# L10&11: Liver cirrhosis and its complications

- Define Cirrhosis.
- Recognize the types of cirrhosis.
- Recognize the causes and the pathogenic mechanisms leading to cirrhosis.
- Describe the pathological findings in cirrhotic livers.
- Recognize the major complications of 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

Black: original content
Red: Important
Green: only found in males slides

Orange: Doctor notes
Grey: Extra/Robbins
Purple: Only found in females slides

Reviewed by: Razan AlRabah & Ibrahim AlDakhil

Editing File

# Liver Cirrhosis

- **Cirrhosis:** diffuse transformation of the liver into **regenerative parenchymal nodules**, surrounded by **fibrosis**.
- The End-stage of chronic liver disease.
- Reversal is usually rare once cirrhosis is established.
- Its mainly **caused** by:
  - **Alcohol abuse**
  - Viral hepatitis (B/C)
  - Other: biliary disease and iron overload. (Hemochromatosis in frequent blood transfusions)

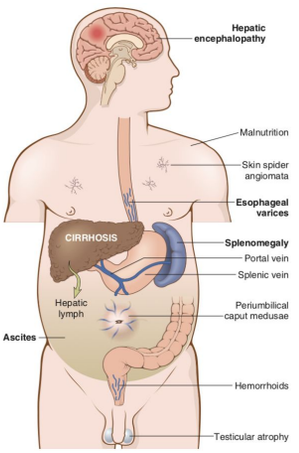
## Main characteristics

1. **Fibrosis:** in the form of delicate bands of broad bridging scars/septae
2. **Nodules:** regenerated hepatocytes, encircled by fibrosis. Varying in size.
3. **Diffuse disruption of architecture** of entire liver, not focal.

- There is **vascular reorganization**, due to damage and fibrosis, leading to abnormal interconnections between vascular inflow and hepatic vein outflow channels.

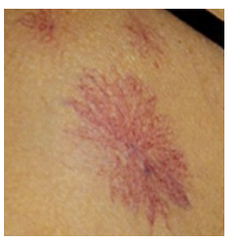
## Classifications (based on causes)

- **Alcoholic liver disease (60-70%)** micronodular
- **Viral hepatitis** (10%)
- **Biliary disease** (5-10%)
- **Primary hemochromatosis** (5%)
- **Wilson disease** (abnormal copper metabolism, genetic) **,** rare
- **α1-Antitrypsin deficiency,** rare
- **Cryptogenic Cirrhosis** (idiopathic)**, (**10-15%)
- **Cardiac cirrhosis,** occur in cases of cardiac disease
- **Drug-induced Cirrhosis (Methotrexate, enalapril, vitamin A)**
- In children, galactosemia and tyrosinosis can lead to cirrhosis




## Clinical features

- May be clinically silent
- Nonspecific features:
  - Anorexia and weight loss, Weakness and frank debilitation.
  - **Skin spider angiomata** (due to unmetabolized circulating estrogen).
  - Osteoporosis.
- **Jaundice**
- **Cause of death:**



**Skin spider angiomata**

1. Progressive liver failure
2. Complication of portal hypertension
3. Hepatocellular carcinoma

# Liver Cirrhosis

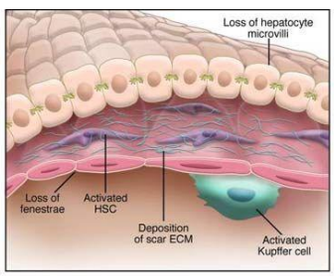
## Pathogenesis

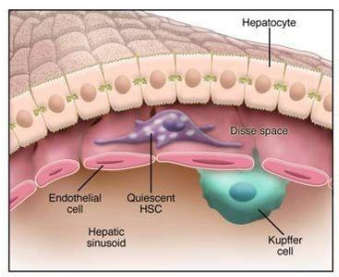
- Perisinusoidal **stellate cells** (ito cells), which are normally storing vitamin A and Fat, become stimulated by:
  - Cytokines due to chronic inflammation.
  - Cytokines from endogenous cells (Kupffer cells, endothelial cells, hepatocytes, bile duct epithelial).
  - Disruption of normal extracellular matrix.
  - Toxins.

