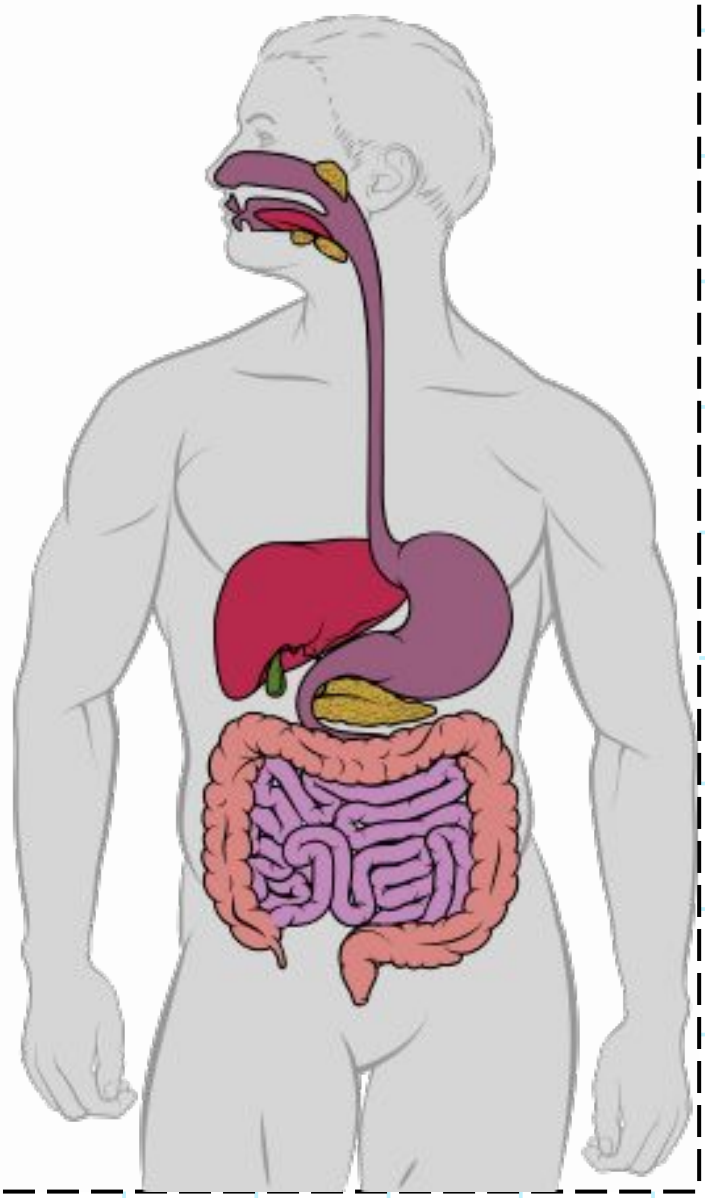
Liver cirrhosis and its complications



Editing File

Color index :
Main text (black)
Female Slides (Pink)
Male Slides (Blue)
Important (Red)
Dr's note (Green)
Extra Info (Grey)

OBJECTIVES

- Define Cirrhosis.
- Recognize the types and classification of cirrhosis.
- Recognize the causes and the pathogenic mechanisms leading to cirrhosis.
- Describe the pathological findings in cirrhotic livers.
- Recognize the major complications of liver cirrhosis.
- Understand the pathogenetic mechanisms underlying the occurrence of the complications.
- Recognize the clinical features inherent to the above-mentioned complications.
- Describe the pathological findings of the different complications.

THIS LECTURE WAS PRESENTED BY DR.WAJD ALTHAGAFI & DR.AHMED ALHUMAIDI

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IF YOU WANT TO WATCH OSMOSIS VIDEO

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Female Slides

Introduction

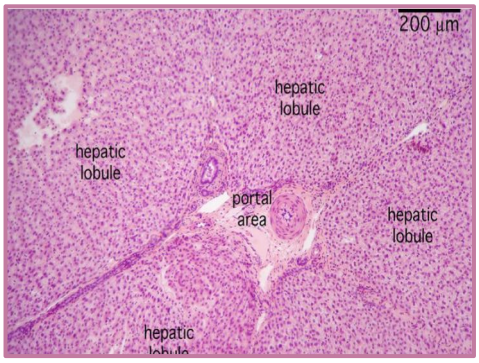
1

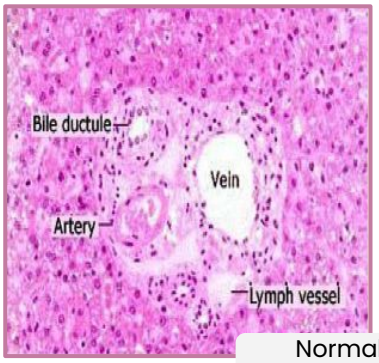
Normal adult liver weighs approximatel y 1400 g in females and 1800 g in males.

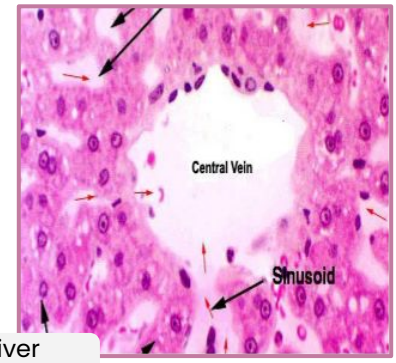
- **Has dual (double)blood supply:**
  ✓ Portal vein providing 60 - 70% of hepatic blood flow
  ✓ Hepatic artery supplies remaining 30 - 40%
- Both portal vein & hepatic artery enter the inferior aspect of the liver through the hilum "porta hepatis".
- Within the liver, the branches of the portal veins, hepatic arteries & bile ducts travel in parallel within portal tracts.

2

Normal histology of the liver







Normal liver lobules

Clinical Note

Patient with autoimmune hepatitis may present with Heterogeneous presentation that ranges from asymptomatic to acute liver failure and/or cirrhosis , Early signs include Fatigue, general malaise, and lethargy , Transient erythematous rash Or Signs of acute liver failure Jaundice , Right upper quadrant (RUQ) pain , Fever , Decreased platelet count

Differential Diagnosis includes: Primary biliary cholangitis (PBC): also presents with fatigue, jaundice, hepatomegaly, and biopsy results similar to AIH.

Primary sclerosing cholangitis (PSC): also presents with fatigue, jaundice, hepatomegaly. One of the best ways to differentiate PSC from AIH is via imaging modalities such as (magnetic resonance cholangiopancreatography)

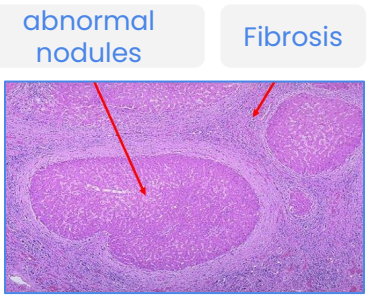
IMPORTANT

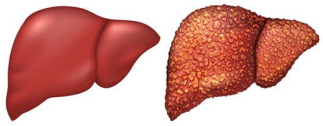
Liver cirrhosis

Osmosis Vid

Liver cirrhosis

- Cirrhosis is the morphologic change most often associated with chronic liver disease.
- It **refers to the diffuse transformation of the liver into regenerative parenchymal nodules surrounded by fibrous bands**
- Defined as a diffuse process characterized by **fibrosis** and the conversion of normal liver architecture into structurally **abnormal nodules**





Epidemiology

Female Slides

- It is among the top 10 causes of death in the Western world.
- It is the end-stage of chronic liver disease.
- Not all chronic liver disease terminates in cirrhosis & not all cirrhosis leads to end stage liver disease.

Cirrhosis, as the end stage of chronic liver disease, is defined by three main morphologic characteristics:

Female Slides

01

Fibrosis

in the form of delicate bands or broad scars/septa (Bridging fibrous septa).

02

Parenchymal nodules

containing hepatocytes encircled by fibrosis, with diameters varying from very small (<0.3 cm, micronodules) to large (several centimeters, macronodules).

03

Disruption

of the architecture of the entire liver.

Female Slides

Liver cirrhosis

Causes

- Generally, liver disease is an insidious process in which the signs & symptoms of hepatic decompensation appear weeks, months, or even years after the onset of injury.
- The hepatic injury may be imperceptible to the patient and to be manifest only by laboratory test abnormalities.

Test category	Blood measurement
Hepatocyte integrity	Cytosolic hepatocellular enzymes • serum aspartate (AST) • Serum alanine aminotransferase (ALT) • Serum lactate dehydrogenase (LDH)
Biliary excretory function	Substances normally secreted in bile • serum bilirubin A. Total : unconjugated B. Direct: conjugated only • Urine bilirubin • serum bile acids • plasma membrane enzymes (from damage to bile canaliculus) A. serum alkaline phosphatase B. serum γ-glutamyl transpeptidase (GGT)
Hepatocyte function	Proteins secreted into the blood : • Serum albumin • Prothrombin time (PT) • Partial thromboplastin time (PTT) Hepatocyte metabolism : • Serum ammonia • Aminopyrine breath test (hepatic demethylation)

Liver cirrhosis

Infrequent types of cirrhosis:

• The classification is based on the underlying etiology.

