جامعة الملك سعود
King Saud University

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Pathology

liver cirrhosis and its complication

439

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- Important
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Objective

01 Define Cirrhosis

02 Recognize the types and classification of cirrhosis

03 Recognize the causes and the pathogenic mechanisms leading to cirrhosis

04 Describe the pathological findings in cirrhotic livers

05 Recognize the major complications of cirrhosis

06 Understand the pathogenetic mechanisms underlying the occurrence of the complications

07 Recognize the clinical features inherent to the above-mentioned complications

08 Describe the pathological findings of the different complications

Overview

LIVER CIRRHOSIS

- Introduction
- Causes
  - Chronic Viral Hepatitis
  - Autoimmune Hepatitis
  - Alcohol Liver Disease
  - Secondary Biliary Cirrhosis
  - Primary Sclerosing Cholangitis
  - Primary Sclerosing Cholangitis
- Complication
  - Portal hypertension
    - Splenomegaly
    - Portosystemic vines shunt
      - Esophageal varices
      - Hemoroid
      - Caput Medusa
  - Liver failure
    - Hyperammonemia
      - Hepatic encephalitis
    - Hyperestrogenemia
    - Hypoalbuminemia
    - Coagulopathy
  - Asites
  - Jaundice and cholestasis
  - Spontaneous bacterial peritonitis
  - Hepatorenal syndrome
  - Hepatocellular Carcinoma

Female's slide

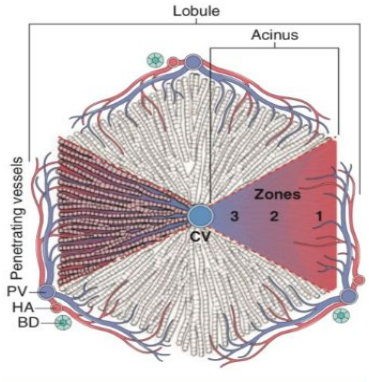
Histology of Liver

Introduction

- Normal adult liver weighs approximately 1400 g in females and 1800 g in males
- Has dual 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**
- Based on Couinaud classification, the liver is divided into **eight independent functional segments**
- Each segment has its own portal pedicle consisting of the hepatic arterial branch, portal branch, and the bile duct with a separate hepatic venous branch

Lobules

- Liver cells "hepatocytes" are arranged radially around the central vein "terminal hepatic vein"
- Porta tract are present at the periphery
- These lobule are often drawn as hexagonal structures
- Smallest structural unit of the liver is the lobule
- The smallest functional unit is the acinus



Physiologically

1. - it is more useful to think of liver architecture in terms of functional unit "acinus"
2. - Depends on position of hepatocytes relative to their blood supply
3. - Three zones are identified in term of oxygenation & nutrient supply
4. - Division of the lobular parenchyma into zones is an important concept because each zone differs with respect to its metabolic activities and susceptibility to certain forms of hepatic injury
5. - Certain hepatic injury occurs in certain zone which means each disease starts at different place/zone near or far from the central vein .

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 (asymptomatic patient)

Mechanism of injury and repair

01

lnjured hepatocytes may show several potentially reversible changes, such as accumulation of fat and bilirubin (cholestasis)

02

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, drug and toxin-induced hepatitis.

Chronic liver failure and cirrhosis

- When there is an injury happening to the liver, the most severe clinical form/ consequence is the liver failure which is NOT the end stage .
- Three types of liver failure: Acute (reversible), Chronic (irreversible → liver cirrhosis) and Acute on top of chronic liver failure .
- 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
- It is among the top 10 causes of death in the Western world
- It is the end-stage of chronic liver disease (liver is not functioning anymore)
- Not all chronic liver disease terminates in cirrhosis & not all cirrhosis leads to end stage liver disease
- Patients may present with the same clinical findings (signs & symptoms) but histologically they are completely different .

Cirrhosis

- is the end stage of chronic liver disease, it's defined by **three main morphologic characteristics**:

1. **Parenchymal/regenerative nodules** containing hepatocytes encircled by fibrosis, with diameters varying from very small (<0.3 cm, micronodules) to large (several centimeters, macronodules)
2. **Fibrosis**: in the form of delicate bands or broad scars/septa (**Bridging fibrous septa**)
3. **Disruption of the architecture of the entire liver**

Causes

Chronic hepatitis B&C → Non-alcoholic fatty liver disease (NAFLD) → Alcoholic liver disease

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

Classification of cirrhosis based on causes (US)

- 60% to 70% — **Alcoholic liver disease**
- 10% — Viral hepatitis
  The most common cause in Saudi Arabia
- 5% to 10% — Biliary diseases
- 5% — Primary hemochromatosis
  Genetic (appears at childhood)
- Rare — Wilson disease
  Genetic (appears at childhood)
- Rare — α1-Antitrypsin deficiency
  Genetic (appears at childhood)
- 10% to 15% — **Cryptogenic cirrhosis**
  = idiopathic

Classification of cirrhosis (Infrequent types of cirrhosis) rare

❖ The classification is based on the underlying etiology

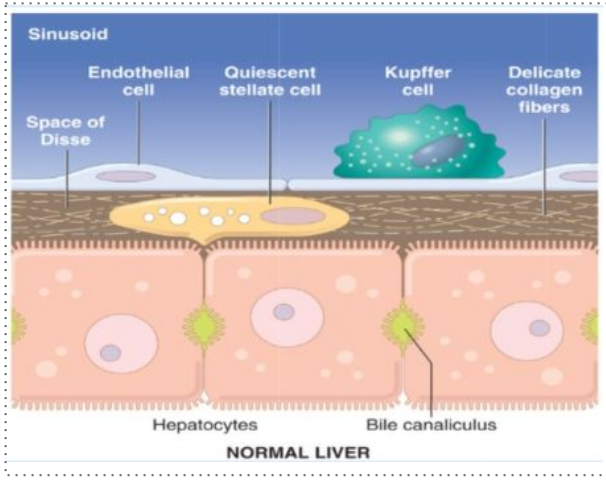
1. The cirrhosis developing in infants and children with galactosemia and tyrosinosis
2. Drug-induced cirrhosis (methotrexate, enalapril, vitamin A) need liver function test frequently
3. Severe fibrosis can occur in the setting of cardiac disease "cardiac cirrhosis"
4. In some cases, there is no cause, and these are referred to cryptogenic cirrhosis
5. Once cirrhosis is established, it is usually impossible to establish an etiologic diagnosis on morphologic grounds alone = in cirrhotic liver, it's difficult to determine the cause of liver failure

