Ministry of Health of the Republic of Belarus
Educational Institution
“Gomel State Medical University”

Department of Pathological Anatomy

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METHODICAL GUIDELINES

for conducting a practical class
in the academic discipline “Pathological Anatomy”
for students
of the 3rd year, Faculty of International Students (instruction in English),
enrolled in the specialty
7-07-0911-01 “General Medicine”

Topic: “Liver pathology: steatosis, hepatitis, cirrhosis”

Duration: 3 hours

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EDUCATIONAL AND INSTRUCTIONAL GOALS, OBJECTIVES, AND MOTIVATION FOR MASTERING THE TOPIC

Educational Goal:

- To study the definition, classification, etiology, pathogenesis, morphology, complications, and outcomes of fatty liver disease (steatosis), hepatitis, and cirrhosis. To analyze steatosis (fatty liver): causes (alcohol, obesity, diabetes, metabolic syndrome, drugs, toxins), morphology (macrovesicular and microvesicular steatosis), progression to steatohepatitis (nonalcoholic steatohepatitis – NASH, alcoholic steatohepatitis). To examine hepatitis: acute hepatitis (viral – A, B, C, D, E; drug-induced, toxic, autoimmune) with histological features (ballooning degeneration, acidophil bodies (Councilman bodies), lobular disarray, spotty necrosis, portal inflammation, cholestasis) and chronic hepatitis (grading – necroinflammatory activity; staging – fibrosis). To discuss viral hepatitis serological and molecular markers. To analyze cirrhosis: definition, etiology (alcohol, viral hepatitis B and C, NASH, biliary diseases, autoimmune hepatitis, metabolic diseases, cryptogenic), morphological types (micronodular, macronodular, mixed), histological features (bridging fibrosis, regenerative nodules, disruption of lobular architecture). To discuss complications of cirrhosis: portal hypertension (ascites, varices, splenomegaly, hepatic encephalopathy), hepatocellular carcinoma, liver failure, coagulopathy, jaundice.

Instructional Goal:

- Within the framework of the educational process for this academic discipline, the student must acquire not only theoretical knowledge, practical skills and abilities in the specialty but also develop their personal potential. They should cultivate qualities of responsibility and patriotism, be prepared to actively participate in the economic, socio-cultural, and public life of the country, recognize the social significance of their future professional activity, understand the norms of medical ethics and deontology, and learn to observe academic and labor discipline. In the course of studying the educational material, students should realize the importance of maintaining a healthy lifestyle and, as an example in the future, when performing professional duties, set an example for those around them and their patients.

Objectives: Upon completion of the practical session, the student must:

***Know*:**

- The definition, causes, and morphological features of hepatic steatosis;
- The histological features of acute and chronic hepatitis;
- The definition, etiology, and morphological types of cirrhosis;
- The complications of cirrhosis (portal hypertension, ascites, varices, hepatic encephalopathy);
- The relationship between chronic hepatitis, cirrhosis, and hepatocellular carcinoma;
- The grading and staging systems for chronic hepatitis.

Be able to:

- Identify macrovesicular and microvesicular steatosis on liver biopsy;
- Recognize the histological features of acute viral hepatitis (ballooning degeneration, acidophil bodies, lobular disarray);
- Diagnose cirrhosis based on macroscopic (nodular surface) and microscopic (fibrosis, regenerative nodules) features;
- Diagnose pathological processes and diseases based on the description of macroscopic and microscopic changes in organs and tissues of the body.

Master:

- Basic techniques for working with a microscope;
- Skills in clinical-anatomical analysis;
- The fundamentals of synthetic generalization of morphological diagnostic signs of diseases and their correct interpretation in cause-and-effect relationships.

Motivation for Mastering the Topic:

Liver diseases, including steatosis (fatty liver), hepatitis, and cirrhosis, are major causes of morbidity and mortality worldwide. Nonalcoholic fatty liver disease (NAFLD) affects approximately 25% of the global population, parallel to the obesity and diabetes epidemics. Chronic viral hepatitis (B and C) affects hundreds of millions of people and is a leading cause of cirrhosis and hepatocellular carcinoma. Understanding the morphological features of these diseases is essential for hepatologists, gastroenterologists, infectious disease specialists, pathologists, and primary care physicians for diagnosis, prognostication, and monitoring of treatment response.

QUESTIONS

1. Hepatosis. Definition. Etiology. Pathogenesis. Classification. Morphology. Complications and outcomes.
2. Autoimmune hepatitis. Definition. Etiology. Pathogenesis. Classification. Morphology. Complications and outcomes.
3. Primary biliary cholangitis (PBC). Definition. Etiology. Pathogenesis. Classification. Morphology. Complications and outcomes.
4. Viral hepatitis. Definition. Etiology. Pathogenesis. Classification. Morphology. Complications and outcomes.
5. Liver cirrhosis. Definition. Etiology. Pathogenesis. Classification. Morphology. Complications and outcomes. Causes of death. Portal hypertension.