• Many forms of cirrhosis (particularly alcoholic cirrhosis) are initially micronodular (less than 3 mm), but there is a tendency for nodules to increase in size with time.

The cirrhosis developing in infants and children with galactosemia and tyrosinosis.

Drug-induced cirrhosis (methotrexate, enalapril, vitamin A).

Severe fibrosis can occur in the setting of cardiac disease "cardiac cirrhosis".

In some cases, there is no cause, and these are referred to cryptogenic cirrhosis.

Once cirrhosis is established, it is usually impossible to establish an etiologic diagnosis on morphologic grounds alone.

Classification of cirrhosis based on causes

- Alcoholic liver disease : 60% to 70%
- Viral hepatitis : 10% (most common in KSA)
- Biliary diseases : 5% to 10%
- Primary hemochromatosis : 5%
- Wilson disease : Rare
- α1-Antitrypsin deficiency : Rare
- Cryptogenic cirrhosis : 10% to 15%

IMPORTANT

Pathogenesis

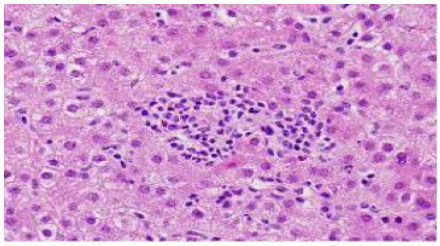
Pathogenesis of liver cirrhosis

Female Slides

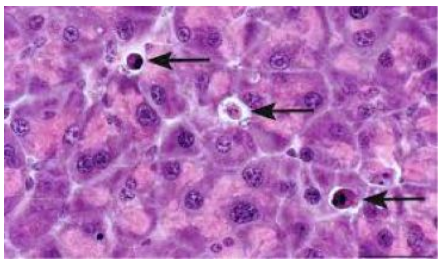
Injured hepatocytes may show several potentially reversible changes, such as accumulation of fat and bilirubin (cholestasis).
• When injury is not reversible, hepatocytes die by necrosis or apoptosis:
✔ Necrosis is commonly seen following hepatic injury caused by hypoxia
& ischemia.
✔ Apoptotic cell death predominates in viral, autoimmune & and drug- and toxin-induced hepatitis.

Mechanism of injury and repair Old Theory

Necrosis is commonly seen following hepatic injury caused by hypoxia & ischemia.



Apoptotic cell death predominates in viral, autoimmune & and drug- and toxin-induced hepatitis.



IMPORTANT

• The major source of /Principal cell type involved in scar deposition/excess collagen in cirrhosis is the perisinusoidal hepatic stellate cell./(**Ito cells**)
• They are pericytes found in the perisinusoidal space of the liver (space of Disse) and in normal liver has a role in the storage of vitamin A.
• Following liver injury, stellate cells become activated by several mechanisms and convert into highly fibrogenic myofibroblasts, (myofibroblast-like cells) which produce the fibrous scar.

Pathogenesis

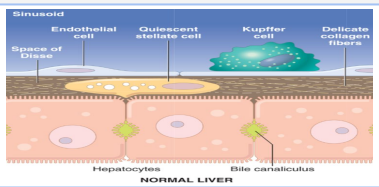
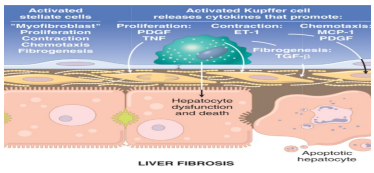
Same in boys slides but with other forms important!!

The stimuli for stellate cell activation may originate from several sources:

1. Proliferation of hepatic stellate cells and their activation into myofibroblasts is initiated by a series of changes that include an increase in the expression of platelet-derived growth factor receptor β (PDGFR-β) in the stellate cells.
2. Chronic inflammation, with production of inflammatory cytokines such as tumor necrosis factor (TNF), lymphotoxin, and interleukin 1β (IL-1β), and lipid peroxidation products.
3. At the same time, Cytokine and chemokine production such as PDJF, TNF, TGFβ1, ext. activated endogenous cells (Kupffer cells and endothelial cells, hepatocytes, and bile duct) epithelial cells leads to direct stimulation of stellate cells by these toxins.

Pathogenesis

Pathogenesis of liver cirrhosis

		
Same in boys slides but with other forms important!!		
Pathogenesis	The pathogenetic processes in cirrhosis are progressive fibrosis and reorganization of the vascular microarchitecture of the liver In the normal liver, interstitial collagens (types I and III) are concentrated in portal tracts and around central veins. The type IV collagen (reticulin) is in the space of Disse	In cirrhosis Types I and III collagen are deposited in the space of Disse, creating fibrotic septal tracts, accompanied by the loss of fenestrations of sinusoidal endothelial cells (capillarization of sinusoids, that is the sinusoidal space comes to resemble a capillary rather than a channel for exchange of solutes between hepatocytes and plasma). Kupffer cell activation leads to secretion of multiple cytokines; These cytokines "activate" stellate cells, and acquire a myofibroblastic state a major source of collagen in cirrhosis. Kupffer cells also are a major source of TNF released into the system circulation.
summary	Severe injury → death of large number of hepatocytes & drop out of liver cells → collapse of the underlying reticulin → prevent orderly regeneration of hepatocytes → activation of stellate cells → replacement of areas of liver cell loss by fibrous septa → fibrous septa encircle surviving, regenerating hepatocytes in late-stage chronic liver disease ➔ cirrhosis.	

Deep Focus Question

Which statement about the hemostatic system in patients with liver cirrhosis is true?

A. Patients with cirrhosis are at risk for thrombi and spontaneous bleeding
B. Traditional tests used to assess bleeding are accurate in clients with liver cirrhosis
C. Patients with liver disease are at higher risk for thrombi than bleeding
D. Patients with liver cirrhosis maintain a consistent and predictable hemostatic system

Answer: A

Female Slides

Pathogenesis

Clinical course of the disease

1

About 40% of patients are asymptomatic until most advanced stages of disease.
All forms of cirrhosis may be clinically silent.

2

Non-specific symptoms such as anorexia, weight loss, weakness & osteoporosis, and, in advanced disease, frank debilitation eventually signs & symptoms of liver failure (jaundice, encephalopathy & coagulopathy), much as the same as in acute liver hepatitis.

3

Widely variable from patient to patient , In some patient's disease remission or cure, however, portal hypertension may persist due to presence of irreversible shunts.
Incipient or overt hepatic failure may develop.

4

In fibrosis regression scars become thinner, more densely compacted & eventually start to fragment.
Adjacent parenchymal regenerating nodules coalesce into larger islands.

Causes of death

01

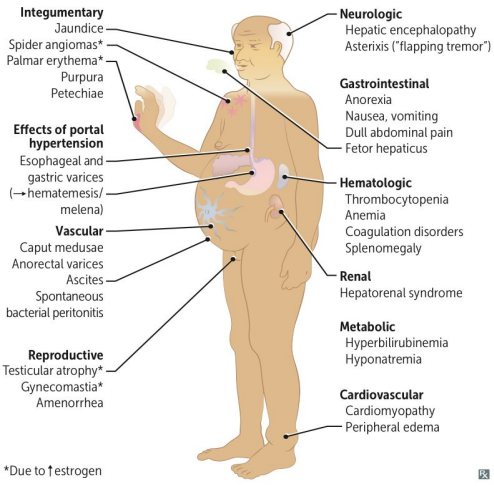
Progressive liver failure.

