Materials
for students for practical classes in pathological anatomy
at the Department of Pathological Anatomy

II year Faculty of Dentistry

Topic: "Immunopathological processes: hypersensitivity reactions. Auto-immune diseases (Hashimoto's struma, systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, periarteritis nodosa) (Topic 5, part 2) ".

1. The purpose of the lesson. To study the issues of etiology, pathogenesis, morphology, complications and outcomes of hypersensitivity reactions; as well as selected diseases as examples of autoimmune diseases.

2. Requirements for the level of the student for mastering the discipline - pathological anatomy. The student should know:

1. Determination of hypersensitivity reactions.

2. Immunopathological features and morphological manifestations of hypersensitivity reactions of I-IV types.

3. Definition of autoimmune diseases.

4. Definition, etiology, pathogenesis, morphological manifestations, complications and outcomes of autoimmune diseases on the example of Hashimoto's struma, systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, periarteritis nodosa.

Theoretical aspects.

There are 4 main types of pathological conditions of the immune system: 1) hypersensitivity reactions, which are immunological tissue damage; 2) autoimmune diseases, which are immune responses directed against one's own body; 3) syndromes of immune deficiency arising from a congenital or acquired defect in the normal immune response; 4) amyloidosis.

Immune tissue damage (hypersensitivity reactions)

Contact of the body with the antigen leads to the development of not only a protective immune response, but also reactions that damage tissues.

Hypersensitivity reactions can be initiated by the interaction of an antigen with an antibody or by cellular immune mechanisms. Immune reactions that damage tissues can be associated not only with exogenous, but also endogenous antigens.

Type I hypersensitivity reactions (anaphylactic type) can be local or systemic. A systemic reaction occurs in response to intravenous administration of an antigen to which the host has been sensitized. Local reactions depend on the site of penetration of the antigen and are manifested in limited skin edema (skin allergy, urticaria), nasal and conjunctival discharge (allergic rhinitis and conjunctivitis), hay fever, bronchial asthma or allergic gastroenteritis (food allergy). The development of type I hypersensitivity reactions in humans is provided by IgE. IgE antibodies formed in response to an allergen attack mast cells and basophils, which have highly sensitive Fc receptors. Upon repeated contact of mast cells and basophils sensitized with cytophilic IgE antibodies with a specific antigen, mediators responsible for clinical manifestations are released.

Systemic anaphylaxis develops after administration of heterologous proteins, such as antisera, hormones, enzymes, polysaccharides, and some drugs, such as penicillin. The severity of the condition depends on the level of prior sensitization. Pathological examination reveals edema and hemorrhages in the lungs in some patients, while others have acute emphysema of the lungs with dilatation of the right ventricle of the heart.

Local anaphylaxis. This condition is sometimes referred to as atopic allergy. About 10% of the population suffers from local anaphylaxis, which occurs in response to allergens entering the body: pollen, animal dandruff, house dust, etc. Diseases based on local anaphylaxis include urticaria, angioedema, allergic rhinitis (hay fever) and some forms of asthma. There is a familial predisposition to this type of allergy.

Type II hypersensitivity reactions. In type II hypersensitivity reactions, antibodies appear directed against their own tissues, which act as antigens. There are three antibody-dependent mechanisms for the development of reactions of this type.

Complement-dependent reactions. There are two mechanisms by which antibodies and complement can induce type II hypersensitivity: *direct lysis* and *opsonization. In the first case*, the antibody (IgM or IgG) reacts with the antigen on the cell surface, causing the activation of the complement system. This triggers the membrane-attacking complex (MAC), which disrupts the integrity of the membrane, "perforating" the lipid layer. *In the second case*, the cells are phagocytosed after fixing the antibody or C3b component of the complement to the cell surface (opsonization). In this variant of type I hypersensitivity, blood cells (erythrocytes, leukocytes and platelets) are most often targeted as targets, but antibodies can also be directed against extracellular structures, for example, against the glomerular basement membrane.

Antibody-dependent cellular cytotoxicity is not accompanied by complement fixation, but it causes leukocyte cooperation. Target cells coated with IgG antibodies at low concentrations are destroyed by nonsensitized cells that possess Fc receptors. These cells bind target cells using receptors for the IgG Fc fragment, and cell lysis occurs without phagocytosis. This type of cytotoxicity involves monocytes, neutrophils, eosinophils, and NK cells.