COURSE OF THE SESSION

Liver cell injury can be caused by a variety of factors such as **microbial infections**, **toxins**, **circulatory disturbances**, or **trauma**, leading to the necrosis of hepatocytes. The extent of involvement within the hepatic lobule varies, resulting in three distinct types of liver cell necrosis: **diffuse** (ranging from submassive to massive), **focal** and **zonal**.

1. **Diffuse (Submassive to Massive) Necrosis**: This form of necrosis involves widespread and diffuse damage to liver cells, affecting entire groups of lobules. It is commonly associated with conditions such as viral hepatitis or drug-induced liver injury.

2. **Focal Necrosis**: Focal necrosis entails the involvement of small clusters of hepatocytes scattered irregularly throughout the hepatic lobule. Microbial infections are the most common cause of this type of necrosis, including viral hepatitis, military tuberculosis, typhoid fever, and various bacterial, viral, and fungal infections. Additionally, drug-induced hepatitis can lead to focal necrosis.

3. **Zonal Necrosis**: Zonal necrosis refers to the necrosis of hepatocytes within specific zones of the hepatic lobule, categorized into three types based on the affected zone and underlying etiology:

- **Centrilobular necrosis** predominantly affects hepatocytes in zone 3, situated around the central vein. It is frequently observed in ischemic insults, such as those seen in shock or congestive heart failure, as zone 3 is the farthest from the blood supply. Additionally, it may result from poisoning with substances like chloroform, carbon tetrachloride, or certain drugs.
- **Midzonal necrosis** involves hepatocytes in zone 2 of the hepatic lobule and is less common. This pattern of necrosis is observed in conditions like yellow fever and viral hepatitis. In viral hepatitis, some necrotic hepatocytes in the mid-zone may transform into acidophilic, rounded structures known as Councilman bodies.
- **Periportal (peripheral) necrosis** affects zone 1, which is closest to the arterial and portal blood supply. This zone is particularly susceptible to the effects of circulating hepatotoxins, as seen in conditions like phosphorus poisoning and eclampsia.

Hepatosis, a group of liver diseases characterized by **hepatocyte dystrophy** and **necrosis**, can manifest as **congenital** or **acquired** conditions, either **acute** or **chronic** in nature.

Acute hepatosis, also known as **toxic liver dystrophy**, presents with **progressive massive liver necrosis** and subsequent liver insufficiency. Its etiology includes poisoning from various sources such as **food products** (e.g., mushroom poisoning), **toxic substances** (e.g., phosphorus), and rare forms of **viral hepatitis**.

During the initial week of acute hepatosis, hepatocytes undergo **fat dystrophy**. Subsequently, necrosis and autolysis of hepatocytes occur, progressing to involve all lobules of the liver by the second week (characterized by **yellow dystrophy**). During the third week, the liver diminishes in size and turns red due to

the resolution of necrotic debris and the development of an inflammatory reaction with hyperemia of blood vessels (known as **red dystrophy**).

Patients with acute hepatosis typically exhibit various manifestations, including **jaundice** due to elevated bilirubin levels, **hemorrhagic syndrome** resulting from coagulation factor deficiency, **acute renal insufficiency** due to tubular epithelium necrosis, and dystrophic changes in internal organs secondary to intoxication. Liver insufficiency can lead to **death**, with survivors often developing **post-necrotic liver cirrhosis**.

Massive liver necrosis, also known as **massive hepatic necrosis** or **fulminant hepatic failure**, is a severe and often life-threatening condition characterized by extensive death of liver cells (hepatocytes) leading to rapid liver dysfunction.

The etiology, morphology, and outcomes of massive liver necrosis vary depending on the underlying cause, but it typically involves a cascade of events that result in widespread hepatocyte death and loss of liver function.

Massive liver necrosis: etiology

1. **Drug-induced Liver Injury**: Certain medications, toxins, and chemicals can cause severe liver damage, leading to massive necrosis. Examples include acetaminophen overdose, certain antibiotics, chemotherapeutic agents, and herbal supplements.

2. **Toxic Hepatitis**: Exposure to toxic substances such as industrial chemicals, mushroom toxins (e.g., Amanita species), or certain herbal remedies can result in acute liver failure with massive necrosis.

3. **Ischemic Hepatitis**: Severe and prolonged liver ischemia, often due to conditions like shock, hypotension, or hepatic artery thrombosis, can lead to extensive liver cell death.

4. **Metabolic Disorders**: Conditions such as Wilson's disease, acute fatty liver of pregnancy, or acute liver failure associated with hemochromatosis can also result in massive hepatic necrosis.

