Materials
for students for practical classes in pathological anatomy
at the Department of Pathological Anatomy
II year Faculty of Dentistry

Topic: "Disorders of chromo proteins metabolism (exogenous and endogenous pigments). Hemosiderosis and hemochromatosis. Jaundice. Disorders of nucleic acids metabolism. Pathological calcification. Formation of stones".

1. The purpose of the lesson. To study the issues of etiology, pathogenesis, morphology, complications and outcomes of disorders of pigment and minerals metabolism; to study the morphological features of pathological accumulation of endogenous and exogenous pigments.

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

1. Terms - hemosiderin, hemosiderosis, hemochromatosis, porphyria, hematoidin, hematins, (hemomelanin) malaria pigment, lipofuscin, melanin.

2. Questions of etiology, pathogenesis, morphology of hemosiderosis, hemochromatosis, porphyria, lipofuscinosis, hypo- and hypermelanosis.

3. Characteristic changes in internal organs in hemosiderosis, hemochromatosis, porphyria, lipofuscinosis, hypo- and hypermelanosis.

4. Types, causes, mechanisms of development and functional significance of disorders in the exchange of nucleoproteins.

5. Mechanisms of development and clinical and morphological characteristics of gout.

6. Pathological calcification: definition, types, morphological characteristics.

7. Formation of stones: examples, mechanisms.

Theoretical aspects.

I. Morphology of pathological accumulation of endogenous and exogenous pigments.

Pigments are colored substances of various chemical nature, which can be found in cells normally or accumulate in pathological conditions. Distinguish: exogenous and endogenous pigments.

Exogenous pigments include coal dust, which, entering the lungs, is captured by alveolar macrophages, through the lymphatic vessels it penetrates into the regional lymph nodes, where it is deposited in the form of a black pigment (anthracosis).

Endogenous pigments include lipofuscin, melanin, and some hemoglobin derivatives.

Endogenous pigmentation can be either acquired or hereditary.

Among the endogenous pigments are hemoglobinogenic, proteinogenic (tyrosinogenic) and lipidogenic.

Hemoglobinogenic pigments are various derivatives of hemoglobin that occur during the synthesis or breakdown of erythrocytes. Ferritin, hemosiderin, bilirubin and porphyrins are normally formed (porphyrins, being the precursors of heme, can be found in minimal amounts in blood and urine in normal conditions). Under pathological conditions, hematoidin and hematins are formed.

Ferritin is an iron protein containing the protein apoferritin and a trivalent iron atom in the composition of phosphate hydroxide. Ferritin molecules are formed intracellularly when iron ions bind to the protein apoferritin. Ferritin is detected in tissues using cadmium sulfate by the Klochkov method, as well as immunohistochemically using specific antisera. In practice, the histochemical method is most often used - the reaction of the formation of Prussian blue or the Prels reaction - a reaction to the detection of salts of iron (III) oxide with the help of iron-cyanide potassium and hydrochloric (hydrochloric) acid.

Hemosiderin is a ferritin polymerization product. According to its chemical structure, it is a colloidal iron hydroxide combined with mucoproteins of the cell. Normally, a small amount of hemosiderin is found in monocytic phagocytes of the bone marrow, spleen and liver. Hemosiderin is an intracellular pigment. Its synthesis takes place in cells called sideroblasts (in specialized organelles - siderosomes). Sometimes, such a large amount of hemosiderin accumulates in sideroblasts that the cells are destroyed and hemosiderin is free lying in the stroma of organs, where it is captured by macrophages (siderophages). In the cytoplasm of these cells, siderosomes are not detected. When stained with hematoxylin and eosin, hemosiderin is detected in the form of brown grains, and with the Perls reaction - in the form of greenish-blue granules (Prussian blue).

In the case of accumulation of catabolic pigment (formed during hemolysis), they usually speak of hemosiderosis.

A disease resulting from an increased intake of iron into the body and also accompanied by massive deposits of hemosiderin is called hemochromatosis.

Hemosiderosis - occurs with increased hemolysis - destruction of erythrocytes; can be local and general, or common.

