

LECTURE 8

Immunopathologic processes

Theme 11. Immune system pathomorphology.

Hypersensitivity reactions and mechanisms.

Theme 12. Autoimmune diseases. Immunodeficiency states.

Amyloidosis

Structural-functional organization of immune system, cellular grounds of immune response

Immune system provides organism protection of infection agents and biologic substances with antigenic features.

Immune protection is done by lymphocytes (immunocytes) forming in the marrow from lymphoid embryo.

■ Immune system includes the following **peripheral organs**:

- -lymph nodes,
- -pharyngeal tonsils,
- - lymph follicles in intestine wall,
- -lymphocytes in peripheral gland,
- - spleen

■ and **central organs**

- thymus,
- marrow.

Immune response

Two types of immune response are differentiated:

- -cellular
- - humoral.

Cellular immunity

Cellular immunity is provided by T-lymphocytes:

- -T-killers,
 - - T-suppressors,
 - - T-helpers.
- They are formed in thymus.

Cellular immunity

- Significant role in cellular immunity realization belongs to cytotoxic cells (**T-killers**) carrying out direct injury of cells by their lysis.

- Besides that T-cells synthesize *lymphokines (cytokines)*:
- -interleukins,
- -interferon
- and others which regulate macrophages and other lymphocytes function.
- Important role in this process is given to **T-helpers (CD4)** and **T-suppressors (CD8)**.

Humoral immunity

■ Humoral immunity is carried out by **B- lymphocytes**, which transform into *plasmacytes* and synthesize *immunoglobulin (antibodies)*.

■ **Immunoglobulin** has antigenic specificity and differs from each other by amino acid composition. Several classes of antibodies are differentiated: **IgA, IgG, IgM, IgD, IgE**.

■ Immunoglobulin molecules consist of light and heavy chains. Each chain has permanent and temporary chains comprising corresponding receptors to antigens providing their contact and destruction.

Immune response

■ Immune response to antigen could be **primary** and **secondary**.

■ **Primary** response occurs in case immune system first contact with antigen. It is realized in several days while B-lymphocytes transform in plasma cells and start to synthesize **IgM**.

■ **Secondary** response occurs after immune system repeated contact with antigen and develops fast (in 2-3 days) with **IgG** assistance.

Thymus disease

The most often thymus disease shows itself with inherited pathology:

- - aplasia,
- - hypo- and dysplasia,
- - atrophy,

- thymomegalia as well as accidental involution,
- hyperplasia from lymphoid elements or neoplastic processes.

Thymus disease

■Under *aplasia, hypo- and dysplasia of thymus*, as well as under its *senile accidental involution or atrophy cellular* or combined immune deficiency develops quite often.

■*Thymomegalia* (inherited or acquired) is also accompanied with immunodeficiency state progress causing severity of infection diseases course and sometimes even fatal consequences of them.

■*Thymus hyperplasia* from lymphoid elements is characteristic for autoimmune diseases.

Immune response of the organism for antigen action

Phases of immune response:

- lymphocyte antigen recognition,
- T- and B- lymphocytes transformation and proliferation,
- Types of immune response are as follows:

- primary
- and secondary.

■**Primary** immune response occurs under the first time meeting with specific antigen. At it **IgM** is produced, further on **IgG** appear.

■**Secondary** immune response occurs under repeated antigen getting into organism and is accompanied with **IgG** accumulation.

■**Immune tolerance** means immune system's insusceptibility to own tissues which are antigens, this is natural tolerance developing in fetal life.

Immunological hypersensitivity

■
It is one of the evidences of dysimmunity, occurring in *sensitized organism* and are connected with humoral and cellular immunity.

■Immediate and delayed type hypersensitivity are differentiated which are morphologically shown with acute or chronic immune inflammation.

■Reactions of hypersensitivity could progress by *four types* of scenarios.

Hypersensitivity of the I-st (immediate) type-Allergy and Anaphylaxis

■develops at participation of tissue basophils and blood basophils which produce IgE in case antigen (allergen) getting into organism.