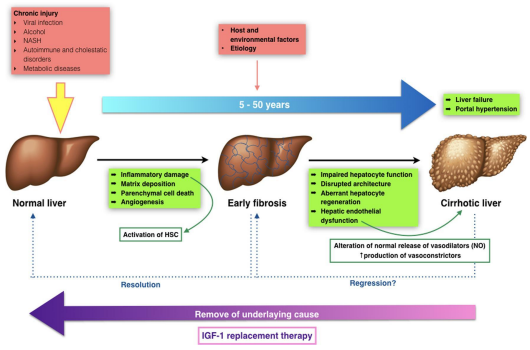
02

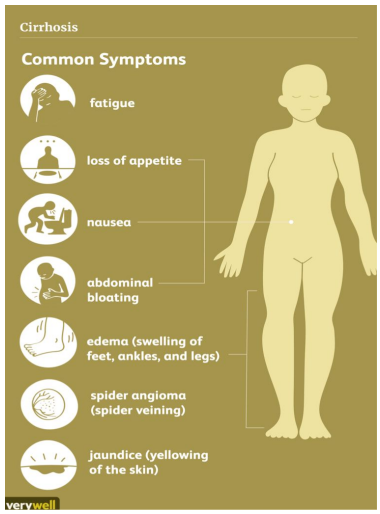
complication related to portal hypertension

03

Hepatocellular carcinoma







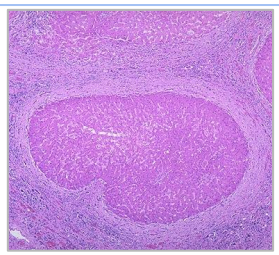
Morphology of liver cirrhosis

Morphology

Microscopic

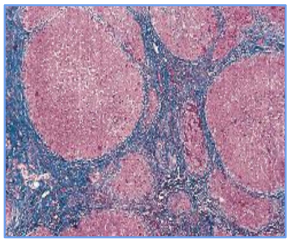
Female Slides

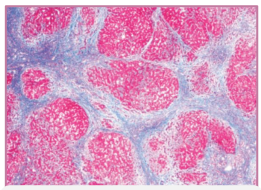
- Regenerative nodules of hepatocytes are surrounded by fibrous connective tissue that bridge between portal tracts
- Within this collagenous tissue are scarred lymphocytes as well as proliferation of bile ducts



- <u>Regenerative parenchymal nodules</u> surrounded by thick fibrous or collagen bands
- Vascular architecture is reorganized with the formation of abnormal interconnections between vascular inflow and hepatic vein outflow.
- **Fibrosis is the key feature of progressive damage to the liver**

Masson trichrome stain

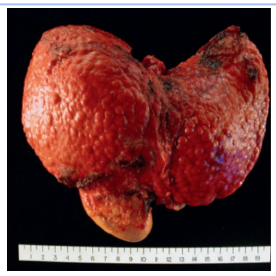
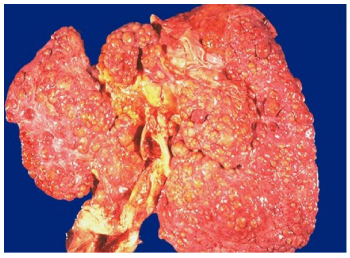
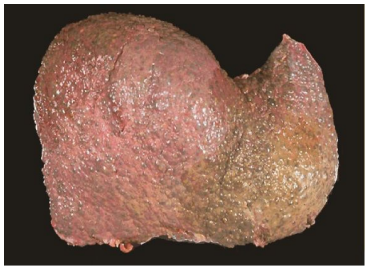




Masson trichrome stain

Gross

Prof Ahmed 443 note:
Not important for your level

Marked by the diffuse transformation of the entire liver into regenerative parenchymal nodules surrounded by fibrous bands	Nodules are larger than 3 mm "macronodular cirrhosis"	The regenerative nodules are small nodules, less than 3 mm in size "Micronodular cirrhosis"
		

Morphology of common causes of liver cirrhosis: Female Slides

01

Infectious disorder:

Viruses (hepatitis B and C virus).

02

Others:

Autoimmune hepatitis.

Alcoholic liver disease.

Biliary Cirrhosis.

Viral Hepatitis

Osmosis Vid

Definition

- Inflammatory disorders of the liver dominate the clinical practice of hepatology.
- Hepatitis is the name applied to viruses (hepatitis A, B, C, D, and E virus) that are hepatotropic, that is have a specific affinity for the liver.
- The morphologic changes in acute and chronic viral hepatitis are shared among the hepatotropic viruses and can be mimicked by drug reactions or autoimmune hepatitis.
- Fibrosis: continued loss of hepatocytes results in fibrous septa formation which ultimately leads to cirrhosis

Classified to:

Female Slides

Acute viral hepatitis

-Predominantly mononuclear inflammatory cell infiltrate, rich in plasma cells (in Hepatitis A infection).

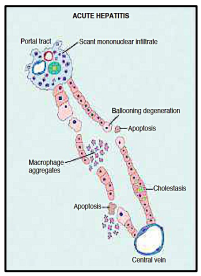
-Portal inflammation: absent or minimal:

1-Confined to portal tracts.

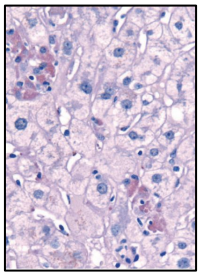
2-Most parenchymal injury is scattered throughout the hepatic lobule as "spotty necrosis" or lobular hepatitis.

3-Bridging inflammation and necrosis (in cases of severe acute hepatitis).

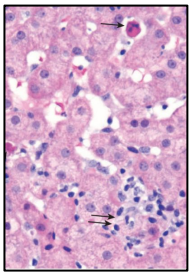
4-hepatocyte injury may result in necrosis or apoptosis.



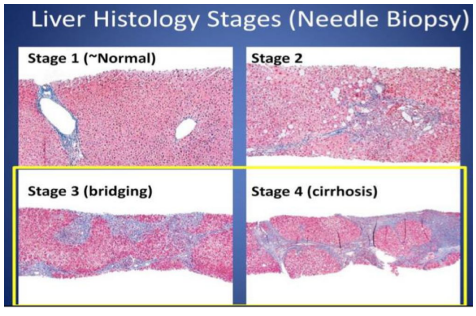
Acute hepatitis



Hepatocyte necrosis

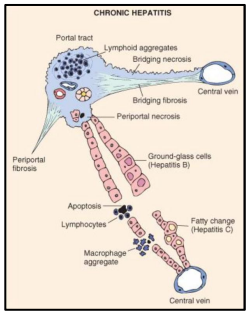


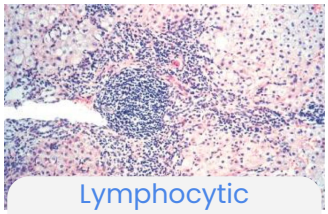
Hepatocyte apoptosis



Chronic viral hepatitis

-some changes are shared with acute hepatitis
-Hepatocyte injury, necrosis, and regeneration
Portal tract Inflammation:
1-Confined to portal tracts, or
2-Spillover into adjacent parenchyma, with necrosis of hepatocytes ("interface hepatitis"), or
3-Bridging inflammation and necrosis
-Mononuclear portal infiltration in portal tract (mild to severe and variable from one portal tract to the other).
-Interface hepatitis is present as well: Located at the interface between hepatocellular parenchyma & portal tract stroma.
-Lobular hepatitis.
-The hallmark of progressive chronic liver damage <u>is scarring;</u>
1-At first, only portal tracts exhibit fibrosis.
2-In some patients, with time, fibrous septa "bands of dense scar" will extend between portal tracts
3-In most severe cases, continued scarring and nodule formation ➔ cirrhosis.
-Cirrhosis: The end-stage outcome



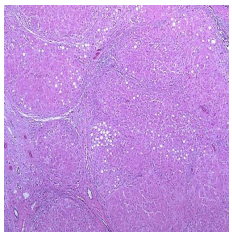
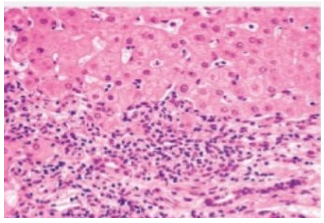
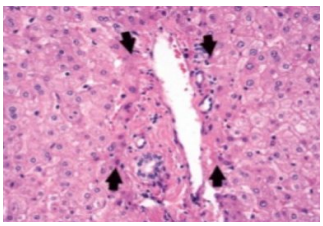
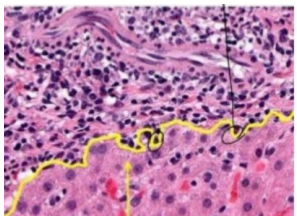


Lymphocytic infiltration of portal tract, a feature of chronic hepatitis

Viral Hepatitis

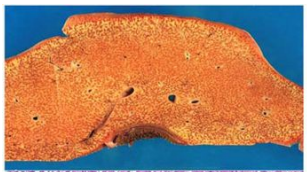
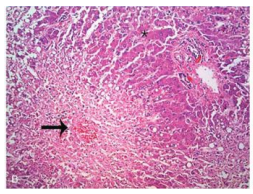
Microscopically

Female Slides

Viral hepatitis C which is at a high stage with extensive fibrosis and progression to macronodular cirrhosis, as evidenced by the large regenerative nodule at the center right	Piecemeal necrosis in Chronic hepatitis	Interface hepatitis: **Spillover into adjacent parenchyma**, with necrosis of hepatocytes
		 

Massive liver necrosis

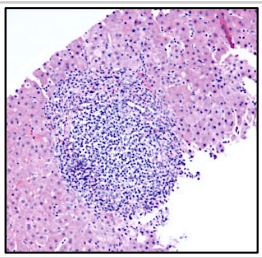
Female Slides

Grossly	The liver is small (700 g), soft, and congested.	
Microscopically	Confluent necrosis is seen in the perivenular region. There is little inflammation with residual normal tissue.	