Massive liver necrosis: morphology

1. Macroscopic Examination: Grossly, the liver appears **enlarged**, **friable**, and may exhibit **areas of discoloration** such as yellow or green due to bile stasis. Hemorrhagic areas may also be present.
2. Microscopic Examination: Microscopically, there is **extensive necrosis of hepatocytes** throughout the liver parenchyma. The necrotic areas are often characterized by loss of cellular architecture, disruption of hepatic cords, and infiltration of inflammatory cells. Bridging necrosis, where necrotic areas extend and merge, is frequently observed.
3. Vascular Changes: In some cases, vascular **congestion** and **thrombosis** may be evident, reflecting impaired blood flow within the liver.
4. Biliary Changes: **Bile duct proliferation** and **bile stasis** may be observed due to impaired bile flow.

Massive liver necrosis: outcomes

1. **Recovery**: Some individuals with acute liver failure due to massive necrosis may recover with supportive care and prompt treatment. Liver regeneration can occur if the damage is not extensive, allowing the liver to regain function over time.

2. **Liver Transplantation**: In cases where liver function does not recover spontaneously, liver transplantation may be the only life-saving option. Transplantation provides a chance for survival and long-term recovery, although it comes with its own set of risks and challenges, including the availability of suitable donor organs and the risk of rejection.

3. **Death**: Despite aggressive medical management, massive liver necrosis can lead to multi-organ failure and death, especially if not promptly recognized and treated. The mortality rate remains high, particularly in cases where fulminant hepatic failure progresses rapidly.

Steatosis

Fatty liver disease, also known as steatosis, is a **chronic condition** characterized by the **abnormal accumulation of lipids** within hepatocytes. It represents a disruption in the normal processes of lipid synthesis and elimination, leading to the retention of triglyceride fats.

Etiology:

1. **Intoxication**: Excessive alcohol consumption or the use of certain medications can contribute to the development of fatty liver disease by impairing liver function and metabolism.

2. **Metabolic Disorders**: Conditions such as diabetes mellitus, Cushing's disease, hypothyroidism, and others can disrupt metabolic processes in the body, leading to the accumulation of fats in the liver.

3. **Dietary Factors**: Consuming a diet high in fats and carbohydrates can contribute to the accumulation of lipids in the liver, especially when coupled with a sedentary lifestyle.

4. **Hypoxia**: Conditions that result in reduced oxygen delivery to the liver, such as anemias or circulatory disorders, can also contribute to fatty liver disease by disrupting normal cellular metabolism.

Steatosis: morphology

In fatty liver disease, excess lipid accumulates within hepatocytes, forming **vesicles that displace the cytoplasm**. This results in characteristic changes in the appearance of the liver:

1. The liver may **increase in size**, often with a smooth surface.

2. The color of the liver may appear **yellowish** or brown-red due to the presence of lipid-laden cells.

3. **Fat droplets**, or inclusions, can be observed within hepatocytes under microscopic examination.

4. These fat inclusions may be distributed throughout the liver parenchyma, occurring in individual hepatocytes (**disseminated obesity**), in groups of hepatocytes (**zonal obesity**), or throughout the entire liver parenchyma (**diffuse obesity**).

When the vesicles are large enough to distort the nucleus, the condition is known as **macrovesicular steatosis**; otherwise, the condition is known as **microvesicular steatosis**. While not particularly detrimental to the cell in mild cases, large accumulations can disrupt cell constituents, and in severe cases, the cell may even burst.

Stages of Steatosis

1. **Simple Lipidosis**: In this stage, there is accumulation of fat inclusions inside cells, but without necrotic changes.
2. **Lipidosis with Necrobiosis of Hepatocytes and Inflammatory Reaction**: Here, lipidosis is accompanied by the death of hepatocytes and an inflammatory response.
3. **Lipidosis with Beginning of Lobular Structure Damage**: This stage involves further damage to the lobular structure of the liver due to lipid accumulation.

Lipid inclusions may lead to the death of hepatocytes and the formation of fat droplets located outside the cells, surrounded by an inflammatory reaction. Understanding the stages of fat hepatosis is essential for evaluating the severity of the condition and guiding treatment decisions.

Alcohol-induced steatosis, also known as **alcoholic fatty liver disease** (AFLD), is a prevalent liver condition characterized by the accumulation of fat within hepatocytes due to chronic alcohol consumption.

It represents one of the **earliest stages of alcoholic liver disease** and can progress to more severe forms of liver damage if alcohol consumption continues unabated.

The primary cause of alcohol-induced steatosis is chronic alcohol consumption. Ethanol, the primary component of alcoholic beverages, undergoes metabolism primarily in the liver. **Chronic alcohol intake disrupts lipid metabolism**, leading to an imbalance between lipid uptake, synthesis, and export within hepatocytes. This imbalance results in the accumulation of triglycerides and other lipids, causing hepatosteatosis.