- This reaction takes place at eczemas,
- dermatitis,
- allergic rhinitis and gastroenteritis,
- atopic asthma – local manifestations,
- anaphylactic reactions and shock - systemic manifestations.

Morphology of the I-st Hypersensitivity:

- alterative and vascular-exudative changes prevail:
- plasma escape,
- mucoid and fibrinoid swelling,
- fibrinoid necrosis,
- accumulation of coarsely dispersed proteins, fibrin, immune complexes, cellular elements – erythrocytes, neutrophils, eosinophils.
- 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.

Morphology of the I-st Hypersensitivity

■**Allergic edema of larynx.** Regular croup. Mucus tunic of larynx is sharply edematous. Lumen is slot-type narrowed.

Hypersensitivity of the IIrd type (antibody-mediated hypersensitivity)

■develops under antibody (IgG or IgM) interaction with antigen on cells surface, with their further damage by lysis, phagocytosis by macrophages, T-lymphocytes cellular cytotoxicity, cells' function change.

■An example of these reactions could be reactions with erythrocytes destruction after hemotransfusion, hemolytic disease of neonates, reactions with neutrophils', thrombocytes', etc. destruction.

Hypersensitivity of the IIIrd type (immune complex hypersensitivity)

■develops in the result of immune complexes formation after antibody and antigen interaction, causing complement activation and acute inflammation and necrosis progress.

■ Immune complex hypersensitivity could be systemic - serum sickness, erythematosus or local – Arthus phenomenon after repeated antigen introduction at vaccination.

Hypersensitivity of the IVth type (delayed-type hypersensitivity)

■ is realized under participation of cells - sensitized lymphocytes and macrophages, which could behave cytotoxically directly (T-killers) or secret lymphokines.

■ 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 tuberculin-type reaction in skin for antigen introduction, contact dermatitis, autoimmune diseases, immunity under viral, fungal and some bacterial infections (tuberculosis, brucellosis).

Autoimmune diseases

occur in case disorder of immune system natural tolerance to own antigens, which is formed in embryonal period.

Autoimmunization is formed, in the other words autoantibodies, circulating immune complexes aggression, which contain autoantibodies to antigens of the own cells of organism.

Aetiology:

■ chronic viral infections,

■ radiation,

■ genetic abnormalities.

■ cells damage mechanisms are differentiated occurring under humoral or cellular hypersensitivity (types II, III and IV) immune system dysfunction – T-lymphocytes and antiidiotype antibodies suppressive activity decrease.

Classification Autoimmune diseases

organ specific

■ (Hashimoto's thyroiditis,

■ insulinresistant diabetes,

■ disseminated sclerosis,

■ encephalomyelitis,

■ polyneuritis,

■ aspermatogenesis, etc.)

■ - *organ nonspecific* or systemic diseases

■ (systemic lupus

■ erythematosus,

■ atrophic arthritis,

■ dermatomyositis

■ and others).

Autoimmune diseases of intermediate type

Organ specific autoimmune diseases

■ develop in connection with immunologic separated organs immune barriers damage (thyroid gland, cerebrum, nerves, testicles, adrenal glands, eyes). Antibodies and sensibilized lymphocytes are formed for unchanged antigens of these organs, morphologic changes develop, characteristic for delayed-type hypersensitivity reaction: tissue is subject to infiltration with lymphocytes, parenchyma dies, conjunctive tissue expands. Lymphoid system failure to control immune homeostasis of organism is characteristic for autoimmune diseases. Most of autoimmune diseases have family inclination (systemic lupus erythematosus, Hashimoto's thyroiditis and others) or are connected with specific HLA antibodies.

Organ specific autoimmune diseases

■ **Nodose goiter. Histologically - Hashimoto's thyroiditis. Thyroid gland is increased. Its surface is coarse-gibbous.**

Autoimmune diseases of intermediate type

are also differentiated:

■ myasthenia gravis,

■ diabetes mellitus of the 1st type,

■ thyrotoxicosis,

■ Goodpasture's syndrome,

■ Sjogren's sicca syndrome, etc.

