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

II year Faculty of Dentistry

Topic: "Immunopathological processes. Immunodeficiency states. Amyloidosis. Morphology of Immunogenesis Disorders (Topic 5, Part 3) ".

1. The purpose of the lesson. Study the morphological and immunological primary and secondary immunodeficiencies; to study the issues of etiology, pathogenesis, morphogenesis, complications and outcomes of various types of amyloidosis, especially the morphology of disorders of immunogenesis.

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

1. Terms - immunodeficiency states, primary immunodeficiency syndromes (primary immunodeficiencies), secondary immunodeficiency syndromes (secondary immunodeficiencies), acquired immunodeficiency syndrome (AIDS), opportunistic infections, amyloid, amyloidosis, primary amyloidosis, old familial amyloidosis.

2. Questions of etiology, pathogenesis, morphology of various types of amyloidosis; the essence and morphological manifestations of primary and secondary immunodeficiencies; questions of etiology, pathogenesis, morphology of acquired immunodeficiency syndrome (AIDS).

3. Characteristic changes in internal organs in amyloidosis; morphological features of changes in the organs of the immune system in primary immunodeficiencies; clinical and morphological characteristics of the stages of AIDS.

4. Morphology of impaired immunogenesis: changes in the thymus with impaired immunogenesis (age-related and accidental involution, hypopalsia and hyperplasia of the thymus, thymic-lymphatic state); changes in peripheral lymphoid tissue with impaired immunogenesis.

Theoretical aspects.

1. Immunodeficiency states.

Immunodeficiencies are divided into *primary*, which are mostly hereditary, and *secondary* (acquired), associated with complications of infectious diseases, impaired absorption, aging, side effects of immunosuppression, radiation, chemotherapy, and other autoimmune diseases.

Primary immunodeficiency syndromes represent a decrease in the intensity of the immune response up to its absence due to impaired development of the immune system, both genetically determined and associated with exposure to various harmful factors during intrauterine development.

The main manifestations of congenital immunodeficiencies:

1) infectious diseases mainly of systems and organs in contact with the external environment;

2) tumor diseases, mainly of the lymphoid system;

3) autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, hemolytic autoimmune anemia, etc.

One of the main criteria of congenital immunodeficiency is a change in the mass of thymus - a decrease in it by 5-10 times or an increase by 3-4 times or more.

Variants of congenital immunodeficiencies:

1) combined immune deficiency;

2) insufficiency of cellular immunity;

3) lack of humoral immunity;

4) unclassified immunodeficiencies;

5) immunodeficiencies associated with a defect in the phagocytic system.

Combined immune deficiency is characterized by a pronounced suppression of the function of T and B cells; usually associated with a dysfunction of the central organs of the immune system.

Varieties of combined immune deficiency:

1*) severe combined immunodeficiency (Swiss type of immune deficiency)* - transmitted in an autosomal recessive manner; microscopic picture of the thymus - the lobules consist of the reticular stroma, the reticuloepithelium is underdeveloped, the thymic bodies are either completely absent, or single, small, there are very few lymphocytes, the division into cortical and medullary layers is not determined; microscopic picture of lymphoid tissue (lymph nodes, spleen) - follicles are not developed, zoning in the lymph nodes is not distinguishable, the tissue of the nodes is represented by reticular stroma, myeloid elements and lymphocytes in very small numbers, pronounced deficiency of mature lymphocytes, plasma cells are absent;

2) *Louis-Bar syndrome (ataxia-telangiectasia)* - transmitted in an autosomal recessive manner, characterized by a deficiency of T-helpers, as well as dysfunction of B-cells; there is a sharp decrease in the size of the thymus, sometimes its partial replacement with adipose tissue, its lobules are very small, without signs of epithelium differentiation, thymic bodies are not detected, peripheral lymphoid organs - a decrease in the number of lymphocytes;

3) *Wiskott-Aldrich syndrome* - transmitted by a recessive type linked to the X chromosome; the morphology of the thymus is diverse - from normal to severe dysplasia, in which a large number of calcified thymic bodies are found in the compact reticular stroma of the organ.