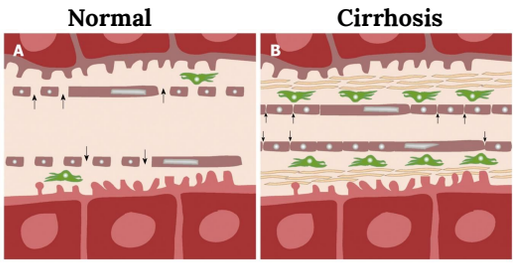
Perisinusoidal **stellate cell** (ito cells) are stimulated into **myofibroblast-like** cells.

Stimulated stellate cells secrete collagen I & III which are deposited into lobules creating septal tracts[1].

Capillarization of sinusoids, or loss of fenestration→ cannot exchange solutes between hepatocytes and plasma.

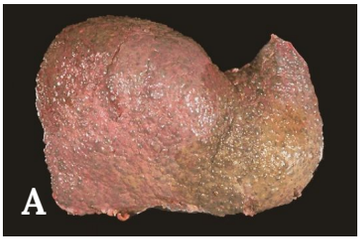


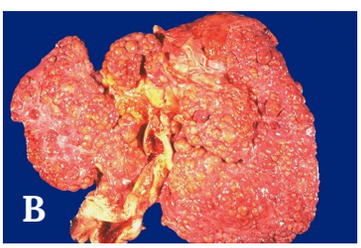



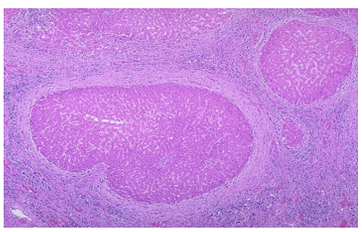



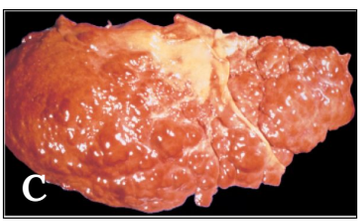

## Morphology

- Once cirrhosis has been established etiology cannot be established based on morphology.
- **Macroscopy**:
  - **Micronodular cirrhosis (A):** nodules <3mm.
    - Most common cause in alcoholism.
  - **Macronodular cirrhosis (B&C):** > 3mm
- **Microscopy:**
  - Regenerative nodule of hepatocytes.
    - Surrounded by fibrosis.
  - Scattered lymphocytes.
  - Proliferation of bile ducts.






1-the reticuticular fiber is replaced by collagen which makes it more stiff .

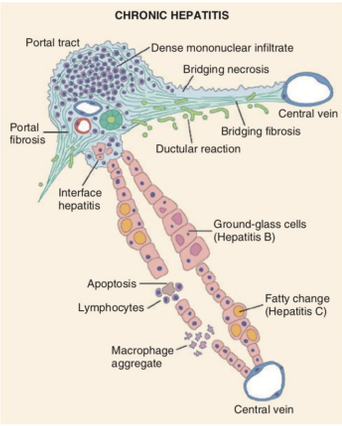
# Chronic Viral Hepatitis

**Fibrosis staging:**

1. Stage I: fibrosis in the portal tract.
2. Stage II: periportal fibrosis.
3. Stage III: Bridging fibrosis.
4. Stage IV: Nodule formation (Cirrhosis).

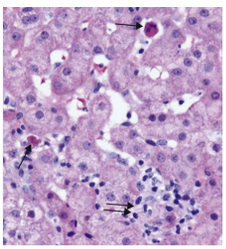
**Inflammation Staging:**

1. Grade I: inflammation in the portal tract.
2. Grade II: inflammation out the portal tract (Interface hepatitis).




## Morphology of Chronic Hepatitis

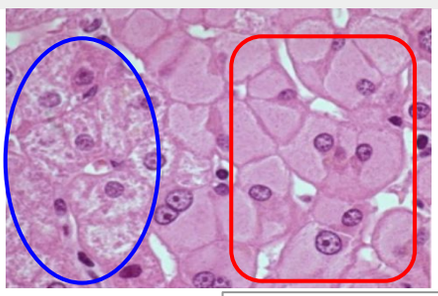
- Hepatocyte injury, necrosis, and regeneration.
- Sinusoidal Cell reactive changes.
- Portal tract Inflammation.
- Fibrosis: Continued loss of hepatocytes results in fibrosis septa formation which ultimately leads to cirrhosis.
- **Cirrhosis:** the end-stage outcome.