Alcohol-induced steatosis occurs due to multiple mechanisms:

1. **Impaired Fatty Acid Oxidation**: Chronic alcohol consumption impairs mitochondrial function and the activity of enzymes involved in fatty acid oxidation, leading to the accumulation of fatty acids within hepatocytes.
2. **Increased Lipogenesis**: Alcohol metabolism promotes the synthesis of fatty acids and triglycerides in the liver. Excessive alcohol consumption enhances the expression of lipogenic enzymes, further contributing to lipid accumulation.
3. **Altered Lipid Secretion**: Alcohol disrupts the secretion of lipids from the liver, leading to the retention of triglycerides within hepatocytes.
4. **Oxidative Stress**: Ethanol metabolism generates reactive oxygen species (ROS), causing oxidative stress and damage to hepatocytes. Oxidative stress exacerbates lipid accumulation and promotes inflammation and fibrosis.

Drug-induced hepatosis, also known as **drug-induced liver injury** (**DILI**), refers to liver damage caused by the ingestion of various medications, herbs, or dietary supplements.

The pathogenesis of drug-induced hepatosis involves complex mechanisms that can lead to various forms of liver injury, **ranging from mild elevations in liver enzymes to severe liver failure**.

Many drugs have the potential to cause **direct hepatotoxicity**, where the drug or its metabolites directly injure liver cells (hepatocytes).

DILI: pathogenesis

1. **Metabolic Activation**: Some drugs require metabolic activation by liver enzymes to become toxic. For example, acetaminophen (paracetamol) undergoes metabolic activation to form a reactive metabolite that can cause oxidative stress and damage hepatocytes.
2. **Formation of Reactive Metabolites**: Certain drugs can undergo bioactivation to form reactive metabolites that covalently bind to cellular proteins and DNA, leading to cellular damage and death.
3. **Inhibition of Mitochondrial Function**: Some drugs can directly impair mitochondrial function within hepatocytes, leading to decreased ATP production, oxidative stress, and cell death. Examples include certain antiretroviral drugs and antibiotics.
4. **Direct Cellular Toxicity**: Some drugs exert direct toxic effects on hepatocytes through mechanisms such as disruption of cell membranes, inhibition of protein synthesis, or induction of apoptosis (programmed cell death).

DILI: pathogenesis

DILI can also involve **immune-mediated mechanisms**:

1. **Hypersensitivity Reactions**: Some individuals may develop hypersensitivity reactions to certain drugs, leading to immune-mediated liver injury. These reactions can manifest as various forms of liver injury, including acute hepatitis, granulomatous hepatitis, or autoimmune-like hepatitis.
2. **Drug-Induced Autoimmune Hepatitis**: Certain drugs can trigger an autoimmune response in susceptible individuals, leading to the development of autoimmune hepatitis. This can involve the production of autoantibodies, infiltration of inflammatory cells, and destruction of hepatocytes.

Several factors can influence the **risk** of DILI:

1. **Genetic Factors**: Genetic polymorphisms in drug-metabolizing enzymes, transporters, or immune-related genes can predispose individuals to drug-induced hepatotoxicity.
2. **Drug Factors**: The chemical structure, dose, route of administration, and duration of drug exposure can all influence the likelihood of drug-induced hepatosis.
3. **Underlying Liver Disease**: Pre-existing liver disease, such as viral hepatitis or non-alcoholic fatty liver disease, can increase susceptibility to drug-induced hepatotoxicity.

Diabetic hepatosis, also known as **non-alcoholic fatty liver disease** (**NAFLD**) in the context of diabetes, is a common liver condition associated with insulin resistance and type 2 diabetes mellitus.

Insulin resistance, a hallmark of type 2 diabetes, plays a central role in the **pathogenesis of diabetic hepatosis**. In insulin-resistant states, peripheral tissues such as muscle and adipose tissue exhibit reduced responsiveness to insulin, leading to compensatory **hyperinsulinemia**. However, the **liver remains sensitive to insulin**, resulting in increased hepatic glucose production and lipogenesis. Consequently, **excess triglycerides are synthesized within the liver**, contributing to the development of hepatic steatosis.

Diabetic hepatic steatosis: pathogenesis

1. **Increased Lipogenesis**: Insulin resistance and hyperinsulinemia promote de novo lipogenesis in the liver, leading to increased synthesis of fatty acids and triglycerides. This excess lipid production overwhelms the capacity of hepatocytes to export or metabolize triglycerides, resulting in the accumulation of fat within liver cells.
2. **Impaired Lipid Clearance**: Insulin resistance also impairs the clearance of lipids from the circulation by reducing the uptake of fatty acids by peripheral tissues such as adipose tissue and skeletal muscle. As a result, circulating free fatty acids are preferentially taken up by the liver, exacerbating hepatic steatosis.
3. **Adipose Tissue Dysfunction**: Adipose tissue dysfunction in obesity and insulin resistance leads to the release of pro-inflammatory cytokines (e.g., TNF-alpha, IL-6) and adipokines (e.g., leptin, adiponectin) into the circulation. These mediators promote inflammation and insulin resistance in the liver, further exacerbating hepatic lipid accumulation.
4. **Mitochondrial Dysfunction**: Oxidative stress resulting from mitochondrial dysfunction contributes to hepatocyte injury and inflammation in diabetic hepatosis. Reactive oxygen species (ROS) generated during mitochondrial respiration damage cellular components and activate inflammatory pathways, promoting liver injury and fibrosis.