Antibody-mediated cell dysfunction. In some cases, antibodies directed against receptors on the surface of cells disrupt their function without causing cell damage or inflammation. For example, in myasthenia gravis, antibodies react with acetylcholine receptors in the motor end plates of skeletal muscle, damaging neuromuscular transmission and thus causing muscle weakness.

Type III hypersensitivity reactions (associated with immune complexes). The development of type III hypersensitivity reactions is associated with antigen-antibody complexes formed as a result of antigen-antibody binding in the bloodstream (circulating immune complexes) or outside the vessels (in situ immune complexes). Circulating immune complexes cause damage when they enter the blood vessel wall or filter structures (glomerular filter in the kidney).

There are two types of immunocomplex damage that occur when an exogenous antigen (foreign protein, bacteria, virus) enters the body and when antibodies are formed against its own antigens. Diseases caused by immune complexes can be generalized if immune complexes are formed in the blood and are deposited in many organs, or associated with individual organs such as the kidneys (glomerulonephritis), joints (arthritis) or small blood vessels of the skin (local Arthus reaction).

Systemic and munocomplex disease. One of its varieties is acute serum sickness resulting from repeated administration of large doses of foreign blood serum used for passive immunization.

The pathogenesis of systemic immunocomplex disease consists of three phases:

- the formation of antigen-antibody complexes in the blood;
- deposition of immune complexes in various tissues;
- inflammatory response.

The first phase begins with the entry of the antigen into the bloodstream and the production of antibodies. Approximately 5 days after the administration of the serum, antibodies are formed against its components, which, while still in the bloodstream, form antigen-antibody complexes.

In the second phase, these complexes are deposited in various tissues. This deposition is influenced by the following factors: the charge of the immune complexes (anionic versus cationic), the valence of the antigen, the avidity (degree of affinity of antibodies to the antigen) of the antibody, the affinity (relationship) of the antigen to the components of various tissues, the three-dimensional structure of the complexes (lattice), and hemodynamic factors. Most often, immune complexes are deposited in the renal glomeruli, joints, skin, heart, serous membranes and small blood vessels. In order for these complexes to leave the circulatory system and settle in the tissues, it is necessary to increase the permeability of the vascular bed. Once the complexes are deposited in the tissues, they initiate an acute inflammatory reaction.

In the third phase (approximately 10 days after the administration of the antigen), clinical manifestations of the disease are observed, such as fever, urticaria, arthralgias, enlarged lymph nodes and proteinuria. Following the deposition of immune complexes, the complement system is activated with the formation of its biologically active components. This activation is

accompanied by pro-inflammatory effects. Phagocytosis of antigen-antibody complexes by leukocytes leads to the release or formation of various additional pro-inflammatory substances, including prostaglandins, vasodilating proteins and chemotactic substances. As a result, vasculitis, glomerulo-nephritis, arthritis, etc. develop.

The morphological picture of immunocomplex damage is dominated by acute necrotizing vasculitis. For example, affected kidney glomeruli are characterized by hypercleo-accuracy (a large number of cells) as a result of swelling and proliferation of endothelial and mesangial cells, as well as infiltration by neutrophils and monocytes. With immunofluorescence microscopy, immune complexes are visible as granular deposits of immunoglobulin and complement, and under an electron microscope - in the form of electron-dense deposits (deposits) along the glomerular basement membrane.

Chronic serum disease occurs with repeated or prolonged exposure to antigen. Constant antigenemia is necessary for the development of chronic immune complex disease, since immune complexes are most often deposited in the vascular bed. For example, systemic lupus erythematosus is associated with long-term preservation (persistence) of autoantigens. Often, however, despite the presence of characteristic morphological changes and other signs that indicate the development of an immune complex disease, the antigen remains unknown. This situation is typical for rheumatoid arthritis, periarteritis nodosa, membranous nephropathy and some vasculitis.

Local immunocomplex disease (Arthus reaction) is expressed in local tissue necrosis resulting from acute immunocomplex vasculitis. This process can be induced experimentally by intradermal administration of antigen to an immune animal that already has circulating antibodies against the antigen. Due to the excess of antibodies, when the antigen enters the vascular wall, large immune complexes are formed, which cause an inflammatory reaction. Arthus's reaction develops within a few hours and reaches a peak 4-10 hours after injection, when a zone of visible edema with hemorrhages appears.

