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Morphology of pigment and mineral metabolism disorders (mixed dystrophies). Morphology of pathological accumulation of endogenous and exogenous pigments. Hemosiderosis, hemochromatosis. Jaundice. Pathological calcification.

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1. **The purpose of the lesson.** To study the issues of etiology, pathogenesis, morphology, complications and outcomes of disorders of pigment metabolism; to study the morphological features of pathological accumulation of endogenous and exogenous products; to characterize the morphological manifestations of pathological calcification.
2. **Requirements for the level of the student** for mastering the discipline - pathological anatomy.

The theoretical basis.

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

Pigments are colored substances of various chemical nature that can be found in cells in normal conditions or accumulate in pathological conditions. Distinguish between: exogenous and endogenous pigments.
Exogenous pigments include coal dust, which, entering the lungs, is captured by alveolar macrophages, penetrates through the lymphatic vessels into the regional lymph nodes, where it is deposited in the form of 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 derivatives of hemoglobin that occur during the synthesis (decay) of erythrocytes. Normally, ferritin, hemosiderin, bilirubin and porphyrins are 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 using 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 that occurs as a result of an increased intake of iron into the body and is 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), on a cut with numerous brownish blotches and interlayers of connective tissue. Microscopically: in the lungs, a large number of cells containing brown pigment are detected, which are 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, which develops:
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 mainly 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, and 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 recurrent 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 picture 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 deposited 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. 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 ensure the absorption and metabolism of dietary 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 (icteric coloration of the skin, sclera, mucous membranes, etc. appears).

Proteinogenic (tyrosinogenic) pigments are pigments associated with the metabolism of tyrosine. These include melanin, pigment of enterochromaffin cell granules and adrenochrome. The accumulation of these pigments in tissues is a manifestation of a number of diseases.
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). Disturbances in melanin metabolism 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 lesions of the adrenal glands in 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 melalin in melanocytes and keratinocytes (epidermal cells, into which melanin is transmitted through the processes of melanocytes) increases, in the dermis, melanin is determined in melanophages; atrophy of the epidermis, hyperkeratosis are noted. 2) Congenital widespread hypermelanosis is observed with 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
- melanoma.

Hypopigmentation.
A) Common 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 leucoderma.

The pigment of granules of enterochromaffin cells, scattered in various sections of the gastrointestinal tract, is a derivative of tryptophan. It can be detected using a number of histochemical reactions - argentafin, chromaffin Falk reaction, pigment formation is associated with the synthesis of serotonin and melatonin. The accumulation of granules containing pigment of enterochromaffin cells is constantly found in tumors from these cells, called carcinoids.

Adrenochrome, a product of adrenaline oxidation, is found in the form of granules in the cells of the adrenal medulla. Gives a characteristic chromaffin reaction, which is based on the ability to be stained with chromic acid in a dark brown color and to restore dichromate. The nature of the pigment has been little studied. The pathology of adrenochrome metabolism disorders has not been studied.

Lipidogenic pigments (lipid pigments) are pigments formed during the metabolism of fats. This group includes fatty protein pigments - lipofuscin, vitamin E deficiency pigment, ceroid and lipochromes. Lipofuscin, vitamin E deficiency pigment and ceroid have the same physical and chemical (histochemical) properties, which gives the right to consider them as varieties of one pigment - lipofuscin. However, at present, lipofuscin is considered a lipopigment of only parenchymal and nerve cells; the pigment of vitamin E deficiency is a type of lipofuscin. A ceroid is a lipopigment of mesenchymal cells, mainly macrophages. The pathology of lipopigment metabolism is diverse.

Lipofuscin is an insoluble pigment, also known as aging, wear pigment; 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 liposcinosis. 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; 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 in color; microscopy: the hepatic tracts are sharply thinned, in the cytoplasm of hepatocytes there are numerous brown granules of lipofuscin.