Hepatitis, characterized by **liver inflammation**, can arise from a multitude of causes, including infectious viruses and noninfectious agents, posing a range of health risks, some of which can be life-threatening.

Chronic hepatitis denotes a persistent inflammatory condition of the liver lasting over 6 months without signs of resolution. It can manifest either as **primary**, independent diseases, or **secondary**, developing alongside other health conditions.

Primary hepatitis often stems from exposure to hepatotropic viruses (particularly hepatitis B and C), alcohol abuse, or certain medications like methyldopa, oxyphenizatin, halotin, isoniazid, nitrofurantoin, among others.

Conversely, **secondary hepatitis** is linked to various factors such as infection, intoxication, gastrointestinal damage, autoimmune processes, metabolic disorders like Wilson's disease, α1-antitrypsin deficiency, and more.

The course of hepatitis can be **acute** or **chronic**.

Histologically, chronic hepatitis is categorized into **chronic persistent hepatitis** (CPH) and **chronic active hepatitis** (CAH). However, this classification transcends mere morphology, as each subtype reflects distinct clinical aspects, including disease activity, symptom severity, and prognosis.

Chronic hepatitis serves as a nonspecific manifestation of numerous chronic liver conditions. Differential diagnosis typically involves an array of histological, laboratory, and clinical assessments.

Chronic hepatitis often **arises from underlying chronic liver diseases**, including iron overload (**hemochromatosis**), **Wilson's disease** (hepatolenticular degeneration), **alpha-1-antitrypsin deficiency**, autoimmune liver diseases (such as **autoimmune hepatitis**), and primary biliary cirrhosis.

Hemochromatosis is a disorder characterized by the accumulation of excessive **iron deposits** in multiple organs, leading to dysfunction. Normally, the body tightly regulates iron absorption because it lacks the ability to eliminate excess iron. However, in hemochromatosis, pathological levels of iron accumulate, causing a range of health issues. Dubbed "**bronze diabetes**", hemochromatosis is often associated with skin discoloration and pancreatic complications. It stands as the most prevalent autosomal recessive disorder among individuals of European descent.

Organs affected by hemochromatosis encompass the liver, pancreas, heart, thyroid, joints, skin, gonads, and pituitary gland. Excessive alcohol consumption and viral hepatitis exacerbate the condition, particularly in terms of liver and pancreatic toxicity. Notably, **cirrhosis is present in 70% of hemochromatosis patients**, significantly elevating the risk of hepatocellular carcinoma, a leading cause of mortality in affected individuals.

Autoimmune hepatitis stands as a chronic condition instigated by an **aberrant immune response targeting liver cells**. Similar to other autoimmune disorders, the presence of circulating auto-antibodies aids in diagnosis. These auto-antibodies include the sensitive yet less specific anti-nuclear antibody (**ANA**), smooth muscle antibody (**SMA**), and atypical perinuclear antineutrophil cytoplasmic antibody (**p-ANCA**).

Triggers for autoimmune hepatitis encompass **drug-induced factors** (such as nitrofurantoin, hydralazine, and methyldopa), **post-liver transplant** occurrences, and **viral infections** (including hepatitis A, Epstein-Barr virus, or measles). Manifestations of autoimmune hepatitis vary widely, spanning from asymptomatic states to acute or chronic hepatitis, and in severe cases, progressing to fulminant liver failure.

Typically, autoimmune hepatitis **predominantly affects young females**, though it can affect individuals of any gender and age. Patients may exhibit classic signs and symptoms of autoimmunity, such as fatigue, anemia, anorexia, amenorrhea, acne, arthritis, pleurisy, thyroiditis, ulcerative colitis, nephritis, and maculopapular rash.

Autoimmune hepatitis: pathology

1. **Inflammatory Infiltrates**: Histologically, autoimmune hepatitis is marked by a dense infiltrate of lymphocytes, plasma cells, and macrophages within the hepatic parenchyma. These inflammatory cells infiltrate the portal tracts, often extending into the lobules.

2. **Interface Hepatitis**: A hallmark feature of autoimmune hepatitis is interface hepatitis, characterized by inflammation at the interface between hepatocytes and the portal tracts. This interface activity can lead to interface hepatitis on liver biopsy, with inflammation and necrosis affecting the limiting plate of hepatocytes.

3. **Liver Cell Necrosis**: Autoimmune hepatitis may exhibit varying degrees of hepatocyte necrosis, ranging from spotty necrosis to confluent necrosis. This necrosis can be accompanied by hepatocyte ballooning and Mallory-Denk bodies, indicative of cellular injury and stress.

