**Immunopathology**

**Disorders of the immune system are divided into three broad categories:**

1. Hypersensitivity reactions (immunologically mediated tissue injury)
2. Autoimmune diseases
3. Immunodeficiency diseases

**1. Hypersensitivity Reactions**

The purpose of the immune response is to protect against invasion by foreign organisms, but they often lead to host tissue damage. An exaggerated immune response that results in tissue injury is broadly referred to as a hypersensitivity reaction. The resulting Ag-Ab reaction increase the release of large quantities of chemicals, enzyme, and cell stimulus.

**1) Type I hypersensitivity (anaphylactic or immediate type) reaction**

**Definition:** Type I hypersensitivity reaction may be defined as a rapidly developing Immunologic reaction occurring, within (1-10) minutes after the combination of an antigen with antibody bound to mast cells or basophilic in individuals previously sensitized to the antigen. The reactions depend on the site of antigen exposure (penicillin, bee venom, pollen, dust).
Activation of mast cells in type I hypersensitivity and release of their mediators. ECF, eosinophil chemotactic factor; NCF, neutrophil chemotactic factor; PAF, platelet-activating factor.

**Morphology of the I-st Hypersensitivity:**

- vascular-exudative changes prevail (plasma escape, mucoid and fibrinoid swelling, fibrinoid necrosis).
- accumulation of proteins, fibrin, immune complexes, cellular elements – erythrocytes, neutrophils, eosinophil.

In case repeated antigen coming these activated cells separate vasoactive substances – histamine and various ferments, which starts bloodstream exudative reaction. In the place of this reaction development intensive eosinophilic infiltration is found which is able to reduce allergic response.
Diseases

① Urticaria and angioneurotic edema
② Asthma
③ Hay fever
④ Anaphylactic shock: serious or fatal anaphylaxis may follow. Edema of larynx, with airway obstruction may occur.

2) Type II hypersensitivity reaction (cytotoxic type).

Definition: Type II hypersensitivity is mediated by antibodies directed towards antigens present on the surface of exogenous antigens, occur at (1-5 hr). Three different antibody-dependent mechanisms are involved in this type of reaction.

1- Increase phagocytic activity.
   develops under antibody (IgG or IgM) interaction with antigen on cells surface, with their further damage by lysis, phagocytosis by microphages, T-lymphocytes cellular cytotoxicity, cells’ function change.

2- complement-dependent reactions.

Schematic illustration of three different mechanisms of antibody-mediated injury in type II hypersensitivity.

Complement-dependent reactions that lead to lysis of cells or render them susceptible to phagocytosis.

3- Antibody-dependent cell-mediated cytotoxicity (ADCC)
   Which increase the activity of natural killer cells.
Antibody-dependent cell-mediated cytotoxicity (ADCC). IgG-coated target cells are killed by cells that bear Fc receptors for IgG (e.g., NK cells, macrophages).

**Diseases**

1. Transfusion reactions (graft rejection).
2. Grave's reaction.
3. Autoimmune hemolytic anemia.
4. Autoimmunothyroiditis.
5. Certain drug reactions.
6. Infertility.

3) **Type III hypersensitivity / immune complex-mediated** *(Arthur's reaction).*

Type III hypersensitivity reaction is induced by antigen-antibody complex circulate in blood and deposition in basement membrane of cell like glomerulus, synovial joint, skin that produces tissue damage as a result of their capacity to activate the complement system. The antibodies involved in this reaction are IgG, IgM or IgA. this reaction occur within (5-24 hr).

Sometime this reaction occur due to Ab against Ag of streptococcus which similar stricture to basement membrane of glomerulus and synovial membrane and heart muscles.

**Disease**

1. glomerulonephritis.
2. Rhmatiod arthritis.
3. Rhmatoid Myocarditis.
4) Type IV hypersensitivity (Cell-mediated) reaction (delay type).

**Definition:** The cell-mediated type of hypersensitivity is initiated by specifically sensitized T lymphocytes.

- is realized under participation of cells - sensitized lymphocytes and macrophages, which could behave cytotoxically directly (T-killers) or secret lymphokine this attract more T lymphocyte cells.

- This reaction develops in 24-72 hours after antigen introduction in sensitized organism and is characterized with granulomatous inflammation with caseous necrosis.

- Clinicopathologic manifestations of delayed-type hypersensitivity include: dermatitis, autoimmune diseases, immunity under viral, fungal and some bacterial infections (tuberculosis, brucellosis).

**Immunologic Tolerance**

Immunologic tolerance is a state in which an individual is incapable of developing an immune response to specific antigens. Self-tolerance refers to lack of responsiveness to an individual’s antigens. Tolerance can be broadly classified into two groups: central and peripheral tolerance.

2. Autoimmune Diseases

- **Definition:** Autoimmunity implies that an immune response has been generated against self-antigens /Autoantigens/. Central to the concept of autoimmune diseases is a breakdown of the ability of the immune system to differentiate between self and non-self-antigens. The presence of circulating autoantibodies does not necessarily indicate the presence of autoimmune disease.