Immunofluorescence microscopy reveals complement, immunoglobulins and fibrinogen deposited in the walls of blood vessels. Fibrinoid vascular necrosis is described in light-optical examination. Vascular rupture leads to local hemorrhage, but thrombosis is most often observed, contributing to the development of local ischemic damage.

IV type of hypersensitivity (cell-mediated). These reactions are caused by specifically sensitized T-lymphocytes.

Type IV includes the classic delayed hypersensitivity reactions induced by CD4+ T cells and direct cellular cytotoxicity mediated by CD8 + T cells. This is the main type of immune response to various intracellular infectious agents, especially mycobacterium tuberculosis, as well as to many viruses, fungi, protozoa and parasites. Contact skin sensitivity to chemicals and rejection reactions are other examples.

Two variants of type IV hypersensitivity reactions are described.

Delayed type hypersensitivity (HRT). An example is the reaction to intradermal tuberculin, a component from the walls of mycobacterium tuberculosis. In a sensitized person, after 8-12 hours, redness and induration appear at the injection site, and the peak of the reaction occurs after 24-72 hours. In highly sensitized patients, necrosis develops in the injection zone.

Light-optically HRT is characterized by the accumulation of mononuclear cells in the subcutaneous tissue and dermis (mainly around small veins and venules) with the appearance of characteristic perivascular cuffs. An increase in vascular permeability is associated with the formation of pores between endothelial cells. The release of plasma proteins outside the vascular bed increases dermal edema and is accompanied by the deposition of fibrin in the interstitium. CD4 + T cells predominate in the damaged areas.

With persistence of the antigen, macrophages are transformed into epithelioid cells surrounded by a shaft of lymphocytes - a granuloma is formed. This type of inflammation is characteristic of type IV hypersensitivity and is called granulomatous inflammation.

T-lymphocyte-mediated cytotoxicity. In this state, sensitized CD8 + T cells destroy target cells that carry antigen (cytotoxic lymphocytes - CTL). T cells that respond to histocompatibility antigens fixed to the cell surface play an important role in transplant rejection. They are also involved in protecting against viral infections. In cells infected with a virus, viral peptides bind to class I molecules of the major histocompatibility complex (MHC) and are transported in the form of complexes to the cell surface. This complex is recognized by cytotoxic CD8 + T cells. The lysis of infected cells is completed before the virus replicates, which leads to the destruction of the latter. It is believed that many tumor antigens are present on the cell surface, and CTLs are involved in anti-tumor immunity.

Graft rejection. The graft rejection reaction is associated with the recognition of the transplanted tissue by the host as foreign. The antigens responsible for rejection are the HLA antigens. Graft rejection is a complex process, during which both cellular immunity and circulating antibodies are important.

Autoimmune diseases

Some human diseases are caused by the development of an immune response directed against their own antigens.

There are three main signs of autoimmune diseases:

1) the presence of an autoimmune reaction;

2) the presence of clinical and experimental data that such a reaction is not secondary to tissue damage, but has a primary pathogenetic significance;

3) the absence of other definite causes of the disease.

There are autoimmune diseases in which the action of autoantibodies is directed against a single organ or tissue and, as a result, local damage develops. For example, in Hashimoto's thyroiditis, antibodies are absolutely specific for the thyroid gland. In systemic lupus erythematosus, autoantitels react with the constituent parts of the nuclei of various cells. In Goodpasture's syndrome, antibodies against the basement membrane of the lungs and kidneys cause damage only in these organs. The pathological anatomy of individual autoimmune diseases will be discussed in the chapters devoted to diseases of the corresponding organs or organ systems.

3. Lesson plan

Macropreparations

1. To study the reaction of type II hypersensitivity according to the macroscopic picture. Describe the macrodrug "**Large variegated kidney**" (subacute glomerulonephritis). Pay attention to the size, consistency, color of the kidney surface and on the cut.

2. Examine Hashimoto's goiter in a macroscopic picture. Describe" **the Hashimoto's Goiter**" macropreparation. Pay attention to the size and surface of the gland, consistency, type of tissue in the section.

Micropreparations

1. To study the reaction of type I hypersensitivity by the microscopic picture. Describe the micropreparation "**Bronchial biopsy in bronchial asthma**" (staining with hematoxylin and eosin). Pay attention to the blood filling and permeability of the vessels of the mucous membrane, the basement membrane of the epithelium, the mucous glands, the composition and localization of the cellular infiltrate, the contents of the bronchus.