Diseases with autoimmune disorders

■ autoantigens appearance at them occurs as the result of tissues and organs antigen features change, tissue proteins denaturation:

■ burns,

■ irradiation,

■ traumas,

- chronic inflammations,
- viral infections.

Immunologic deficiency

■is manifested with immunodeficiency state progress, which could be **primary** in the result of underdevelopment (hypoplasia, aplasia) of central or peripheral organs of immunogenesis – **congenital or heritable immunodeficiencies** and **secondary** (acquired) – occur under sicknesses and other exogenous influences.

Primary (congenital) immune deficiencies

are manifested with cells humoral immunity deficiency or combined immunodeficiency. The most investigated are the following types of congenital immune deficiencies:

- severe combined immunodeficiency,
- hypoplasia of thymus (DayJorge syndrome),
- congenital agamoglobulinemia (Brutton's disease),
- isolated IgA deficit,
- complement deficit,
- Nezelof-type thymic dysplasia,
- immune deficiencies connected with heritable diseases (Wiskott-Aldrich syndrome,
- ataxy- telangiectasia Lui-Barre), etc.

Clinicopathological manifestations of primary immune deficiencies

- often are presence of thymus congenital anomalies, spleen, lymphatic nodes underdevelopment.
 - Aplasia, hypoplasia of thymus is accompanied with cellular immunity deficiency or combined immunodeficiency.
 - At aplasia (agenesia) thymus is absent completely,
 - at hypoplasia it is of smaller size, division into cortex and medullary substance is abnormal, lymphocytes quantity is sharply reduced.
 - In spleen follicles size is noticeably reduced, light centers and plasma cells are absent.
 - In lymphatic nodes follicles and cortex layer (B-dependent zones) are absent, only pericortex layer (T-dependent zone) is kept.
- The course of patients' death is infection diseases (purulent infections, tuberculosis, sepsis, etc.) progress and organism inability to struggle against microorganisms.

Secondary (acquired) immunodeficiencies

■are met rather often

■Aetiology:

■*various diseases:*

- infection diseases,
- leucosis,
- malignant lymphomas (lymphogranulomatosis),
- thymomas,
- sarcoidosis.

■or *drug therapy*(Yatrogenic immune deficiencies):

- radiation therapy,
- administration of corticosteroids,
- immunosuppressants,
- antilymphocytic serum,
- thymectomy,
- thoracic duct, drainage.

Yatrogenic immune reactions - “ graft-versus-host”.

At various organs and tissues transplantation graft-versus-host reaction often develop. At that graft antigens induce specific antibodies creation and sensibilized erythrocytes production, infiltrating graft and causing its destruction and rejection by the way of direct cytotoxic action or by the way of lymphoquins 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 body big amount of HLA-incompatible and viable lymphocytes, 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 oppression of immune system.

Etiology – Acquired immune deficiency syndrome (AIDS)

■ T-lymphotropic virus of human immunodeficiency (HIV).

■ 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. On the capsule surface there are two glycoproteins providing virus binding with cells which on their surface carry CD4+ antigen. These cells include as follows: T-CD4+ lymphocytes (helpers), B-lymphocytes, which have CD4+ receptors, monocytes, macrophages, microglia, dendritic cells, endotheliocytes.

Epidemiology Acquired immune deficiency syndrome (AIDS)

■ AIDS expansion is of pandemic character.

■ Approximately every 8-10 months amount of those ill with AIDS doubles, half of them die in 3 years period. Most of them are found in USA, West European countries, Africa. In certain regions of Central Africa up to 60 % of adults are infected.

■ The source of infection is sick person - virus carrier. The highest concentration of virus is found in blood, sperm, cerebrospinal fluid, it is lower in saliva, tears, in cervical and vaginal secretions of sick people.

■ Three ways of infecting were proved: sexual, parenteral (by the way of virus introduction with blood preparations or with contaminated instruments utilization), transplacental and with mother's milk. According to the data of American Center of Sickness Rate Control risk of medical employees infection in case contaminated syringe needle prick or in case cut equals to 4,7:1000.