**Etiology:**

1- Hereditary
2- chronic viral infections
3- radiation,
4- Genetic abnormalities.
5- cells damage mechanisms are differentiated occurring under humoral or cellular hypersensitivity (types II, III and IV) immune system dysfunction.
6- Malignant tumor.
Classification Autoimmune diseases

A. **organ specific**
1- Hashimoto's thyroiditis
2- insulin resistant diabetes
3- disseminated sclerosis
4- encephalomyelitis
5- polynueritis,
6- aspermatogenesis.

B. **organ nonspecific or systemic diseases**
1- systemic lupus erythematosus.
2- atrophic arthritis
3- dermatomyositis.

C. **Autoimmune diseases of intermediate type** are also differentiated:
1- myasthenia gravis.
2- diabetes mellitus.
3- thyrotoxicosis.

D. **Diseases with autoimmune disorders**
- autoantigens appearance at them occurs as the result of tissues and organs antigen features change, tissue proteins denaturation:
1- burns,
2- irradiation,
3- traumas,
4- chronic inflammations,
5- Viral infections.

**Organ nonspecific autoimmune diseases**

**Systemic lupus erythematosis (SLE).**
- Systemic lupus erythematosis is a chronic of non-organ specific autoimmune disease characterized by loss self-tolerance and production of autoantibodies particularly antinuclear antibodies (ANAS). characterized principally by injury to the skin, joints, kidney and serosal membranes. Each and very part of the body may be affected. It is common among women and a female to male ratio of 9:1
Etiology and pathogenesis

- The cause of SLE remains unknown but it appears to be a complex disorder of multifactorial origin resulting from interactions including:

1. **Genetic factors**
2. **Hormonal factors:** Estrogens confer increased risks (10 times more common in females than males) that accelerate during pregnancy and menses. Androgens however, confer decreased risk.
3. **Environmental factors**
4. **Drugs** such as hydralazine, penicillin etc induce SLE–like illness in which all acting in concert to cause activation of helper T-cells and B-cells that results in the secretion of several species of autoantibodies.
5. **Ultraviolet rays**
6. **Surgery**
7. **Immunologic factors**
   i) B cell hyperactivity with hypergammaglobulinemia
   ii) Autoantibodies present with reactivity to DNA, RNA, or phospholipids thus, antinuclear antibodies (ANA) are the ones that are directed against several nuclear antigen grouped into four categories:
   1. Antibodies to DNA
   2. Antibodies to histone
   3. Antibodies to non-histone proteins bound to RNA
   4. Antibodies to nucleolar antigens

- In tissues, nuclei of damaged cells react with ANAs, lose their chromatin pattern, and become homogenous to produce so–called lupus erythematosus (LE) bodies or hematoxylin bodies.
Morphologic changes in SLE

The most characteristic lesions result from the deposition of immune complexes found in the blood vessels, kidneys, connective tissue and skin. Acute necrotizing vasculitis of small arteries and arterioles is characterized by fibrinoid necrosis.

Kidney: 60 – 70% involvement by SLE. Anti-dsDNA (60-90% associated with nephritis.

Skin: Acute lesions “butterfly” rash (50%) where histology shows liquefactive degeneration of the basal layer of the epidermis. Sunlight exposure incites or accentuates the erythema. Chronic lesion: Descoid (plaques with scales, scarring with central atrophy)

Serositis - Acute, subacute or chronic inflammations of the serosal linings pluralitis pericarditis peritonitis

Myocarditis leading to arrhythmias, congestive heart failures. Accelerated coronary atherosclerosis with evidence of angina pectoris.

Spleen - is moderately enlarged with focal hyperplasia

Lungs - Pleuritis and pleural effusion are the most common pulmonary manifestations.

3. Immunodeficiency Diseases

The term immunodeficiency covers a group of disorders of specific immune responses, neutrophil, macrophage and natural killer cells functions, as well as defects in the complement system that lead to impaired resistance to microbial infections.

Classification: These diseases are crudely classified into primary and secondary types.

1) Primary immunodeficiency diseases (exceedingly rare)

These disorders usually manifest in early childhood and are almost always genetically determined. Though, some overlap exists primary immunodeficiency diseases are further divided into:

Deficiencies of antibody (B – cells) immunity.

a. Infantile X-linked gammaglobinemia: those family have normal cell mediated immunity but no humeral immunity.
Deficiencies of cell mediated (T-cell) Immunity

b. Thymic hypoplasia or aplasia: this case mostly common in mice and calf in this case have normal humeral immunity but no cell mediated immunity.

c. **Combined T-cell and B-cell deficiencies**: Severe combined immunodeficiency disease (SCID) in this case no humeral immunity no cell mediated immunity.

d. dysgammaglobulinemia: in this case normal Ab formation from B cell but difficult to release from plasma cell.