Local hemosiderosis - occurs with extravascular hemolysis in the foci of hemorrhage: hemosiderin accumulates in the cells surrounding the hemorrhage: macrophages, leukocytes, endothelium, epithelium. An example of local hemosiderosis can be brown induration of the lungs, which occurs during chronic venous congestion in patients with chronic heart diseases (magpies, cardiosclerosis, etc.). *Macroscopically*: the lungs are enlarged, dense (induration), in section with numerous brownish blotches and interlayers of connective tissue. *Microscopically:* in the lungs, a large number of cells containing brown pigment are detected, found both in the stroma of the lung and in the lumens of the alveoli and bronchi. The interalveolar septa are significantly thickened due to the proliferation of connective tissue.

General hemosiderosis - occurs with intravascular hemolysis, developing: a) with diseases of the blood system (anemia, leukemia, congenital defects of erythrocytes and hemoglobin); b) in case of poisoning with hemolytic poisons; c) with infectious diseases (malaria, sepsis, relapsing fever, etc.); d) with transfusions of incompatible blood and Rh-conflict (hemolytic disease of the newborn). Hemosiderin appears initially and predominantly in mononuclear phagocytes of the spleen, liver, lymph nodes and bone marrow, as well as in macrophages scattered throughout other organs - in the skin, pancreas, kidneys, lungs. In the future, hemosiderin can appear in the cells of the parenchyma (hepatocytes), and in the stroma of organs and in the walls of blood vessels. As the pigment accumulates, the organs acquire a brown (rusty) color.

Idiopathic pulmonary hemosiderosis or Celen-Gellerstedt syndrome. It occurs in children aged 3-8 years and is characterized by repeated hemorrhages in the pulmonary parenchyma, followed by massive hemosiderosis and sclerosis, hemoptysis and the development of secondary iron deficiency anemia. In the lungs there is a typical pattern of brown induration, but there is no heart damage in patients.

Hemochromatosis - the disease is associated with an overload of the body with iron, which is de-ponded in the form of ferritin and hemosiderin mainly in the parenchymal elements of various organs, as a result of which they acquire a brown color. It is accompanied by damage to the parenchymal organs with the development of sclerosis and atrophy.

There are two forms of hemachromatosis: primary and secondary.

Primary (idiopathic) hemochromatosis is a hereditary disease from the thesaurismosis group, caused by an enzyme defect, in which iron absorption in the small intestine increases. The disease is transmitted in an autosomal recessive manner.

Morphology. At the stage of expanded changes, the most characteristic triad is liver cirrhosis (in most cases), diabetes mellitus (in 75-80%) and bronze skin pigmentation (in 75-80%). Secondary hemochromatosis - develops in the case of acquired deficiency of enzyme systems that provide absorption and metabolism of food iron.

Reasons: 1) excessive intake of iron from food, intake of iron-containing preparations, parenteral administration of iron (prolonged hemodialysis, etc.); 2) alcoholism; 3) repeated blood transfusions; 4) after resection of the stomach; 5) with hemoglobinopathies - hereditary diseases - sideroachrestic anemia, thalassemia, congenital atransferrinemia. Typical are liver damage (cirrhosis), pancreas (diabetes mellitus), myocardium - with the development of heart failure.

Bilirubin is the main bile pigment, the end product of hemolysis. With an excessive accumulation of bilirubin in the blood (more than 2-2.5 mg%), **jaundice** develops in the tissues (jaundice appears on the skin, sclera, mucous membranes, etc.).

Disruption of bilirubin metabolism is associated with a disorder of its formation and excretion. This leads to an increased content of bilirubin in the blood plasma and yellow coloration of the skin, sclera, mucous and serous membranes and internal organs - jaundice.

The mechanism of development of jaundice is different, which makes it possible to distinguish three types of it: suprahepatic (hemolytic), hepatic (parenchymal) and subhepatic (mechanical).

The causes of suprahepatic (hemolytic) jaundice are intravascular hemolysis when:

a. infections

b. intoxications

v. isoimmune disorders

d. autoimmune disorders

e. massive hemorrhages

Suprahepatic jaundice morphology:

1.increase in the blood of unconjugated bilirubin

2.in the urine, the urobilin content is sharply increased, there is no bilirubin

3.the feces are sharply colored in a dark color (pleochromia) due to the large amount of stercobilon

4.general hemosiderosis

5.Icteric coloration of the skin, sclera, mucous membranes with a lemon-yellow tint

Pallor of the skin and enlargement of the spleen (due to anemia) are often present

The causes of hepatic (parenchymal jaundice) - damage to hepatocytes with:

a. acute and chronic hepatitis b. cirrhosis of the liver c. medication damage d. autointoxication e. pregnancy with intrahepatic cholestasis f. enzymopathies with impairment of one of the phases of bilirubin metabolism.

