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Necrosis and apoptosis. Infarction. Biological death.

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1. Purpose: to consider the main types of cell death: necrosis, apoptosis, their significance for the body. Consider the main morphological (macro- and microscopic) signs of necrosis and apoptosis. To study the varieties of heart attacks, their morphological and clinical significance for the body.
2. Requirements for the student's level of mastering the discipline - pathological anatomy.
Theoretical aspects: Damage and death of cells and tissues. There are two types of cell death - necrosis and apoptosis. Necrosis is the most common type of cell death due to exogenous influences, including ischemia and chemical stimuli. It is manifested by a sharp swelling or destruction of the cell, denaturation and coagulation of cytoplasmic proteins, destruction of cellular organelles.

Apoptosis - the natural death of a cell - serves to eliminate (eliminate) unnecessary cell populations during embryogenesis and during various physiological processes. The main morphological feature of apoptosis is the condensation and fragmentation of chromatin. Although the mechanisms of necrosis and apoptosis are different, there are many similarities between these processes.
There are three main types of cell damage:
1) ischemic and hypoxic;
2) caused by free oxygen radicals;
3) toxic.
In classical morphology, non-lethal cell damage is called dystrophy, or reversible cell damage. Light-optically distinguish two types of such changes: swelling and fatty changes. Swelling develops when cells are unable to maintain ionic and fluid homeostasis. Fatty changes can also be a sign of reversible cell damage. Light-optically, they are characterized by the appearance of small or large lipid inclusions in the cytoplasm. They are found in hypoxic and various forms of toxic damage, mainly in cells involved in or dependent on fat metabolism, such as hepatocytes and myocardiocytes.
Necrosis is a spectrum of morphological changes that develop following cell death in living tissue. This is the result of the destructive action of enzymes on a plaquely damaged cell. In fact, two competing processes develop: enzymatic cell digestion and protein denaturation.
Macroscopic signs of necrosis can manifest themselves in different ways: they depend on the originality of the organ in which necrosis occurs, as well as on the nature of the damaging factor.
Microscopic signs relate to both the nucleus and the cytoplasm of cells, as well as the extracellular matrix.
Kernel changes include:
- karyopyknosis - shrinking of the nuclei due to the condensation of chromatin;
- karyorexis - disintegration of nuclei into lumps;
- karyolysis - dissolution of the nucleus due to the activation of hydrolases (ribonuclease and deoxyribonuclease; RNase and DNase).
Changes in the cytoplasm are expressed in:
- plasma coagulation - protein denaturation and coagulation with the appearance of bright pink lumps in the cytoplasm;
- plasmorexis - the decay of the cytoplasm into lumps;
- plasmolysis - melting of the cytoplasm.
Changes in the extracellular matrix are manifested:
- in the splitting of reticular, collagen and elastic fibers under the influence of proteases, elastases, collagenases. Necrotic masses are often impregnated with fibrin with the development of fibrinoid necrosis.

There are 5 types of necrosis: coagulation, colliquation (wet), gangrenous (gangrene), caseous (cheesy, cheese-like) and fatty (enzymatic, or steatonecrosis).
Coagulation necrosis is the maintenance of the general contours of the focus for at least several days. In this type of necrosis, damage or subsequently increasing intracellular acidosis denature not only structural proteins, but also enzymes and thereby block proteolysis of the cell. Coagulation necrosis is characteristic of hypoxic tissue death in all organs except the brain.
One of the most common types of such necrosis is a heart attack. Heart attack is tissue necrosis that occurs when blood circulation is impaired (vascular, ischemic necrosis). A heart attack develops as a result of thrombosis, embolism, prolonged spasm of the arteries or functional overstrain of organs in conditions of insufficient blood supply (the latter applies only to myocardial infarction).

