VOLGOGRAD STATE
MEDICAL UNIVERSITY
Department of Pathological Anatomy

Diseases of the liver and biliary system. Hepatitis. Cirrhosis of the liver. Liver cancer. Cholelithiasis.

Guidelines for students
III year of medical faculty
for practical exercises in pathological anatomy

Volgograd, 2020

Diseases of the liver and biliary system

1. The purpose of the lesson. To study the etiology, pathogenesis, morphological characteristics, complications and outcomes of diseases of the liver and biliary system.

2. Requirements for the level of the student in the development of the discipline - pathological anatomy. The student must know:

1. Definition, etiology, classification, pathological anatomy of fatty hepatosis.
2. Definition, etiology, classification, pathological anatomy, complications of massive liver necrosis.
3. Definition, etiology, classification, pathological anatomy, complications of hepatitis.
4. Definition, classification, pathological anatomy, complications of cirrhosis.
5. Definition, classification, pathological anatomy of liver tumors.
6. Definition, classification, pathological anatomy, complications of appendicitis.

3. Theoretical aspects.

The liver is vulnerable to a wide variety of metabolic, toxic, microbial, circulatory, and neoplastic insults. In some instances, the disease is primary to the liver, as in viral hepatitis and hepatocellular carcinoma. More often the hepatic involvement is secondary, often to some of the most often diseases in humans, such as cardiac decompensation, disseminated cancer, alcoholism, and extrahepatic infections.

Some general aspects of liver disease are reviewed 1) morphologic patterns of hepatic injury, 2) hepatitis, and 3) cirrhosis.

MORPHOLOGIC PATTERNS OF HEPATIC INJURY

MORPHOLOGY. The liver is an inherently simple organ, with a limited repertoire of responses to injurious events. Regardless of cause, five general reactions may occur.

Necrosis. Virtually any significant insult to the liver may cause hepatocyte necrosis. In ischemic necrosis, poorly stained mummified hepatocytes remain (coagulative necrosis). In necrosis, that is toxic or immunologically mediated, isolated hepatocytes round up to form shrunken, pyknotic, and intensely eosinophilic Councilman bodies (a process known as apoptosis). Alternatively, hepatocytes may osmotically swell and rupture, the so-called hydropic degeneration. Necrosis may be limited to scattered cells within the hepatic lobules (focal necrosis) or involve particular regions of the lobule (zonal necrosis), entire lobules (submassive necrosis), or the whole liver (massive necrosis). Focal necrosis is the most characteristic of microbial infections, particularly smoldering forms of viral hepatitis. Centrilobular necrosis is characteristic of ischemic injury and many drug and toxic chemical reactions. Midzonal necrosis is a rare pattern, seen in yellow fever. Strictly periportal necrosis is seen primarily in phosphorus poisoning and eclampsia.

Massive necrosis is most commonly caused by severe chemical and drug toxicity or viral hepatitis. In other conditions, such as typhoid fever, tularemia, brucellosis, and herpes or adenovirus infection, expanding regions of the parenchyma are destroyed (geographic necrosis). With disseminated candidal or bacterial infection, macroscopic abscesses may occur.

Degeneration. Short of outright necrosis, hepatocytes may take on a swollen, edematous appearance (ballooning degeneration) with irregularly clumped cytoplasm and large, clear spaces. Alternatively, retained biliary material may impart a diffuse foamy swollen appearance to the hepatocyte (cholestasis). Accumulation of specific substances in viable hepatocytes, such as iron, copper, and viral particles, may be of particular diagnostic value.

Inflammation. Inflammation is defined as the influx of acute or chronic inflammatory cells into the liver and is termed hepatitis. Although inflammation may be secondary to hepatocellular necrosis, lymphocytic attack of viable antigen-expressing liver cells is a common cause of the liver damage. Inflammatory cells may be limited to the site of entry (portal tracts) or spill over into the parenchyma. In the case of focal hepatocyte necrosis, scavenger macrophages quickly generate

scattered clumps of inflammatory cells in an otherwise innocuous parenchyma. Foreign bodies, organisms, and a variety of drugs may incite a granulomatous reaction.

Regeneration. The liver has enormous reserve, and regeneration occurs in all but the most fulminant diseases. Regeneration is signified by thickening of the hepatocyte cords (the result of hepatocyte proliferation) and some disorganization of the parenchymal structure. When massive hepatocellular necrosis occurs and leaves the connective tissue framework intact, almost perfect restitution can occur.

Fibrosis. Fibrous tissue is formed in response to inflammation or direct toxic insult to the liver.

Deposition of collagen has lasting consequences on hepatic patterns of blood flow and perfusion of hepatocytes. In the initial stages, fibrosis may develop around portal tracts or the central vein or may be deposited directly within the space of Disse. With continuing fibrosis, the liver is subdivided into nodules of regenerating hepatocytes surrounded by scar tissue, termed cirrhosis.

VIRAL HEPATITIS

Viral hepatitis is reserved for infection of the liver caused by a small (but growing) group of viruses having a particular affinity for the liver: Hepatitis A Virus, Hepatitis B Virus, Hepatitis C Virus, Hepatitis D Virus, and Hepatitis E Virus.