Morphology of hepatic jaundice:

1.disorder of the uptake and conjugation of bilirubin by damaged hepatocytes an increase in the level of conjugated and unconjugated bilirubin in the blood

2.urobilin and bilirubin in urine

3.Dark colored feces (although less intense than with hemolytic jaundice)

4.jaundice with a reddish tinge

5.enlargement of the liver, sometimes an increase in the spleen

Subhepatic (mechanical) jaundice - obstruction of the bile ducts due to:

a. bile stone disease

b. biliary tract cancer

c. pancreatic head and / or duodenal papilla cancer

d. biliary atresia e. cancer metastases in periportal lumen.

Subhepatic jaundice morphology:

1.disorder of bile excretion a sharp increase in the blood of conjugated bilirubin

2. bilirubin in urine

3.Acholia feces (due to lack of stercobilinogen)

4.jaundice of a greenish tint

5.cholestasis:

a) stagnation of bile in the liver

Melanin is a brownish-black pigment synthesized in specialized structures - melanosomes in cells called melanocytes, from tyrosine under the action of the enzyme tyrosinase. The main histochemical method for identifying melanin is the argentaffin reaction, based on the ability of melanin to reduce an ammoniacal solution of silver nitrate to metallic silver (Masson-Fontana method). Melanin metabolism disorders are expressed in the development of widespread and local hyperpigmentation and hypopigmentation. They can be congenital and acquired.

Hyperpigmentation (hypermelanosis).

A) Common:

1) acquired widespread hypermelanosis develops in Addison's disease: the disease is associated with damage to the adrenal glands with tuberculosis, bilateral tumors or metastases, amyloidosis, autoimmune damage, hemochromatosis, etc.; with a decrease in the function of the adrenal glands, there is an increase in the synthesis of ACTH, which has a melanin-stimulating effect; the synthesis of melanin increases in the skin, it acquires a brown color (melasma), becomes dry, flaky; in the basal layers of the epidermis, the content of melanin in melanocytes and keratinocytes increases (epidermal cells into which melanin is transmitted through the processes of melanocytes), in the dermis, melanin is determined in melanophages; atrophy of the epidermis, hyperkeratosis are noted.

2) Congenital widespread hypermelanosis is observed in pigmented xeroderma (a hereditary disease in which the skin's sensitivity to ultraviolet rays increases); manifests itself as spotty

pigmentation of the skin with the occurrence of hyperkeratosis and edema; can lead to the development of malignant skin tumors.

B) Local hyperpigmentation is manifested in the form of freckles, dark brown spots - lentigo, benign melanocytic formations - nevi and malignant tumors - melanomas.

Hypopigmentation.

A) Widespread hypomelanosis, or albinism: associated with hereditary tyrosinase deficiency; manifests itself as white skin, colorless hair, red eyes.

B) Local hypopigmentation (more often acquired, less often congenital) are called vitiligo, or leukoderma.

Lipofuscin is an insoluble pigment, also known as aging pigment, from patching; forms golden brown granules in the cell; consists of polymers of lipids and phospholipids associated with protein. The accumulation of lipofuscin in cells is called lipofuscinosis. Lipofuscin most often accumulates in the cells of the myocardium, liver, skeletal muscles during aging or exhaustion, which is accompanied by the development of brown atrophy of organs: a) the heart becomes small, the amount of fatty tissue under the epicardium is significantly reduced, the vessels acquire a convoluted course, the myocardium is dense, brown in color; microscopy: the cardiomyocytes are reduced in size, granules of the brown pigment lipofuscin are visible in the cytoplasm, b) the liver is significantly reduced, its edge is sharp, the liver tissue is dense, brown; microscopy: the hepatic tracts are sharply thinned, in the cytoplasm of hepatocytes there are numerous brown granules of lipofuscin.

Pathological calcification

With pathological calcification, an abnormal loss of calcium salts occurs simultaneously with small amounts of iron, magnesium and other mineral salts. There are two forms of pathological calcification: dystrophic and metastatic.