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. Then it occupies new cells with CD4+ receptors. In CD4+ lymphocytes-helpers HIV could stay in latent state for indefinitely long 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.

Clinical periods of AIDS:

■ incubation period (asymptomatic carrier),

■ lymphadenopathy syndrome (LAS),

■ pre-AIDS (syndrome, associated with AIDS),

■ acquired immune deficiency syndrome (AIDS).

Incubation period of AIDS

■ could last from 6 months up to 12 years and longer.

■ As a rule there are no symptoms manifested at this stage.

■ Anti-HIV – antibodies are found in blood.

■ Various factors reducing organism resistance could provoke clinical symptoms.

■ Approximately in 20 % cases acute signs of primary AIDS infection appear in 3-6 weeks from the moment of contamination.

■ Major signs of disease beginning is high and long-term fever (38-39 C) with lymphatic nodes injury, more often it is neck lymphatic nodes enlargement, skin rash appearance and mononucleosis syndrome. Signs frequency: fever 92%, myalgia – 83 %, Skin rash – 50 %, mononucleosis and plasmacytosis in blood formula – 70 %.

AIDS

■ **Period of persistent generalized lymphadenopathy** 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

■ *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.

Changes in lymphatic nodes by AIDS manifestations

■ *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, their composition is polymorphous: round of irregular shape lymphocytes, plasmacytes, immunoblasts, eosinophils, tissue basophils.
- Follicles atrophied, little.
- Sometimes follicle centers' hyalinosis is found.

Changes in lymphatic nodes by AIDS manifestations

- *Stage of lymphoid emaciation.*
- Lymphatic nodes are represented with stroma only.
- Sinuses are dilated, 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, lymphoid apparatus of bowel.

AIDS

■ *Injuries caused by opportunistic infections* are various in their localization and nature: bacterial, fungi, parasitogenic, viral. Opportunistic are called infections caused by conditionally-pathogenic causative agents contamination with which healthy people does not accompanied with pathologic changes. At AIDS opportunistic infections are characterized with recurrent course, process generalization. Treatment is ineffective. Interstitial pneumonia, esophagitis, gastroenterocolitis, encephalitis, meningitis, abscess, sepsis.

AIDS

■ *Malignant tumors* at AIDS are mostly of two types:

- -Kaposi's sarcoma,
- -malignant lymphomas among elderly people.
- At AIDS they are often early manifestation of disease.
- Besides cutis mucus tunics, lymphatic nodes are subject to injury, sometimes multiple visceral lesions are observed.
- Microscopically Kaposi's sarcoma is represented with numerous neoplasms, thin walled vessels localized in random way.
- Malignant lymphomas injure central nervous system, lymphatic nodes, digestive tract, upper air passages, bone marrow.
- AIDS always ends mortally caused by purulent infections, sepsis, tuberculosis or malignant growth progress.

Amyloidosis

■ *It* is characterized with abnormal fibrillar protein (*F-component*) accumulation in tissues which is connected with blood plasma glucoproteins (*P-component*) with characteristic physics-chemical features. This composite substance is called *amyloid-glycoprotein*, that is protein with carbohydrates admixture and subject to iodine and sulphuric acid is colored in blue (*Virhov's reaction*).

Amyloidosis

■ Amyloid consists of

- albumines,
- fibrin,
- complement,
- blood plasma
- globulins,
- lipids,
- lipoproteins,
- calcium salts,
- acid glycosaminoglycans of main substance - chondroitin sulfate and heparitin sulfate.
- Fibrillar and globular proteins of amyloid are closely connected with polysaccharides.

stages of *Amyloidosis*

- Amyloidosis morphogenesis, in accordance with V.V.Serov, goes through a number of stages :
- 1-stage transformation of reticuloendothelial system cells, plasmacytes and lymphocytes into amyloidoblasts,
- 2-stage amyloidoblasts' synthesis of amyloid's fibrillar component,
- 3-stage fibrils aggregation with amyloid framework formation,
- 4-stage amyloid fibrils combination with plasma components (proteins, glycoproteins, lipids, immune complexes, etc.) and glycosaminoglycans of main substance.