4. **Fibrosis and Cirrhosis**: Over time, chronic inflammation and hepatocellular injury can lead to fibrosis and cirrhosis. Fibrosis manifests as collagen deposition within the portal tracts and periportal areas, eventually progressing to bridging fibrosis and micronodular or macronodular cirrhosis in advanced cases.

5. **Regenerative Nodules**: In cirrhotic livers, regenerative nodules composed of hepatocytes surrounded by fibrous septa may develop. These nodules represent attempts at liver regeneration in response to ongoing injury and fibrosis.

Primary biliary cholangitis (PBC), previously identified as primary biliary cirrhosis, represents an **autoimmune** liver ailment characterized by the **gradual destruction of the liver's small bile ducts**. This destruction leads to the accumulation of bile and other toxins within the liver, a condition termed cholestasis. Over time, this ongoing damage can result in the formation of scar tissue, fibrosis, and eventual cirrhosis.

Common symptoms of PBC include fatigue, itching, and, in more advanced stages, jaundice. In early stages, changes may only be detectable through blood tests.

PBC is relatively uncommon, affecting approximately one in 3,000–4,000 individuals. It exhibits a notable predilection for women, with a female-to-male ratio of at least 9:1.

From a morphological standpoint, PBC is characterized by **dense lymphocytic infiltration in portal tracts**, along with **granulomatous destruction** and loss of medium-sized interlobular bile ducts. These changes are focal and variable within the liver. Additional morphological features include periportal accumulation of Mallory hyaline, minimal neutrophils, and variable portal eosinophils.

Viral hepatitis is a broad term encompassing **liver inflammation caused by infection with hepatitis viruses**, which are classified into five main types: hepatitis A, B, C, D, and E. Each virus exhibits distinct epidemiological characteristics, routes of transmission, clinical manifestations, and outcomes.

Hepatitis A and E: These viruses are primarily transmitted through contaminated food or water, especially in regions with inadequate sanitation. Hepatitis A and E infections typically result from ingesting contaminated food or water, leading to acute illness characterized by jaundice, fatigue, and gastrointestinal symptoms. However, hepatitis E can occasionally cause severe acute liver failure, particularly in pregnant women and individuals with underlying liver disease.

Hepatitis B, C, and D: Transmission of these viruses occurs primarily through exposure to infected blood or body fluids, including sexual contact, needle sharing among intravenous drug users, and perinatal transmission from mother to child. Hepatitis B and C infections can lead to chronic liver disease, cirrhosis, and hepatocellular carcinoma if left untreated. Hepatitis D is a defective virus that requires concurrent infection with hepatitis B to replicate and cause liver disease, resulting in more severe outcomes than hepatitis B infection alone.

Viral hepatitis: pathogenesis

The pathogenesis of viral hepatitis involves a complex interplay between viral factors, host immune responses, and environmental factors:

1. **Viral Replication**: Hepatitis viruses target hepatocytes, where they replicate and produce viral particles, leading to direct cytopathic effects on liver cells.

2. **Immune Response**: The host immune system recognizes viral antigens and mounts an immune response, resulting in inflammation and tissue damage within the liver. Chronic hepatitis is characterized by persistent inflammation and immune-mediated destruction of hepatocytes.

3. **Cytokine Dysregulation**: Dysregulation of pro-inflammatory and anti-inflammatory cytokines contributes to the pathogenesis of liver injury and fibrosis in chronic hepatitis.

4. **Genetic Susceptibility**: Host genetic factors, such as human leukocyte antigen (HLA) polymorphisms, influence susceptibility to viral hepatitis and disease progression.

Viral hepatitis: morphology

1. **Hepatocellular Injury**: Hepatitis viruses cause varying degrees of hepatocellular injury, ranging from mild inflammation to hepatocyte necrosis and apoptosis.

2. **Portal Inflammation**: Inflammatory infiltrates consisting of lymphocytes, plasma cells, and macrophages are observed in the portal tracts, often extending into the liver lobules.

3. **Fibrosis and Cirrhosis**: Chronic inflammation triggers the deposition of extracellular matrix proteins, leading to progressive fibrosis and eventual cirrhosis, characterized by regenerative nodules surrounded by fibrous septa.

4. **Extrahepatic Manifestations**: In addition to liver involvement, viral hepatitis can manifest with extrahepatic complications, such as autoimmune phenomena, renal disease, dermatological manifestations, and neurological symptoms.

Viral hepatitis: clinical presentation

1. **Acute Hepatitis**: Patients with acute viral hepatitis may present with nonspecific symptoms, including fatigue, anorexia, nausea, vomiting, abdominal pain, and jaundice. Laboratory tests typically reveal elevated liver enzymes, bilirubin, and markers of viral infection.

2. **Chronic Hepatitis**: Chronic hepatitis may be asymptomatic or present with fatigue, malaise, abdominal discomfort, and signs of liver dysfunction. Long-term complications of chronic hepatitis include liver cirrhosis, hepatocellular carcinoma, and end-stage liver disease.