Lack of cellular immunity.

Variants:

1) *Di-Giorgi syndrome* (congenital aplasia or hypoplasia of the thymus) - characterized by agenesis or hypoplasia, sometimes ectopia of the thymus in combination with malformations of the cardiovascular system, face and parathyroid glands;

2) *Nezelof's syndrome* (alimphocytosis) - inherited in an autosomal recessive manner, characterized by lymphopenia with a significant decrease in the number of T-lymphocytes with a normal number of B-cells; Histologically, thymic dysplasia with an almost complete absence of lymphocytes and the presence of glandular structures is revealed, thymic bodies are absent;

3) *Immunodeficiency in Down syndrome* - characterized by lymphopenia with a relative increase in the activity of T-suppressors.

Lack of humoral immunity - the main disease in that group is *Bruton's disease* (congenital agammaglobulinemia - is transmitted by a recessive type linked to the X chromosome; characterized by a sharp decrease in the level of Ig in blood serum, the absence of formation of plasma cells in the body with complete preservation of reactions In families, the disease manifests itself in half of the cases. Spontaneous mutations are possible, heredity in such cases is not traced. The pathogenesis is not clear, it is believed that there are no precursors of B-lymphocytes. Characteristic are bacterial infections that develop at an early age, either up to 1 year of age, or after 4-5 years. There are repeated pneumonia with bronchiectasis, otitis media, meningitis, sepsis, the causative agents of which are gram-positive cocci. Vaccination and viral infections are unremarkable. Antibodies are not formed during immunization. Lymphopenia is not observed ...

Pathological anatomy.

Thymus: untimely fatty metamorphosis with a pronounced collapse of lobules, a decrease in the number of lymphocytes and the appearance of large areas of adipose tissue both in the interlobular connective tissue septa and in the parenchyma of the organ. Thymic bodies are not formed correctly, or may be absent.

Lymph nodes: no follicles and no cortical zone, but only a T-dependent paracortical zone.
Spleen: Very small follicles may be observed, however, light cents are missing. Plasma cells are not detected anywhere. Particularly indicative is the complete absence of plasma cells in the intestinal mucosa (normally found in large numbers). The absence of plasma cells can be established during life with a biopsy of the rectal mucosa. Along with the absence of plasma cells in the mucous membrane, abscesses are often found with an accumulation of decaying leukocytes in crypts.

Secondary immunodeficiencies are not associated with a genetically mediated block of any link of immunity; they develop under the influence of a wide variety of pathological processes that affect the initially unchanged immune system. Secondary immunodeficiencies can cause infectious diseases of parasitic, bacterial and viral etiology, diseases associated with

malnutrition, malignant neoplasms, kidney diseases, metabolic diseases, as well as diseases caused by prolonged use of hormones and cytostatics. From a morphological point of view, the thymus has IY-Y phases of accidental transformation, and in the peripheral organs of immunogenesis, the devastation (delimphotization) of structural and functional zones is observed.

Acquired Immunodeficiency Syndrome (AIDS) is an infectious disease caused by the Human Immunodeficiency Virus (HIV), a retrovirus belonging to the lentivirus family. The main targets for HIV are 1) the immune system and 2) the central nervous system.

The immunopathogenesis of AIDS is characterized by:

1) the development of profound immunosuppression, which is mainly associated with a pronounced decrease in the number of CD4 + T cells, which causes a change in the CD4 / CD8 ratio in the peripheral blood;

2) infection of monocytes and macrophages, which turn into a "factory" for the production of viruses and a reservoir for their storage;

3) the ability of macrophages to transport the virus throughout the body, especially to the nervous system;

4) a decrease in the number of peripheral blood monocytes, a decrease in antimicrobial activity, chemotaxis, secretion of IL-1, TNF;

5) damage to the function of B-lymphocytes (development of hypergammaglobulinemia and circulating immune complexes associated with polyclonal activation of B cells).

