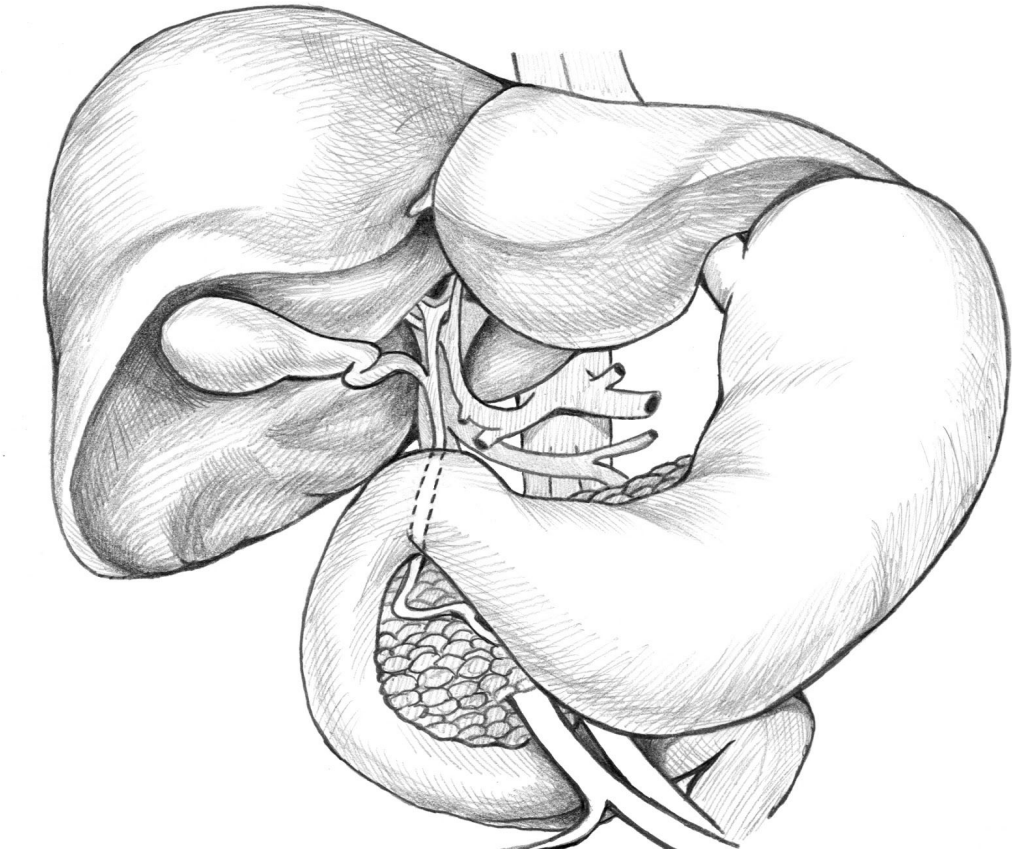
Liver cirrhosis and complications

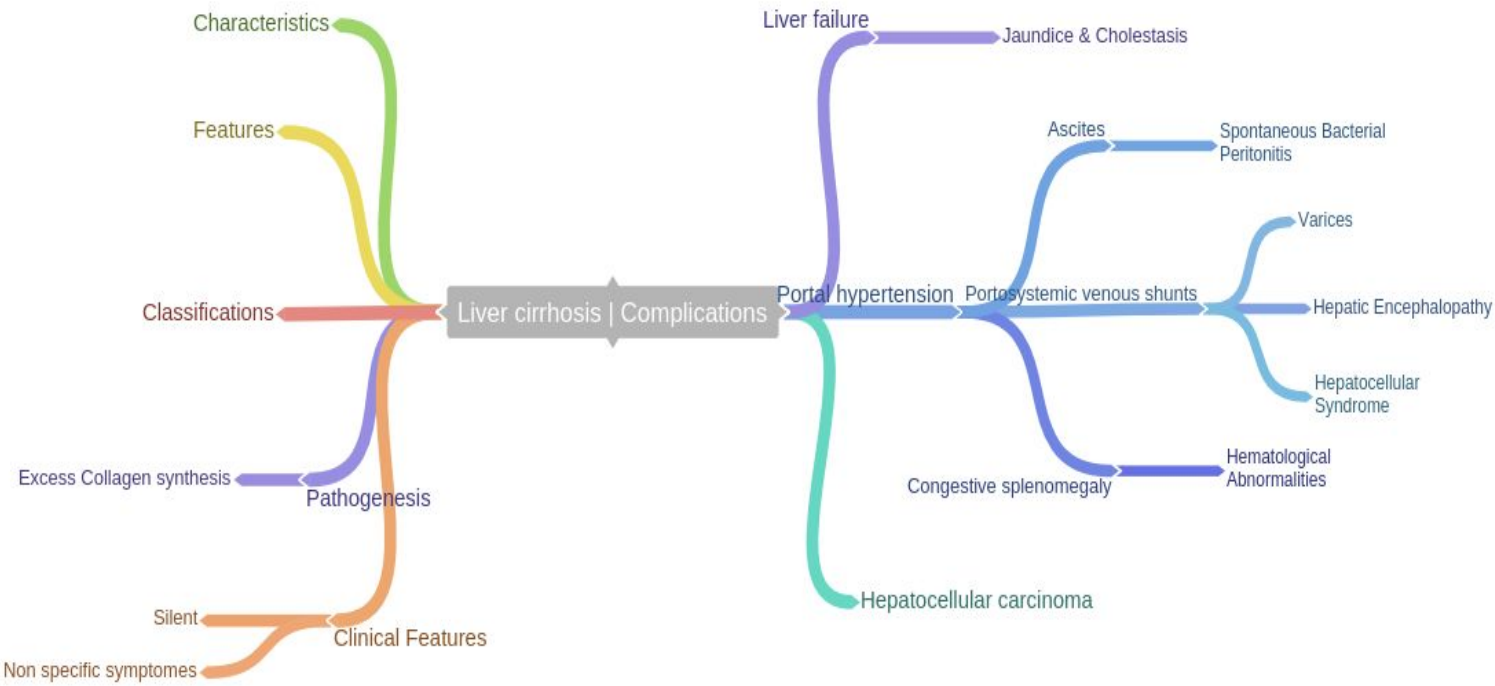


Objectives:

1. *Define Cirrhosis.*
2. *Recognize the types of cirrhosis.*
3. *Recognize the major causes and the pathogenetic mechanisms leading to cirrhosis.*
4. *Describe the pathological findings in cirrhotic livers.*
5. *Recognize the major complications of cirrhosis.*
6. *Understand the pathogenetic mechanisms underlying the occurrence of the complications.*
7. *Recognize the clinical features inherent to the above mentioned complications.*
8. *Describe the pathological findings of the different complications.*

Important note: **Please check out this link before viewing the file to know if there are any additions or changes. The same link will be used for all or our work: Pathology Edit.**

Mind Map:



Cirrhosis:

Cirrhosis is among the top 10 causes of death in the Western world. The chief worldwide contributors are:

- **Alcohol abuse**
- **Viral hepatitis**
- Other causes such as **biliary disease, and iron overload**.

Cirrhosis is defined by three characteristics:

1. **Fibrosis** in the form of delicate bands or broad scars/septa.
2. **Nodules containing regenerating hepatocytes encircled by fibrosis, with diameters varying from very small (<3 mm micronodules) to large (several centimeters, macronodules).**
3. **Disruption of the architecture of the entire liver.**

Features of cirrhosis:

Vascular architecture is reorganized by **the parenchymal damage** and **scarring**, with the formation of abnormal interconnections between **vascular inflow** and **hepatic vein outflow** channels.