Pathogenesis of liver cirrhosis

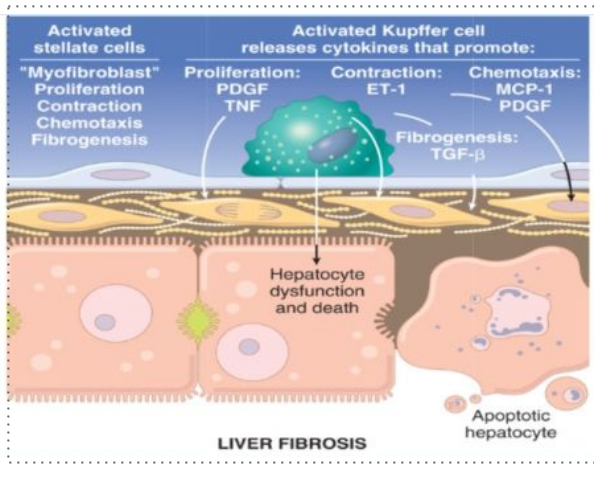
❖ Principal cell type involved in scar deposition and The major source of excess collagen in cirrhosis is the perisinusoidal hepatic stellate cell (older name : ito cells)
❖ These cells are located in the space of Disse and in normal liver has a role in the storage of vitamin a fat-storing cells
❖ Following liver injury,(during the development of cirrhosis)stellate cells become activated by several mechanisms and convert into highly fibrogenic myofibroblasts (myofibroblast-like cell) , which produce the fibrous scar
❖ In injury, stellate cells undergo modifications and activation into myofibroblasts that produce fibrous tissue (fibrosis) leading to fibrous scar

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

➢ 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.
➢ Chronic inflammation, with production of inflammatory cytokines such as tumor necrosis factor (TNF), lymphotoxin, and interleukin 1β (IL-1β), and lipid peroxidation products
➢ At the same time, Cytokine and chemokine production by Kupffer cells, endothelial cells leads to direct stimulation of stellate cells by these toxins
➢ Cytotoxin production by Kupffer cell , endothelial cell , hepatocytes , and bile duct epithelial cell



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



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)

❖ 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

Clinical manifestation

- About 40% of patients are asymptomatic until most advanced stages of disease
- Non-specific symptoms such as anorexia, weight loss, weakness & eventually signs & symptoms of liver failure (jaundice, encephalopathy & coagulopathy , osteoporosis and in advanced disease , frank debilitation), much as the same as in acute liver hepatitis
- Incipient or overt hepatic failure may develop

Clinical course

★ Female's slide

- 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
- In fibrosis regression scars become thinner, more densely compacted & eventually start to fragment Adjacent parenchymal regenerating nodules coalesce into larger islands = start as small nodules then get larger into micronodules

Causes of death in patient with liver cirrhosis

★Female's slide

Progressive liver failure

1. A complication related to portal hypertension
2.
3. Hepatocellular carcinoma

Summary

Female's slide

1. Severe injury
2. death of large number of hepatocytes & drop out of liver cells
3. collapse of the underlying reticulin
4. prevent orderly regeneration of hepatocytes
5. activation of stellate cells
6. replacement of areas of liver cell loss by fibrous septae
7. fibrous septa encircle surviving, regenerating hepatocytes in late-stage chronic liver disease
8. cirrhosis

Chronic Hepatitis Morphology ★Male's slide

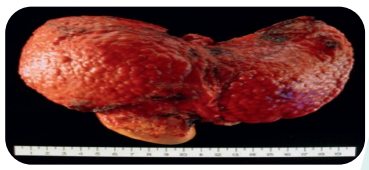
Some changes are shared with acute hepatitis

- Hepatocyte injury, necrosis, and regeneration
- **Portal tract Inflammation:**
  - Confined to portal tracts, *or*
  - Spillover into adjacent parenchyma, with necrosis of hepatocytes ("interface hepatitis"), or
  - Bridging inflammation and necrosis
- **Fibrosis:**
  - continued loss of hepatocytes results in fibrous septa formation which ultimately leads to cirrhosis
- HBV: "ground-glass" hepatocytes, "sanded" nuclei
- HCV: bile duct damage, lymphoid aggregate formation
- **Cirrhosis: The end-stage outcome**

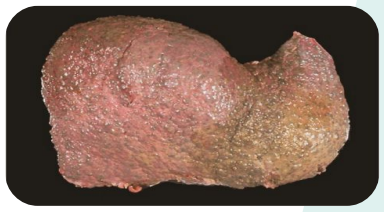
Gross Morphology

The images found in both slides while the content was only in female slides

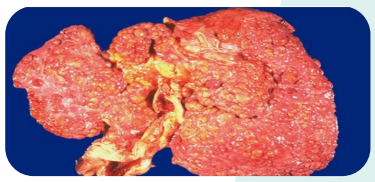
- The broad scars separating bulging regenerative nodules over the liver surface (nodular outer surface)



- **Micronodular cirrhosis** : The regenerative nodules are quite small, averaging less than 3 mm in size, but there is a tendency for nodules to increase in size with time
- The most common cause for this is **chronic alcoholism**

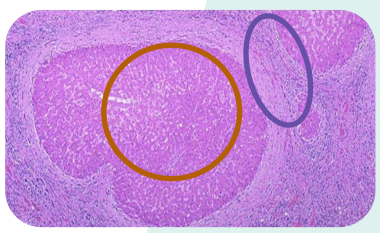


- The nodules seen here are larger than 3 mm
- this is an example of "macronodular" cirrhosis

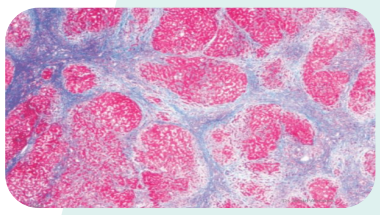


Microscopically ★Female's slide

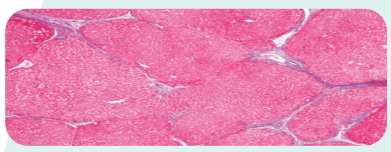
- Regenerative nodules of hepatocytes are surrounded by fibrous connective tissue/thick fibrous band that bridges between portal tracts. Within this collagenous tissue are scattered lymphocytes as well as a proliferation of bile ducts
- Defined as a diffuse process characterized by **fibrosis** and the conversion of normal liver architecture into structurally abnormal **nodules**