Disease development mechanisms:

1) death of infected CD4 + T cells;

2) a decrease in the number of immature precursors of CD4 + T cells (associated with their direct infection in the thymus, as well as infection of cells that secrete cytokines necessary for the differentiation of CD4 + T cells);

3) the formation of syncytium (giant cells) by fusion of infected and uninfected cells (with this, autoimmune destruction of both infected and uninfected CD4 + T cells occurs.

The course of AIDS consists of three phases reflecting the dynamics of the interaction of the virus with the host: 1) early acute phase (high level of virus formation, viremia, widespread seeding of lymphoid tissue, infection is controlled by an antiviral immune response); 2) the middle chronic phase (the period of relative containment of the multiplication of the virus, the immune system is intact, however, weak replication of the virus is observed mainly in the lymphoid tissue); 3) the final crisis phase (opportunistic infections, secondary tumors, signs of neurological disease).

2. Amyloidosis.

It is characterized by the appearance in the stroma of organs and in the walls of blood vessels of a complex protein amyloid, which is not normally found. Severe amyloidosis leads to parenchymal atrophy and organ sclerosis, which is accompanied by the development of their functional insufficiency. There are two main forms (amyloid from light chains - AL and linked amyloid - AA) and several small biochemical forms. For each type of fibrillar protein, precursor proteins normally found in blood have been identified. The heterogeneity of amyloid explains the diversity of its clinical and morphological forms, which can be independent diseases or complications of other diseases.

Microscopic diagnostics of amyloidosis:

1) when stained with hematoxylin and eosin, amyloid is represented by amorphous eosinophilic (pink) masses;

2) when Congo is colored red (specific coloring for amyloid), the amyloid is painted brick-red;

3) when viewing preparations stained with Congo red in a polarizing microscope, two colors are detected - dichroism: reddish and green-yellow glow on a black background;

4) when examining preparations stained with thioflavin S or T in a luminescent microscope, a specific yellow glow is detected, stained with thiazine red - red glow

5) In an electron microscope, amyloid consists of unbranched fibrils with a length of about 7.5-10.0 nm (F-component).

The classification of amyloidosis is based on the chemical structure of the amyloid molecule (AL, AA, ATTR) and clinical syndromes.

There are: 1) primary amyloidosis (the formation of AL-amyloid is characteristic, based on the development of plasma cell dyscrasia in patients with multiple myeloma);

2) reactive systemic (secondary) amyloidosis (formation of AA-amyloid is characteristic; associated with chronic inflammation, accompanied by tissue destruction; occurs in tuberculosis, bronchiectasis, chronic osteomyelitis, rheumatoid arthritis and other connective tissue diseases);

3) congenital familial amyloidosis (familial Mediterranean fever - an autosomal recessive variant - characterized by attacks of fever, polyserositis, amyloid is represented by the AA variant; autosomal dominant familial amyloidosis - is characterized by amyloid prolapse mainly in peripheral nerves, amyloid is represented by the ATTR variant);

4) amyloidosis associated with hemodialysis (occurs due to the loss of -microglobulin; characterized by deposits of amyloid deposits in the synovium of joints and tendons),

5) localized amyloidosis (amyloid deposits - in the form of nodules, only in one organ - most often in the lungs, larynx , skin, bladder, tongue and around the eyes), 6) endocrine amyloidosis (amyloid deposits - in some endocrine tumors - medullary carcinoma, pancreatic islet tumors, in the islets of Langerhans in type II diabetes mellitus),

7) amyloidosis of aging (senile cardiac amyloidosis and senile cerebral amyloidosis).

4. Changes in the thymus with impaired immunogenesis.

Age-related involution of the thymus is a decrease in the mass and volume of the parenchymal organ with age, a decrease in the production of hormones and T-lymphocytes. The volume and mass of the thymus parenchyma slightly increases in the first months of life, and then progressively decreases at a fairly high rate until the age of 40, after which the rate of involution slows down. The medullary zone decreases with age more than the cortex. In the thymus stroma, there is an overgrowth of adipose and connective tissue, the volume of which increases especially rapidly from the age of 10-25. Calcified forms are found among thymic bodies.

