**Immunopatholog**

 Body immune responses are normal defense mechanisms designed to overcome invasion by various environmental factors such as microorganisms & toxic chemicals. immunopathology is concerned with the pathological changes that occur in the tissues as a result of improper immune response.

Immune response in general include:

• Non-specific host defense mechanisms (innate immunity)

 • Specific immunity (adaptive immunity, acquired immunity) i.e., the **humoral** and **cellular**

**The major components of innate immunity are:**

1. Physiological barriers (skin & mucous membr.)that block entry of microbes,
2. cells (phagocytic cells) mainly neutrophils and macrophages, dendritic cells, non - phagocytic are natural killer (NK) cells,
3. soluble proteins: complement proteins
4. chemokines, cytokines( IL1,6,)induce fever, and already formed antimicrobial substances (lysozymes and peroxidase Es)
5. Receptors: toll like receptors
6. Compounds: lactoferrine and defensiness
7. Microbial agents: normal flora

**Specific (adaptive, acquired) immune response:** started by Agengulfment by Ag presenting cells with subsequent CD4(helper Tcell TH) activation that ended by either humeral immune response (Ab formation) or cellular immune response (Tcytotoxic and other immune cells activated like macrophage, natural killer cells, neutrophils and others) or both cellular and humeral.

**Diseases (immunopathology) may result from**:

 1. Inadequate immune response = lead to immunodeficiency

2. Excessive immune response = hypersensitivity reactions

3. Inappropriate immune response = autoimmune diseases and graft rejection

**Inadequate immune responses:**

These can result from immuno-deficiency states. There are two classes of immunodeficiency syndromes:

 1. Primary; which is present at birth & often the result of a genetic disorder

2. Secondary; which is much more common than the primary. It can be secondary to a. Drugs b. Diseases

**1-Primary immunodeficiency**

1. **X-linked agammaglobulinemia (Bruton disease)** This is one of the more common forms of primary immunodeficiency. It is due to failure of pre-B-cells to differentiate into B-cells that result in the absence of gamma globulin in the blood (agammaglobulinemia). The disease is seen primarily in males. In most cases, there are recurrent bacterial infections. For obscure reasons, auto-immune diseases (such as SLE & dermatomyositis) also occur in up to 20% of patients.
2. **Isolated IgA-deficiency** :This is the most common of all primary immunodeficiency states. There is marked reduction in the level of serum IgA but other immunoglobulins are normal. In most cases it is asymptomatic & detected accidentally, but some patients have recurrent respiratory infections & diarrhea. There is also a significant, unexplained association with autoimmune diseases.
3. **Severe combined immune deficiency (SCID)** :This condition may be inherited as a recessive disorder either autosomal or an X-linked. The condition is due to failure of development of both B-cell & Tcell precursors from primitive stem cells.

**2-secondary immunodeficiency** : Acquired immunodeficiency syndrome (AIDS). AIDS is a common and important example.

**Acquired immunodeficiency syndrome (AIDS)**

 retroviral disease caused by human immunodeficiency virus (HIV) and characterized by profound immuno-suppression leading to: 1. Opportunistic infections 2. Secondary neoplasms and 3. Neurological manifestations.

**Etiology**: It caused by RNA virus that have T helper cell tropism. This is a human retrovirus belonging to the lentivirus family. The virion is spherical & surrounded by a lipid envelope derived from the host cell membrane.

**Immunopathogenesis of HIV disease:** The major targets of HIV infection is cells express CD4 receptors. AIDS leads to severe impairment of the cell-mediated immunity system due to destruction of CD4 lymphocytes & a **decreased helper/suppressor T-cell ratio** in the blood. The virus gains entry to T-cells by attaching to surface CD4 molecules; this explains the selective tropism of the virus for **CD4 +Tcells** ,**macrophages & dendritic cells that express CD4 receptors**. The virus core containing the HIV genome enters the cytoplasm of the cell. The viral genome then **undergoes reverse transcription**, leading to formation of complementary DNA (cDNA). In the dividing T-cells, the cDNA enters the nucleus & integrates into the host genome. After integration, the provirus may remain non-transcribed for months or years & the infection becomes latent; alternatively, proviral DNA may be transcribed to form complete viral particles that bud from the cell membrane, leading to cell death. Due to loss of CD4+ cells, patients will have an inversion of the CD4- /CD8 ratio in the peripheral blood; normally it is about 2, while in AIDS patients the ratio ≤ 0.5. ADIS patients will also have qualitative defects in Tcell function. This depression in CD4 +ve cells lead to depression in cell mediated immunity that explain the fungal apportunistic infection, viral infection and tumor development.