Certain histologic features point to specific viral etiologies:

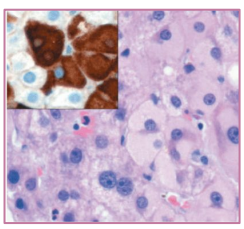
HCV

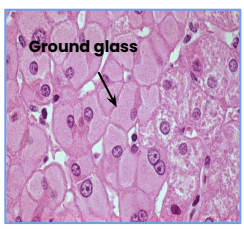
1-Large lymphoid aggregates in portal tract
2-Mild steatosis (fatty changes)
3-Bile duct injury/damage



HBV

1-Ground glass hepatocytes,sanded nuclei
"finely granular eosinophilic cytoplasm = massive amount of HBsAg within endoplasmic reticulum".
2-Can be confirmed by immunostaining.





Autoimmune hepatitis

Female Slides

Osmosis Vid

Definition

- Is a chronic, progressive hepatitis with all the features of autoimmune diseases in general:
  1. Genetic predisposition.
  2. Association with other autoimmune diseases.
  3. Presence of autoantibodies.
  4. Therapeutic response to immunosuppression Like steroids
- Risk for AIH is associated with certain HLA alleles, such as the DRB1 allele in Caucasians.

Clinical features

1

Associated with other autoimmune diseases e.g. rheumatoid arthritis, Sjogren's syndrome etc.

2

Immunosuppressive therapy is usually effective ➔ remission in 80% of patients & enables long-term survival.

3

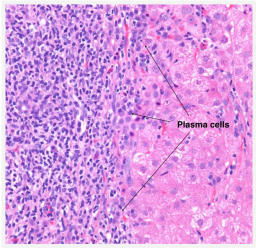
End-stage disease is an indication for liver transplantation:

-The 10-year survival rate after liver transplant is 75%.
- Recurrence in the transplanted organ occurs in 20% of cases.

Clinicopathologic features

- The annual incidence is highest among white northern Europeans, but all ethnic groups are susceptible
- Female predominance (78%)
- Classified into two types, based on the patterns of circulating antibodies:

Type 1	Type 2
1-More common in middle-age & older individuals 2-Characterized by the presence of anti-nuclear (ANA), anti–smooth muscle actin (SMA), anti-mitochondrial (AMA) & anti–soluble liver antigen/liver-pancreas antigen (anti-SLA/LP) antibodies.	• Usually seen in children and teenagers • Characterized by the presence of anti–liver kidney microsome-1 antibodies & anti–liver cytosol-1 antibodies.

Morphology For both types	-AIH shares patterns of injury with acute or chronic viral hepatitis, but with some difference. -There is a nearly phase of severe parenchymal destruction followed rapidly by scarring.	Typical features of AIH: 1. Necrosis and inflammation 2. Plasma cell predominance 3. Hepatocyte "rosettes" in areas of marked activity.	

Alcoholic Liver Disease

Female Slides

Osmosis Vid

Definition

- Excessive ethanol consumption causes more than 60% of chronic liver disease in Western countries and accounts for 40% to 50% of deaths due to cirrhosis.
- It is estimated that 15 to 20 years of excessive drinking are necessary to develop alcoholic cirrhosis.
- Cirrhosis typically develops after more than 10 years of heavy drinking.
- Alcoholic cirrhosis has similar clinical signs and symptoms as cirrhosis caused by viral hepatitis.

Causes

The cause of alcoholic hepatitis is uncertain, but it may stem from one or more of the following toxic products of ethanol and its metabolites:

01

Acetaldehyde

a major metabolite of ethanol)

02

Alcohol

directly affects mitochondrial function and membrane fluidity.

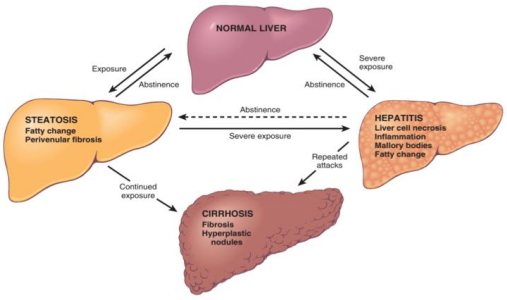
03

Reactive oxygen species.

Damaging hepatocytes

Death

- Hepatic failure.
- Massive gastrointestinal hemorrhage.
- Intercurrent infection (to which affected individuals are predisposed).
- Hepatorenal syndrome.
- Hepatocellular carcinoma(3%–6%) of cases.



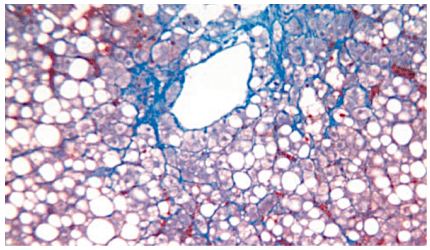
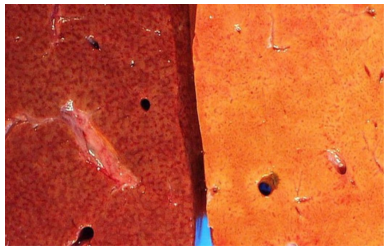
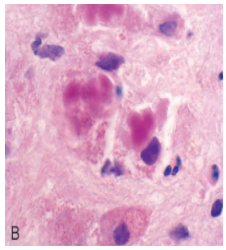
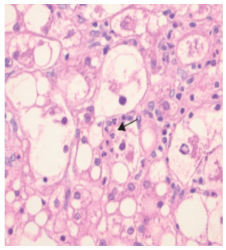
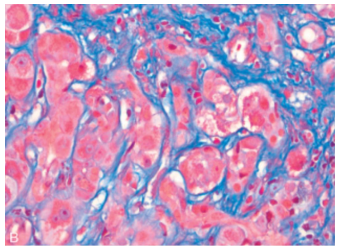
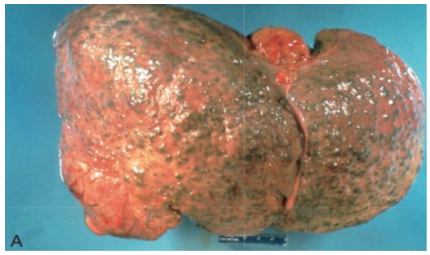
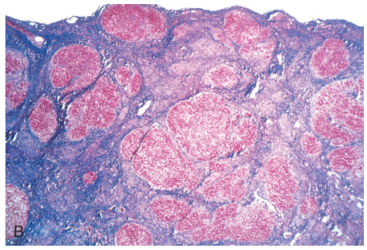
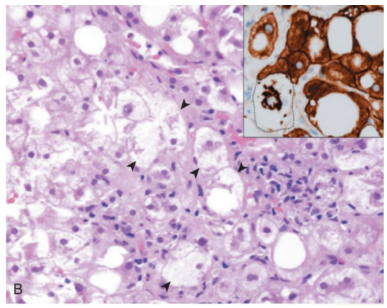
All In females Slide Except The Picture with blue frame & its description in both

Female Slides

Alcoholic Liver Disease

Morphology

IMPORTANT

Hepatic Steatosis (Fatty Liver)	 
Alcoholic Hepatitis (Alcoholic Steatohepatitis): 1. Hepatocyte swelling necrosis. **2. Mallory bodies.** 3. Neutrophilic reaction. 4. Fibrosis	  
Regenerative nodules (Micronodular cirrhosis)	 
A: • Cluster of inflammatory cells • Mallory-Denk bodies B : Ballooned hepatocytes (seen with CK IHC)	 

Deep Focus Question

Why does portal hypertension occur in patients that have liver cirrhosis?

A. High systemic blood pressure
B. Scar tissue of the liver blocks blood flow
C. Stenosis of the portal vein
D. Increased blood from the intestines

Answer: B

Deep Focus Question

Which of the following is a non-respiratory cause of clubbing?

A. Liver cirrhosis
B. Cholelithiasis
C. Ruptured spleen
D. Renal failure

Answer: A

Intrahepatic Biliary Tract Disease

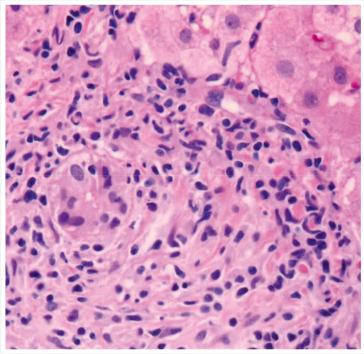
Distinguishing features of the major intrahepatic bile duct disorders			
	Secondary biliary cirrhosis	Primary biliary cirrhosis	Primary sclerosing cholangitis
Etiology	Extrahepatic bile duct obstruction : biliary atresia , gallstones, stricture , carcinoma of pancreatic head	Possibly autoimmune	Unknown , possibly autoimmune 50% to 70 % associated with inflammatory bowel disease
Sex prediction	None	Female to male 6:1	Female to male 1:2
Symptoms and Signs	Pruritus , jaundice, malaise ,dark urine, light stools, hepatosplenomegaly	Same as Secondary biliary cirrhosis; insidious onset	Same as Secondary biliary cirrhosis; insidious onset
Laboratory Findings	Conjugated hyperbilirubinemia,increased serum alkaline phosphatase,bile acids,cholesterol	Same as Secondary biliary cirrhosis; plus elevated serum IgM autoantibodies (especially M2 form of antimitochondrial antibody)	Same as secondary biliary cirrhosis ;plus elevated serum IgM , hypergammaglobulinemia
Important pathologic findings before cirrhosis develops	Prominent bile stasis in bile duct , bile ductular proliferation with surrounding neutrophils , portal tract edema	Dense lymphocytic infiltrate in portal tract with granulomatous destruction of bile duct	Periductal portal tract fibrosis , segmental stenosis of extrahepatic and intrahepatic bile duct .