A ceroid is formed in macrophages by heterophagy during the resorption of lipids or lipid-containing material; the basis of the ceroid is formed by lipids, to which proteins are reattached. Endocytosis leads to the formation of heterophagic vacuoles (lipophagosomes). Lipophagosomes are transformed into secondary lysosomes (lipophagolysosomes). Lipids are not digested by lysosomal enzymes and remain in lysosomes, residual bodies appear, that is, telo'lysosomes. Under pathological conditions, the formation of a ceroid is most often observed with tissue necrosis, especially if lipid oxidation is enhanced by hemorrhage (therefore, earlier ceroid was called hemofuscin, which is fundamentally incorrect) or if lipids are present in such an amount that their autooxidation begins earlier than digestion.

Lipochromes are represented by lipids, in which carotenoids are present, which are the source of the formation of vitamin A. Lipochromes give a yellow color to adipose tissue, adrenal cortex, blood serum, yellow body of the ovaries. Their identification is based on the detection of carotenoids (color reactions with acids, green fluorescence in ultraviolet light). In conditions of pathology, excessive accumulation of lipochromes can be observed. For example, in diabetes mellitus, pigment accumulates not only in adipose tissue, but also in the skin and bones, which is associated with a sharp violation of lipid-vitamin metabolism. With a sharp and rapid weight loss, lipochromes condense in the fatty tissue, which turns yellow.

II. 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) in 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.

Dystrophic calcification produces crystalline minerals 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 spread, develops both in cells and extracellularly. The initiation of intracellular calcification occurs in the mitochondria of deceased or dying cells, which accumulate Ca2.

Outside of cells, the initiation phase takes place in membrane-surrounded vesicles about 200 nm in diameter, formed during aging or destruction of the cell. 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. Causes of hypercalcemia are hyperparathyroidism, vitamin C intoxication, systemic sarcoidosis and other granulomatosis, hyperthyroidism, idiopathic hypercalcemia, Addison's disease (adrenocortical insufficiency), increased bone destruction associated with multiple myeloma or metastases, decreased 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 a hydroxyapatite crystal structure. Most often, mineral salts do not clinically cause organ dysfunction, however, massive calcification, for example, of lung or kidney tissue (nephrocalcinosis), can disrupt the function of these organs.

3. Lesson plan.

Macropreparations:

1. Macropreparation. 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.
2. Macropreparation. Nutmeg liver - determine the size of the liver, pay attention to its surface, texture, thickness, color and uniformity of color on the cut.
3. Macropreparation. Melanoma metastases to the liver (optional). Pay attention to the color of the nodes characteristic of this disease, to the state of the organ surface.

Skin in Addison's disease (optional) - pay attention to the skin color characteristic of this disease, to the condition of the skin surface.

4. Macropreparation. 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.
5. Macropreparation. Gallbladder stones (optional)- pay attention to the size, shape, color, consistency and surface condition of the stones.
6. Macropreparation. “Petrification in the lung”. Pay attention to the localization, number, shape, size, color and consistency of the lesions in the lung tissue.
7. Macropreparation. Lung anthracosis - pay attention to the color, localization of focal black inclusions (pigment) in the lung.

Micropreparations:
1. Micropreparation. Brown induration of the lung - find capillaries that are sharply overflowing with blood, pay attention to the thickness of the walls of the interalveolar septa and the walls of blood vessels; find brown pigment grains, mark its localization (intracellular, extracellular). Hematoxylin and eosin staining, Perls reaction.
2. Micropreparation. Nutmeg liver - find deposits of pigment granules, determine the type of pigment, its color and localization (in which parts of the lobule and which cell it accumulates); to determine the size of the liver cells and their nuclei, the state of the organ stroma.
3. Micropreparation. Skin with Addison's disease - find pigment deposits in the epidermis and dermis; determine the color, amount and localization of the pigment.
4. Micropreparation. Liver with 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 necrosis of the parenchyma, stained with bile, accumulation of leukocytes in the area of necrosis.
5. Micropreparation. Lymph node anthracosis (optional) - pay attention to the color, localization of inclusions (pigment), the condition of the sinuses and tissue of the lymph node.
6. Micropreparation. "Calcareous metastases in the myocardium" (staining with hematoxylin and eosin). Pay attention to the color and localization of calcium salt deposits, the state of damaged cardiomyocytes, changes in the myocardial stroma.
7. Micropreparation. "Calcareous metastases in the kidney" (staining with hematoxylin and eosin). Pay attention to the color and localization of calcium salt deposits, the state of damaged cells.