The diagnosis of viral hepatitis involves a combination of clinical evaluation, **serological testing** for viral markers, imaging studies, and liver biopsy when indicated. Treatment strategies vary depending on the type of viral hepatitis and may include antiviral therapy, immunomodulatory agents, supportive care, and lifestyle modifications. **Vaccination against hepatitis A and B viruses** is an effective preventive measure to reduce the burden of viral hepatitis worldwide.

Cirrhosis

Liver cirrhosis is a **progressive and irreversible condition** characterized by the **replacement of normal liver tissue with fibrous scar tissue**.

This fibrotic scarring disrupts the liver's structure and function, leading to impaired liver function and the development of complications such as **portal hypertension**, **ascites**, **hepatic encephalopathy**, and **hepatocellular carcinoma**.

Cirrhosis: etiology

1. **Chronic Viral Hepatitis**: Chronic infection with hepatitis B or C viruses is a leading cause of cirrhosis worldwide.

2. **Alcohol Abuse**: Prolonged excessive alcohol consumption is a major risk factor for the development of alcoholic liver cirrhosis.

3. **Non-Alcoholic Fatty Liver Disease** (NAFLD) and **Non-Alcoholic Steatohepatitis** (NASH): Obesity, insulin resistance, and metabolic syndrome contribute to the accumulation of fat in the liver, leading to inflammation, fibrosis, and cirrhosis.

4. **Autoimmune Liver Diseases**: Autoimmune hepatitis, primary biliary cholangitis (formerly primary biliary cirrhosis), and primary sclerosing cholangitis are autoimmune conditions that can progress to cirrhosis.

5. **Hemochromatosis**: Iron overload disorders, such as hereditary hemochromatosis, can cause iron deposition in the liver, leading to fibrosis and cirrhosis.

6. **Wilson's Disease**: This rare inherited disorder results in copper accumulation in the liver and other organs, leading to cirrhosis if untreated.

7. **Biliary Tract Disorders**: Chronic biliary obstruction, gallstones, and other biliary tract diseases can cause bile stasis, inflammation, and fibrosis, ultimately leading to cirrhosis.

Cirrhosis: pathogenesis

1. **Hepatocyte Injury**: Chronic liver injury, whether due to viral hepatitis, alcohol abuse, or other causes, triggers a cascade of inflammatory responses and tissue repair processes.

2. **Inflammation and Fibrosis**: In response to hepatocyte injury, hepatic stellate cells become activated and transform into myofibroblasts, which produce excessive amounts of extracellular matrix proteins, particularly collagen. This results in the formation of fibrous scar tissue that disrupts the liver's normal architecture and impairs its function.

3. **Progression to Cirrhosis**: Chronic inflammation and ongoing hepatocyte injury perpetuate the fibrotic process, leading to progressive fibrosis and ultimately cirrhosis. As the liver becomes increasingly scarred, its ability to regenerate and perform essential functions diminishes, resulting in the development of complications associated with cirrhosis.

Cirrhosis: morphology

The morphology of cirrhosis, particularly on pathohistological examination, reveals distinct changes reflective of the progressive **fibrotic remodeling** and **architectural distortion** within the liver parenchyma.

1. **Fibrous Septa Formation**: A hallmark feature of cirrhosis is the development of fibrous septa, which are dense bands of collagen that extend from the portal areas to surround regenerative nodules. These septa compartmentalize the liver parenchyma, disrupting the normal lobular architecture and impairing blood flow within the liver sinusoids.

2. **Regenerative Nodules**: In response to chronic injury and fibrosis, the liver undergoes attempts at regeneration, resulting in the formation of regenerative nodules composed of hepatocytes surrounded by fibrous septa. These nodules vary in size and shape and are distributed irregularly throughout the liver parenchyma.

3. **Nodular Transformation**: With disease progression, the liver undergoes nodular transformation, characterized by the replacement of normal hepatocytes with regenerative nodules surrounded by fibrous septa. This nodular transformation contributes to the development of the characteristic micronodular or macronodular appearance observed in cirrhotic livers.

4. **Hepatocyte Alterations**: Hepatocytes within cirrhotic livers often exhibit features of cellular injury and regeneration, including ballooning degeneration, cytoplasmic vacuolization, and increased mitotic activity. These changes reflect ongoing hepatocyte turnover in response to chronic injury and fibrosis.

5. **Portal Tract Changes**: The portal tracts in cirrhotic livers may exhibit various histological alterations, including inflammation, fibrosis, and bile duct proliferation. Chronic inflammation and fibrosis within the portal tracts contribute to portal hypertension, a key pathophysiological feature of cirrhosis.

6. **Microvascular Changes**: Microscopic examination of cirrhotic livers may reveal alterations in the hepatic microvasculature, including sinusoidal dilation, congestion, and endothelial dysfunction. These changes impair blood flow within the liver sinusoids and contribute to the development of portal hypertension and associated complications.