Intrahepatic Biliary Tract Disease

Morphology

Primary Biliary cirrhosis

Pre-cirrhotic stage	With time
-Portal tracts and bile ducts are infiltrated by lymphocytes, macrophages, plasma cells, and occasional eosinophils -Noncaseating granulomatous inflammation -Bile duct destruction	-Progressive obstruction ➔ damage bile ducts and ductular proliferation, inflammation, and necrosis of the adjacent periportal hepatic parenchyma -Over years to decades, relentless portal tract scarring and bridging fibrosis lead to cirrhosis.

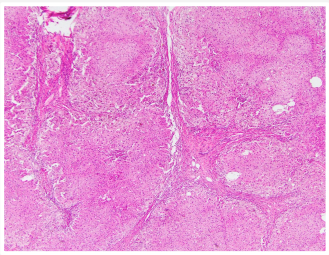


Secondary Biliary cirrhosis

Female Slides

The end-stage obstructed liver shows

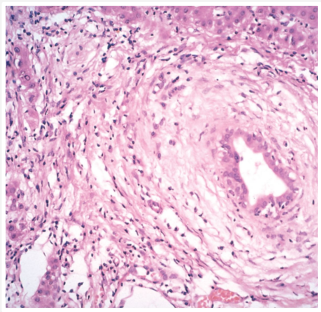
- Yellow-green pigmentation . On cut surface the liver is hard, with a finely granular appearance.
- Coarse fibrous septa that subdivide the liver in a **jigsaw-like pattern.**
- Extensive proliferation of smaller bile ductules.
- Cholestasis
- Ascending bacterial infection incites a robust neutrophilic infiltration of bile ducts.



Primary sclerosing cholangitis

onion-skin fibrosis

- Fibrosing cholangitis of bile ducts, with a lymphocytic infiltrate, progressive atrophy of the bile duct epithelium, and obliteration of the lumen
- The concentric periductal fibrosis around affected ducts "onion-skin fibrosis"
- As the disease progresses, the liver becomes cirrhotic like that seen with primary and secondary biliary cirrhosis



Complications Of Liver Cirrhosis

Clinical features

Female Slides

01

About 40% of patients are asymptomatic until most advanced stages of disease.

02

Non-specific symptoms such as anorexia, weight loss, weakness & eventually signs & symptoms of liver failure discussed earlier (jaundice, encephalopathy & coagulopathy) , much as the same as in acute liver hepatitis.

03

Additional significant manifestations and Complications.

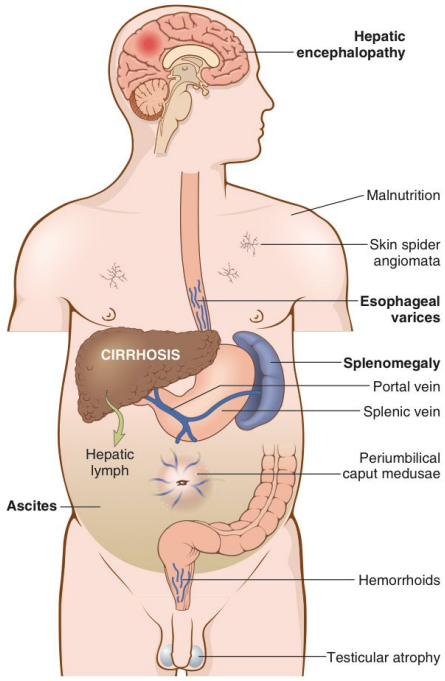
Bilirubin metabolism and elimination

Bilirubin is the end product of heme degradation is derived primarily from the breakdown of senescent circulating erythrocytes.

Bilirubin thus formed outside the liver is bound to serum albumin and delivered to the liver.

Hepatocellular uptake and conjugation with one or two molecules of glucuronic acid in the endoplasmic reticulum generate bilirubin monoglucuronide and diglucuronides, (water soluble).

Gut bacteria deconjugate the bilirubin it to colorless urobilinogen. The urobilinogen are excreted in the feces, with some reabsorption and excretion into urine.



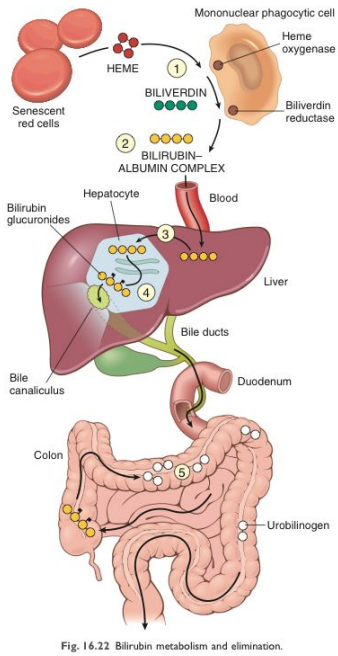


Fig. 16.22 Bilirubin metabolism and elimination.

Complications Of Liver Cirrhosis

Female Slides

jaundice & Cholestasis

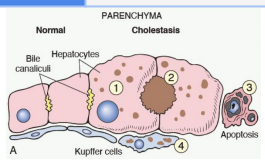
Definition

- Yellowish or greenish pigmentation of the skin and sclera of the eyes respectively due to high bilirubin levels.
- Jaundice occurs when the equilibrium between bilirubin production and clearance is disturbed.
- To understand the pathophysiology of jaundice it is important first to become familiar with the major aspects of bile formation and metabolism.

Causes

Predominantly Unconjugated Hyperbilirubinemia	Excess Production of Bilirubin	• Hemolytic anemias • Resorption of blood from internal hemorrhage (e.g., alimentary tract bleeding, hematomas) • Ineffective erythropoiesis (e.g., pernicious anemia, thalassemia)
	Reduced Hepatic Uptake	• Drug interference with membrane carrier systems
	Impaired Bilirubin Conjugation	• Physiologic jaundice of the newborn • Diffuse hepatocellular disease (e.g., viral or drug-induced hepatitis, cirrhosis)
Predominantly Conjugated Hyperbilirubinemia	Decreased Hepatocellular Excretion	• Drug-induced canalicular membrane dysfunction (e.g., oral contraceptives, cyclosporine) • Hepatocellular damage or toxicity (e.g., viral or drug-induced hepatitis, total parenteral nutrition, systemic infection)
	Impaired Intrahepatic or Extrahepatic Bile Flow	• Inflammatory destruction of intrahepatic bile ducts (e.g., primary biliary cirrhosis, primary sclerosing cholangitis, graft-versus-host disease, liver transplantation) • Gallstones • External compression (e.g., carcinoma of the pancreas)

Pathogenesis

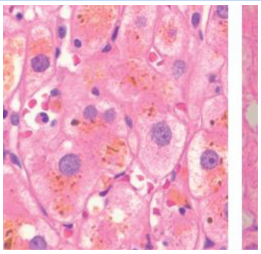


Condition of impaired bile formation and bile flow, leading to accumulation of bile pigment in the hepatic parenchyma.

Symptoms

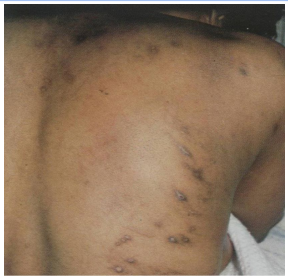
Patients may have jaundice, pruritus, skin xanthomas (focal accumulation of cholesterol), or symptoms related to intestinal malabsorption, including nutritional deficiencies of the fat-soluble vitamins A, D, or K.

Morphology



1. Cholestatic hepatocytes are enlarged.
2. Associated with dilated canalicular spaces.
3. Apoptotic cells may be seen.
4. Kupffer cells frequently contain regurgitated bile pigments.
5. Characteristic accumulation of bile pigments in the cytoplasm

Pruritus

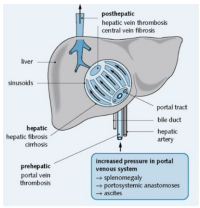


- Chronic severe jaundice ➔ itching.
- May be so profound ➔ risk of repeated bouts of potentially life-threatening infection.
- Severe pruritis in some patients is 1ry indication for liver transplantation.
- Is also frequently seen in other disorders associated with cholestasis.
- Precise pathogenesis is unknown.

Complications of liver cirrhosis

Portal Hypertension

Definition



- More frequent and more complex than in acute liver failure.
- Due to Resistance to blood flow and. by diminished flow through the portal venous system.
- Causes could be because obstruction at the prehepatic, intrahepatic, or post hepatic level.