Colliquation (wet) necrosis occurs as a result of autolysis or heterolysis, is more common in lesions by bacterial infectious agents and is caused by the diluting action of proteolytic leukocyte enzymes. As for wet necrosis during hypoxic death of brain tissue, the reasons for its appearance remain unclear. The nature of such necrosis is explained by the fact that the brain tissue is rich in water and the processes of autolysis in it prevail over coagulation changes.
Gangrene is a black or dark brown necrosis that develops in the tissues, directly or through the anatomical channels in contact with the external environment. In addition to limbs, gangrene occurs in the lungs, intestines, cheeks, and elsewhere. The dark color of gangrenous tissue is caused by iron sulfite, which is formed from iron, hemoglobin and hydrogen sulfide in the air. There are three morphological types of gangrene: dry, wet, and bedsore.
Dry gangrene is accompanied by mummification, a well-pronounced zone of demarcation inflammation, often occurs in the lower extremities. Macroscopically necrotic tissues (more often foot tissues) are reduced in volume, dry, black, and the demarcation zone is well defined.
Wet gangrene develops when dead tissue is infected with bacteria, usually anaerobic bacteria (for example, from the Clostridium group). With wet gangrene, the tissue swells, becomes edematous, the demarcation zone is not defined. This gangrene occurs in the intestines, lungs, uterus, limbs.
A bedsore is a type of dry or wet gangrene that occurs as a result of trophoneurotic disorders in weakened bedridden patients in areas of the body exposed to the greatest pressure.
Gas gangrene is rare. With it, bubbles with hydrogen sulfide, usually produced by the microbe Clostridii ,uersinii, are inside the necrotic tissue.
Caseous (cheesy, cheese-like) necrosis as a type of coagulation is most often found in tuberculous foci. Macroscopically, it really resembles cottage cheese or soft cheese. Microscopically represented by structureless pink masses surrounded by a zone of granulomatous inflammation, consisting of tuberculous tubercles.
Fatty (enzymatic) necrosis, or steatonecrosis, is a focus of destroyed fatty tissue of a pale yellow color, putty-like appearance, of various shapes and sizes. More often this is a consequence of the release of activated pancreatic lipases, acting directly in the abdominal cavity in acute pancreatitis.
The outcomes of necrosis are associated with reactive changes: processes of demarcation and repair, spreading from the zone of demarcation inflammation:
- organization, or scarring, replacement of necrotic masses with connective tissue;
- encapsulation, delimitation of the site of necrosis with a connective tissue capsule;
- petrification, saturation of the necrosis area with calcium salts (degenerative calcification);
- ossification - the appearance in the area of bone tissue necrosis (occurs very rarely, in particular, in the foci of Gon - healed foci of primary tuberculosis);
- cyst formation at the end of colliquation necrosis.
Under unfavorable circumstances, purulent fusion of necrotic masses occurs, and sepsis may develop.
APOPTOSIS. If necrosis is considered a pathological form of cell death resulting from a sharp damaging effect on the cell, then apoptosis is opposed to it as a controlled process of cell self-destruction.The morphological manifestations of apoptosis are the condensation of nuclear heterochromatin and cell shrinkage while maintaining the integrity of the organelles and the cell membrane. The cell breaks down into apoptotic bodies, which are membrane structures with organelles and nucleus particles enclosed inside. Then the apoptotic bodies are phagocytosed and destroyed by lysosomes by the surrounding cells.
The characteristic signs of apoptosis are determined by the type of exposure and the type of cells. Chromatin condensation is associated with the cleavage of nuclear DNA, which occurs at the site of bonds between nucleosomes and leads to the formation of fragments. Violation of the volume and size of cells is explained by the activity of transglutaminase. This enzyme catalyzes the cross-linking of cytoplasmic proteins that form a membrane under the plasma membrane. Phagocytosis of apoptotic bodies by macrophages and other types of cells is provided by the latter's receptors. One of the important features of apoptosis is its dependence on gene activation and protein synthesis. Induction of apoptosis-specific genes is provided by special stimuli such as heat shock proteins and protooncogenes. Several genes involved in the emergence and growth of an elogenous tumor (oncogenes and suppressor genes) play a regulatory role in the induction of apoptosis. For example, the p53 oncogene stimulates normal apoptosis.
Apoptosis is responsible for numerous physiological and pathological processes in the body:

- mediates the programmed removal of cells during embryogenesis (including implantation, organogenesis and involution);
- due to apoptosis, hormone-dependent involution of cells occurs in adults (for example, rejection of endometrial cells during the menstrual cycle, atresia of follicles in the ovaries during menopause, regression of the lactating mammary gland after cessation of feeding the child);
- ensures the destruction of cells in proliferating cell populations, such as the epithelium of the crypts of the small intestine, and cell death in tumors;
- death of autoreactive clones of T-lymphocytes and pathological atrophy of hormone-dependent tissues (for example, atrophy of the prostate gland after castration and the disappearance of lymphocytes in the thymus after the injection of glycoproteins) are realized through apoptosis;
- apoptosis underlies the pathological atrophy of the parenchymal organs after the closure of the duct (for example, pancreas, parotid salivary gland, kidney);
- apoptosis is associated with cell death caused by cytotoxic T cells (for example, in transplant rejection), and cell death in certain viral diseases (for example, in viral hepatitis, in which cell fragments during apoptosis are known as Kaunsilman's bodies);
- apoptosis underlies cell death caused by various weak damaging effects, which in high doses lead to cell death (thermal effects, radiation, cytotoxic anticancer drugs and, possibly, hypoxia).

3. Lesson plan.

Mandatory Micro-, Macropreparations:

1. **Micropreparation** “Necrosis and apoptosis of spleen follicle lymphocytes in relapsing fever ”(staining with hematoxylin and eosin). At low magnification, pay attention to changes in the center of the follicles, and at high magnification, to changes in the nuclei, characteristic of necrosis and apoptosis.
2. **Micropreparation** Apoptotic bodies (Kaunsilman's little bodies) in hepatitis "(staining with hematoxylin and eosin). Pay attention to the localization, shape, structure and color of Kaunsilman's bodies.
3. **Micropreparation** "Necrosis of the epithelium of the convoluted tubules of the kidney" (staining with hematoxylin and eosin). Pay attention to the state of the nuclei and cytoplasm of the epithelium of the tubules, the blood filling of the capillaries of the glomeruli and vessels of the renal medulla.
4. **Macropreparation**"Ischemic cerebral infarction" Pay attention to the shape, consistency and color of the necrosis focus.
5. **Macropreparation**"Ischemic spleen infarction". Pay attention to the shape, color and consistency of the necrosis focus.
6. **Micropreparation** "Ischemic kidney infarction" (staining with hematoxylin and eosin). Pay attention to changes in the focus of necrosis and the zone of demarcation inflammation.
7. **Macropreparation**"Gangrene of the foot". Pay attention to the volume of necrotic tissues, their color and consistency, note the presence of a demarcation line.
8. **Macropreparation**"Intestine gangrene". Note the condition of the mucous membrane, color, thickness, consistency of the intestinal wall, the standing of the serous membrane and mesenteric vessels.
9. **MacropreparationTuberculosis** of lymph nodes ”. Pay attention to the color, shape, consistency of necrosis foci in the lymph nodes.
10. **Macropreparation**"Pancreatonecrosis" (fatty (enzymatic) necrosis, steatonecrosis). Pay attention to the color, shape, consistency and localization of necrotic changes.

Electronogram "Apoptotic body". Pay attention to changes in chromatin, the structure of the apoptotic body.

4. QUESTIONS

Choose one correct answer

1. At an autopsy performed on the 3rd day after the death of a patient with myocardial infarction, pronounced signs of autolysis in all organs were macroscopically revealed, which made it difficult to confirm the clinical diagnosis. In such a situation, for the differential diagnosis between necrosis and postmortem autolysis, you can use:
a) karyolysis,
b) plasmorexis,
c) plasmolysis,
d) demarcation inflammation,
e) karyorexis.