Hepatitis A Virus does not cause chronic hepatitis or a carrier state and only rarely causes fulminant hepatitis, and so the fatality rate associated with Hepatitis A Virus is about 0.1 %.

Hepatitis B Virus can produce 1) acute hepatitis, 2) chronic nonprogressive hepatitis, 3) progressive chronic disease ending in cirrhosis, 4) fulminant hepatitis with massive liver necrosis, and 5) an asymptomatic carrier state with or without progressive disease. Furthermore, Hepatitis B Virus plays an important role in the development of hepatocellular carcinoma.

Transfusion, blood products, dialysis, needle-stick accidents among health care workers, intravenous drug abuse, and homosexual activity constitute primary risk categories for Hepatitis B Virus infection.

Hepatitis C Virus has a high rate of progression to chronic disease and eventual cirrhosis, exceeding 50 %.

ACUTE VIRAL HEPATITIS

Any of the hepatotropic viruses can cause acute viral hepatitis. Whatever the agent is, the disease is more or less the same and can be divided into four phases: 1) an incubation period, 2) a symptomatic preicteric phase, 3) a symptomatic icteric phase, and 4) convalescence.

MORPHOLOGY. The morphologic changes in acute viral hepatitis are virtually the same regardless of the causative agent and can be mimicked by drug reactions. Grossly, the liver is slightly enlarged and more or less green depending on the phase of the acute disease and the degree of jaundice. Histologically the major findings are 1) necrosis of random isolated liver cells or small cell clusters; 2) diffuse liver cell injury; 3) reactive changes in Kupffer cells and sinusoidal lining cells and an inflammatory infiltrate in portal tracts, and 4) evidence of hepatocytic regeneration during the recovery phase. Necrotic hepatocytes may be evident as fragmented, eosinophilic Councilman bodies or may be phagocytosed leading to the accumulation of clumps of lymphocytes and macrophages. Confluent necrosis may lead to bridging necrosis connecting portal-to-portal, central-to-central, or portal-to-central regions of adjacent lobules, signifying a more severe form of acute hepatitis.

Lobular disarray results from the cellular swelling (ballooning), necrosis, and regeneration of cells producing compression of the vascular sinusoids and loss of the normal, more or less radial array. Fatty change is unusual except with Hepatitis C Virus. An inconstant finding is bile stasis within the lobule. Inflammation is a characteristic, usually prominent feature of acute hepatitis. Kupffer cells and sinusoidal lining cells undergo hypertrophy and hyperplasia and are often laden with lipofuscin pigment owing to phagocytosis of hepatocellular debris. The portal tracts are usually

infiltrated with a mixture of inflammatory cells; this infiltrate may spill over into the parenchyma, particularly where adjacent hepatocytes have undergone necrosis. The bile duct epithelia may proliferate, particularly in cases of Hepatitis C Virus hepatitis, forming poorly defined ductular structures (cholangioles).

In the recovery phase of acute hepatitis, the lobule remains somewhat disorganized because hepatocytes can proliferate faster than normal cord-sinusoid-cord relationships can be established. Regenerating hepatocytes lack uniformity in size and are pale, the result of diminished numbers of cytoplasmic organelles. Double and triple nuclei in regenerating cells are commonly observed. Residual clumps of inflammatory cells may persist for some time.

CHRONSC VIRAL HEPATITIS

Symptomatic, biochemical or serologic evidence of continuing or relapsing hepatic disease for more than 6 months, optimally with histologically documented inflammation and necrosis, is taken to mean chronic hepatitis. Although the hepatitis viruses are responsible for most cases of chronic hepatitis, there are many other etiologies (each described later): Wilson's disease, alpha-1-antitrypsin deficiency, chronic alcoholism, drugs (isoniazid, alpha-methyldopa, methotrexate), and autoimmunity.

Since 1968, chronic hepatitis has been classified according to the extent of inflammation:

1. Chronic persistent hepatitis, in which inflammation is confined to the portal tracts.

2. Chronic active hepatitis, in which portal tract inflammation spills into the parenchyma and surrounding regions of necrotic hepatocytes.

3. Chronic lobular hepatitis, in which persistent inflammation is confined to the lobule.

It is now apparent that the primary determinant of disease progression, and therefore prognosis, is the etiologic form of hepatitis. Therefore, although histologic information may provide information helpful for patient management, classification of chronic hepatitis strictly by histologic criteria is obsolete and should not be used. This is particularly important because therapy that is effective for one cause of chronic hepatitis may be ineffective, or potentially detrimental, in other forms of the disease.

The likelihood of chronic hepatitis following acute viral infection can be summarized:

Hepatitis A Virus: Extremely rare.

Hepatitis B Virus: Develops in more than 90% of infected neonates and *5 %* of infected adults, of whom one-fourth progresses to cirrhosis.

Hepatitis C Virus: Develops in more than 50 % of infected patients, of whom half progresses to cirrhosis.

Hepatitis D Virus: Rare in acute Hepatitis D Virus/ Hepatitis B Virus coinfection; a more severe chronic hepatitis is the most frequent outcome of Hepatitis D Virus superinfection.

Hepatitis E Virus: Does not produce chronic hepatitis.