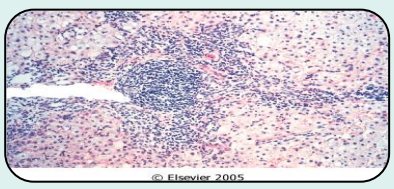
- Diffuse transformation of liver parenchyma into regenerative parenchymal nodules surrounded by thick fibrous or collagen bands
- Vascular architecture is reorganized with the formation of abnormal interconnections between vascular inflow and hepatic vein outflow
- Fibrosis is the key feature of progressive damage to the liver
- Masson trichrome stain (bluish coloration, shows the amount of fibrosis)



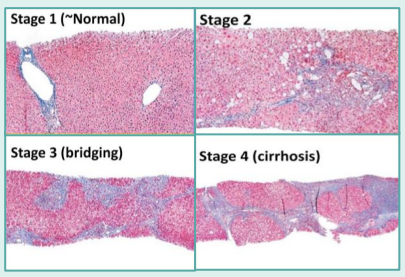
- Regression of fibrosis and most scars are gone.
- Scars become thinner and more densely compact



- Lymphocytic infiltration of portal tract, a feature of chronic hepatitis



- Stage 1: Normal
- Stage 2: Beginning of fibrosis
- Stage 3: Fibrosis forms a bridge
- Stage 4: Fibrosis forms a nodules , in this stage we call it cirrhosis



Morphology of common causes of liver cirrhosis

- **Infectious :**
  - Viruses (hepatitis B & C virus)
- **Others :**
  - Autoimmune hepatitis (AIH)
  - Alcoholic liver disease
  - Biliary cirrhosis

Viral Hepatitis

Overview

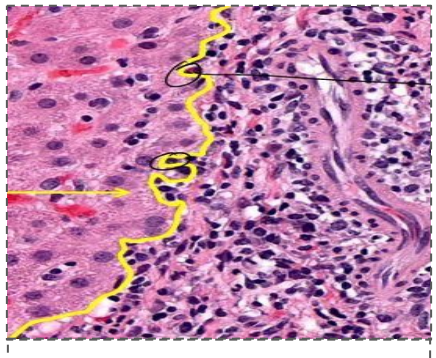
- Inflammatory disorders of the liver dominate the clinical practice of hepatology
- Hepatitis is the name applied to viruses (hepatitis A, B, C, D, and E virus) that are hepatotropic, that is, have a specific affinity for the liver
- The morphologic changes in acute and chronic viral hepatitis are shared among the hepatotropic viruses and can be mimicked by drug reactions or autoimmune hepatitis (the same criteria is shared between these viruses)

Hepatitis Morphology

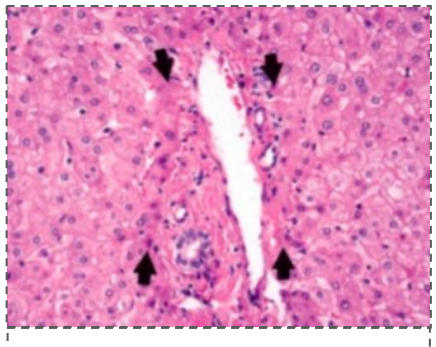
- Some changes are shared with acute hepatitis:

1. Hepatocyte injury, necrosis, and regeneration
2. Sinusoidal cell reactive changes
3. Portal tract Inflammation:

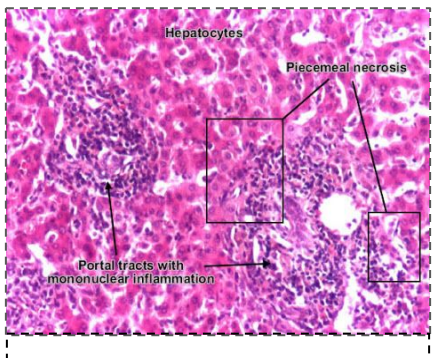
- Confined to portal tracts or
- Spillover into adjacent parenchyma, with necrosis of hepatocytes "interface hepatitis" or
- Bridging inflammation and necrosis



Spillover into adjacent parenchyma, with necrosis of hepatocytes "interface hepatitis"



Piecemeal necrosis of chronic hepatitis



Extra

Morphology of acute viral hepatitis ★ Female's slide

01 Predominantly mononuclear inflammatory cell infiltrate (lymphocytes), rich in plasma cells in hepatitis A infection

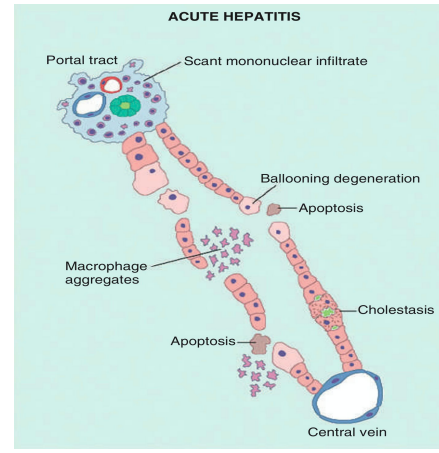
02 Portal inflammation: Minimal or absent

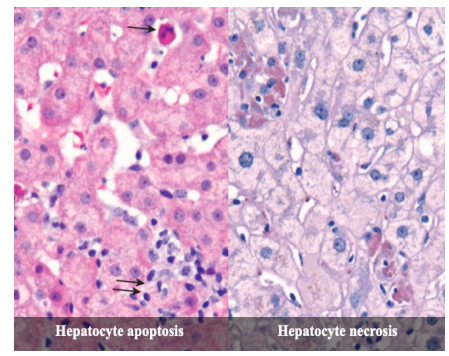
03 Scattered parenchymal injury throughout the hepatic lobules "spotty necrosis or lobular hepatitis"

04 Hepatocyte injury may result in either:

1. Necrosis: Cytoplasm appears empty with eventual rupture of cell membrane → "drop out " of hepatocytes ➔ collapse in sinusoidal collagen reticulin framework
2. Apoptosis ➔ shrunken, intensely eosinophilic cells with pyknotic & fragmented nuclei