2. Early signs of necrosis are detected using a histochemical reaction:
a) with triphenyltetrazolium,
b) according to Shueninov,
c) with toluidine blue,
d) according to Brachet,
e) according to Felgen.

H. Sign of apoptosis:
a) activation of DNA synthesis,
b) activation of endonucleases,
c) karyolysis,
d) demarcation inflammation,
e) a decrease in the content of free calcium in the cytosol.

4. Programmed cell death that normally occurs in the organs of the fetus is called:
a) apoptosis,
b) autolysis,
c) heterolysis,
d) fibrinoid necrosis,
e) heterophagy.

5, a 71-year-old patient suffering from atherosclerosis developed pain in the left groan. I did not go to the doctor. By the time of examination: the moan is increased in volume, the tissues are flabby, black, the skin is macerated. The demarcation zone is not expressed. All provisions are correct, except:
a) diagnosis - wet gangrene,
b) the most likely causes of development - thrombosis or thromboembolism of the mesenteric artery,
c) the color of the tissues is associated with the accumulation of iron sulfite,
d) fuzzy boundaries of the affected areas are a favorable sign,
e) there was an addition of putrid flora.

6. The features of irreversible damage to myocardiocytes in myocardial ischemia are:
a) the inclusion of lipids in the cytoplasm,
b) the disappearance of glycogen from the cytoplasm,
c) swelling of cells,
d) condensation of chromatin,
e) overcontraction lines in the cytoplasm.

7. Red heart attack develops as a result of:
a) coronary artery thrombosis,
b) embolism of the branch of the pulmonary artery,
c) testicular torsion,
d) embolism of the superior mesenteric artery,
e) portal vein thrombosis.

Select all correct answers

8. Choose correct statements:
a) the cytoplasm of necrotic cells is more eosinophilic,
b) pyknotic nuclei are stained with hematoxylin weaker,
c) fatty necrosis is represented by precipitates of calcium soaps,
d) with caseous necrosis, the cells retain their outlines,
e) colliquation necrosis develops as a result of infection.

9. Serum creatine kinase levels increase with necrosis:
a) the brain,
b) kidneys,
c) striated muscles,
d) pancreas,
e) myocardium.

10. Choose correct statements:
a) gangrene - necrosis of tissues in contact with the external environment,
b) sequestration - a type of gangrene,
c) gangrene of the intestine is always wet,
d) gangrene of the limb can be either dry or wet,
e) the color of tissues in gangrene is due to the accumulation of hematin chloride.

11. Patient 67 years old, suffering from atherosclerosis of the mesenteric vessels, was admitted to the surgical department with symptoms of acute abdomen. With laparotomy - loops of the small intestine with pronounced necrotic changes. Choose the correct positions:
a) wet gangrene has developed in the intestine,
b) a pressure sore has developed in the intestine,

c) the intestine is swollen, purple-black, fibrinous overlays on the serosa,
d) the most likely cause is thrombosis of the mesenteric artery,
e) the presence of intestinal flora does not play a role.

12. A patient with transmural myocardial infarction developed back pain, hematuria. After another 2 days, right-sided hemiplegia and speech disorder developed. The patient died with symptoms of increasing cerebral edema. Choose the correct positions:
a) myocardial infarction is a focus of coagulation necrosis,
b) a heart attack has developed in the kidney,
c) a heart attack has developed in the brain,
d) kidney infarction is a focus of colliquation necrosis,
e) red myocardial infarction.

13. Choose correct statements:
a) coagulation necrosis is accompanied by tissue compaction and dehydration,
b) colliquation necrosis - enzymatic softening and melting of tissue,
c) caseous necrosis - a type of coagulation necrosis,
d) gangrene - necrosis of tissues in contact with the external environment,
e) sequestration - ischemic necrosis.

15. Localization of infarction is usually combined with the following morphological signs of the pathological process:
1) myocardium, a) white with a hemorrhagic corolla,
2) lung, b) can lead to ulceration,
3) the brain, c) leads to bleeding,
4) the small intestine. d) leads to the formation of a cyst,
e) triangular shape.