Classification of amyloidosis

- -generalized:
 - primary,
 - secondary,
 - hereditary,
 - senile;
- - localized amyloidosis includes
 - tumor like,
 - separate forms of hereditary amyloidosis,
 - cardiac,
 - insular,
 - cerebral amyloidosis of elderly people,
 - APUD-amyloidosis, etc.

Amyloidosis

■ *Localized amyloidosis* is characterized with nodular shape amyloid masses appearance, which are seen microscopically in one organ: lungs, larynx, skin, urinary bladder, tongue. Lymphocytic or plasmacytic infiltration is often observed surrounding amyloid masses being a proof of their immune origin.

■.

Amyloidosis

■ *Endocrine amyloidosis* is characterized with amyloid masses appearance in endocrine tumors: medullary carcinoma, pancreatic islets' tumors, pheochromocytoma, poorly differentiated gastric carcinoma; in islet of Langerhans at II type diabetes mellitus.

Amyloidosis

■ *Senile amyloid* is manifested in two variants:

- - amyloid depositing in the heart (in ventricles or auricle) and lungs, spleen, pancreatic gland of elderly people;
- - senile cerebral amyloidosis, when amyloid deposits in blood vessel walls and plaques of cerebral cells at Alzheimer's dementia

Amyloidosis

■ By etiology:

- - primary (idiopathic);
- - secondary (acquired, reactive);
- - hereditary (genetic);
- - senile.

Amyloidosis

■ The most often *secondary (acquired) amyloidosis* is observed. It occurs as complication of sicknesses accompanied by tissues decay: chronic abscesses,

- osteomyelitis,
- pulmonary tuberculosis,
- extensive burns,
- multiple bronchiectasis,
- chronic pneumonias,
- tumors disintegration.

Amyloidosis

secondary (acquired) amyloidosis

■ **Tissues decay products are absorbed in blood, hyper- and dysproteinemia develops.**

■ **During this process first of all discharge organs (kidneys) are littered, second – organs depositing blood (spleen, liver) and third turn – other organs (heart, skeletal muscles, adrenal glands, etc.). This causes intoxication and autoimmunization.**

Amyloidosis

of kidney

■ **In kidney amyloid accumulates in mesangium, capillary walls.**

■ *Macroscopically* kidneys enlarge, harden. Organ is pale on section, looks like wax or lard - “lardaceous kidney”.

Amyloidosis

of kidney

■ **Renal amyloidosis.** Kidney is enlarged, of hard consistence. Section surface is of wax-like, tallowy color. Cortical layer is of yellow-white color, incrassate. This kidney is named “large tallow kidney”.

Amyloidosis

of kidney

■ **Renal amyloidosis.** Specimen is colored with iodine-grune. Amyloid masses depositing is observed in glomerules. Capillary glomerules acuteness is decreased. There are homogenous masses (cylinders) in renal tubules' lumens

Amyloidosis

of spleen

■ **In spleen amyloid appears first as homogenous mass around vessels - “sago” spleen, later on in all the pulp – “lardaceous spleen”.**

Amyloidosis

of spleen

■ **Spleen amyloidosis.** Specimen is colored with gentian violet. Amyloid is deposited like it does in lymphatic follicles – “sago” spleen.

Amyloidosis

■ In heart,

■ skeleton

■ muscles amyloid

■ deposits mostly downstream vessels.

Amyloidosis

■ **Microscopically** in case hematoxylin and eosin coloration amyloid is represented with amorphous eosinophilic masses, and in case colored with Congo-red (specific coloration of amyloid) amyloid is colored in brick-red color.

Consequence of amyloidosis

■ is unfavorable,

■ the process is irreversible,

■ function of tissue or organ sharply decreases or completely stops,

■ for example, renal insufficiency at renal amyloidosis.

■

Thanks for your attention