Chronic hepatitis with Hepatitis B Virus, and apparently with Hepatitis C Virus, contributes significantly to the development of primary hepatocellular carcinoma.

The clinical features of chronic hepatitis are extremely variable and are not predictive of outcome. In some patients, the only signs of chronic disease are persistent elevations of serum transaminases, hence the facetious designation "transaminitis." The most common symptom is fatigue; less common symptoms are malaise, loss of appetite, and occasional bouts of mild jaundice. Physical findings are few, if any, the most common being spider angiomas, palmar erythema, mild hepatomegaly, hepatic tenderness, and mild splenomegaly. Laboratory studies may reveal prolongation of the prothrombin time and, in some instances, hyperglobulinemia, hyperbilirubinemia, and mild elevations in alkaline phosphatase. Occasionally in cases of Hepatitis B Virus, and rarely in Hepatitis C Virus, immune-complex diseases may develop secondary to the presence of circulating antibody-antigen complexes, in the form of vasculitis (subcutaneous or visceral, i.e., polyarteritis nodosa) or glomerulonephritis.

MORPHOLOGY. The morphology of chronic hepatitis ranges from exceedingly mild to severe, to eventual cirrhosis. In the mildest form, an inflammatory infiltrate is limited to portal

tracts, consisting of lymphocytes, macrophages, occasional plasma cells, and occasional rare neutrophils or eosinophils. Liver architecture is usually well preserved but may exhibit vestiges of acute disease.

The histologic hallmark of progressive disease is piecemeal necrosis, whereby the chronic inflammatory infiltrate spills out from portal tracts into adjacent parenchyma, with associated necrosis of hepatocytes in the limiting plate. There may be lobular inflammation with focal necrosis of hepatocytes. As with acute hepatitis, bridging necrosis may connect adjacent portal-portal, central-central, and portal-central zones. Although piecemeal and bridging necrosis do not imply inevitable progression of disease, continued loss of hepatocytes results in fibrous septum formation, which, accompanied by hepatocyte regeneration, results in cirrhosis.

The aforementioned features are common to all forms of chronic hepatitis (viral or otherwise). In patients with chronic Hepatitis C Vims hepatitis, lymphoid aggregates in portal tracts and mild fatty change are seen in about 50 % of cases, and bile duct damage is seen in more than 90 %. Conversely, "ground-glass" hepatocytes are sometimes present in chronic Hepatitis B Virus hepatitis. Despite the use of immunohistochemical techniques, it is frequently impossible to identify the etiology of chronic hepatitis on tissue samples, so great reliance must be placed on clinical, virologic, and serologic observations.

The clinical course is unpredictable. Patients may experience spontaneous remission or may have indolent disease without progression for many years. Conversely, some patients have rapidly progressive disease and develop cirrhosis within a few years. The major causes of death are cirrhosis, with liver failure and hepatic encephalopathy or massive hematemesis from esophageal varicose and, in those with long-standing Hepatitis B Virus (particularly neonatal) or Hepatitis C Virus infection, hepatocellular carcinoma.

4. Оснащение занятия:

Макропрепараты: острая язва желудка, хроническая язва желудка, рак желудка, флегмонозный аппендицит, жировой гепатоз печени, цирроз печени.

Микропрепараты: хроническая язва желудка, флегмонозный аппендицит, массивный некроз печени, острый вирусный гепатит, цирроз печени.

Электронограммы: 1) Скопление Helicobacter pilori (HP) в разрушенной мышечной пластинке (МП) слизистой оболочки желудка; 2) В цитоплазме макрофага (слизистая оболочка желудка) - множество вакуолей, различный включений и фагоцитированный Helicobacter pilori; 3) Helicobacter pilori в цитоплазме макрофага - завершенный фагоцитоз; 4) Вирусный гепатит: в пространстве Диссе множественные вирусные частицы, ядро гепатоцита сморщено; 5) Алкогольный гиалин (Ги) в цитоплазме гепатоцита; 6) Портальный цирроз печени: синусоид (С) сдавлен, в перисинусоидальном пространстве фибробласты (Фб) и пучки коллагеновых волокон (КлВ) (ПД - подоцит, Гл - гликоген).

CIRRHOSIS

Cirrhosis is among the top ten causes of death in the world, largely the result of alcohol abuse, chronic hepatitis, biliary disease, and iron overload. This end stage of liver disease is defined by three characteristics:

- Fibrosis is present in the form of delicate bands or broad scars replacing multiple adjacent lobules.

- The parenchymal architecture of the entire liver is disruptured by interconnecting fibrous scars.

- Parenchymal nodules are created by regeneration of hepatocytes, The nodules may vary from micronodules (less than 3 mm in diameter) to macronodules (3 mm to several centimeters in diameter).

Several features should be understood:

- The parenchymal injury and consequent fibrosis are diffuse, extending throughout the liver; focal injury with scarring does not constitute cirrhosis.

- Nodularity is requisite for the diagnosis and reflects the balance between regenerative activity and constrictive scarring.

- Fibrosis, once developed, is generally irreversible; some regression has been observed in humans with treated schistosomiasis and hemochromatosis.

- Vascular architecture is recognized by parenchymal damage and scarring, with formation of abnormal interconnections between vascular inflow and hepatic vein outflow.