Apoptotic hepatocytes (acidophil bodies)

### HBV

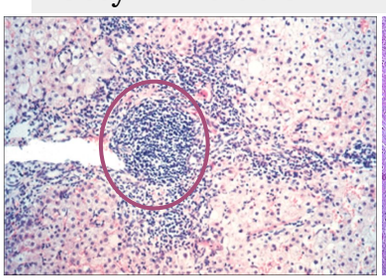
- Ground-glass hepatocytes with sanded nuclei.
- Normal hepatocytes.

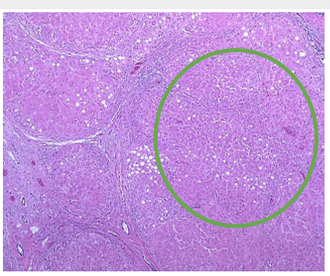


### HCV

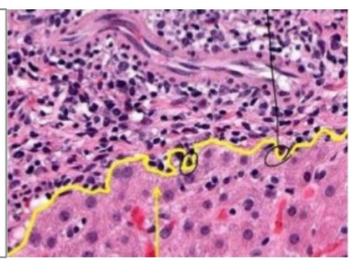
- **Bile duct damage**, **lymphoid aggregate** formation.

**Pic:** high stage with extensive fibrosis and progression to macronodular cirrhosis, as evidenced by the large regenerative nodule at the center right, and some fatty infiltration





Portal tract Inflammation: Confined to portal tracts, or Spillover into adjacent parenchyma, with necrosis of hepatocyte (interface hepatitis or Piecemeal necrosis).



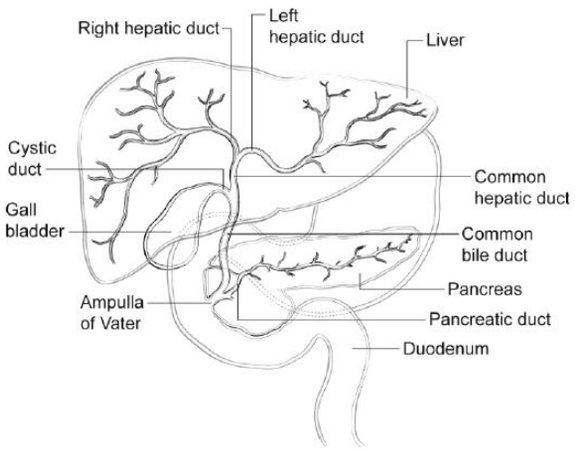
# Autoimmune Hepatitis

- **Autoimmune hepatitis:** is a chronic hepatitis with histologic features like that of chronic viral hepatitis.
- **Absence** of viral serologic markers.
- Elevated serum **IgG and Gamma-globulin levels** (> 1.5 times normal).
- High serum titres of auto-antibodies in 80% of cases.
- In untreated severe disease:
  - 40% of patients die within 6 months of diagnosis.
  - Cirrhosis develops in at least 40% of survivors.
  - Progressing to hepatic encephalopathy within 8 weeks of onset.
- **Pre-cirrhosis findings:**
  - Necrosis and inflammation
  - Plasma cell predominance
- **Two primary types of autoimmune hepatitis:**

| | Type 1 | Type 2 |
|---|---|---|
| **Age group** | • Most often in middle-age women. | • Most often seen in children or teenagers. |
| **Antibodies** | ○ Characteristically associated with increase in:<br>■ Antinuclear antibodies (ANA).<br>■ **Antismooth muscle antibodies (SMA).**<br>■ Anti-mitochondrial antibodies. | ○ Associated with increase in:<br>■ **Anti-liver kidney microsomal auto-antibodies.**<br>■ Anti-liver cytosol-1 antibodies. |
| **Association** | • Associated with other autoimmune disease:<br>○ Rheumatoid arthritis<br>○ Sjogren's syndrome | |
| **Treatment** | • Immunosuppressive therapy, and liver transplantation. | |

# Intrahepatic Biliary Diseases

- There are 3 disorders of the intrahepatic biliary ducts:
  - Primary
    - Primary biliary cholangitis.
    - Primary sclerosing cholangitis.
- Secondary biliary cirrhosis.
- After cirrhosis (end-stage) the pathological picture is Indistinguishable from 1ry or 2ry cirrhosis.