2) **Secondary immunodeficiencies States**

These immunodeficiency states may be acquired secondary to various disease processes or drug effects:

a. Viral infection (AIDS).

b. Protein deficiency

Lack of protein leads to cell mediated immunity and hypocomplementamia

c. **Hematologic malignancies**

Leukemia and lymphomas where normal functioning cell replaced by neoplastic ones here both humeral and cell mediated immunity are impaired.

“**graft-versus-host**”. At various organs and tissues transplantation graft-versus-host reaction often develop. At that graft antigens induce specific antibodies creation and sensebilized erythrocytes production, infiltrating graft and causing its destruction and rejection by the way of direct cytotoxic action or by the way of lymphokines secretion. Graft immunity manifestations are similar to delayed-type hypersensitivity reaction. In these cases immunosuppressive agents ought to be used. These statuses occur in case introduction into recipient’s suffering from immunodeficiency for example at bone marrow transplantation or intestine transplantation, or at lymphocytes transfusion together with blood. Diseases is manifested with skin rash, diarrhea, liver impairment, anemia, neutropenia.
Acquired immune deficiency syndrome (AIDS):

This is chronic, rarely – acute disease with prevailing injury of immunogenesis organs and blood cells, the final stage of which is complete suppression of immune system.it is slow progress and it is usually fatal.

Etiology

- T- lymphotropic virus of human immunodeficiency (HIV),(lenti retro virus ).
- In the recent years this virus was defined as HIV - 2 (African AIDS virus), in Japan HIV-3 was also revealed. Because of infinite inclination to mutation, there are various viral strains.
- Virus contains two RNA molecules – virus genome and reversible transcriptase.

Pathogenesis of Acquired immune deficiency syndrome (AIDS)

- In human blood virus hitches cells with CD4+,
- penetrates inside with receptor and
- builds in cell’s genetic code.
- By the way of reversible transcriptase virus codes production of particles similar to it until cell dies. Than it occupies new cells with CD4+ receptors. In CD4+ lymphocytes-helpers HIV could stay in latent state for indefinitely log time.
- Cells with immunodeficiency virus on their surface stimulate immune response by the way of HIV-antibodies and cytotoxic lymphocytes production which cause both damaged and undamaged T-lymphocytes-helpers’ cytolysis. All that cause cellular and humoral immunity decrease which in the final of disease ends with complete loss of delayed-type hypersensitivity for various antigens.

Transmission

1- Sexual contact
2- Contaminated needle
3- Infected Blood transfusion and its products.
Incubation period of AIDS

- could last from 6 months up to 12 years and longer there are no symptoms manifested at this stage.
- Anti-HIV – antibodies are found in blood.
- Approximately in 20 % cases acute signs of primary AIDS infection appear in 3-6 weeks from the moment of contamination.

Period of persistent generalized lymphadenopathy.

- Major signs of disease beginning is high and long-term fever (38-39 С) with lymphatic nodes injury, more often it is neck lymphatic nodes enlargement, skin rash appearance and mononucleosis syndrome. Is characterized with persistent enlargement of various groups of lymphatic nodes. Morphologically lymphatic nodes follicles increase is revealed. Period duration is 3-5 years.

Pre-AIDS (syndrome associated with AIDS)

- progresses on the ground of moderate immunodeficiency and is characterized with body weight decrease up to 20 %,
- development of fever,
- diarrhea
- progressive lymphadenopathy,
- Recurring acute viral respiratory infections.

Period of acquired immune deficiency syndrome (AIDS)

- considerable loss of body weight, up to cachexia,
- Sharp immunity depression causing opportunistic infections and malignant tumors (lymphoma, Kaposi's sarcoma) progress.
- AIDS manifestations are really various but they are grouped in three main syndromes –
- Lymphatic nodes injury,
- Lesions caused by opportunistic infections,
malignant tumors progress.

Changes in lymphatic nodes by AIDS manifestations

1- Stage of follicular hyperplasia is characterized with follicles size increase with large light centers Peripheral lymphocytic crown surrounding follicles is narrow or completely absent, medullary tension bars are hard to determine.

2- Stage of diffuse hyperplasia similar to angioimmunoblast lymphadenopathy is characterized with lymphatic nodes usual structure loss. Histologically vessels prevail in lymphatic node, the amount of cells is small, and their composition is polymorphous: round of irregular shape lymphocytes, plasmacytes, immunoblasts, eosinophils, tissue basophils. Follicles atrophied, little. Sometimes follicle centers’ hyalinosis is found.

3-Stage of lymphoid emaciation. Lymphatic nodes are represented with stroma only.

- Sinuses are dilates, filled with mononucleate cells.
- Lymphatic nodes and diminished, sclerosed,
- amount of lymphoid elements is not big, plasmacytes and immunoblasts are found.
- Similar changes are observed in spleen, thymus gland, and lymphoid apparatus of bowel.