All forms of cirrhosis may be clinically silent. The ultimate mechanism of most cirrhotic deaths is 1) progressive liver failure, 2) a complication related to portal hypertension, or 3) the development of hepatocellular carcinoma. Portal hypertension (increased resistance to portal flow) can be caused by prehepatic, intrahepatic, and posthepatic causes. The dominant intrahepatic cause is cirrhosis. The four major clinical consequences are 1) ascites, 2) the formation of portosystemic venous shunts, 3) congestive splenomegaly, and

4) hepatic ehcephalopathy.

POSTNECROTIC CIRRHOSIS

This pattern of cirrhosis is characterized by irregularly sized nodules separated by variable but mostly broad scars. The most common known cause is previous viral infection; in about 20 to 25 % of cases it evolves from chronic Hepatitis B Virus infection; the contribution of chronic Hepatitis C Virus may be even greater. In a small number of instances, there is a well-documented history of acute liver damage caused by some hepatotoxin, such as phosphorus; carbon tetrachloride; mushroom poisoning; or a drug, such as acetaminophen, oxyphenisatin, or alpha-methyldopa. Undoubtedly some cases represent end-stage alcoholic cirrhosis, readily misinterpreted as postnecrotic cirrhosis in the absence of a history of chronic alcoholism. After all these possibilities have been excluded, there remains a large residue of uncertain origin. A single attack of massive hepatic necrosis only infrequently gives rise to postnecrotic cirrhosis because either it is fatal, or regeneration of the liver cells permits survival with little or no residual scarring.

MORPHOLOGY. Typically some time after an acute event or following years of chronic hepatitis, the liver exhibits nodules of varying size (some several centimeters in diameter) and broad bands or areas of depressed scarring . Severe collapse may leave a shrunken liver less than 1 kg in weight. Microscopically tabular architecture may be completely lost in the developing nodules and scar. Alternatively, progressive chronic hepatitis of any etiology inexorably transforms a more normalized liver into a patchwork of variably sized nodules alternating with broad septal scars. Eventually active liver cell necrosis becomes inconspicious. Residual of portal tracts may be evident; bile stasis is variable. Ultimately the diagnosis rests on excluding other bases for cirrhosis.

ALCOHOLIC LIVER DISEASE

Alcohol abuse constitutes the major form of liver disease in many countries. Chronic alcohol consumption has a variety of adverse effects. Of greatest impact, however, are the three distinctive, albeit overlapping, forms of liver disease: 1) hepatic steatosis, 2) alcoholic hepatitis, and 3) cirrhosis, collectively referred to as alcoholic liver disease.

HEPATIC STEATOSIS (FATTY LIVER)

MORPHOLOGY. Following even moderate intake of alcohol, small (microvesicular) lipid droplets accumulate in hepatocytes. With chronic intake of alcohol, lipid accumulates to the point of creating large clear macrovesicular spaces, compressing and displacing the nucleus to the periphery of the hepatocyte. This transformation is initially centrilobular, but in severe cases, it may involve the entire lobule. The liver is often grossly enlarged, up to 4 to 6 kg, and is a soft, yellow, greasy organ. Although there is little or no fibrosis at the outset, with continued alcohol abuse, fibrous tissue develops around the central veins and extends into the adjacent sinusoids. Up to the time that fibrosis appears, the fatty change is completely reversible if there is further abstention from alcohol.

ALCOHOLIC HEPATITIS

MORPHOLOGY. Alcoholic hepatitis exhibits the following:

1. Liver cell necrosis - single or scattered foci of cells undergo swelling (ballooning) and necrosis, more frequently in the centrilobular regions of the lobule.

2. Mallory bodies - scattered hepatocytes accumulate tangled skeins of cytokeratin intermediate filaments and other proteins, visible as eosinophilic cytoplasmic inclusions. These may also be seen in primary biliary cirrhosis, Wilson's disease, chronic cholestatic syndromes, focal nodular hyperplasia and hepatocellular carcinoma.

3. Neutrophilic reaction - neutrophils permeate the lobule and accumulate around degenerating liver cells, particularly those having Mallory bodies. Lymphocytes and macrophages also enter portal tracts and spill into the lobule.

4. Fibrosis - alcoholic hepatitis is almost always accompanied by a brisk sinusoidal and perivenular fibrosis; occasionally periportal fibrosis may predominate, particularly with repeated bouts of heavy alcohol intake. Fat may be present or entirely absent. Deranged iron processing in the alcoholic typically leads to a modest accumulation of hemosiderin in hepatocytes and Kupffer cells.