 **Pathogenesis of central nervous system involvement (AIDS):** The nervous system is a major target of HIV infection. Macrophages & their equivalents in the CNS; the microglia, are mainly infected with HIV. The virus is mostly carried into the brain by infected monocytes. The mechanism of HIV induced damage of the brain remains obscure. It is believed that neurologic deficit is caused indirectly by viral products & soluble factors e.g. cytokines produced by macrophages/microglia.

**Inappropriate immune response:**

**A-Transplant rejection:** Organ transplantation is used increasingly to treat irreversible diseases of the kidney, liver, heart, lung, & bone marrow. Unfortunately, the action of the immune system of the recipient can lead to destruction of the transplanted tissue a process termed "transplant rejection". The recipient immune response involving both cell- and humoral-mediated hypersensitivity responses directed against histocompatibility antigens (human leukocytes antigens (HLA)) on the donor transplant.

 Patterns of transplant rejection: Rejection reactions have been classified as

 1. Hyperacute 2. Acute 3. Chronic rejection

 **Hyperacute rejection**: This occurs within a very short time from the moment the organ is perfused by the host's blood (minutes to a few hours). In this form there is a widespread intravascular thrombosis in small vessels, with focal necrosis**. It is the result of pre-formed humoral host antibodies reacting with antigens in the graft**. These preformed antibodies developed due to:

**1. Previous rejection of a transplant**

**2. Multiparous women** who develop anti-HLA antibodies against paternal antigens shed from the fetus (a rejection in this instance will affect the transplanted organ donated by the husband and offspring)

**3. Prior blood transfusions** because platelets and WBCs are rich in HLA antigens.

The hyperacutely rejected kidney rapidly becomes cyanotic, mottled, & flaccid & may excrete only a few drops of blood-stained urine.

 **Acute rejection**: It occurs within days or weeks of transplantation. It is **mediated by both humoral & cell-mediated mechanisms**. Acute cellular rejection is mediated by T-cells reacting against donor HLA antigens, particularly class II. It is accompanied by signs of failure of transplanted organ.

 **Chronic rejection**: In recent years, acute rejection has been significantly controlled by immunosuppressive therapy. Chronic rejection occurs slowly & progressively after transplantation (months to years). It is the **result of slow breakdown of the host's tolerance to the graft and may be due to inadequate immune suppression**. The condition is manifested by a progressive decline in function of transplanted organs.

**B-Autoimmune diseases:** Autoimmune diseases are the result of immune reactions against self-antigen. Sometimes the immune response is an antibody response (autoantibody), or it is a cell-mediated immune response. In autoimmune diseases, the normal mechanisms ensuring tolerance for self-antigens have broken down. (Self tolerance indicates lack of immune responsiveness to one's own tissue antigens).

 **Mechanisms of Autoimmunity**: Autoimmunity arises from a combination of :

* **Bypass of helper T-cell tolerance (activation of autoreactive T helper cells) by drug or infection**
* **Molecular mimicry** : Microbes share epitopes with self-antigens eg. Streptococci and rheumatic heart disease
* **Polyclonal lymphocyte activation (Endotoxin, EBV , AIDS , CMV)**
* **Emergence of sequestered antigens (e.g., eye, brain ,thyroid , sperm )**
* **Inaproperiate expresion of class II MHC molecules : Normally only on APC s. After viral infection or trauma the released gamma IFN leads to expressing class II MHC molecules on some cells like Pancreatic beta cells lead to IDDM or thyroid cells lead to autoimmune thyroiditis**
* **Genetic predisposing (association with MHC gene(:**

**Ankylosing spondilitis HLA B27, SLE DR 2,3 , IDDM DR 3,4**

Mechanisms have been postulated to explain the link between infections and autoimmunity.