05 In sever acute hepatitis ➔ central portal bridging necrosis ➔ parenchymal collapse

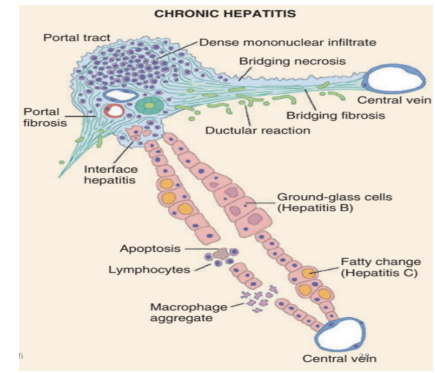


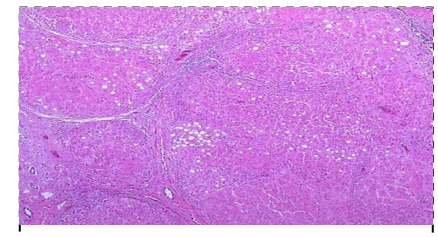


Morphology of chronic viral hepatitis

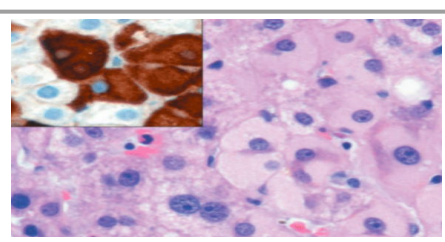
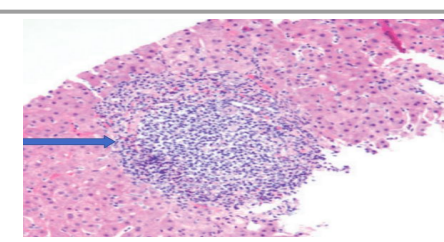
- Hepatocyte injury, necrosis, and regeneration
- Portal tract inflammation
- Fibrosis: Continued loss of hepatocytes results in fibrosis septa formation which ultimately leads to cirrhosis.
- Cirrhosis:the end stage outcome
- Mononuclear portal infiltration in portal tract
- Interface hepatitis is present as well: Located at the interface between hepatocellular parenchyma & portal tract stroma
- Lobular hepatitis
- The hallmark of progressive chronic liver damage is scarring At first, only portal tracts exhibit fibrosis→ In some patients, with time, fibrous septa "bands of dense scar" will extend between portal tracts , In most severe cases, continued scarring and nodule formation ➔ cirrhosis

- Certain histologic features point to specific viral etiologies





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

HBV	HVC
❖ Ground glass hepatocytes "finely granular eosinophilic cytoplasm = massive amount of HBsAg within endoplasmic reticulum" (Ballooning of cells) ❖ sanded nuclei ❖ Can be confirmed by immunostaining (Brown color)	❖ Large lymphoid aggregates in portal tract (lymphoid follicles with lymphocytes) ❖ Mild steatosis (fatty changes) ❖ Bile duct injury
	

Autoimmune Hepatitis

Overview

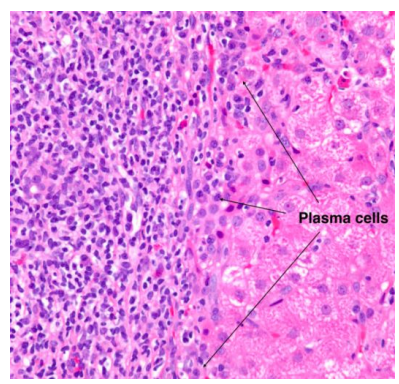
- ❖ Is a chronic, progressive hepatitis with all the features of autoimmune diseases in general:
  - ➢ Genetic predisposition
  - ➢ Association with other autoimmune diseases
  - ➢ Presence of autoantibodies
  - ➢ Therapeutic response to immunosuppression Like steroids
- ❖ Risk for AIH is associated with certain HLA alleles, such as the DRB1 allele in Caucasians
- ❖ But as in other autoimmune disorders the mechanistic basis for this relationship is unclear
- ❖ Triggers for the immune reaction may include viral infections or drug or toxin exposures

Clinical features	❖ Diagnosis & intervention are imperative ❖ Acute clinical illness is a common presentation (40%) ❖ Sometimes the disease is fulminant, progressing to hepatic encephalopathy within 8 weeks of onset ❖ Mortality for patients with severe untreated AIH is ~ 40% within 6 months of diagnosis & cirrhosis develops in at least 40% of survivors
Incidence	❖ The annual incidence is highest among white northern europeans, but all ethnic groups are susceptible ❖ Female predominance (78%)
Association	❖ Associated with other autoimmune diseases eg. rheumatoid arthritis, Sjogren's syndrome, SLE etc
Treatment	❖ Immunosuppressive therapy is usually effective ➔ remission in 80% of patients & enables long-term survival ❖ 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

Types "Classified into two types, based on the patterns of circulating antibodies"	Type 1	Type 2
	❖ More common in middle-age & older individuals. ❖ 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

- ❖ 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

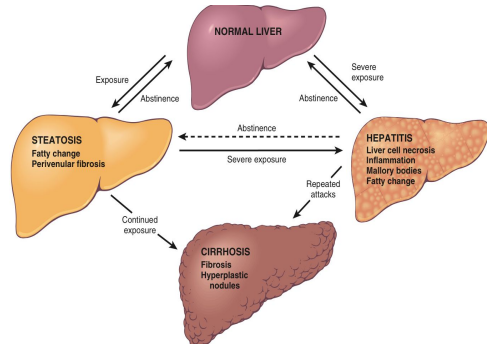
Overview

- 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
- Cirrhosis occurs in a small proportion of chronic alcoholics
- Alcoholic cirrhosis has similar clinical signs and symptoms as cirrhosis caused by viral hepatitis

Features

Hepatic steatosis (reversible) → Alcoholic hepatitis (irreversible) → Fibrosis and cirrhosis

- may develop sequentially or independently, so they do not necessarily represent a sequential continuum of changes.
- Short-term ingestion (8 gm of ethanol/day) → usually mild hepatic changes that are reversible (e.x. steatosis)
- Long-term ingestion (40-80 gm of ethanol/day) → considered as border line risk factor for severe liver injury which is usually irreversible (e.x. hepatitis)



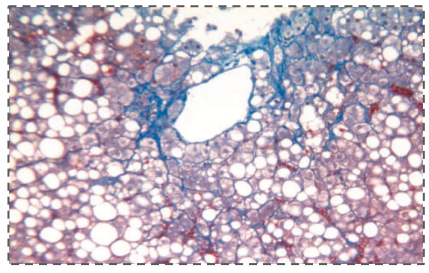
Causes

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

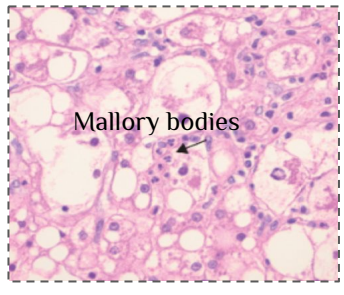
1. Acetaldehyde → (a major metabolite of ethanol) induces lipid peroxidation which may disrupt cytoskeleton and membrane function.
2. Alcohol → directly affects mitochondrial function and membrane fluidity.
3. Reactive oxygen species → generated during oxidation of ethanol by the microsomal ethanol oxidizing system react with and damage membranes and proteins