ALCOHOLIC CIRRHOSIS

MORPHOLOGY. The final and irreversible form of alcoholic liver disease usually evolves slowly and insidiously. At first the cirrhotic liver is yellow-tan, fatty, and enlarged, usually weighing more than 2 kg. Over the span of years it is transformed into a brown, shrunken, nonfatty organ, sometimes less than 1 kg in weight. Cirrhosis may develop within 1 to 2 years in the setting of alcoholic hepatitis. Initially the developing fibrous septa are delicate and extend from central vein to portal regions as well as from portal tract to portal tract. Regenerative activity of the entrapped parenchymal acini generates fairly uniformly sized "micronodules." With time, the nodularity becomes more prominent; scattered nodules may become quite large, and occasionally nodules more than 2 cm in diameter may develop. As fibrous septa dissect and surround nodules, the liver becomes more fibrotic, loses fat, and shrinks progressively in size. Parenchymal islands are engulfed by ever wider bands of fibrous tissue, and the liver is converted into a mixed micronodular and macronodular pattern. Further ischemic necrosis and fibrous obliteration of nodules eventually create broad expanses of tough, pate scar tissue, leaving residual parenchymal nodules that protrude like "hobnails" from the surface of the liver ("Laennec's cirrhosis"). By microscopy, the septa contain variable amounts of scattered lymphocytes and some reactive bile duct proliferation. Bile stasis often develops; Mallory bodies are only rarely evident at this stage. Thus end-stage alcoholic cirrhosis comes to resemble, both macroscopically and microscopically, postnecrotic cirrhosis.

SECONDARY BILIARY CIRRHOSIS

Prolonged obstruction to the extrahepatic biliary tree results in profound alteration of the liver itself. The most common cause of obstruction is an impacted gallstone in the common bile duct; other conditions include biliary atresia, malignancies of the biliary tree and head of the pancreas, and strictures resulting from previous surgical procedures. The initial morphologic features of cholestasis were described earlier and are entirely reversible with correction of the obstruction. Initiation of periportal fibrosis secondary to inflammation, however, eventually leads to secondary biliary cirrhosis. Secondary bacterial infection ("ascending cholangitis") may contribute to the damage; enteric organisms such as coliforms and enterococci are common culprits.

MORPHOLOGY. The end-stage obstructed liver exhibits extraordinary yellow-green pigmentation and is accompanied by marked icteric discoloration of body tissues and fluids. On cut surface, the liver is hard, with a finely granular appearance. Microscopically, large and small bile ducts are distended and frequently contain inspissated bile. Portal tracts are interconnected by inflamed fibrous septa and appear edematous; there is frequently a narrow zone of edema and ductular proliferation at the junction of parenchyma and septa. Cholestatic features may be severe, with cytoplasmic and canalicular accumulation of bile, extensive feathery degeneration of hepatocytes, and the formation of bile lakes (see earlier discussion of cholestasis). Once the

regenerative nodules of cirrhosis have formed, however, bile stasis may become less conspicuous. Ascending bacterial infection incites a supervening robust neutrophfilic infiltration of bile ducts and cholangitic abscesses.

PRIMARY BILIARY CIRRHOSIS

Primary biliary cirrhosis is a chronic, progressive, and often fatal cholestatic liver disease, characterized by the destruction of intrahepatic bile ducts, portal inflammation and scarring, and the eventual development of cirrhosis and liver failure. The primary feature of this disease is a nonsuppurative, granulomatous destruction of medium-sized intrahepatic bile ducts; cirrhosis appears only late in the course.

- This is primarily a disease of middle-aged women, with a female-to-male predominance in excess of 6:1. Age of onset is between 20 and 80 years, with the peak incidence between 40 and 50 years.

- The onset is insidious, usually presented with pruritus. Jaundice develops late in the course.

- Hepatomegaly is typical. Xanthomas and xanmelasmas arise as a result of cholesterol retention. Stigmata of chronic liver disease are late features.

- The disease may be asymptomatic for years, running its course over two or more decades.

MORPHOLOGY. Primary biliary cirrhosis is the prototype of all conditions leading to small-duct biliary fibrosis and cirrhosis. Historically, four histologic stages have been described:

1. The florid duct lesion (granulomatous destruction of interlobular bile ducts).
2. Ductular proliferation with periportal hepatitis.
3. Scarring, with bridging necrosis and septal fibrosis.
4. Cirrhosis.

Although conceptually useful, these four stages cannot be reliably assessed histologically because primary biliary cirrhosis is a focal and variable disease, and exhibits different degrees of severity in different portions of the liver. Therefore it is more useful to regard primary biliary cirrhosis as being marked by damage restricted to portal tracts, followed by progressive damage to the parenchyma..

Portal Tract Lesion. There is random, focal destruction of interlobular and septal bile ducts by granulomatous inflammation, entitled the florid duct lesion. Affected portal tracts exhibit a dense infiltrate of lymphocytes (including lymphoid follicle formation), histiocytes, plasma cells, and a few eosinophils. Approximately 50 % of biopsy specimens obtained early in the disease show ductal lesions. Granulomas and a lymphocytic infiltrate may be present within the lobular parenchyma. Cholestasis is variably present.

Progressive Lesion. With more global hepatic involvement, normal interlobular bile ducts become infrequent, and secondary obstructive changes develop, similar to those seen in extrahepatic obstruction. Mallory bodies may be present in hepatocytes adjacent to portal tracts. Initially portal tract inflammation may be marked and spilled over into the parenchyma, causing destruction of adjacent hepatocytes (piecemeal necrosis). With time, inflammation subsides, and granulomas and florid duct lesions become infrequent. Hepatocyte loss, fibrosis, and nodular regeneration lead to the gradual development of true cirrhosis. Macroscopically the liver does not at first appear abnormal, but as the disease progresses, bile stasis stains the liver green. The capsule remains smooth and glistening until a fine granularity appears, culminating in a well-developed, uniform micronodularity. Liver weight is at first normal to increased (owing to inflammation); ultimately liver weight is slightly decreased. In most cases, the end-stage picture may be difficult to distinguish from secondary biliary cirrhosis or cirrhosis that follows chronic active hepatitis.