Complications

Osmosis Vid

Splenomegaly

Definition

Massive splenomegaly may secondarily induce hematologic abnormalities attributable to hypersplenism, such as thrombocytopenia or even pancytopenia

Pathogenesis

Long-standing congestion may cause congestive splenomegaly , The degree of splenic enlargement varies widely and may reach as much as 1000 gm.

IMPORTANT Esophageal varices

Female Slides

Definition

-Venous blood from the GI tract is delivered to the liver via the portal vein before reaching the inferior vena cava.
-This circulatory pattern is responsible for the first-pass effect in which drugs and other materials absorbed in the intestines are processed by the liver before entering the systemic circulation.
-Diseases that impede this flow cause portal hypertension and can lead to the development of esophageal varices, an important cause of esophageal bleeding.

Pathogenesis

-Portal hypertension results in the development of collateral channels at sites where the portal and caval systems communicate.
-Although these collateral veins allow some drainage to occur, they lead to development of a congested subepithelial and submucosal venous plexus within the distal esophagus (varices). 90% of cirrhotic patients
-Most commonly in association with alcoholic liver disease and hepatic schistosomiasis.
-Variceal rupture results in hemorrhage into the lumen or esophageal wall : Medical emergency
-Treated by sclerotherapy, balloon tamponade, rubber band ligation
-Half of patients die from the first bleeding episode either as a direct consequence of hemorrhage or following hepatic coma triggered by hypovolemic shock, Additional 50% within 1 year.

Female Slides

Morphology

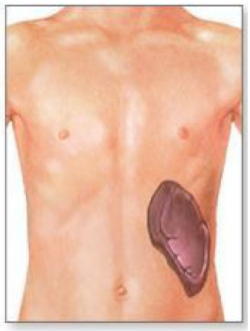
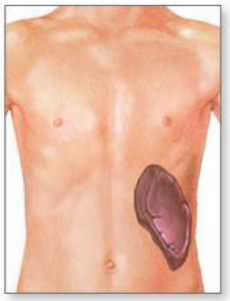
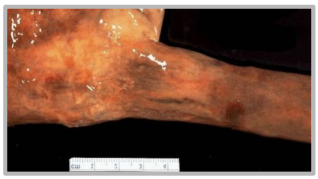
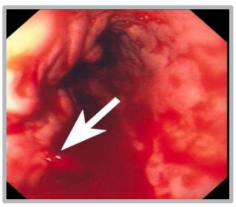
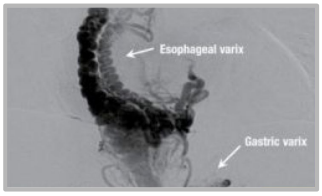
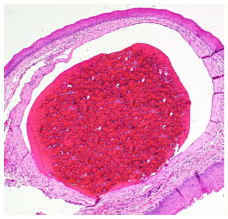
Grossly :
-Varices can be detected by venogram: tortuous dilated veins lying primarily within the submucosa of the distal esophagus and proximal stomach.
-Venous channels directly beneath the esophageal epithelium may also become massively dilated.
-Varices may not be grossly obvious in surgical or postmortem specimens, because they collapse in the absence of blood flow.
-Variceal rupture results in hemorrhage into the lumen or esophageal wall, in which case the overlying mucosa appears ulcerated and necrotic.
-If rupture has occurred in the past, venous thrombosis, inflammation, and evidence of prior therapy may also be present.

Complications of liver cirrhosis

Portal Hypertension

Complications

Female Slides

	Splenomegaly	Esophageal varices
Morphology	 Splenomegaly  Splenomegaly	    Microscopic : Dilated, thin-walled vessels, mostly in the submucosa 

Consequences

wherever the systemic and portal circulations share capillary beds

- Portal hypertension
  - Portosystemic venous Shunt
    - Rectum (hemorrhoids)
    - Abdominal wall collaterals (**caput medusae**)
    - Cardioesophageal junction (esophagogastric varices)

Clinical features

Female Slides

- Asymptomatic or rupture -> massive hematemesis
- Inflammatory erosion of thinned overlying mucosa.
- Increased tension in progressively dilated veins.
- Increased vascular hydrostatic pressure associated with vomiting (with blood) are likely to contribute to medical emergency that is treated by any of several methods: in both slides & mentioned above

1. Sclerotherapy
2. Endoscopic balloon tamponade
3. Endoscopic rubber band ligation

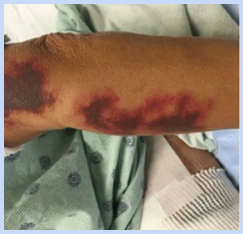
Complications of liver cirrhosis

Hepatic failure

Coagulopathy

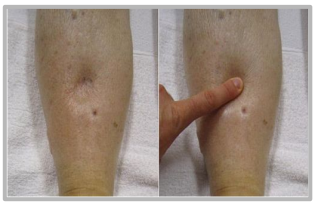
- Coagulation factors that decline in the face of liver failure, leading to easy bruising and bleeding. Paradoxically, disseminated intravascular coagulation
- Hypercoagulation state also may occur due to failure of the damaged liver to remove activated coagulation factors.

Complication in addition to Jaundice



Hypoalbuminemia

- Hypoalbuminemia from decreased synthesis of albumin
- Produces dependent pitting edema and ascites due to a decrease in plasma oncotic pressure.



Hyperestrogenemia

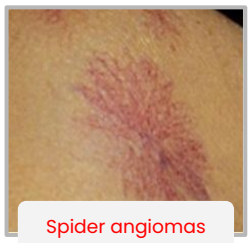
IMPORTANT

- Due to impaired estrogen metabolism:

1. Liver cannot degrade estrogen and 17-ketosteroids (Androstenedione).
2. Androstenedione is aromatized into estrogen in the adipose cells.

- Palmar erythema "due to local vasodilatation.
- **Spider angiomas of skin.**

Females	Males
hypogonadism → oligomenorrhea, amenorrhea & sterility.	• Hypogonadism • Female distribution of hair. • **Gynecomastia**



Spider angiomas

Palmar erythema

Gynecomastia

Hepatic encephalopathy

IMPORTANT

MOSTLY HEPATITIS C

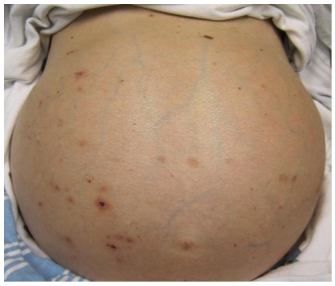
Definition	A spectrum of disturbances in consciousness, ranging from subtle behavioral abnormalities to confusion & stupor, to coma & death.
Course	develop over days, weeks, or a few months after acute injury. Reversible if the underlying hepatic condition can be corrected.
Features	fluctuating neurologic signs, including rigidity, hyperreflexia, and asterixis , only minor morphologic changes in the brain, such as edema and an astrocytic reaction.
Mechanism	appears to be associated with elevated ammonia levels in blood and the central nervous system correlate with impaired neuronal function and promote generalized brain edema.

Complications of liver cirrhosis

Ascites

Definition

- Is the accumulation of excess fluid in the peritoneal cavity.
- 85% of cases are caused by cirrhosis.
- Clinically detectable when at least 500 mL have accumulated.
- The fluid is generally serous, having less than 3 gm/dL of protein (largely albumin), and a serum to ascites albumin gradient of ≥1.1 gm/dL.



peritonitis

Spontaneous bacterial peritonitis:
Increased risk for spontaneous bacterial infection on top of ascites.

pathogenesis

The pathogenesis of ascites is complex, involving the following mechanisms:

1. Increase in portal vein hydrostatic pressure , Leakage of hepatic lymph into the peritoneal cavity
2. Decreases oncotic pressure : Hypoalbuminemia : Albumin comprises 75-80% of normal plasma colloid oncotic pressure and 50% of protein content. When plasma proteins, especially albumin, no longer sustain sufficient colloid osmotic pressure to counterbalance hydrostatic pressure, edema develops.
3. Liver is unable to metabolize aldosterone.
4. Sinusoidal hypertension, drives fluid into the space of Disse, which is then removed by hepatic lymphatics;

IMPORTANT Hepatorenal syndrome

Detention

Is a form of renal failure occurring in individuals with liver failure (severe chronic liver disease) in whom there are no intrinsic morphologic or functional causes for kidney dysfunction/ renal failure .

incidence

The incidence of this syndrome is about 8% per year among patients who have cirrhosis and ascites , The prognosis is poor, with a median survival of only 2 weeks in the rapid -onset form and 6 months with the insidious-onset form.

abnormalities

Main functional abnormalities:

- Sodium retention, impaired free-water excretion, ↓ renal perfusion & ↓ glomerular filtration rate.

Features

↓ Urine output, ↑ blood urea nitrogen & creatinine levels.