## 1- Secondary Biliary Cirrhosis:

- Prolonged obstruction of the **extrahepatic biliary** tree resulting in alteration of the liver.
- Biliary obstruction initiate periportal fibrosis leading to hepatic scarring and nodule formation → Hepatic cirrhosis.

| | | |
|---|---|---|
| **Etiology** | **Adults** | - **Gallstones** (most common cause).<br>- Malignancies of the biliary tree or head of the pancreas.<br>- Post surgical strictures. |
| | **Children** | - Biliary atresia.<br>- Cystic Fibrosis.<br>- Choledochal cyst. |
| **Sex** | None | |
| **Symptoms** | Pruritus, jaundice, malaise, dark urine, light stool, hepatosplenomegaly. | |
| **Findings** | - Increased serum conjugated bilirubin, bile acids, and cholesterol.<br>- Increased **serum ALP** (alkaline phosphatase).<br>- **NO increase in serum AMA nor IgM.** | |
| **Pre-cirrhosis findings** | - Bile stasis in ducts with duct proliferation.<br>- Neutrophil infiltration with portal tract edema. | |
| **Complications** | - Obstruction can lead to 2ry infection (ascending cholangitis).<br>- Common organisms: coliforms and enterococci. | |

# Intrahepatic Biliary Diseases

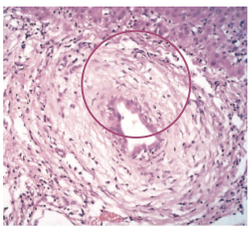
## 2- Primary Biliary Cholangitis:

- Chronic, progressive, and often fatal cholestatic liver disease, characterized by the destruction of **intrahepatic bile ducts**,
- Destruction can lead to portal inflammation and scarring and nodular formation → Hepatic cirrhosis

| | |
|---|---|
| **Etiology** | Possibly autoimmune. |
| **Sex** | **Female**:male 6:1 (middle aged women). |
| **Symptoms** | Pruritus, jaundice, malaise, dark urine, light stool, **Xanthomas and xanthelasmas** arise owing to cholesterol retention. |
| **Findings** | - Increased serum conjugated bilirubin, bile acids, and cholesterol.<br>- Increased **serum ALP** (alkaline phosphatase).<br>- **Increase in serum AMA** (anti-mitochondrial antibody). |
| **Pre-cirrhosis findings** | - Dense lymphocytic infiltration in portal tracts.<br>- Non-suppurative **granulomatous** destruction of bile ducts. |
| **Associations** | - Associated with Sjögren syndrome. |

## 3- Primary Sclerosing Cholangitis: (unknown pathology)

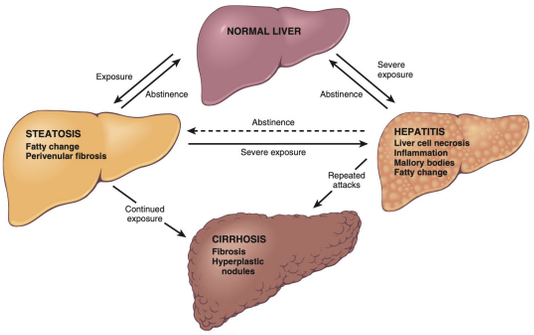
- Characterized by inflammation and obliterative fibrosis of **intrahepatic** and **extrahepatic** bile ducts, with **dilation** of preserved segments.