- **Fibrosis** is the key feature of **progressive** damage to the liver.
- Once cirrhosis has developed, reversal is thought to be **rare**.

Classification of cirrhosis:

The classification is based on the underlying etiology:

1. **Alcoholic liver disease** "alcoholic cirrhosis" (60% to 70%).
2. **Viral hepatitis** (10%)."viral cirrhosis"
3. Biliary diseases (5% to 10%).
4. Primary hemochromatosis (5%).
5. Wilson[1] disease (Rare).
6. α 1-Antitrypsin deficiency (Rare).
7. **Cryptogenic cirrhosis** "idiopathic cirrhosis" (10% to 15%).

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

- **Infrequent types** of cirrhosis also include :
  - The cirrhosis developing in **infants and children** with **galactosemia**[2] and **tyrosinosis**[3].
  - **drug-induced** cirrhosis.
  - Severe fibrosis can occur in the setting of **cardiac disease** (sometimes called "cardiac cirrhosis").

Once cirrhosis is established, it is usually impossible to establish an etiologic diagnosis on morphologic grounds alone (you have to check the history).

Pathogenesis of cirrhosis:

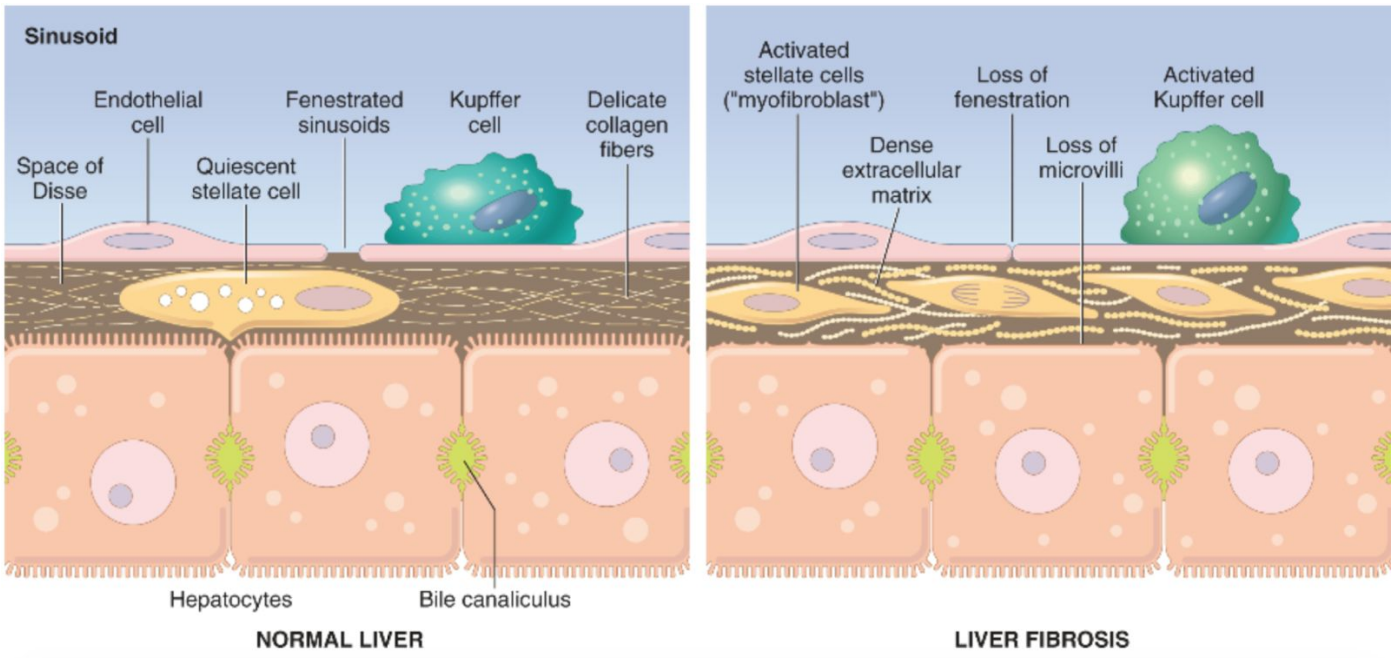
- The pathogenetic processes in cirrhosis are **progressive fibrosis** and **reorganization** of the vascular microarchitecture of the liver.(the connection between the portal vein and IVC is blocked due to fibrosis → reorganization).