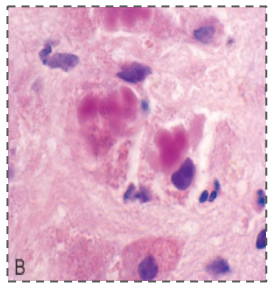
Morphology

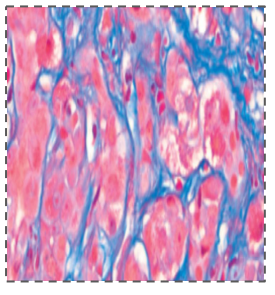
- Hepatic Steatosis (Fatty Liver) "predominant"



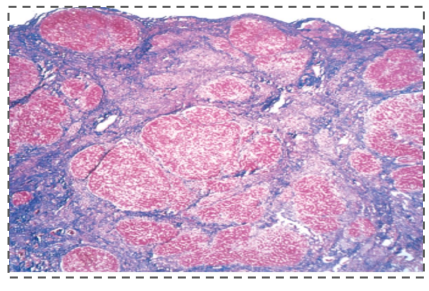
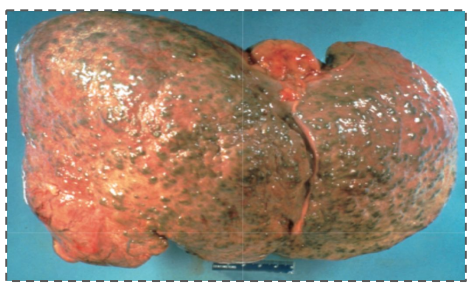

- Alcoholic Hepatitis (Alcoholic Steatohepatitis):
  - Hepatocyte swelling necrosis
  - **Mallory bodies** = eosinophilic inclusions in the hepatocytes
  - Neutrophilic reaction = inflammation
  - fibrosis "end stage"







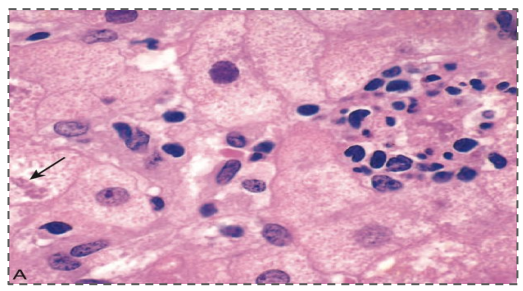
- Alcoholic Cirrhosis (Micronodular cirrhosis) that is separated by fibrous bands

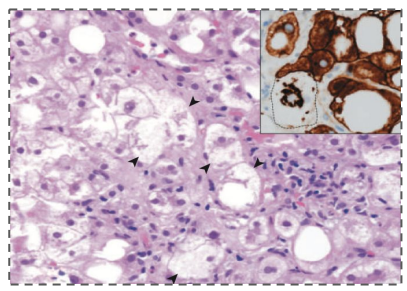



- Hepatocyte injury

•Cluster of inflammatory cells
•Mallory-Denk bodies

Ballooned/enlarged hepatocytes (seen with CK IHC)





Causes of death

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

- Summary of the (liver cirrhosis , Autoimmune Hepatitis , Alcoholic liver disease was only found in female slid , click here

Intrahepatic biliary tract disease

Distinguishing features of the major intrahepatic bile duct disorders ★

	Secondary biliary cirrhosis	Primary biliary cirrhosis	Primary sclerosing cirrhosis
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
Symptom and sign	Pruritus , jaundice, malaise , dark urine, light stools , hepatosplenomegaly	Same as secondary biliary cirrhosis; insidious onset	Same as secondary biliary cirrhosis; insidious onset
Laboratory finding	Conjugated hyperbilirubinemia, increased serum alkaline phosphatase, bile acids , cholesterol	Same as secondary biliary cirrhosis, puls elevated serum **IgM autoantibodies** (especially M2 form of anti-mitochondrial antibody)	Same as secondary biliary cirrhosis, puls 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 .

Secondary biliary cirrhosis

Overview		❖ Secondary inflammation resulting from biliary obstruction initiates periportal fibrosis, which eventually leads to hepatic scarring and nodule formation, generating secondary biliary cirrhosis
Etiology		❖ **The most common cause of obstruction in adults** is extrahepatic **cholelithiasis** (gallstones), followed by malignancies of the biliary tree or head of the pancreas and structures resulting from previous surgical procedures ❖ **Cholestasis** (stagnant of bile) are entirely reversible with correction of the obstruction ❖ **Obstructive conditions in children** include biliary atresia, cystic fibrosis, choledochal cysts (a cystic anomaly of the extrahepatic biliary tree) ❖ Subtotal obstruction may promote secondary bacterial infection of the biliary tree (ascending cholangitis), which aggravates the inflammatory injury. Enteric organisms such as coliforms and enterococci are common culprits
Sex predilection		❖ None
Symptoms and signs		❖ Pruritus, jaundice, malaise, dark urine, light stools, hepatosplenomegaly
Morphology	Grossly	❖ The end-stage obstructed liver shows: Yellow-green pigmentation that is accompanied by marked icteric discoloration (Patients present with jaundice), body tissues and fluids ❖ On cut surface the liver is hard, with a finely granular appearance
	Microscopically	❖ Characterized by coarse fibrous septa that subdivide the liver in a **jigsaw-like pattern (Puzzle-like pattern)** ❖ Extensive proliferation of smaller bile ductules ❖ Cholestatic may be severe, with extensive feathery degeneration and formation of bile lakes ❖ Ascending bacterial infection incites a robust neutrophilic infiltration of bile ducts which is usually detected by gram stain
Laboratory findings		❖ Conjugated **hyperbilirubinemia**, increased serum alkaline phosphatase, bile acids, cholesterol No increase in serum AMA or IgM
Important pathologic findings before cirrhosis develops		❖ Prominent bile stasis in bile ducts, bile ductular proliferation with surrounding neutrophils, portal tract edema