| | |
|---|---|
| **Etiology** | Possibly autoimmune. |
| **Sex** | Female:**male** 1:2 |
| **Symptoms** | Pruritus, jaundice, malaise, dark urine, light stool, hepatosplenomegaly |
| **Findings** | - Increased serum conjugated bilirubin, bile acids, and cholesterol.<br>- Increased **serum ALP** (alkaline phosphatase).<br>- **Increase in serum IgM** (hypergammaglobulinemia).<br>- **Beading appearance in radiology.** |
| **Pre-cirrhosis findings** | - Concentric periductal fibrosis (onion-skin fibrosis).<br>- Segmental stenosis of both intra- and extrahepatic ducts. |
| **Associations** | - Associated with IBD especially Ulcerative colitis |

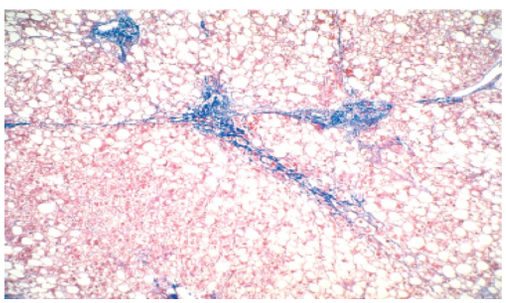
# Alcohol Liver Disease

- Alcoholic liver disease has 3 features:
  1. **Steatosis** (fatty change)
     ➔ It is due to continuous exposure of alcohol.
  2. **Hepatitis**
     ➔ It is due to severe exposure of alcohol.
  3. **Fibrosis**
     ➔ Can be either due to hepatitis or steatosis.
- If a steatosis was followed by a hepatitis it's called **steatohepatitis.**

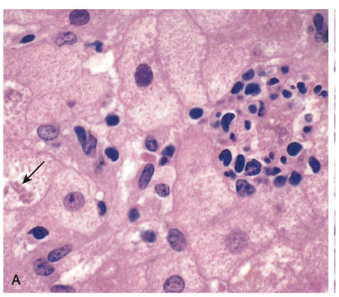



## Morphological Features

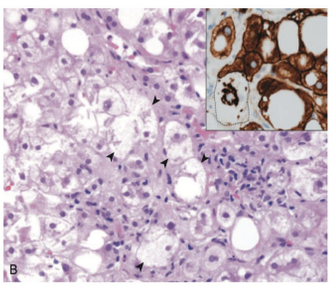
- Alcohol liver disease is marked by fatty changes or neutrophilic infiltrate leading to cirrhosis, key features include
  1. Mallory-Denk bodies (eosinophilic bodies)
  2. Neutrophil infiltrate
  3. Hepatocyte ballooning



Fibrosis appears as blue of **masson trichrome** stain



Mallory-Denk bodies
(damaged intermediate filaments)



Ballooning hepatocytes

## Causes of death:

- Hepatic failure
- Massive gastrointestinal hemorrhage
- Intercurrent infection
- Hepatorenal syndrome
- Hepatocellular carcinoma

# Complications of liver cirrhosis

## 1. Portal hypertension

| | |
|---|---|
| **Definition** | Resistance to blood flow |
| **Types** | **1. Prehepatic:** E.g portal vein thrombosis.<br>**2. Intrahepatic:** the dominant cause is cirrhosis ( most cases of portal hypertension)<br>**3. Posthepatic:** E.g Budd-Chiari syndrome[1]. |
| **Complications Of Portal hypertension** | **A. Splenomegaly.**<br>**B. Portosystemic shunt:**<br>1. Rectum (Hemorrhoids).<br>2. Cardioesophageal junction (esophagogastric varices).<br>3. Abdominal wall collaterals (caput medusae) |

### A. Splenomegaly:

- Long-standing congestion may cause congestive splenomegaly (spleen weight may reach up to 1000 gm)
- The massive splenomegaly may **induce hematologic abnormalities** attributable to hypersplenism, such as thrombocytopenia or pancytopenia.

### B. Portosystemic shunt:

- Portosystemic shunts develop when blood flow is reversed from the portal to systemic circulation.
- due to intrasinusoidal hypertension from regenerative nodule compression.