16. Localization of necrosis is usually combined with the following type of pathological process:
Organ: Type of necrosis:
1) heart, a) coagulation,
2) kidney, b) colliquation,
3) muscles, c) fibrinoid,
4) brain, d) waxy,
5) the spleen. e) gangrenous.

Situational tasks.

Situational task 1.
During a colon resection for cancer, a patient developed bleeding from the vessel of the transverse colon mesentery and a drop in blood pressure. In the postoperative period, the picture of acute renal failure.
1. What changes in the kidneys led to the development of acute renal failure?
2. What is the mechanism of their development in this patient.

Situational task 2.
The patient was admitted to the clinic with an attack of angina pectoris. Sudden death occurred three days later. Autopsy: atherosclerosis of the aorta, blood vessels of the heart and brain, In the anterior wall of the left ventricle - a scar field. In the right hemisphere of the brain, in the region of the subcortical nuclei, an extensive focus of tissue destruction was found.
1. What clinical and morphological form of necrosis developed in the patient?
2. The outcome of what process is the myocardial scar?

Situational task 3.
A 65-year-old patient suffering from atherosclerosis developed pain in the right leg, tissues of 1 toe became black, the epidermis exfoliated.
1. What clinical and morphological form of necrosis has developed?
2. What kind of this form?
H. What is the cause of this necrosis?
4. How to explain the black color of necrotic tissues.

5. List of recommended literature:
Basic literature:

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

Additional literature:

1. “Pathology. Quick Review and MCQs” Harsh Mohan, 2004.
2. “Textbook of Pathology ” Harsh Mohan, 2002.
3. “General and Systemic Pathology” Joseph Hunter, 2002.
4. “General and Systematic Pathology ” Ed. J.C.E. Underwood – Edinburgh: Churchill Livingstone, 1996 (2^{th}).
5. “Histology for Pathologist” Ed. S.S.Sternberg – Philadelphia: Lippincott Raven Publ, 1997 (2^{th}).
6. “Histopathology. A Color Atlas and Textbook” Damjanov I., McCue P.A. – Baltimore, Philadelphia, London, Paris etc.: Williams and Wilkins, A Waverly Co., 1996.
7. “Muir’s Textbook of Pathology” Eds. R.N.M. MacSween, K. Whaley London: ELBS, 1994 (14^{th}).
8. “Pathology” Eds. Rubin, J.L. Farber – Philadelphia: Lippincott Raven Publ, 1998 (3^{th}).
9. “Pathology Illustrated” Govan A.D.T., Macfarlane P.S., Callander R. – Edinburgh: Churchill Livingstone, 1995 (4^{th}).
10. “Robbins Pathologic Basic of Disease” Eds. R.S.Cotran, V.Kumar, T.Collins – Philadelphia, London, Toronto, Montreal, Sydney, Tokyo: W.B.Saunders Co., 1998 (6^{th}).
11. “Wheater’s Basic Histopathology. A Color Atlas and Text” Burkitt H.G., Stevens A.J.S.L., Young B. – Edinburgh: Churchill Livingstone, 1996 (3^{th}).
12. “Color Atlas of Anatomical Pathology” Cooke R.A., Steward B. – Edinburgh: Churchill Livingstone, 1995 (10^{th}).
13. “General Pathology ” Walter J.B., Talbot I.C. – Edinburgh: Churchill Livingstone, 1996 (7^{th}).
14. “Concise Pathology” Parakrama Chandrasoma, Glive R. Taylor.
15. “Pathology” Virginia A. LiVolsi, Maria J. Merino, John S. J. Brooks, Scott H. Saul, John E. Tomaszewski, 1994.
16. “Short lectures on pathology” Zagoroulko A., 2002
17. “Robbins pathologic basis of diseases” Cotran R., Kumar V., Collins T.
18. “General pathology” Dr. Fatma Hafez, 1979.
19. “Anderson’s Pathology ” Damjanov I., Linder J. – St. Louis: Mosby Inc., 1995 (10^{th}).

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