Female's slide

Parameter	Primary Biliary Cirrhosis	Primary Sclerosing Cholangitis
Age	Median age 50 years (30–70)	Median age 30 years
Gender	90% female	70% male
Clinical course	Progressive	Unpredictable but progressive
Associated conditions	Sjögren syndrome (70%) Scleroderma (5%) Thyroid disease (20%)	Inflammatory bowel disease (70%) Pancreatitis (≤25%) Idiopathic fibrosing diseases (retroperitoneal fibrosis)
Serology	95% AMA-positive 20% ANA-positive 40% ANCA-positive	0–5% AMA-positive (low titer) 6% ANA-positive 65% ANCA-positive
Serology	Normal	Strictures and beading of large bile ducts; pruning of smaller ducts
Duct lesion	Florid duct lesions and loss of small ducts only	Inflammatory destruction of extrahepatic and large intrahepatic ducts; fibrotic obliteration of medium and small intrahepatic ducts

Primary biliary cirrhosis

Overview	❖ Is an autoimmune disease whose primary feature is nonsuppurative, inflammatory destruction of small- and medium-sized intrahepatic bile ducts (no bacterial infection or ascending cholangitis) ❖ It is accompanied by portal inflammation, scarring, and eventual development of cirrhosis and liver failure
Epidemiology	❖ Middle-aged ❖ Female predominance over males in excess of 6 : 1 ❖ It may occur between the ages of 20 and 80 years, with peak incidence between 40 and 50 years of age
Clinical course	❖ Insidious onset ❖ Patients may be symptom-free for many years ❖ Eventually, pruritus, fatigue, and abdominal discomfort develop ❖ **General features** of jaundice and hepatic decompensation, including portal hypertension and variceal bleeding, mark entry into the end stages of the disease ❖ **Secondary features**: skin pigmentation (jaundice), xanthelasmas, steatorrhea, and vitamin D malabsorption–related osteomalacia and/or osteoporosis ❖ May also have **extrahepatic manifestations** of autoimmunity, including Sjögren syndrome; systemic sclerosis
Symptoms and signs	❖ Pruritus, jaundice, malaise, dark urine, light stools, hepatosplenomegaly
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 ❖ With time: ➢ Progressive obstruction of the main bile duct ➔ 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
Laboratory findings	❖ **Serum alkaline phosphatase** and cholesterol are almost always elevated ❖ **Antimitochondrial antibodies (AMA)** are present in 90% to 95% of patients (highly characteristic of PBC) ❖ Hyperbilirubinemia is a late development and usually signifies incipient hepatic decompensation
Important pathologic findings before cirrhosis develops	❖ Dense lymphocytic infiltrate in portal tracts with granulomatous destruction of bile ducts

Primary sclerosing cirrhosis

- In most cases, the end-stage picture is indistinguishable from secondary biliary cirrhosis or the cirrhosis that follows chronic hepatitis from other causes

Overview	❖ chronic cholestatic disorder Characterized by 1) inflammation and obliterative fibrosis of intrahepatic and extrahepatic bile ducts, with dilation of preserved segments 2) irregular biliary strictures and dilations cause the characteristic "beading" of the intrahepatic and extrahepatic biliary tree seen by MRI.
Etiology	❖ Unknown, possibly autoimmune ❖ commonly seen in associated with inflammatory bowel disease 50-70% , particularly chronic ulcerative colitis
Sex predilection	❖ Female to male: 1:2
Clinical course	❖ Asymptomatic patients may come to attention only because of persistent elevation of serum alkaline phosphatase ❖ Progressive fatigue, pruritus, jaundice may develop & weight loss ❖ Approximately 7% of individuals with PSC develop cholangiocarcinoma
Symptoms and signs	❖ Same as secondary biliary cirrhosis (Pruritus, jaundice, malaise, dark urine, light stools, hepatosplenomegaly) insidious onset
Morphology	❖ 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**" is followed by their disappearance, leaving behind a solid, cordlike fibrous scar ❖ As the disease progresses, the liver becomes cirrhotic like that seen with primary and secondary biliary cirrhosis
Pathogenesis	❖ unknown
Laboratory finding	❖ Same as secondary biliary cirrhosis (Conjugated hyperbilirubinemia, increased serum alkaline phosphatase, bile acids, cholesterol) plus elevated serum IgM, hypergammaglobulinemia
Important pathologic findings before cirrhosis develops	❖ Periductal portal tract fibrosis, segmental stenosis of extrahepatic and intrahepatic bile ducts

COMPLICATION OF CIRRHOSIS

1) Portal hypertension

Definition	❖ More frequent and more complex in chronic than in acute liver failure Due to Resistance to blood flow and. by diminished flow through the portal venous system
Causes of portal hypertension	❖ could be because obstruction at the **prehepatic**, **intrahepatic**, or **post hepatic** level
In summary :	Portal hypertension ⟶ Portosystemic shunt which may lead to A. Rectum (hemorrhoids) B. Abdominal wall collaterals (caput medusae) C. Cardioesophageal junction (esophagogastric varices)

Complications of Portal hypertension

Portosystemic shunt:	splenomegaly
❖ Develop when blood flow is reversed from portal to systemic circulation ❖ Produced by dilation of collateral vessels ❖ Most clinically important is esophageal varices which appear in ~ 40% of patients with advanced-stage liver disease ❖ often cause massive, frequently fatal hematemesis, particularly with compounding coagulopathy	❖ Long-standing congestion may cause congestive splenomegaly ❖ The degree of splenic enlargement varies widely and may reach as much as 1000 gm ❖ Massive splenomegaly may secondarily induce hematologic abnormalities attributable to hypersplenism, such as thrombocytopenia or even pancytopenia

Portosystemic shunt count..

1. Caput Medusa

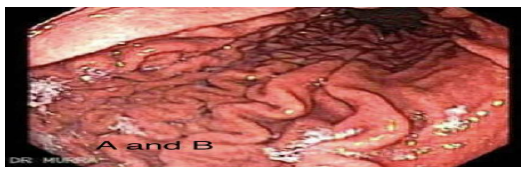
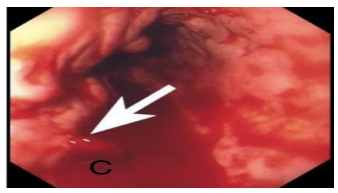
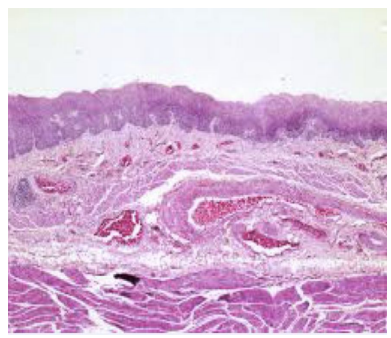
Overview	increased blood flow into veins at the paraumbilical veins of the abdominal wall (forming a caput medusae)

2. Hemorrhoid

Overview	increased blood flow into veins at the rectum (forming hemorrhoids)

Portosystemic shunt count..