2. To study the reaction of type III hypersensitivity by the microscopic picture. Describe the micropreparation "**Lupus nephritis**" (staining with hematoxylin and eosin). Pay attention to the necrosis of the vascular loops of the glomeruli, the thickness of the basement membranes of the capillaries, blood clots in the lumen of some capillaries, changes in cell nuclei.

3. To study the reaction of type IV hypersensitivity on the microscopic picture. Describe the micropreparation "**Viral chronic active hepatitis**" (staining with hematoxylin and eosin). Pay attention to the thickness of the portal tracts, localization and cellular composition of the infiltrate, localization and size of foci of necrosis of hepatocytes, apoptotic bodies.

4. To study the reaction of type IV hypersensitivity according to the microscopic picture. Describe the micropreparation "**Leprosy granuloma**" (staining with hematoxylin and eosin, according to Tsi-lu - Nielsen). Pay attention to the localization and cellular composition of the infiltrate, mark the large macrophages - Virchow's leprosy cells. To detect in the cytoplasm of these cells when staining according to Ziehl-Nielsen the accumulation of the pathogen.

5. Examine Hashimoto's goiter by a microscopic picture. Describe the micropreparation "**Hashimoto's Goiter**" (staining with hematoxylin and eosin). Pay attention to the localization and cellular composition of the infiltrate, the state of the parenchyma.

Electronograms

1. To study fibrinoid necrosis using electron microscopy. Describe the electronogram "**Fibrinoid necrosis**". Pay attention to the state of collagen fibrils, the accumulation of fibrin in the necrosis zone.

2. To study the effect of a lymphocyte on a hepatocyte in viral chronic active hepatitis using electron microscopy. Describe the electronogram "**Cellular cytolysis in chronic viral hepatitis B**". Pay attention to the contact of the killer lymphocyte with the hepatocyte, changes in the cytoplasmic membrane of the hepatocyte.

Situation case.

Situation case 1

Patient A., 75 years old, suffering from an atopic form of bronchial asthma, died in a state of asthmatic status from acute pulmonary heart failure.

Questions to the situational case 1

1. What pathological process has developed in this patient in the lungs? 2. What is the pathogenesis of anaphylactic reaction in the lungs?

3. Explain if this reaction is local or general?

4. Describe the micropreparation of the lungs of this patient.

5. With what pathological processes should this pathological process in the bronchi be differentiated?

6. What is the role of mast cells in this process? List the main mediators of mast cells.

Situation case 2

Patient B. with Goodpasture's syndrome and lung damage died from rapidly progressing chronic renal failure.

Questions to the situation case 2

1. Name and describe the microscopic changes in the kidneys that were the cause of the patient's death.

2. Explain the pathogenesis of renal and pulmonary pathology.

3. Another name for Goodpasture's syndrome in the lungs.

4. What is the method of laboratory diagnosis of Goodpasture's syndrome?

5. What pigment accumulates in the lungs and by what reaction is it detected in histological preparations?

Situation case 3

Patient P., 28 years old, consulted a doctor about an increase in body temperature to 39-40 ° C, increasing weakness, headache, sleep disorders, appetite, the appearance of pain in muscles and joints, reddish eruptions on the skin of the face in the form of a "butterfly", in the upper half of the chest in the form of a "neckline". A blood test revealed LE cells.

Questions for situation case 3

1. What disease can be suspected in the patient?

2. Explain what are LE cells?

3. What other blood changes will confirm the diagnosis?

4. What is the pathogenesis of systemic lupus erythematosus?

5. The patient was treated, however, after several years persistent proteinuria appeared in the urine. What changes in the kidneys can cause this symptom? Describe these changes.

6. Explain the pathogenesis of lupus nephritis?

Situation case 4

Patient R., 40 years old, turned to the outpatient department with complaints about the disc-fort in the neck, chilliness, drowsiness, lethargy, memory loss, decreased ability to work, dry skin, fragility and hair loss on the head ... The anamnesis was normal. Heredity for endocrine pathology is not burdened. On examination, the thyroid gland is slightly enlarged and dense.

Questions for situation case 4

1. What research is advisable to conduct to clarify the diagnosis?

2. The level of thyroid-stimulating hormone (TSH) is increased during repeated studies, T3 and T4 are normal. A cytological examination of the material obtained with a fine-needle biopsy revealed a large number of lymphoid cells and B cells. What is the presumptive diagnosis? How else can you confirm it?

3. Describe the appropriate micropreparation.

Literature to the Topic 5

Basic literature:

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Additional literature:

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