Dystrophic calcification. With it, the level of Ca2 + in the blood does not change, calcium salts are deposited in areas of necrosis and sclerosis. Calcification occurs, for example, in fibrous plaques with decay (atheromatosis) with atherosclerosis (which is accompanied by damage to the intima of the aorta and large arteries), in the lungs during the healing of foci of caseous necrosis in tuberculosis. Focuses of calcification acquire a stony density and are called petrification. With aging and rheumatic diseases, calcium salts are deposited in the valves of the heart.

With dystrophic calcification, crystalline minerals are formed, consisting of calcium phosphate, in the form of apatite, similar to bone hydroxyapatite. The process of dystrophic calcification consists of two phases: initiation (nucleation) and propagation, develops both in cells and extracellularly. The initiation of intracellular calcification occurs in the mitochondria of deceased or dying cells, which accumulate Ca2 +.

Outside the cells, the initiation phase takes place in membrane-surrounded vesicles of about 200 nm in diameter, formed during cell aging or destruction. It is believed that Ca2 + is concentrated in these vesicles due to its affinity for acidic phospholipids contained in vesicles, and then phosphate groups formed as a result of the action of membrane-associated phosphatases are

attached to Ca2 +. This process is cyclical, as a result, microcrystals are formed, which gradually increase in size (phase of propagation or growth). The formation of crystals depends on the concentration of calcium and phosphorus ions in the extracellular spaces, the presence of mineral inhibitors, collagen and other proteins. Osteopontin, an acidic phosphoprotein involved in bone mineralization, can also play a role in the development of dystrophic calcification. Dystrophic calcification is usually a sign of damage, although it can also cause organ dysfunction, such as calcification of the heart valves and atherosclerosis.

Metastatic calcification. This process occurs in normal tissues with hypercalcemia. The causes of hypercalcemia are hyperparathyroidism, vitamin D intoxication, systemic sarcoidosis and other granulomatosis, hyperthyroidism, idiopathic hypercalcemia, Addison's disease (adrenocortical insufficiency), increased bone destruction associated with the formation of multiple myeloma or bone metastases, reduced cancer immobilization, and leukemia. In some cases, hypercalcemia also develops in severe renal failure with phosphorus retention, leading to secondary hyperparathyroidism.

Calcium salts are deposited in various tissues, but necessarily in the interstitium of the mucous membrane of the stomach, kidneys, lungs, myocardium, arteries and pulmonary veins. All these tissues, during their functioning, lose acid and become alkalized, which predisposes to metastatic calcification. Calcium salts can be in the form of non-crystalline amorphous deposits or the structure of hydroxyapatite crystals. Most often, mineral salts do not clinically cause organ dysfunction, however, massive calcification, for example, of lung or kidney tissue (nephrocalcinosis), can impair the function of these organs.

3. Lesson plan.

Macropreparations

1. **Pigmental nevus** - pay attention to the skin color characteristic of this disease, to the condition of the skin surface.

2. **Metastasis of melanoma in the liver** – pay attention to the color and sizes of metastatic foce in the liver, to the color of the liver.

3. **Anthracosis of the lung** – pay attention to color and consistency of the lung tissue.

4. **Brown myocardial atrophy** - to determine the size of the heart, as well as the color of the myocardium from the surface and on the cut, to characterize the state of the coronary arteries.

5. **Brown induration of the lung** - pay attention to the consistency of the organ, its appearance, the degree of airiness, the color of the organ in the section.

6. **Gallbladder stones** - pay attention to the size, shape, color, consistency and surface condition of the stones.

Micropreparations

1. **Anthracosis of the lung** - pay attention to the color, localization of inclusions (pigment), the state of the sinuses and tissue of the lymph node.
2. **Hemosiderosis of the liver (H&E)** - find capillaries that are sharply overflowing with blood, find brown pigment grains, mark its localization (intracellular, extracellular).
3. **Hemosiderosis of the liver (Prussian blue reaction)** - find capillaries that are sharply overflowing with blood, find blue pigment grains, mark its localization (intracellular, extracellular).
4. **Liver in obstructive jaundice** - pay attention to yellowish grains of bile pigment in the cytoplasm of hepatocytes; find dilated and filled with bile (bile clots) bile ducts; pay attention to focal parenchymal necrosis, stained with bile, accumulations of leukocytes in the necrosis zone.
5. **Calcareous metastases in the myocardium** (staining with hematoxylin and eosin) - pay attention to the type, color and localization of calcium salt deposits, the state of damaged cardiomyocytes, changes in the myocardial stroma, lack of a cellular reaction to calcium salt deposition.
6. **Calcinosis of the ovary vesseles** (staining with hematoxylin and eosin) - pay attention to the appearance, color and localization of calcium salt deposits, lack of cellular reaction to calcium salt deposition.
7. **Dystrophic calcification** - (staining with hematoxylin and eosin) - pay attention to the appearance, color and localization of calcium salt deposits, lack of cellular reaction to calcium salt deposition.