Causes

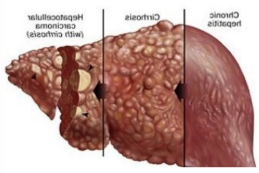
Several factors are involved in its development, including

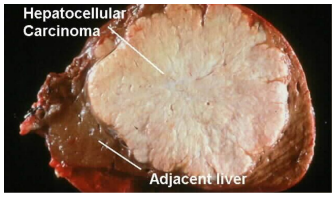
1. **Decreased renal perfusion pressure due to systemic vasodilation.**
2. Activation of the renal sympathetic nervous system with vasoconstriction of the afferent renal arterioles.
3. Increased synthesis of renal vasoactive mediators (activation of the renin/angiotensin axis), that decrease glomerular filtration.

Female Slides Hepatocellular Carcinoma

Definition

Most chronic liver disease predispose to development of hepatocellular carcinoma





Keywords

Cirrhosis		• Parenchymal nodules containing hepatocytes • Fibrosis in form of Bridging fibrous septa
Viral hepatitis	Morphology	• Predominantly mononuclear inflammatory cell infiltrate, • Portal tract inflammation -Spillover into adjacent parenchyma, with necrosis of hepatocytes ("interface hepatitis") or -Confined to portal tracts or -Bridging inflammation and necrosis
	Microscopically	• **HBV:** ground glass hepatocytes
		• **HCV:** lymphoid aggregates in portal tract - mild steatosis
Autoimmune hepatitis	Type 1	Characterized by the presence of: • anti-nuclear (ANA), • anti–smooth muscle actin (SMA), • anti-mitochondrial (AMA) • anti–soluble liver antigen/liver-pancreas antigen (anti-SLA/LP) antibodies.
	Type 2	Characterized by the presence of: • anti–liver kidney microsome-1 antibodies • anti–liver cytosol-1 antibodies .
Alcohol liver disease	Morphology	• Hepatic Steatosis (Fatty Liver) "predominant" • **Mallory bodies** = eosinophilic inclusions in the hepatocytes • Neutrophilic reaction = inflammation
Intrahepatic biliary tract disease	Primary biliary cirrhosis	**Morphology:** • Pre-cirrhotic stage: ➢ Portal tracts and bile ducts are infiltrated by lymphocytes, macrophages, plasma cells, and occasional eosinophils (NO neutrophils) ➢ Noncaseating granulomatous inflammation ➢ Bile duct destruction
		Laboratory findings: • ↑Serum alkaline phosphatase • Antimitochondrial antibodies (AMA)
	Secondary biliary cirrhosis	The most common cause of obstruction in adults is extrahepatic cholelithiasis
		Microscopically: • **jigsaw-like pattern**
		Laboratory findings: • Conjugated hyperbilirubinemia
	Primary sclerosing cirrhosis	**Etiology:** • commonly seen in associated with inflammatory bowel disease particularly **chronic ulcerative colitis**
		Morphology: • Atrophy of the bile duct epithelium • The concentric periductal fibrosis around affected ducts **"onion-skin fibrosis"** followed by their disappearance, leaving behind a solid, **cordlike fibrous scar**

Keywords

Complication of cirrhosis	Portal hypertension	**Complication of portal hypertension :** • Splenomegaly • Portosystemic Shunt : – **Caput medusae** – Hemorrhoids ★ **Esophageal varices:** • rupture a massive hematemesis
	Liver failure	1. Coagulopathy 2. Hypoalbuminemia 3. Hyperestrogenemia
	Hyperestrogenemia	**In males:** • Palmar erythema "due to local vasodilatation" • **Spider angiomas of skin** • Hypogonadism • Female distribution of hair • **Gynecomastia**
		in females: • hypogonadism (infertility) ➔ oligomenorrhea,amenorrhea & sterility
	Hyperammonemia	**Hepatic encephalopathy :** • A spectrum of disturbances in consciousness, ranging from subtle behavioral abnormalities to confusion & stupor, to coma & death
	Ascites	• Sinusoidal hypertension • Hypoalbuminemia • Leakage of hepatic lymph into the peritoneal cavity.
	Cholestasis	-
	Jaundice	-
	Pruritus	-
	Spontaneous bacterial peritonitis	increased risk for spontaneous bacterial infection on top of ascites
	Hepatorenal syndrome	**Definition:** • Is a form of renal failure occurring in individuals with liver failure in whom there are NO intrinsic morphologic or functional causes for kidney dysfunction.
		Causes: • Decreased renal perfusion pressure due to systemic vasodilation • Decreased GFR

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DR AHMED CASES & QUESTIONS CLICK HERE

YOU Vs MCQs

1

A 63 year old man is known to hepatic cirrhosis and has been vomiting blood which of the following is most likely the cause of this complication

A-Ascites

B- Esophagus varices

C-Periumbilical medusa

D- Spider angioma

2

Mallory bodies can be seen in?

A- HCV

B- HBV

C- Alcoholic liver

D- Steatosis

3

Which of the following is a clinical finding of portal hypertension in case of liver cirrhosis?

A-Caput medusae

A-Fistula formation

C-Toxic megacolon

D- peptic ulcer

4

A patient had developed liver cirrhosis secondary to hepatitis C virus , he had loss conscious and coma. what is the cause of the coma

A- Urease

B- lactase

C- Ammonia

D-Co_2

1-B / 2-C / 3-A / 4-C

YOU Vs MCQs

5

The major complications of liver cirrhosis include all of the following, except:

A- Portal hypertension

B- Asites

C- Liver failure

D- Pancreatitis

6

Which of the following antibodies indicate primary biliary cirrhosis?

A- Antismooth muscle

B- Anti mitochondrial

C- Antinuclear

D-None of these

7

patient presented with jaundice and they take a biopsy, on microscope it shows “onion skin fibrosis” , what is the diagnosis?

A- Primary sclerosing cirrhosis

B- Secondary sclerosing cirrhosis

C- Primary Biliary cirrhosis

D- secondary biliary cirrhosis

8

Spider angioma in liver cirrhosis is caused by:

A- Hyper-ammonia

B- Hyperestrogenemia

C- Hepatic encephalopathy

D- Ascites

5-D / 6-B / 7-A / 8-B

YOU VS CASES

1. A 62-year-old man is brought to the emergency room in a disoriented state. Physical examination reveals signs of poor hygiene and an odor of alcohol, as well as jaundice, splenomegaly, and ascites. The patient has a coarse fl apping tremor of the hands, palmar erythema, and diffuse spider angiomata. The abdomen displays dilated paraumbilical veins. Serum levels of ALT, AST, alkaline phosphatase, and bilirubin are all mildly elevated. Soon after admission, the patient vomits a large amount of blood. Which of the following is the most likely underlying cause of hematemesis in this patient?

A.Acute alcoholic hepatitis	B.Acute gastritis	C.Cirrhosis	D.Hepatic steatosis

2.For the patient described in Q 1, which of the following pathophysiologic mechanisms is most directly associated with the development of ascites?

A.Decreased aldosterone secretion	B.Decreased intravascular volume	C.Increased intravascular oncotic pressure	D.Increased portal hydrostatic pressure

3.A 20-year-old woman presents with a 2-week history of fever, malaise, and brown-colored urine. She recently visited Mexico. Physical examination reveals jaundice, mild hepatomegaly, and tenderness in the right upper quadrant. The serum bilirubin is 7.8 mg/dL, with 60% in the conjugated form. Serum levels of AST and ALT are markedly elevated (400 and 392 U/L, respectively). Serum albumin and immunoglobulin levels are normal. Serum IgM anti–hepatitis A virus (anti-HAV) is positive. IgG anti–hepatitis B surface antigen (anti-HBsAg) antibodies are positive. Anti–hepatitis C virus antibodies are negative. What is the most likely diagnosis?

A.Acute viral hepatitis A	B.Acute viral hepatitis B	C.Acute viral hepatitis C	D.Chronic viral hepatitis B

4.A 20-year-old woman presents with a 4-week history of dry mouth, fatigue, fever, and yellow sclera. Physical examination shows mild jaundice and hepatomegaly. Serum total bilirubin is 3.3 mg/dL. Serologic markers for viral hepatitis are negative. The anti–mitochondrial antibody test is negative. A liver biopsy discloses parenchymal and periportal inflammatory cell infi ltrates composed primarily of lymphocytes and plasma cells. The patient's signs and symptoms abate following 2 months of treatment with steroids. Which of the following is the most likely diagnosis?