### B-1. Esophageal varices:

- Esophageal varices is an important cause of esophageal bleeding.
- 90% of cirrhotic patients develop varices most commonly in association with alcoholic liver disease.
- Can be caused by Hepatic schistosomiasis.
    - **Pathogenesis:**

Portal hypertension causes portosystemic shunts to dilate. → These shunts allow drainage to occur, leading to congested **subepithelial** and **submucosal** venous plexus within the distal esophagus (varices).

1- The obstruction of two or more major hepatic veins produces liver enlargement, pain, and ascites.

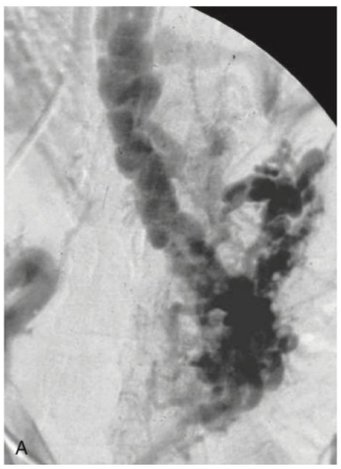
# Complications of liver cirrhosis

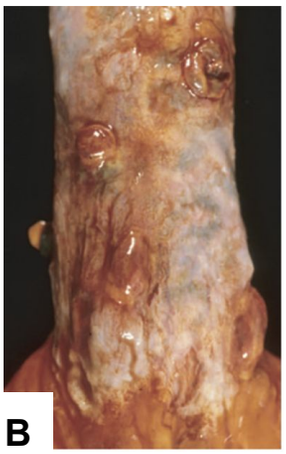
- **Morphology:**

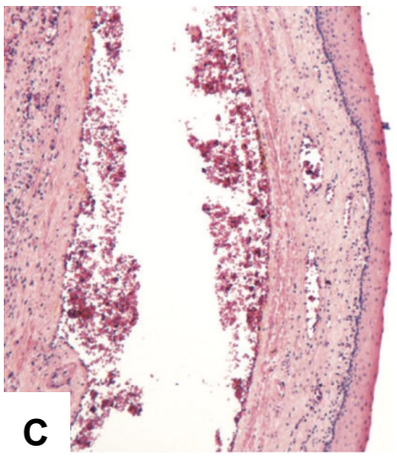
**A: Venogram**: tortuous dilated veins lying primarily within the submucosa of the distal esophagus and proximal stomach.
Venous channels directly beneath the esophageal epithelium may also become massively dilated.

**B:** Varices may not be grossly obvious in surgical or postmortem specimens, because they collapse in the absence of blood flow.

**C:** Rupture results in hemorrhage into the lumen or esophageal wall.
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.




| | |
|---|---|
| **Clinical features** | • Asymptomatic or rupture → massive hematemesis.<br>• Inflammatory erosion of thinned overlying mucosa<br>• Increased tension in progressively dilated veins<br>• Increased vascular hydrostatic pressure associated with vomiting are likely to contribute to medical emergency that is treated by any of several methods:<br>  ○ Sclerotherapy<br>  ○ Endoscopic balloon tamponade<br>  ○ Endoscopic rubber band ligation. |
| **Prognosis** | • 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)<br>• Each episode has a similar rate of mortality.<br>• Over half of deaths among individuals with advanced cirrhosis result from variceal rupture. |

# Complications of liver cirrhosis

## 2. Hepatic Failure

| | |
|---|---|
| **A. Coagulopathy** | The liver is the source of a number of coagulation factors that decrease by liver failure, leading to easy bruising and bleeding. |
| **B. Hypoalbuminemia** | • Hypoalbuminemia from decreased synthesis of albumin → Produces dependent pitting edema and ascites due to a decrease in plasma oncotic pressure. |
| **C. Hepatic encephalopathy** | • A spectrum of disturbances in consciousness ranging from subtle behavioral abnormalities, to confusion and stupor, to coma and death.<br>• may develop over days, weeks, or a few months<br>• Due to elevated ammonia levels in blood and CNS.<br>• Protein is converted from urea into ammonia in colon bacteria (cannot be metabolized in sick liver and with portosystemic shunts, ammonia go to brain). |

## 3. Ascites

- is the accumulation of excess fluid in the peritoneal cavity:
- 85% of cases are caused by cirrhosis.
- Serous: less than 3 gm/dL of protein
  - **Pathogenesis:**

**Increase in portal vein hydrostatic pressure** → **Decreases oncotic pressure** → **Liver is unable to metabolize aldosterone**

## 4. Spontaneous bacterial peritonitis

- Increased risk for spontaneous bacterial infection on top of ascites.