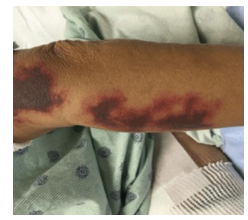
3.Esophageal varices

Overview (Female's slide)	• 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.
Caused by	•Diseases that impede this flow cause portal hypertension. and can lead to the development of esophageal varices, an important cause of esophageal bleeding. •90% of cirrhotic patients
Pathogenesis (Female's slide)	• 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) • Most commonly in association with alcoholic liver disease and hepatic schistosomiasis
Morphology:	**Grossly** : A.Can be be detected by venogram A.tortuous dilated veins lying primarily within the submucosa of the distal esophagus and proximal stomach (mainly above the gastroesophageal junction). B.Venous channels directly beneath the esophageal epithelium may also become massively dilated. C.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   **Microscopically** : (Female's slide) Dilated, thin-walled vessels are seen, mostly in the submucosa 
Clinical features:	Asymptomatic or rupture a massive hematemesis • Inflammatory erosion of thinned overlying mucosa • Increased tension in progressively dilated veins • Increased vascular hydrostatic pressure associated with vomiting are likely to contribute to medical emergency that is treated by any of several methods: 1. Sclerotherapy 2. Endoscopic balloon tamponade 3. Endoscopic rubber band ligation "most common used method" 4.sclerotherapy, balloon tamponade, rubber band ligation
Prognosis: (Female's slide)	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 • Each episode has a similar rate of mortality • Over half of deaths among individuals with advanced cirrhosis result from variceal rupture & bleeding

2) Liver failure

★Female's slide

Hepatic failure

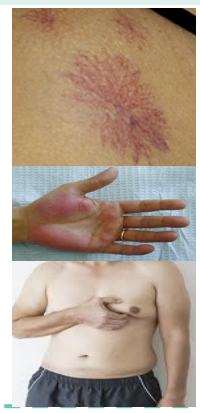
1- Coagulopathy	• Coagulation factors that decline in the face of liver failure, leading to easy bruising (which can occur after touching the skin only) and bleeding. Paradoxically, disseminated intravascular coagulation • Hypercoagulation state also may occur due to failure of the damaged liver to remove activated coagulation factors 
2- Hypoalbuminemia	• Hypoalbuminemia from decreased synthesis of albumin • Produces dependent **pitting edema** (usually felt in the legs)and ascites due to a decrease in plasma oncotic pressure
3- Hyperestrogenemia	- Due to impaired estrogen metabolism : • Liver cannot degrade estrogen and 17-ketosteroids (Androstenedione) • Androstenedione is aromatized into estrogen in the adipose cells

In females ♀

hypogonadism (infertility) ➔ oligomenorrhea, amenorrhea & sterility

In males ♂

- ❖ Palmar erythema "due to local vasodilatation
- ❖ Spider angiomas of skin
- ❖ Hypogonadism
- ❖ Female distribution of hair
- ❖ **Gynecomastia**

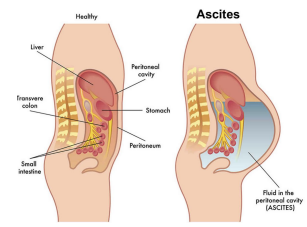


4- Hyperammonemia	**Hepatic encephalopathy :** ❖ A spectrum of disturbances in consciousness, ranging from subtle behavioral abnormalities to confusion & stupor, to coma & death ❖ only minor morphologic changes in the brain, such as edema and an astrocytic reaction ❖ Reversible if the underlying hepatic condition can be corrected

1. Course: → develop over days, weeks, or a few months after acute injury
2. Features: → fluctuating neurologic signs, including rigidity, hyperreflexia, and asterixis
3. Mechanism: → elevated ammonia levels in blood and the central nervous system correlate with impaired neuronal function and brain edema

3) Ascites

Overview	❖ Is the accumulation of excess fluid in the peritoneal cavity 85% ❖ 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
Cause	❖ 85% of cases are caused by cirrhosis (ascites is also caused by congestive heart failure & renal failure)
Pathogenesis	1-Sinusoidal hypertension, drives fluid into the space of Disse, which is then removed by hepatic lymphatics; 2-Hypoalbuminemia 3-Leakage of hepatic lymph into the peritoneal cavity



Pathogenesis:

★Female's slide

Increase in portal vein hydrostatic pressure → Decreases oncotic pressure → Liver is unable to metabolize aldosterone (affects Na/water retention)

Female's slide

4) Cholestasis, Jaundice and Pruritus

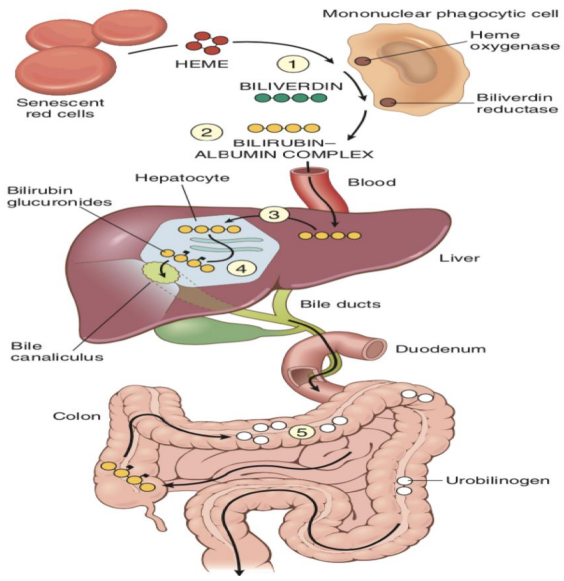
Jaundice and icterus

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

Cause of Jaundice	
Bilirubin overproduction	❖ hemolytic anemias ❖ resorption of blood from internal hemorrhage ❖ ineffective erythropoiesis
reduced hepatic uptake	❖ drug interference with membrane carrier systems
impaired bilirubin conjugation	❖ physiologic jaundice of the newborn ❖ diffuse hepatocellular disease
decreased hepatocellular excretion	❖ drug induced canalicular membrane dysfunction ❖ hepatocellular damage or toxicity
impaired intrahepatic or extrahepatic bile flow	❖ inflammatory destruction of intrahepatic bile ducts ❖ **gallstones** ❖ external compression