A.Autoimmune hepatitis	B.Primary biliary cirrhosis	C.Primary sclerosing cholangitis	D.Wilson disease

1-C / 2-D / 3-A / 4-A

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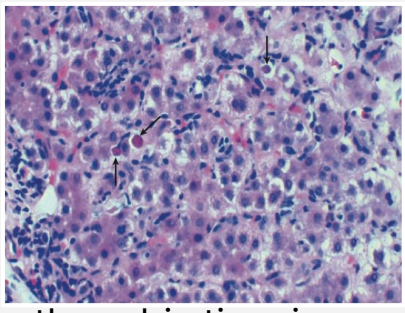
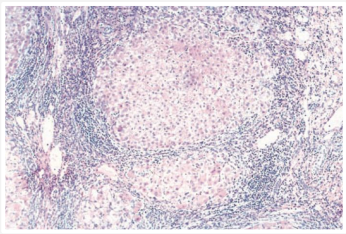
YOU VS CASES

5. A previously healthy 38-year-old man complains of yellow discoloration of his eyes, abdominal pain, and low-grade fever of 1-month duration. Physical examination demonstrates a distended abdomen, right upper quadrant tenderness, and a palpable liver edge 2 cm below the right costal margin. Total serum bilirubin is 7.4 mg/dL. Serum levels of AST and ALT are elevated (229 and 495 U/L, respectively). The prothrombin time is prolonged (18 seconds). A liver biopsy is shown in the image. The arrows point to Councilman bodies. The pathologic findings are indicative of which of the following liver diseases?



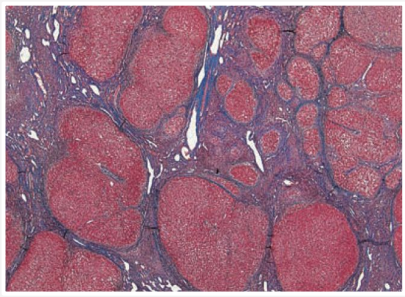
A.Acute viral hepatitis	B.Alcoholic cirrhosis	C.Cardiac cirrhosis	D.Primary biliary cirrhosis

6.A 30-year-old man presents with a 9-month history of fatigue and recurrent fever. He also complains of yellow skin and sclerae, abdominal tenderness, and dark urine. Physical examination reveals jaundice and mild hepatomegaly. Laboratory studies demonstrate elevated serum bilirubin (3.1 mg/ dL), decreased serum albumin (2.5 g/dL), and prolonged prothrombin time (17 seconds). Serologic tests reveal antibodies to hepatitis B core antigen (IgG anti-HBcAg). The serum is positive for HBsAg and HbeAg. A liver biopsy is shown in the image. What is the most likely diagnosis?



A.Acute hepatitis B	B.Alcoholic hepatitis	C.Chronic hepatitis B	D.Subacute hepatic necrosis secondary to hepatitis B infection

7.A 60-year-old man is found in a state of disorientation and is brought to the emergency room in a comatose state. He lived alone, ate poorly, and drank large amounts of hard liquor. Physical examination reveals an emaciated man with a distended abdomen, jaundice, ascites, and a slightly enlarged liver and spleen. A liver biopsy is shown in the image. What blood test would confirm a diagnosis of hepatic coma?



A.Alanine aminotransferase	B.Alkaline phosphatase	C.Ammonia	D.Bilirubin

5-A / 6-C / 7-C

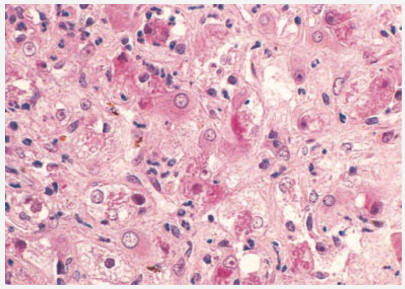
NEED EXPLANATION ? CLICK HERE

YOU VS CASES

8. A 58-year-old man with longstanding alcoholic cirrhosis presents with abdominal pain, fever, and an episode of hematemesis. Physical examination reveals jaundice and a markedly distended abdomen. The patient is disoriented and has a coarse flapping tremor of the hands. Laboratory studies reveal modestly elevated serum levels of AST and ALT (96 and 92 U/L, respectively) and a high serum level of alkaline phosphatase (320 U/L). Prothrombin time is prolonged (20 seconds). The WBC count is 18,000/μL. Shortly after admission, the patient develops coma, adult respiratory distress syndrome, and renal failure (oliguria and elevated serum levels of BUN and creatinine), leading to death within 3 days. Histologic examination of the patient's kidney at autopsy would most likely show which of the following?

A.Interstitial nephritis	B.Membranous nephropathy	C.No histologic changes	D.Proliferative glomerulonephritis

9.A 49-year-old woman presents with a 1-month history of yellow discoloration of her eyes, abdominal pain, malaise, weight loss, and low-grade fever (38.4°C, 101°F). Physical examination shows a distended abdomen with right upper quadrant tenderness and a palpable liver 2 cm below the right costal margin. Laboratory studies reveal decreased serum albumin (2.6 g/dL), elevated serum AST (225 U/L) and ALT (150 U/L), and increased alkaline phosphatase (210 U/L). The prothrombin time is prolonged (15 seconds). A moderate leukocytosis (13,500/μL, 80% neutrophils) is observed. A liver biopsy is shown in the image. These pathologic findings are most commonly associated with which of the following liver diseases?



A.Alcoholic hepatitis	B.Acute hepatitis B	C.Chronic hepatitis B	D.primary biliary cirrhosis

10.A 65-year-old man is brought to the emergency room in a disoriented state. The patient has an odor of alcohol on his breath. Physical examination reveals palmar erythema, diffuse spider angiomata on the upper trunk and face, and gynecomastia. A liver biopsy shows micronodular cirrhosis, massive steatosis, and Mallory hyaline. Serum levels of ammonia are elevated. Which of the following is the most likely underlying cause of gynecomastia in this patient?

A.Hyperbilirubinemia	B.Hyperestrogenism	C.Hypersensitivity vasculitis	D.Hypoalbuminemia

8-C / 9-A / 10-B

NEED EXPLANATION ? CLICK HERE

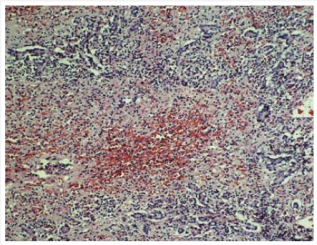
YOU Vs CASES

EXTRA CASES NOT IN THE LECTURE BUT **IN ROBINS** & MENTIONED IN OTHER SUBJECTS

1.A 48-year-old woman has a 3-week history of fatigue as well as yellow skin and sclerae. Physical examination is unremarkable except for mild jaundice. The serum bilirubin level is 3.7 mg/dL, mostly in the unconjugated form. Liver function tests including serum AST, ALT, and alkaline phosphatase are normal. The hemoglobin level is 6.0 g/dL. After corticosteroids are administered, the jaundice resolves. Which of the following diseases is the most likely cause of hyperbilirubinemia in this patient?

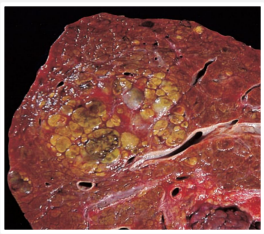
A.Acute hepatitis B infection	B.Autoimmune hemolytic anemia	C.Primary biliary cirrhosis	D.Primary sclerosing cholangitis

2.A 25-year-old heroin addict presents in a disoriented state with a 5-day history of fatigue, malaise, and dark-colored urine. Physical examination reveals jaundice and multiple petechial hemorrhages on the upper extremities. Laboratory studies show serum bilirubin of 15.6 mg/dL, mostly in the conjugated form, 10-fold elevations of serum AST and ALT, high levels of blood ammonia, and increased prothrombin time (15 seconds). The patient's condition deteriorates and he develops stage 4 hepatic encephalopathy. A liver biopsy is shown in the image. Which of the following viruses is most likely responsible for the clinical and pathologic findings in this patient?



A.Hepatitis A virus	B.Hepatitis B virus	C.Hepatitis C virus	D.Hepatitis E virus

3.A 66-year-old man presents with a 2-week history of abdominal bloating, weight loss, and pain in the right upper quadrant. The patient had a serious motor vehicle accident 16 years ago, in which he required transfusion of 10 U of whole blood. On physical examination, he exhibits massive distension of the abdomen. The liver is hard on palpation and occupies the entire right side of the abdomen. Laboratory studies show a low serum albumin (2.2 g/dL) and a markedly elevated serum alpha-fetoprotein. An abdominal ultrasound examination reveals ascites. The patient expires 6 months later. The liver at autopsy is shown in the image. Which of the following is the most common cause of this disease worldwide?



A.Alcoholic hepatitis	B.Chronic hepatitis B	C.Chronic hepatitis C	D.Hepatitis E

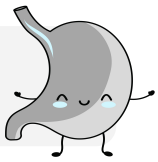
4.A 22-year-old woman from India presents with a 1-week history of fever, malaise, and nausea. The patient is 6 months pregnant. Physical examination reveals jaundice and right upper quadrant pain. Results of laboratory studies include serum bilirubin of 5.2 mg/dL (60% conjugated), AST of 400 U/L, ALT of 392 U/L, alkaline phosphatase of 70 U/L, anti-HAV antibodies negative, HBsAg negative, and IgM anti–hepatitis E virus (anti-HEV) antibodies positive. The patient is at high risk for which of the following?

A.Diabetes mellitus	B.Fulminant liver failure	C.Pulmonary thromboembolism	D.Renal failure

1-B /2 -C/ 3-B /4-B

Pathology Team

Leader زياد العتيبي



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