## 5. Hyperestrinism in males

- **Pathogenesis:**

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

- **Clinical findings:**
  - Gynecomastia
  - Spider telangiectasia
  - Female distribution of hair
  - Sparse hair and hair does not extend from the pubic area to the umbilicus.
  - **Impotence**: due to increased estrogen, there will be increases synthesis of sex hormone–binding protein, which increases binding of free testosterone.

# Complications of liver cirrhosis

## 6. Jaundice and Cholestasis

- **Jaundice and icterus:** a yellowish or greenish pigmentation of the skin and sclera of the eyes respectively due to high bilirubin levels.
- **Cholestasis:** characterized by systemic retention of not only bilirubin but also other solutes eliminated in bile.
- **Cause of Jaundice:**

| | |
|---|---|
| **1. Prehepatic (Bilirubin overproduction)** | • Due to hemolysis and hematoma resorption, which lead to elevated of unconjugated (indirect) bilirubin. |
| **2. Intrahepatic** | • Can lead to unconjugated or conjugated hyperbilirubinemia. The conjugated (direct) bilirubin level is often elevated by:<br>○ Alcohol<br>○ Infectious hepatitis<br>○ Drug reactions<br>○ Autoimmune disorders |
| **3. Posthepatic (Obstruction of the flow of bile)** | • Can cause conjugated hyperbilirubinemia.<br>• Gallstone formation is the most common posthepatic process that causes jaundice; however, the differential diagnosis also includes serious conditions such as:<br>○ Biliary tract obstruction<br>○ Pancreatitis<br>○ Malignancies |

## 7. Hepatorenal syndrome

- Appearance of renal failure in individuals with severe chronic liver disease - no intrinsic morphologic or functional causes for the renal failure.
- **Pathogenesis:**

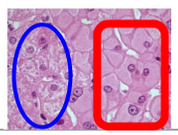
**Decreased renal perfusion pressure due to systemic vasoconstriction.** → **Activation of the renal sympathetic nervous system with vasoconstriction of the afferent renal arterioles** → **Increased synthesis of renal vasoactive mediators, that decrease glomerular filtration.**

## 8. Hepatocellular Carcinoma

# Summary

| Liver Cirrhosis | |
|---|---|
| **Definition** | End-stage liver damage characterized by disruption of the normal hepatic parenchyma by bands of fibrosis and regenerative nodules of hepatocytes |

**causes**

| Chronic Viral Hepatitis | |
|---|---|
| **Pathogenesis** | Continued loss of hepatocytes results in fibrosis septa formation which ultimately leads to cirrhosis.<br>Cirrhosis: the end-stage outcome. |
| **Characterized** | **Portal tract Inflammation:** Confined to portal tracts, or Spillover into adjacent parenchyma, with necrosis of hepatocyte (interface hepatitis or Piecemeal necrosis). |
| **Histology of HBV** | Ground-glass hepatocytes with sanded nuclei.<br>Blue: normal hepatocytes.  |

| Autoimmune Hepatitis | |
|---|---|
| **Type 1** | **Type 2** |
| • Middle-age women<br>• Antismooth muscle antibodies (SMA) | • Children or teenagers<br>• Anti-liver kidney antibodies. |

**Secondary Biliary Cirrhosis**

- Prolonged obstruction of the extrahepatic biliary tree resulting in alteration of the liver.
  Most common etiology is gallstone
- Increased serum ALP
- NO increase in serum AMA nor IgM

**Primary Biliary Cholangitis**

- Autoimmune granulomatous destruction of **intrahepatic bile ducts**
- Increased serum ALP
- Increase in serum AMA

**Primary Sclerosing Cholangitis**

- Inflammation and obliterative fibrosis of intrahepatic and extrahepatic bile ducts, with dilation of preserved segments.
- Increased serum ALP.
- Increase in serum IgM.
- Beading appearance in radiology.
- **Onion-skin fibrosis.**
- Associated with Ulcerative colitis.