Normal liver	Cirrhosis
Interstitial collagens (types I and III) are concentrated in portal tracts and around central veins.	Types I and III collagen are **deposited in the lobule**, creating delicate or broad septal tracts.
The type IV collagen (reticulin) is in the space of Disse.	Stellate cells **'ito cells'** (which lie in the space of Disse) are activated → transform into **myofibroblast-like** cells → produce **excess collagen** that is deposited in the perisinusoidal space → collagen deposition blocks the endothelial fenestrations (**loss of fenestrations**) → capillarization of sinusoids → prevents the free exchange of solutes between hepatocytes and plasma. **Ito cells**: normally functioning as vitamin A and fat-storing cells.

[1] Inherited disorder that causes too much copper to accumulate in your liver, brain and other vital organs.
[2] Rare genetic metabolic disorder that affects an individual's ability to metabolize the sugar galactose properly.
[3] Metabolism disorder of tyrosine marked by the excretion of unusual amounts of tyrosine in the urine.

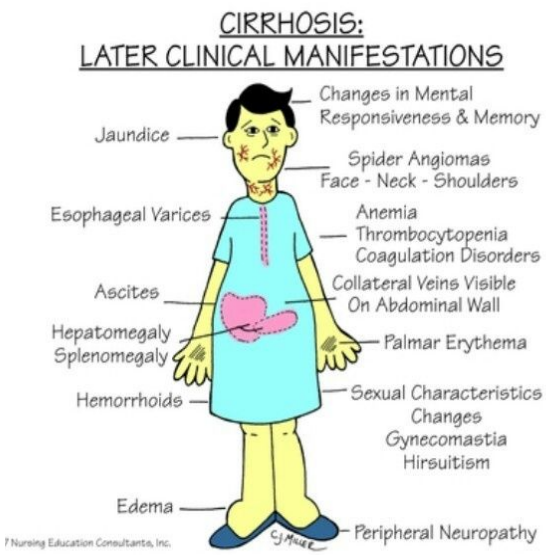
Collagen synthesis is stimulated by:

Activation of endogenous cells (Kupffer cells, endothelial cells, hepatocytes, and bile duct epithelial cells) ⇒ production of inflammatory cytokines ⇒ chronic inflammation ⇒ disruption of the normal extracellular matrix ⇒ stimulation of stellate cells by toxins ⇒ collagen formation.



Clinical Features:

- The cirrhotic patient may develop **jaundice** and even **hepatic failure**.
- All forms of cirrhosis may be clinically **silent**.
- When symptomatic they lead to nonspecific clinical manifestations: anorexia, weight loss, weakness, osteoporosis, and in advanced disease, frank debilitation (because liver responsible metabolic function).
- Incipient (not clear) or overt(clear) **hepatic failure** may develop.

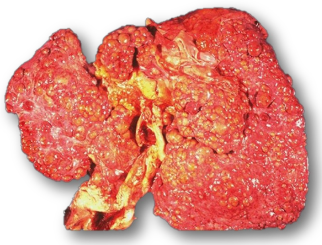
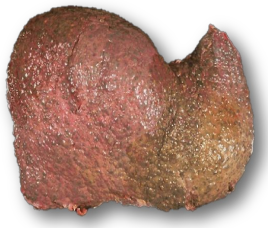
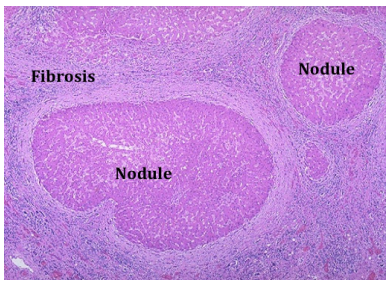