Electronograms
Explore the atlas.
1. Siderophage of the lung - pay attention to the numerous granules of hemosiderin.
2. Lipofuscin in cardiomyocyte - pay attention to the numerous lipofuscin granules.
3. Calcareous metastases in the kidney. Pay attention to the organelles that are the place of fixation of calcium salts.
4. Molecules of ferritin in the hemosiderin granule. Please note that during electron microscopic examination, the hemosiderin granule consists of ferritin molecules with a characteristic tetrahedral shape.

4. QUESTIONS

Choose one correct answer

1. . The accumulation of hemosiderin leads to organ dysfunction in:
a) hemosiderosis,
b) hemochromatosis,
c) hemomelanosis,
d) hemophilia.

2. Hemosiderin in tissues reveals the reaction:
a) CHIC (PAS),
b) Wasserman,
c) Brachet,
d) Felgen,
e) Perls.

3. Brown induration of the lungs is accompanied by the accumulation of:
a) hemosiderin,
b) melanin,
c) coal,
d) lipofuscin,
e) silicon dioxide.

4. Changes in the lungs and regional lymph nodes with the accumulation of coal particles in them are called:
a) hemosiderosis,
b) anthracosis,
c) melanosis,
d) lipofuscinosis,
e) silicosis.

5. Metastatic calcification is caused by:
a) hypercalcemia,
b) hypocalcemia,
c) inflammation,
d) foci of necrosis.

6. Hereditary storage diseases are called:
a) thesaurismoses,
b) systemic,
c) autoimmune,
d) cerebrovascular,
e) immunocomplex.

7. The widespread acquired hypermelanosis develops with the disease:

a) Alzheimer's,
b) Crohn,
c) Addison,
d) Graves.

Choose one or more correct answers
8. Microscopic features of pulmonary hemosiderosis
1) granulomas in the walls of the bronchi
2) inflammatory infiltration
3) proliferation of connective tissue
4) chronic venous congestion
5) multiple small hemorrhages
6) hemosiderin in siderophages and sideroblasts

9. General hemosiderosis occurs when
1) myocardial diseases
2) blood diseases
3) infectious diseases
4) diapedetic hemorrhage
5) transfusion of incompatible blood
6) poisoning with hemolytic poisons

10. Hemosiderosis of the lungs - a manifestation
1) cachexia
2) brown atrophy
3) general hemosiderosis
4) local hemosiderosis
5) suprahepatic jaundice

11. Condition of occurrence of metastatic calcification
1) hypoxia
2) atherosclerosis
3) foci of necrosis
4) hypocalcemia
5) hypercalcemia

12. With degenerative calcification, the level of calcium in the blood
1) increases
2) does not change
3) decreases

13. Features of metastatic calcification
1) hypercalcemia
2) the level of calcium in the blood does not change
3) calcium is deposited in the foci of necrosis
4) calcium salts are in the form of amorphous deposits
5) calcium salts are deposited in various organs

14. Petrification in the outcome of caseous necrosis occurs when
1) rheumatism
2) tuberculosis
3) hemosiderosis
4) idiopathic hypercalcemia.

Situational tasks.

Situational task 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 brownish-brown pigment, macrophages. In the cytoplasm of which the pigment is brown-brown.
Questions: 1) What pathological process took place in the leaflets of the mitral valve?
2) What histochemical stains should be used to identify the pigment found in the lungs?
H) 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?

Situational task 2.
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?

Situational task 3.
Patient Sh., 69 years old, suffered from stomach cancer with metastases to internal organs for a long time, died of cancer cachexia. Autopsy: the heart is reduced in size, dense, brown; histological examination revealed yellow pigment granules in the cytoplasm of cardiomyocytes.
Questions: 1) What pathological process took place in the myocardium?
2) What are the causes and mechanisms of development of the described pathological process?

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.
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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.
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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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