4. Lesson plan

1) To study the following macropreparations, to describe them according to the scheme for the description of macrodrugs.

Macropreparations.

Fatty liver hepatosis - describe size of the liver, its consistency and its color from the surface and in the section.

Liver cirrhosis - determine the size, type and color of the organ from the surface and in the section, note the approximate size of the regenerating nodes and interlayers of connective tissue between them.

Acute liver necrosis - describe to the size, type and color of the organ from the surface and in the section, note the approximate sizes, type, color of the pathological process in the section.

Acute cholecystitis - describe size of the gallbladder, the condition of the outer shell (appearance, degree of blood supply, the nature of plaque), the thickness and type of wall in the section, the nature of the contents in the lumen.

Gallbladder stones - describe size of the gallbladder, the condition of the outer shell (appearance, degree of blood supply, plaque), the thickness and type of wall in the section, the nature of the contents in the lumen, the shape, color, size and number of stones.

2) Examine the following micropreparations, sketch them, indicate and mark the pathological changes with arrows, using the atlas of micropreparations.

Micropreparations.

Massive liver necrosis (stained with hematoxylin and eosin) - note the condition of the parenchyma and stroma (sinusoids, Kupffer cells) in the center and on the periphery of the hepatic lobules.

Hepatic steatosis (stained with hematoxylin and eosin) - pay attention to the state of hepatocytes (the presence of dystrophy, the position of the cell nucleus), note the nature and localization of the pathological process.

Acute viral hepatitis (hematoxylin and eosin staining) - pay attention to the state of hepatocytes (the presence of dystrophy, necrosis), note the nature and localization of inflammatory infiltrate.

Chronic viral hepatitis (stained with hematoxylin and eosin) - pay attention to the state of hepatocytes (the presence of dystrophy, necrosis), note the nature and localization of inflammatory infiltrate.

Cirrhosis of the liver (stained with hematoxylin and eosin) - find morphological signs characteristic of cirrhosis of the liver; pay attention to the thickness of the septum, the severity and nature of dystrophic and necrotic changes in hepatocytes, the severity and cellular composition of inflammatory infiltration.

Liver cirrhosis (van Gieson stain) - to find morphological signs characteristic of liver cirrhosis; pay attention to the thickness of the septum, the severity and nature of dystrophic and necrotic changes in hepatocytes, the severity and cellular composition of inflammatory infiltration.

3) Examine the following electron diffraction patterns using an atlas of micropreparations.

Electron micrograph.

1. Viral hepatitis. In the Disse space there are multiple viral particles, the core of the hepatocyte is wrinkled.
2. Alcoholic hyaline (Gi) in the cytoplasm of hepatocyte.
3. Portal cirrhosis of the liver. Sinusoid (C) is squeezed, in the perisinusoidal space fibroblasts (Fb) and bundles of collagen fibers (CL) (GL - glycogen).

4) Solve the following situational problems (case study) using the tutorial.

Situational tasks (case study).

Case 1

Patient K., 38 years old, was admitted to the hospital with complaints of jaundice, nausea, vomiting, weakness, dizziness, fever up to 38 ° C, dark urine, discoloration of feces. Sick 4 days. On examination: the condition is extremely serious, stiff, from the mouth - hepatic odor, severe yellowness of the skin and sclera; Blood Bi - 320 μmol / L (indirect - 230 μmol / L, direct - 90 μmol / L); anti-HAV IgM antibodies were detected in the blood. In a hospital, the patient's condition progressively worsened, despite intensive therapy being carried out, a coma developed, from which the patient died. At autopsy: pronounced yellowness of the skin and mucous membranes; cerebral edema; the liver is reduced in size, flabby, red-brown in color (microscopically: against the background of hydropic degeneration of hepatocytes, multiple hepatocyte necrosis is noted, around which there is pronounced mononuclear and lymphocytic infiltration, vascular congestion.

Questions: 1) What disease did the patient have? 2) What complication developed and caused death? 3) Describe extrahepatic changes in this disease.

Case 2

Patient P., 22 years old, a drug addict, ill for the past 5 years, was admitted to the hospital in an extremely serious condition; Objectively: coma, icteric staining of the skin and visible mucous membranes; Bi blood - 480 μmol / L (indirect - 360 μmol / L, direct - 120 μmol / L); anti-HCV antibodies were detected in serum. After 3 days, death occurred with coma. At autopsy: the liver is sharply reduced in size, red-brown, microscopically: multiple bridge-like centro-central and centro-portal necrosis, intense inflammatory infiltration, sclerosis of the portal tracts, a combination of fatty and hydropic degeneration of hepatocytes, lymphocyte chains in sinusoids, protrusion of gall .

Questions: 1) What disease did the patient have? 2) What complication developed?

