammatory response.

Amyloidosis may be localized or systemic. It is seen in association with a variety of primary disorders, including:

1- Monoclonal B-cell proliferations in which the amyloid deposits consist of immunologlobulin light chains.

2- Chronic inflammatory diseases such as rheumatoid arthritis (deposits of amyloid A protein, derived from an acute-phase protein produced in inflammation).

3- Alzheimer disease (amyloid β protein).

4- Familial conditions in which the amyloid deposits consist of mutants of normal proteins

5- Amyloidosis associated with dialysis (deposits of β2- microglobulin, whose clearance is defective).

**Histological appearance:**

With the light microscope and standard tissue stains, amyloid appears as an amorphous eosinophilic hyaline extracellular substance that with progressive accumulation will produce pressure atrophy of the adjacent cells. To differentiate between amyloid and other hyaline deposits like collagen and fibrin, a special stain can be used which is, Congo red that give amyloid a pink or red colour.