1. ■ Infections may up-regulate the expression of costimulators on APCs. If these cells are presenting self-antigens, the result may be a breakdown of anergy (self tolerance) and activation of T cells specific for the self-antigens.
2. ■ Molecular mimicry. Microbes may express antigens that have the same amino acid sequences as self-antigens. Example of such mimicry is rheumatic heart disease, in which antibodies against streptococcal proteins cross-react with myocardial proteins and cause myocarditis.
3. ■Some viruses, such as Epstein-Barr virus (EBV) and HIV, cause polyclonal B-cell activation, which may result in production of autoantibodies.
4. ■The tissue injury by infections may release self-antigens and structurally alter self-antigens so that they are able to activate T cells that are not tolerant to these new, modified antigens.

Autoimmune diseases divided to:

 ■Organ specific (response directed against a single component of a single tissue): type I diabetes, graves disease, pemphigus vulgaris …..

 ■ non-organ-specific (systemic) autoimmune disease (response directed against a component that present in many tissues & organs throughout the body): SLE, Rhumatoid arthritis.

**Systemic lupus erythematosus (SLE):** SLE is an autoimmune disease and one of the ''connective tissue disorders''. SLE is a complex disorder of multifactorial origin resulting from interactions among genetic, immunological, and environmental factors that act in concert to cause activation of helper T cells and B cells and result in the production of several species of pathogenic autoantibodies.

**Etiology & pathogenesis**: SLE is a complex disease of multifactorial origin including genetic, hormonal, & environmental factors leading to the apoptosis of cells. Inadequate clearance of the nuclei of these cells results in a large burden of nuclear antigens. lymphocytes are stimulated by self-nuclear antigens, and antibodies are produced against these antigens ANA (antinuclear antibodies). The net result is a cycle of antigen release and immune activation resulting in the production of high affinity autoantibodies. test for ANAs Antibodies to double -stranded DNA and the so-called Smith (Sm) antigen are virtually diagnostic of SLE. –

Mechanisms of Tissue Injury: Regardless of the exact mechanisms by which autoantibodies are formed, they are clearly the mediators of tissue injury.

■Most of the visceral lesions are caused by immune complexes (type III hypersensitivity). This will lead to attraction of phagocytic cells (cellular immunity) to deal with the damaged tissue.

 ■Autoantibodies specific for red cells, white cells, and platelets opsonize these cells and promote their phagocytosis and lysis type II hypersensitivity reaction.

**Rheumatoid Arthritis (RA):** RA is a multi-system connective tissue disease in which the dominant effects are on the joints.

 Pathogenesis: Although much remains uncertain, it is currently believed that rheumatoid arthritis is triggered by exposure of a genetically susceptible host to an arthritogenic antigen resulting in a breakdown of immunological self-tolerance and a chronic inflammatory reaction. In this manner, an acute arthritis is initiated, but it is the continuing autoimmune reaction, the activation of CD4+ helper T cells, and the local release of inflammatory mediators and cytokines that ultimately destroys the joint. **About 80% of the patients have rheumatoid factors (RF) in their serum & synovial fluid. RF represents an autoantibody mainly of IgM class directed against the Fc portion of IgG. RF & IgG form immune complex that fix complement, attract neutrophils, & lead to injury by a type III hypersensitivity reaction**.

An arthritogen thought to be the initiator of the disease remains uncertain. 1-Microbial agents including Epstein-Barr virus, retroviruses, parvoviruses, mycobacteria, Borrelia, Proteus mirabilis, and Mycoplasma 2-Recently, citrullinated proteins (ccp) (proteins modified by the enzymatic conversion of arginine to citrulline, many of which are fibrins) formed in the body (especially in the lungs of smokers) have been implicated in the pathogenesis of rheumatoid arthritis.

Pathologic changes: In the early stage there will be rheumatoid synovitis. There is a great increase in chronic inflammatory cells mainly lymphocytes, plasma cells & macrophages with formation of lymphoid follicles. There is marked synovial hypertrophy & hyperplasia, often with increased vascularity due to angiogenesis. With time there is articular cartilage destruction with replacement by vascular granulation tissue (pannus). After that destruction of the articular cartilage & erosion of the subarticular bone occur and the pannus fills the joints space. Subsequent fibrosis & calcification may cause permanent ankylosis of the affected joint.

**Excess immune response**

**Hypersensitivity reaction**

Hypersensitivity refers to undesirable (damaging, discomfort and sometimes fatal) reactions produced by the normal immune system. Hypersensitivity reactions require a pre-sensitized (immune) state of the host. Hypersensitivity reactions can be divided into four types: type I, type II, type III and type IV, based on the mechanisms involved and time taken for the reaction. Frequently, a particular clinical condition (disease) may involve more than one type of reaction.