Case 3

In patient B., 28 years old, anti-HBV antibodies were detected in the blood; complaints of recurrent pain in the right hypochondrium, nausea, vomiting, at present - icteric skin and sclera. Performed a puncture biopsy of the liver. Microscopically revealed in the biopsy specimen: hepatocyte necrosis, hydropic hepatocyte dystrophy, Councilman's bodies, lymphohistiocytic infiltrates, portal tract sclerosis, “matte vitreous hepatocytes” (direct marker HbsAg) and “sand nuclei” (direct marker HbcAg).

Questions: 1) What disease did the patient have? 2) What is the prognosis of this disease?

Case 4

Patient K., 55 years old, died with ongoing gastrointestinal bleeding. A history of viral hepatitis 20 years ago. At the autopsy: the liver — the surface is coarse and fine tuberous, the sections have coarse and finely knotted tissue, yellow-brown in color (microscopically: multiple fibrotic septa, convergence of triads, protein and fatty hepatocyte dystrophy, severe lymphohistiocytic and neutrophilic septum infiltration, infiltrate exit sites into the parenchyma with the formation of step necrosis); the esophagus - there is blood in the lumen, the mucous membrane is pale, thickened, convoluted veins bulge out from under the mucosa, in the wall of one of which there is an opening covered by a bundle of blood; in the stomach - about 1 liter of “coffee grounds” type contents, the contents of the intestines are black; spleen enlarged 1.5 times, dense, in the abdominal cavity about 3 liters of clear, colorless liquid.

Questions: 1) What liver disease did the patient have? 2) What complications developed? 3) Explain the genesis of the development of the described complications.

Case 5

Patient M. died of acute bilateral pneumonia on the 5th day after the operation of cholecystectomy performed for acute calculous phlegmonous cholecystitis. At autopsy: acute bilateral lower lobar focal confluent bronchopneumonia; liver: slightly enlarged, test-like consistency, ocher-yellow liver tissue on sections, microscopically: in the hepatocyte cytoplasm

there are multiple small and large optically “empty” vacuoles stained with orange-red color by Sudan III.

Questions: 1) What pathological process took place in the liver? 2) What is the possible reason for the development of the described pathological process in the liver?

5) Answer the following questions of the current test control.

QUESTIONS OF THE CURRENT TEST CONTROL:

LIVER DISEASES

Choose one correct answer

1. Liver cells involved in the accumulation and metabolism of vitamin A:
a) hepatocytes,
b) stellate cells (Ito cells),
c) stellate reticuloendotheliocytes (Kupffer cells),
g) endothelial cells,
e) fibroblasts of portal tracts.

Select all correct answers.

2. Macrovesicular steatosis can occur with:
a) viral hepatitis C,
b) alcoholic disease,
c) obesity,
g) viral hepatitis B,
e) diabetes.

Choose one correct answer

3. The appearance of inflammatory infiltrate in the liver:
a) regeneration
b) cirrhosis,
c) hepatoma
d) dystrophy,
e) hepatitis.

Choose one correct answer

4. A change in the color of the skin, sclera, serous and mucous membranes of the internal organs as a result of an increase in the concentration of bilirubin in the blood serum is:
a) melanosis
b) vitiligo, c) jaundice,
g) cyanosis,
e) nevus.

Select all correct answers.

5. Hereditary hyperbilirubinemia occurs in the syndrome:
a) Krigler — Nayyar type I,
b) Gilbert,
c) Krigler — Nayyar type II,
g) Peitz-Yegers,
e) Dhabi to — Johnson.

Select all correct answers.

6. Hepatic cell failure can develop with:
a) microvesicular steatosis,
b) massive necrosis of hepatocytes,
c) acute inflammation of the liver,
g) cirrhosis of the liver,
e) chronic inflammation of the liver.

Select all correct answers.

7. Morphological changes in cirrhosis of the liver:
a) violation of the structure of the liver,
b) regenerative nodes from hepatocytes,
c) bridged fibrous septa,
d) proliferation of stellate cells (Ito cells),
d) a change in the vascular network of the liver.

Select all correct answers.

8. Causes of death of patients with viral cirrhosis of the liver:

a) pulmonary embolism,
b) liver cell failure,
c) complications of portal hypertension,
g) hepatocellular carcinoma,
e) generalized infection.

Select all correct answers.

9. The synthesis of collagen by activated myofibroblasts begins as a result of:
a) destruction of the extracellular matrix,
b) direct stimulation of toxins,
c) apoptosis of stellate cells (Ito cells),
g) production of cytokines by hepatocytes,
e) cytokine production by infiltrate cells.

Select all correct answers.

10. Manifestations of portal hypertension:
a) bleeding from the veins of the esophagus,
b) congestive splenomegaly,
c) ascites,
g) the expansion of the veins of the anterior abdominal wall,
e) cerebral hemorrhage.

Choose one correct answer

11. Liver biopsy of a 65-year-old man with jaundice revealed severe cholestasis, a foamy type of hepatocyte cytoplasm and lake bile. Conclusion:
a) cirrhosis of the liver,
b) obstruction of the biliary tract,
c) Gilbert's syndrome,
g) viral hepatitis B,
e) viral hepatitis C.