Accidental involution of the thymus is a morphological manifestation of the stereotypical response of the thymus to various adverse effects. Accidental involution reflects the gradually increasing process of suppression of the active functioning of the organ up to the onset of its acquired atrophy, which is equivalent to the state of acquired immunodeficiency syndrome.

Accidental involution is observed in various diseases of both non-infectious and non-infectious nature, with leukemias and other malignant tumors, with metabolic disorders in the body of various etiologies, with steroid and cytostatic drugs therapy, with the use of X-ray irradiation, the importance of cooling and hy- poxia.

Accidental involution is a progressive decrease in the mass, volume, and functional activity of the thymus. In children, the accidental involution of the thymus has a pronounced phase character, easily traced during histological examination. The beginning of the expanded involutive changes should be considered the II phase, which is characterized by the picture of the "starry sky" in the cortical substance, arising as a result of the increase in the number of macrophages in the cortex, the process of pronounced apoptosis of T-lymphocytes is also noted. The most characteristic feature of phase III is the inversion of layers and an increase in the number of thymic bodies with their appearance outside the medullary zone. In phase IV, due to the continuing death of lymphocytes, the medullary zone is emptied and the inversion of the layers is lost.

Thymic ones only take the form of homogeneous formations consisting of epithelial cells with a pronounced collapse of their network. Only a few lymphocytes remain. Thymic bodies are homogenized, with sharply flattened epithelial cells along the periphery, some of them are calcified. In phase V, coarsening and collagenization of the stroma increase. From the thymic lobules, in places, only narrow strands of cell accumulations remain with thymic bodies included in them, partially or completely calcified. Sclerosis and lipomatosis develop in the interlobular stroma and intralobular perivascular spaces.

3. Lesson plan

Macropreparations

1. **<u>Amyloidosis of the spleen</u>** - pay attention to the size of the organ, consistency, appearance and color in the section.

2. **Amyloidosis of the kidney** - pay attention to the size of the organ, consistency, appearance and color in the section.

Micropreparations

1. **Amyloidosis of the spleen** (staining with hematoxylin-eosin and Congo-red) - find deposits of amyloid masses and establish their localization, pay attention to the state of cells and intercellular substance of lymphoid follicles.

2. **Amyloidosis of the kidney** (Congo red) - find deposits of amyloid masses and establish their localization, pay attention to the condition of the tubules and stroma.

3. **Di Giorgi's syndrome** - pay attention to the characteristic changes in the thymus (lobules, stroma, cells).

4. **Lymph node in congenital agammaglobulinemia** - pay attention to the characteristic changes in the lymph node (lymphoid follicles, cells).

5. **Spleen in congenital agammaglobulinemia** - pay attention to the characteristic changes in the spleen (lymphoid follicles, red and white pulp, cells).

6. **Thymus in congenital agammaglobulinemia** - pay attention to the characteristic changes in the thymus (lobules, stroma, cells).

7. **Accidental transformation of the thymus** - pay attention to the characteristic changes in the thymus (lobules, stroma, cells).

8. **Age-related atrophy of the thymus** - pay attention to the characteristic changes in the thymus (lobules, stroma, cells).

9. **Lymph node in AIDS** - pay attention to the characteristic changes in the lymph node (lymphoid follicles, cells).

10. **Hypoplasia of T-dependent zones of the spleen** - pay attention to the characteristic changes in the spleen (lymphoid follicles, red and white pulp, cells).

Electronograms

1. **Amyloidosis of the eye** - pay attention to the fibrillar structure of amyloid.

Situation case.

Situation case 1

Patient S., 47 years old, has been suffering from rheumatoid arthritis for 20 years. During the last year, there was a progressive chronic renal failure, which was the cause of the patient's death. Autopsy: the kidneys are enlarged, pale yellow, with a greasy cut surface; the spleen is slightly

enlarged, small, dense, whitish specks are determined on the cuts in the spleen pulp; the liver is enlarged, dense, the liver tissue is light brown on the sections. Microscopic examination revealed homogeneous eosinophilic staining of vascular walls, glomeruli and stroma of the kidneys, spleen follicles, vascular walls and liver stroma.