The ultimate mechanism of most cirrhotic deaths is:

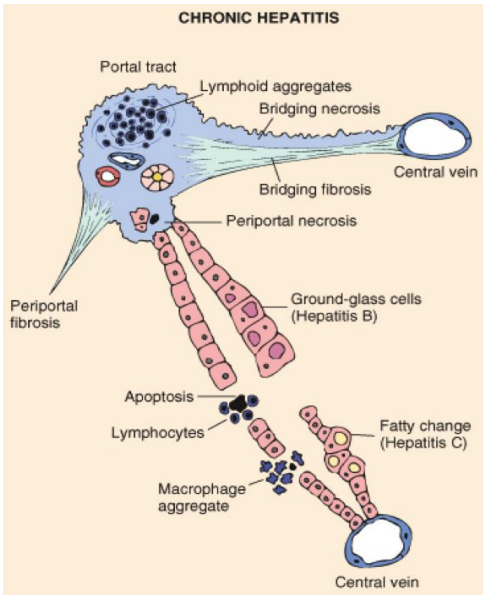
Mnemonic=**Fa**ncy **Carport**

1. Progressive **liver Failure.**
2. The development of hepatocellular **Carcinoma**.
3. A complication related to **Portal hypertension**.

Morphological changes

Gross		Microscopic
		
The nodules seen here are larger than 3 mm and, hence, this is an example of "**macronodular**" cirrhosis.	**Micronodular** cirrhosis: The regenerative nodules are quite small, averaging less than 3 mm in size as seen in **Chronic alcoholism.**	Regenerative nodules of hepatocytes are surrounded by **fibrous connective** tissue that bridges between portal tracts. Collagenous tissue , lymphocytes as well as a proliferation of bile ducts.

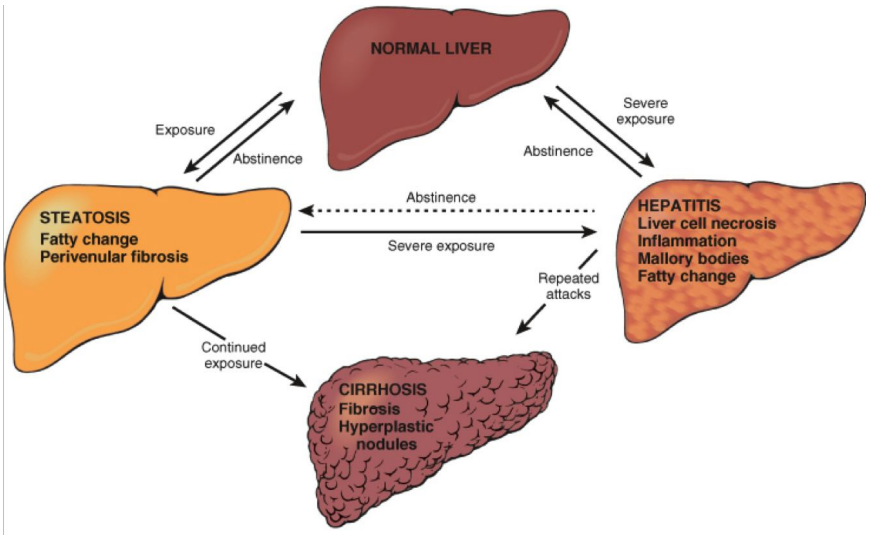
Chronic Hepatitis:



- Hepatocyte injury, necrosis, and regeneration.
- **Sinusoidal** cell reactive changes.
- **Portal tract Inflammation** in three forms:
  1. Confined to portal tracts.
  2. Spillover into adjacent parenchyma, with necrosis of hepatocytes "interface hepatitis[4]".
  3. Bridging inflammation and necrosis (extension of the necrosis from the portal tract to a central vein or to other portal tracts).
- **Fibrosis**:
  - Continued loss of hepatocytes results in fibrous septa formation which ultimately leads to cirrhosis (the fibrous tissue replace the normal parenchyma and eventually result in formation of nodules → cirrhosis).
- **HBV[5]: "ground-glass"** hepatocytes, "sanded" nuclei (the SER in the hepatocytes are filled with HBV antigen, giving the glassy appearance).
- **HCV[6]:** bile duct damage, **lymphoid aggregate** formation.
- **Alcoholic hepatitis: Mallory bodies.**
- **Cirrhosis** is The end-stage outcome.

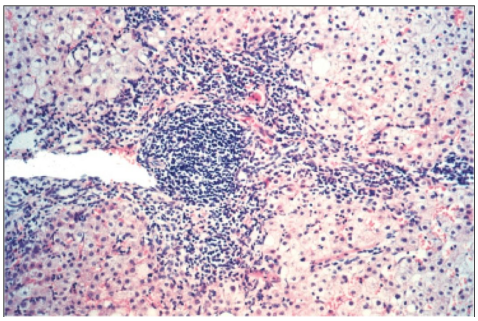
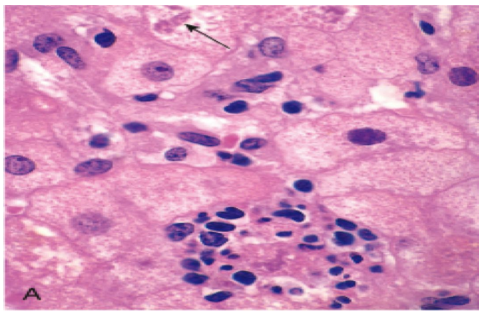
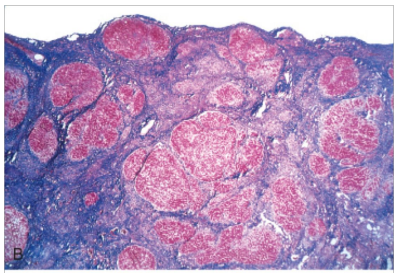
Some of these changes are shared with acute hepatitis.

[4] is a process of inflammation and erosion of the hepatic parenchyma at its junction with portal tracts or fibrous septa.
[5] Hepatitis B virus
[6] Hepatitis C virus



Fatty liver: reversible damage of liver،usually caused by alcohol.
Liver cirrhosis: irreversible damage of liver and it results from many causes،

Morphological changes:

Chronic viral hepatitis	Alcoholic hepatitis	
		
• Portal tract expansion with inflammatory cells. • Fibrosis. • **Lymphoid aggregate (HCV)**.	• The cluster of inflammatory cells marks the site of a necrotic hepatocyte. • **Mallory body** is present in a second hepatocyte (*arrow*). • Eosinophilic Mallory bodies are seen in hepatocytes, which are surrounded by fibrous tissue **(H&E)**.	• Nodules of varying sizes entrapped in blue-staining fibrous tissue. • The liver capsule is at the top. • **Masson's trichrome stain** (commonly used in cirrhosis)

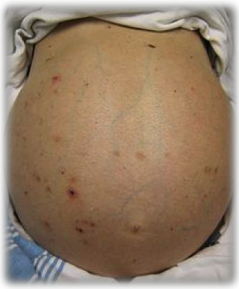
Complications

A- Portal hypertension:

- Resistance to blood flow.
- It can be prehepatic, intrahepatic, or posthepatic (eg.cardiac cirrhosis).
- The dominant intrahepatic cause is **cirrhosis**, accounting for most cases of portal hypertension.