# Summary

| Alcohol Liver Disease |
|---|
| • **Three features**<br>a) Steatosis, b) Hepatitis, c) Fibrosis<br>• **Steatohepatitis** : when steatosis was followed by a hepatitis. |

## Complications of liver cirrhosis

| Portal hypertension | |
|---|---|
| **Portosystemic shunt** | **Splenomegaly** |
| **a)Esophageal varices**<br>blood flows into smaller blood vessels instead of flowing through portal vein this will result in rupture of those vessels<br>b) **Hemorrhoids**<br>c) **caput medusae** | • Long-standing congestion may cause congestive splenomegaly<br>• This might induce hematologic abnormalities, such as **thrombocytopenia** or **pancytopenia**. |

| Hepatic Failure | |
|---|---|
| **Coagulopathy** | ↓number of coagulation factors= easy bleeding |
| **Hypoalbuminemia** | ↓synthesis of albumin = edema + ascites |
| **Hepatic encephalopathy** | ↑ ammonia levels in blood → disturbances in consciousness |

| | | |
|---|---|---|
| **Ascites** | is the accumulation of excess fluid in the peritoneal cavity | |
| **Spontaneous bacterial peritonitis** | Increased risk for spontaneous bacterial infection on top of ascites. | |
| **Jaundice** | **Prehepatic** | Due to hemolysis and hematoma resorption |
| | **Intrahepatic** | lead to unconjugated or conjugated hyperbilirubinemia. |
| | **Posthepatic** | cause conjugated hyperbilirubinemia.<br>Gallstone formation is the most common posthepatic |
| **Hepatorenal syndrome** | renal failure in individuals with severe chronic liver disease due to vasoconstriction | |
| **Hyperestrinism in males** | Because the liver is unable to metabolize estrogen & 17-ketosteroids | |

| Hepatocellular Carcinoma. |
|---|

# Quiz

**Q1: The most common cause of Cirrhosis:**

**A)** Viral hepatitis
**B)** Biliary diseases
**C)** Alcoholic liver disease
**D)** Wilson's disease

**Q2: Ground-glass hepatocytes and sanded nuclei are found in:**

**A)** Chronic Viral hepatitis (B)
**B)** Chronic Viral hepatitis (A)
**C)** Chronic Viral hepatitis (C)
**D)** Chronic Viral hepatitis (E)

**Q3: Type 2 autoimmune is most often seen in:**

**A)** Adults
**B)** Middle-aged women
**C)** Infants
**D)** Teenagers

**Q4: Which of the following antibodies are associated with Type 1 autoimmune hepatitis?**

**A)** Anti-liver kidney microsomal
**B)** Anti-liver cytosol-1
**C)** Anti-nuclear & anti-smooth muscle
**D)** Both A & B

**Q5: Which of the following antibodies is associated with Primary Biliary Cholangitis**

**A)** Anti-nuclear
**B)** Anti-smooth muscle
**C)** Anti-liver cytosol-1
**D)** Anti-mitochondrial

**Q6: Mallory-Denk bodies are found in:**

**A)** Primary Biliary cholangitis
**B)** Hepatic failure
**C)** Kidney disease
**D)** Alcoholic liver disease

**Q7: A Patient present to the GP with thrombocytopenia and pancytopenia, what is your differential diagnosis?**

**A)** Hepatocellular carcinoma
**B)** Hepatic failure
**C)** Esophageal varices
**D)** Splenomegaly secondary to portal hypertension

**Q8: Alcoholic liver disease is commonly associated with which of the following diseases?**

**A)** Hepatic schistosomiasis
**B)** Esophageal varices
**C)** Hematoma
**D)** Hyperestrinism

**Q9: The most common cause of Extrahepatic jaundice:**

A) Bilirubin overproduction
B) Infectious hepatitis
C) Gallstones
D) Drug reactions

1.C 2.A 3.D 4.C 5.D 6.D 7.D 8.B 9.C

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# THANK YOU