 **Type I Hypersensitivity** It is also known as immediate or anaphylactic hypersensitivity. The reaction may involve skin (urticaria and eczema), eyes (conjunctivitis), nasopharynx (rhinorrhea, rhinitis), bronchopulmonary tissues (asthma) and gastrointestinal tract (gastroenteritis). The reaction may range from minor inconvenience to death. The reaction takes 15-30 minutes from the time of exposure to the antigen. Immediate hypersensitivity is mediated by IgE. The primary cellular component in this hypersensitivity are mast cell and basophil. IgE has very high affinity for its receptor on mast cells and basophils. In first exposure IgE bound to mast cell and this called mast cell sensitization. A subsequent exposure to the same allergen **cross links** the cell-bound IgE and triggers the release of various pharmacologically active substances. Mast cell degranulation is preceded by increased Ca++ influx, which is a crucial process promote degranulation. Early mediators cause immediate symptoms e.g. histamine (preformed in granules) leukotriene C4 and prostaglandin D2.

. Eosinophil may control the local reaction (modulate the immune response) by releasing arylsulphatase, histaminase, phospholipase-D and prostaglandin-E . complement not involved in this type.

**Type II Hypersensitivity** It is also known as cytotoxic hypersensitivity and may affect a variety of organs and tissues. The antigens are normally endogenous, although exogenous chemicals (haptens) which can attach to cell membranes can also lead to type II hypersensitivity. **hemolytic anemia** (RBC destruction due to Rh incompatibility between mother and blood transfusion reaction**), granulocytopenia and thrombocytopenia** are such examples. The reaction time is minutes to hours. It is primarily mediated by antibodies of IgM or IgG class, this will activate complement. C3b complement component and IgG opsonize the target antigen this will activate phagocytes (macrophages and other phagocytic cells). NK natural killer cells may also play a role. This cellular activation called (antibody dependent cell cytotoxicity). Diagnostic tests include detection of circulating antibody against tissues involved and the presence of antibody and complement in the lesion (biopsy) by immunofluorescence.

**Type III Hypersensitivity** It is also known as immune complex hypersensitivity. The reaction may be general (e.g., serum sickness) or may involve individual organs including skin (e.g., systemic lupus erythematosus, Arthus reaction), kidneys (e.g., lupus nephritis), lungs (e.g., aspergillosis), blood vessels (e.g., polyarteritis), joints (e.g., rheumatoid arthritis) or other organs. This reaction may be the pathogenic mechanism of diseases caused by many microorganisms. The reaction may take 3-10 hours after exposure to the antigen. **It is mediated by soluble immune complexes. They are mostly of IgG class, although IgM may also be involved. The antigen may be exogenous (chronic bacterial, viral or parasitic infections), or endogenous (non-organ specific autoimmunity: e.g., systemic lupus eythematosus, SLE). The antigen is soluble and not attached to the organ involved. Immuno-complex deposition in tissues with activation of complement and inflammatory cells infiltration is the cause of tissue destruction**.

**Type IV Hypersensitivity It is also** known as cell mediated or delayed type hypersensitivity. The classical example of this hypersensitivity reaction:

1. all causes of granulomatous inflammation like foreign body and tumors,
2. infection that provoke cellular immune response like TB infection , virus and fungal infection.
3. Contact dermatitis and tuberculin (Montoux) reaction which peaks 48 hours after the injection of antigen (PPD or old tuberculin) The lesion is characterized by induration and erythema.

 Type IV hypersensitivity is involved in the pathogenesis of many autoimmune and infectious diseases (tuberculosis, leprosy, blastomycosis, histoplasmosis, toxoplasmosis, leishmaniasis, etc.) and granulomas due to infections and foreign antigens. Another form of delayed hypersensitivity is contact dermatitis (poison ivy, chemicals, heavy metals, etc.) in which the lesions are more papular.

**Mechanisms of damage in delayed hypersensitivity include T lymphocytes activation which inturn activate both Cytotoxic T cells (Tc) cause direct damage and helper T (TH1) cells secrete cytokines which activate activate monocytes and macrophages, which cause the bulk of the damage.**

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