Situation cases.

Situation case 1.

Patient K., 48 years old, suffered from rheumatic heart disease (mitral stenosis) for a long time, died from progressive cardiovascular failure. Autopsy: the left ventricle of the heart is reduced in volume, the cusps of the mitral valve are sharply thickened, inactive, dense, gray-pink in color (similar to hyaline cartilage), cut with a crunch; lungs - enlarged, dense, brownish-red, histologically: in the lumens of the alveoli - erythrocytes, free-lying pigment of brownish-brown color, macrophages, in the cytoplasm of which the pigment is brownish-brown.

Questions: 1) What pathological process took place in the cusps of the mitral valve?

2) What histochemical stains should be used to identify the pigment found in the lungs?

3) What pathological process took place in the lungs?

4) What are the causes and mechanisms of the development of the pathological process in the lungs?

Situation case 2.

Patient M., 45 years old, suffered from diabetes mellitus for a long time, died of intoxication due to the developed gangrene of the right lower limb. A histological examination of the autopsy material of the kidneys revealed small PIC-positive drops in the epithelium of the renal tubules; in the cytoplasm of hepatocytes - colorless vacuoles when stained with hematoxylin and eosin, when stained with Sudan III - orange-red vacuoles; in the nuclei of hepatocytes - SHIK-positive inclusions.

Questions: 1) What pathological process took place in the kidneys?

2) What pathological process took place in the cytoplasm of hepatocytes?

3) What pathological process took place in the nuclei of hepatocytes?

4) What are the mechanisms of the described pathological processes in the kidneys and liver?

Situation case 3.

Patient S., 39 years old, has a tumor of the sigmoid colon. A fragment of the tumor was taken for histological examination, during which a diagnosis was made of adenocarcinoma (a malignant tumor from the glandular epithelium of the intestine), the histological description of the tumor indicated the presence of a weakly stained eosinophilic substance in which the tumor cells are located, staining with mucycarmine is positive.

Questions: 1) What pathological process took place in the tumor tissue?

2) What other histochemical stain could be used to clarify the nature of the pathological process?

3) What is the possible mechanism for the development of this pathological process?

Situation case 4.

A histological examination of the hemorrhage site revealed that in the center of the hemorrhage there are bright orange plates, at the hemorrhage periphery there are accumulations of brownish-brown pigment.

Questions: 1) What pigments were found in the area of hemorrhage?

2) What histochemical stains should be used to identify the described pigments?

Situation case 5.

Patient Sh., 69 years old, suffered from gastric cancer with metastases to the internal organs for a long time, died from cancer cachexia. Autopsy: the heart is reduced in size, dense, brown in color; histological examination in the cytoplasm of cardiomyocytes revealed yellow pigment granules.

Questions: 1) What pathological process took place in the myocardium?

2) What are the causes and mechanisms of development of the described pathological process?

Situation case 6

Patient V., 65 years old, consulted a doctor with complaints of constipation, loss of appetite, convulsions, frequent urination, including at night. The analysis of blood in the serum revealed a persistent increase in the total calcium content up to 11 mg%; further examination revealed signs of osteoporosis, hypertension, bradycardia, slight azotemia, microhematuria; in the blood serum, the level of parathyroid hormone is increased. An ultrasound examination revealed an increase in one of the parathyroid glands. The patient underwent surgery, after which the level of calcium in the blood returned to normal.

Questions for situation case 6

1. Name the cause of hyperparathyroidism.

2. What operation was performed on the patient to normalize the total calcium levels in the blood?

3. Explain the mechanism of action of parathyroid hormone.

4. What pathological processes are associated with the symptoms of kidney damage? Describe the appropriate drugs.

5. What other organs, besides the kidneys, can be affected in the presence of hypercalcemia? Name the pathological process, describe the microscopic manifestations using the example of the myocardium.

Literature to the Topic 3

Basic literature:

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Additional literature:

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