7. **Mallory-Denk Bodies**: Mallory-Denk bodies, eosinophilic cytoplasmic inclusions composed of aggregated intermediate filaments, are frequently observed in hepatocytes within cirrhotic livers, particularly in the setting of alcoholic liver disease. These cytoplasmic inclusions are indicative of cellular injury and stress.

Histopathological evaluation plays a **crucial role** in assessing disease **severity**, predicting **prognosis**, and **guiding therapeutic interventions** in individuals with advanced liver disease.

Alpha-1 antitrypsin deficiency, an **inherited genetic disorder**, impacts both the lungs and liver. In the liver, this deficiency can manifest as **benign neonatal hepatitis syndrome**, while a minority of adults may develop **liver fibrosis** progressing to **cirrhosis** and **hepatocellular carcinoma**.

The condition results in the accumulation of **mutant alpha-1 antitrypsin** molecules within hepatocytes, leading to **significant liver injury** even in individuals with a heterozygous state.

These accumulations are notable for their affinity to stain with the **PAS reaction** and resistance to cleavage by diastase, indicating their glycoprotein nature.

Portal hypertension is a condition characterized by **elevated pressure within the portal venous system**, typically defined as a hepatic venous pressure gradient (HVPG) exceeding 5 mmHg.

The pathogenesis of portal hypertension involves complex hemodynamic changes and structural alterations within the liver and splanchnic vasculature:

1. **Increased Resistance to Portal Blood Flow**: The primary cause of portal hypertension is increased resistance to portal blood flow within the liver sinusoids and intrahepatic portal veins. This increased resistance is primarily attributed to fibrotic remodeling, vascular constriction, and architectural distortion within the liver parenchyma, as seen in conditions such as cirrhosis, fibrosis, and schistosomiasis.

2. **Collateral Vessel Formation**: As portal pressure rises, collateral vessels develop to bypass the hepatic circulation and divert blood flow away from the liver. These collateral vessels include portosystemic shunts, such as esophageal varices, gastric varices, and rectal varices, as well as paraumbilical veins and caput medusae.

3. **Splanchnic Vasodilation**: In response to portal hypertension, there is systemic vasodilation within the splanchnic circulation, leading to increased blood flow to the splanchnic organs, including the stomach, intestines, and spleen. This splanchnic vasodilation further exacerbates portal hypertension by increasing portal blood inflow and contributing to the development of collateral vessels.

4. **Nitric Oxide and Endothelin Dysregulation**: Dysregulation of vasoactive mediators, such as nitric oxide and endothelin, plays a key role in the pathogenesis of portal hypertension. Increased nitric oxide production within the splanchnic vasculature promotes vasodilation and contributes to splanchnic hyperemia, while elevated endothelin levels enhance vasoconstriction and exacerbate intrahepatic resistance to portal blood flow.

5. **Angiogenesis and Fibrosis**: Chronic liver injury and inflammation stimulate angiogenesis and fibrogenesis within the liver parenchyma, leading to the formation of new blood vessels and deposition of extracellular matrix proteins. These structural changes further contribute to intrahepatic vascular resistance and exacerbate portal hypertension.

Portal hypertension

The **clinical manifestations** of portal hypertension result from both the **increased portal pressure** and the **development of collateral vessels**:

1. **Variceal Bleeding**: The most serious complication of portal hypertension is the development of varices, particularly esophageal varices, which are prone to rupture and cause life-threatening upper gastrointestinal bleeding. Patients may present with hematemesis, melena, hematochezia, and signs of hemodynamic instability.

2. **Ascites**: Portal hypertension leads to fluid transudation into the peritoneal cavity, resulting in the accumulation of ascitic fluid. Ascites may be asymptomatic or manifest with abdominal distension, discomfort, and respiratory compromise.

3. **Hepatic Encephalopathy**: The accumulation of neurotoxic substances, such as ammonia and mercaptans, due to impaired hepatic clearance contributes to the development of hepatic encephalopathy. Patients may present with altered mental status, confusion, asterixis, and coma.

4. **Hepatorenal Syndrome**: Progressive renal dysfunction, characterized by oliguria, azotemia, and electrolyte imbalances, may occur in the setting of advanced portal hypertension and severe circulatory dysfunction.

5. **Hepatopulmonary Syndrome**: Abnormal pulmonary vascular dilations and arteriovenous shunting may lead to hypoxemia and dyspnea, a condition known as hepatopulmonary syndrome.

6. **Portosystemic Encephalopathy**: The presence of portosystemic shunts, such as spontaneous portosystemic shunts or surgical shunts, may result in the development of portosystemic encephalopathy, characterized by neurological symptoms and cognitive impairment.

Splenomegaly, enlargement of the spleen, occurs in 35 to 50% of cases of portal hypertension. Increased portal pressure causes congestion and engorgement of the spleen, leading to its enlargement.

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