Choose one correct answer

12. With hepatorenal syndrome in a patient with viral cirrhosis of the liver in a kidney biopsy, you can find:
a) focal necrosis of the glomeruli,
b) proliferative glomerulonephritis,
c) necrotic nephrosis,
g) the usual histological picture,
e) interstitial nephritis.

Choose one correct answer

13. A man of 50 years for 20 years suffers from alcoholic cirrhosis of the liver with the development of syndromes of portal hypertension and hepatic cell failure. For this patient, a symptom is characteristic:
a) hypoalbuminemia,
b) thrombocytosis,
c) hypogammaglobulinemia,
g) hirsutism,
d) increased levels of testosterone in the blood.

Choose one correct answer

14. Often the hepatitis virus causes a fulminant course of hepatitis:
a) A
b) B,
c) C, r) D, D) E.

Select all correct answers.

15. Characterization of viral hepatitis A:
a) benign cyclic course,

b) fecal-oral transmission,
c) low mortality,
g) the development of cirrhosis of the liver,
e) lifelong immunity.
Select all correct answers.
16. Characterization of viral hepatitis B:
a) vertical transmission path,
b) the small size of the virus with defective RNA,
c) prolonged persistence of the virus in the body,
g) the formation of carriage,
e) parenteral route of transmission.
Select all correct answers.
17. Characterization of viral hepatitis C:
a) parenteral route of transmission,
b) lack of effective immunity,
c) low incidence of liver cirrhosis,
d) high frequency of chronicity,
e) mild clinical course.
Select all correct answers.
18. Characterization of viral hepatitis D:
a) low frequency of chronicity,
b) occurs in homosexuals,
c) transforms hepatitis B into a fulminant form,
g) occurs in patients with hemophilia,
e) hepatic cell carcinoma develops.
Select all correct answers.
19. In a liver biopsy sample of a 38-year-old man with acute viral hepatitis B, the following were found:
a) hydropic degeneration of hepatocytes,
b) infiltrate in the parenchyma and portal tracts,
c) the expansion of portal tracts due to fibrosis,
d) apoptotic bodies (Councilsilmen's bodies),
e) merging and / or bridge necrosis of hepatocytes.
Select all correct answers.
20. In a liver biopsy sample of a 40-year-old woman with mild chronic hepatitis B virus, the following were found:
a) preserved lobular and beam structure,
b) periportal fibrosis,
c) infiltration in portal tracts,
g) severe cholestasis,
e) apoptotic bodies (Kaunsilmen's bodies).
Select all correct answers.
21. In a liver biopsy of a man of 25 years with chronic viral hepatitis C found:
a) macrovesicular steatosis of hepatocytes,
b) the formation of lymphoid follicles in the portal
tracts
c) merging and / or bridge necrosis of hepatocytes,
d) apoptotic bodies (Councilsilmen's bodies),
d) the expansion of portal tracts due to fibrosis.
Select all correct answers.
22. Macroscopic characteristics of alcoholic liver steatosis:
a) an increase in the size of the organ,

b) soft consistency,
c) smooth surface
d) yellow color
e) many rounded foci in the parenchyma.

SITUATIONAL OBJECTIVE

A 60-year-old patient suffers from chronic alcoholism for 30 years. When examining the liver is dense, the surface is tuberous. On the anterior abdominal wall, the veins are dilated, the spleen is palpated. A liver biopsy was performed.

Select all correct answers.

23. The following were detected in the biopsy sample:
a) monomorphic small nodes-regenerates,
b) wide septa with close triads,
c) macrovesicular steatosis of hepatocytes,
g) leukocyte infiltrate in the stroma,
e) Mallory bodies in hepatocytes.

SITUATIONAL OBJECTIVE

A woman 50 years old for 10 months is concerned about skin itching, fatigue. Serum levels of transaminases are slightly increased, the amount of alkaline phosphatase is significantly increased, high titers of antimitochondrial antibodies. During the examination, obstruction of the biliary tract was not detected. A liver biopsy was performed.

Select all correct answers.

24. The following were detected in the biopsy sample:
a) granulomatous cholangitis,
b) opaque vitreous hepatocytes,
c) a decrease in the number of bile ducts,
g) portal tract infiltration,
d) the expansion of portal tracts due to fibrosis.

Choose one correct answer

25. To detect sclerosis in the liver, use:
a) hematoxylin and eosin,
b) PAS reaction
c) toluidine blue,
d) Sudan Sh,
e) Perls reaction,
e) picrofuxin.

4. 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 (14th).

8. “Pathology” Eds. Rubin, J.L. Farber – Philadelphia: Lippincott Raven Publ, 1998 (3th).

9. “Pathology Illustrated” Govan A.D.T., Macfarlane P.S., Callander R. – Edinburgh: Churchill Livingstone, 1995 (4th).

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 (6th).

11. “Wheater’s Basic Histopathology. A Color Atlas and Text” Burkitt H.G., Stevens A.J.S.L., Young B. – Edinburgh: Churchill Livingstone, 1996 (3th).

12. “Color Atlas of Anatomical Pathology” Cooke R.A., Steward B. – Edinburgh: Churchill Livingstone, 1995 (10th).

13. “General Pathology ” Walter J.B., Talbot I.C. – Edinburgh: Churchill Livingstone, 1996 (7th).

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 (10th).

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