Questions to the situation case 1:

1) What pathological process in the kidneys, liver and spleen can you think of?

2) What histochemical stains should be used to clarify the nature of the described pathological process?

3) What kind of the described pathological process is this?

Situation case 2

Patient K., 58 years old, suffered from Alzheimer's disease for the last several years, died of bilateral pneumonia. Microscopic examination of the brain substance revealed eosinophilically stained plaques and vascular walls; luminescent examination of preparations stained with thioflavin S revealed a yellow glow of plaques and vascular walls.

Questions to the situation case 2:

1) What pathological process took place in the brain?

2) What kind of the described pathological process is this?

3) What other types of the described pathological process do you know?

Situation case 3

A 7 month old child with inflammatory necrotic skin lesions died of sepsis. Autopsy: the mass of the thymus, lymph nodes, spleen is reduced by 7 times; microscopic examination of the thymus revealed the absence of thymic bodies, a meager number of lymphocytes, pronounced reticuloepithelium underdevelopment; lymph nodes and spleen - the absence of follicles and zoning, plasma cells, a small number of mature lymphocytes.

Questions for situation case 3:

1) What pathology of the immune system does the patient have? 2) What is the variety of the described pathology of the immune system (congenital or acquired)? 3) What is the type of the described pathology of the immune system? 4) What term can be used to describe changes in the thymus?

Situation case4

A 14-year-old boy died of generalized herpes infection. From blood tests: lymphopenia, Ig content is slightly reduced. Autopsy: a decrease in the mass of the thymus, a microscopic examination of which revealed glandular structures, the complete absence of thymic bodies, a sharp decrease in the number of lymphocytes; microscopic examination of lymph nodes and spleen - a sharp decrease in the number of lymphocytes, especially T-dependent zones, single plasmablasts and plasma cells.

Questions for situation case 4:

1) What pathology of the immune system does the patient have? 2) What is the variety of the described pathology of the immune system (congenital or acquired)? 3) What is the type of the described pathology of the immune system? 4) What term can be used to describe changes in the thymus?

Situation case 5

A 1.5-year-old child suffering from congenital hypoparathyroidism died of pneumocystic pneumonia. From blood tests: the amount of calcium in the blood is reduced, the level of phosphorus is increased, the number of lymphocytes in the peripheral blood is normal. Autopsy: hypertelorism, Mongoloid eye incision, small mouth, micrognathia, cleft uvula. Microscopic examination in the thymus in place of the lobules revealed adipose tissue and fibrous connective tissue, in the peripheral lymphoid tissue - devastation of the paracortical zones of the lymph nodes and periarterial zones of the spleen, lymphoid follicles with pronounced light centers; the parathyroid glands were not found.

Questions for situation case 5:

1) What pathology of the immune system does the patient have?

2) What kind of the described pathology of the immune system is it (congenital or acquired)?

3) What is the type of the described pathology of the immune system?

Situation case 6

Patient 0., 30 years old, consulted a doctor with complaints of weight loss, fever, diarrhea, vesicular rashes on the mucous membrane of the mouth, generalized enlargement of lymph nodes. From the anamnesis it is known that about a year ago the patient after a traffic accident was hospitalized, where he was repeatedly transfused with blood.

Questions for situation case 6:

1. What disease can be suspected in the patient? What is

specific diagnostics?

2. What is the most likely route of infection in this case?

3. Explain the mechanism of development of immunodeficiency in HIV infection.

4. What other cells can be affected by the virus?

5. Describe the changes in the lymph nodes in HIV infection.

6. List AIDS-associated diseases, explain the mechanism of their occurrence

Literature to the Topic

Basic literature:

1. "Basic pathology" Vinay Kumar, Ramzi S. Cotran, Stanley L. Robbins, 1997.

Additional literature:

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