Bilirubin metabolism and elimination

Metabolism of bilirubin by the liver consists of four separate but interrelated events:
1. Uptake from the circulation
2. Intracellular storage
3. Conjugation with glucuronic acid
4. Biliary excretion



Bilirubin metabolism and elimination. 1, Normal bilirubin production (0.2 to 0.3 g/day) is derived primarily from the breakdown of senescent circulating red cells, with a minor contribution from degradation of tissue heme-containing proteins. 2, Extrahepatic bilirubin is bound to serum albumin and delivered to the liver. 3 and 4, Hepatocellular uptake (3) and glucuronidation (4) by glucuronosyltransferase in the hepatocytes generate bilirubin monoglucuronide and glucuronides, which are water-soluble and readily excreted into bile. 5, Gut bacteria deconjugate the bilirubin and degrade it to colorless urobilinogens. The urobilinogens and the residue of intact pigments are excreted in the feces, with some reabsorption and excretion into bile.

4) Cholestasis, Jaundice and Pruritus

Cholestasis

- Condition of impaired bile formation and bile flow, leading to accumulation of bile pigment in the hepatic parenchyma
- It can be caused by extrahepatic or intrahepatic obstruction of bile channels, or by defects in hepatocyte bile secretion
- Patients may have jaundice, pruritus, skin xanthomas (focal accumulation of cholesterol) usually around the eyelid, or symptoms related to intestinal malabsorption, including nutritional deficiencies of the fat-soluble vitamins A, D, or K

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

5) Spontaneous bacterial peritonitis

Overview

- As a result of fluid accumulation (ascites), the patient will have an increased risk for spontaneous bacterial infection on top of ascites

6) 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. ❖ The incidence of this syndrome is about 8% per year among patients who have cirrhosis and ascites
Functional abnormalities of the condition ★	❖ Sodium retention, impaired free-water excretion, ↓ renal perfusion & ↓ glomerular filtration rate
Features ★	❖ ↓ Urine output, ↑ blood urea nitrogen & creatinine levels
causes	❖ Decreased renal perfusion pressure due to systemic vasodilation ❖ Activation of the renal sympathetic nervous system with vasoconstriction of the afferent renal arterioles ❖ Increased synthesis of renal vasoactive mediators (activation of the renin/angiotensin axis), that decrease glomerular filtration.
prognosis	❖ is poor, with a median survival of only 2 weeks in the rapid-onset form and 6 months with the insidious-onset form.

Female's slide

7) Hepatocellular Carcinoma

Definition	❖ Most chronic liver disease predispose to development of hepatocellular carcinoma

QUIZ!

MCQs

01 | Cytokines that are seen in liver chronic inflammation ?			
A) TNF	B) lymphotoxin	C) IL-1β	D) all
02 | which one of the following isn't a death cause of liver cirrhosis ?			
A) Progressive liver failure	B) A complication related to portal hypertension	C) renal failure	D) Hepatocellular carcinoma
03 | damage to the liver can be evaluated by?			
A) presence of regenerative parenchymal nodules	B) fibrosis	C) Vitamin A deficiency	D) elevated ALT
06 | Which of these things can cause hepatitis?			
A) Viruses	B) Medicines and alcohol	C) Immune system that's not working as it should	D) all of the above
05 | In which of the following Mallory-Denk bodies are found ?			
A) Viral hepatitis	B) Primary Biliary cholangitis	C) Autoimmune hepatitis	D)Alcoholic liver disease
06 | Which of the following antibodies are associated with Type 2 autoimmune hepatitis?			
A) Anti-liver kidney microsomal	B) Anti-nuclear & anti-smooth muscle	C) Anti-liver cytosol-1	D) Both A & C

MCQs Answer key	01	02	03	04	05	06
	D	C	B	D	D	D

MCQs

QUIZ!

01 | A 58-year-old woman is brought to the emergency department 4 hours after vomiting blood and experiencing bloody stools. The patient was diagnosed with alcoholic cirrhosis 2 years ago. The patient subsequently goes into shock and expires. Which of the following is the most likely underlying cause of hematemesis and hematochezia in this patient?			
A) Alcoholic hepatitis	B) Peptic ulcer disease	C) Portal hypertension	D) Mallory-Weiss syndrome
02 | A 58-year-old woman is brought to the emergency department 4 hours after vomiting blood and experiencing bloody stools. The patient was diagnosed with alcoholic cirrhosis 2 years ago. Endoscopy reveals large esophageal varices, one of which is actively bleeding. Which of the following best explains the pathogenesis of dilated esophageal veins in this patient?			
A) Decreased intravascular oncotic pressure	B) Vasoconstriction of arterioles	C) Vasodilation of capillaries	D) Increased intravascular hydrostatic pressure
03 | 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) No histologic changes	C) Membranous nephropathy	D) Proliferative glomerulonephritis
04 | The most common cause of extrahepatic jaundice :			
A) bilirubin overproduction	B) infectious hepatitis	C) gallstones	D) drug reactions
05 | Is the accumulation of excess fluid in the peritoneal cavity			
A) ascites	B) jaundice	C) pruritus	D)Esophageal varices
06 | Elevated ammonia levels in blood and the central nervous system correlate with impaired neuronal function and brain edema Mechanism of :			
A) Ascites	B) splenomegaly	C) Hepatic failure	D) Hepatic encephalopathy

MCQs Answer key	01	02	03	04	05	06
	C	D	B	c	A	D

" اللهم علمنا ماينفعنا ، وانفعنا بما علمتنا وزدنا علما يارب العالمين "

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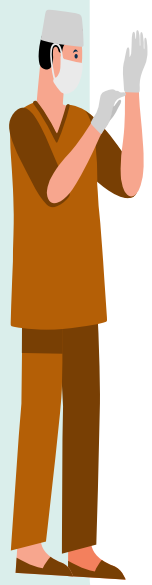

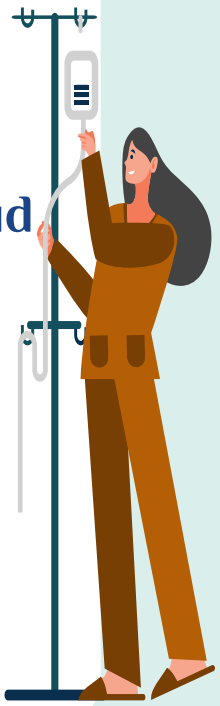

This Lecture done by

- Organizer
- Member
- Note taker
- Reviser

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