It leads to:

1. Ascites:



- Is the accumulation of excess fluid in the **peritoneal cavity** 85%.
- ***Serous**:* less than 3 gm/dL of protein.
- ***Pathogenesis:***

→ Sinusoidal hypertension and hypoalbuminemia → drives fluid into the space of Disse, which is then removed by hepatic lymphatics.

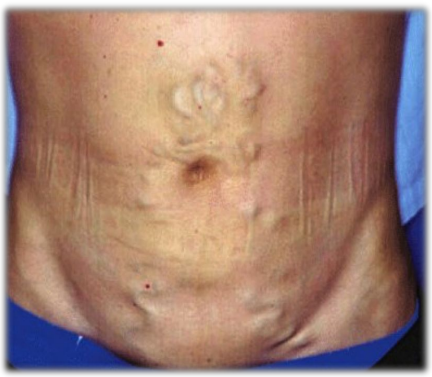
→ Leakage of hepatic lymph into the peritoneal cavity (due to exceeding thoracic duct capacity).

2. Splenomegaly (hypersplenism):

- Long-standing congestion (portal HTN) may cause congestive splenomegaly (1000 gm).
- Hematologic abnormalities attributable to hypersplenism, such as thrombocytopenia[7] or pancytopenia[8].
- Thrombocytopenia + decrease vit K (because of liver insufficiency)→ bleeding into the tissues, bruising, and slow blood clotting.

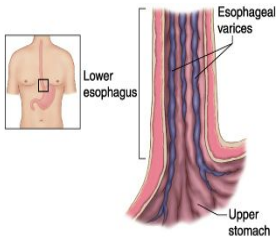
3. Portosystemic venous shunts:

- Rectum → hemorrhoids.
- Abdominal wall → caput medusae 'The appearance of distended and engorged superficial epigastric veins, which are seen radiating from the umbilicus across the abdomen (see pic)'.
- Cardioesophageal junction → **esophagogastric varices** (next page).



[7] Deficiency of platelets in the blood
[8] Deficiency of all three cellular components of the blood (RBCs, WBCs, and platelets).

Esophageal Varices:



- **Varices:** congested **subepithelial and submucosal** venous plexus within the **distal** esophagus.
- Venous blood from the GI tract normally 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** (Variceal bleeding).
- 90% of cirrhotic patients.
- **Half of patients die** from the first bleeding episode either as a direct consequence of hemorrhage (variceal rupture) or following hepatic coma triggered by **hypovolemic shock**, Additional 50% within 1 year.

Pathogenesis of esophageal varices:

Portal hypertension results in the development of collateral channels at sites where the portal and caval systems communicate. Although these collateral(reorganization) veins allow some drainage to occur, they lead to development of varices.

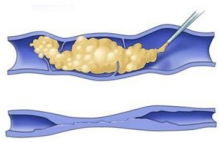
Morphology:

- 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.

Clinical features:

- Asymptomatic or rupture → massive **hematemesis**.
- **Increased tension** in progressively dilated veins.
- **Increased vascular hydrostatic pressure** associated with vomiting are likely to contribute.

Medical emergency that is treated by any of several methods:



- Sclerotherapy (involves injecting a solution directly into the vein. The solution causes the vein to scar and collapse, forcing blood to reroute through healthier veins).
- Endoscopic balloon tamponade.

B- Liver failure

1. Jaundice and icterus[9]:

- **Bilirubin overproduction, hepatitis** 'alter the conjugation process of bilirubin', and **obstruction** of the flow of bile.
- ***Cholestasis***: characterized by systemic **retention** of bilirubin and other solutes which are eliminated in bile.

2. Spider angiomas, hypogonadism, gynecomastia → Hyperestrogenemia.

3. Hepatic encephalopathy:

- A spectrum of disturbances in consciousness, ranging from subtle behavioral abnormalities to deep coma and death.
- Appears to be associated with **elevated blood ammonia** levels (important sign of hepatitis), which impair neuronal function and promote generalized brain edema.
- only **minor morphologic changes** in the brain, such as edema and an astrocytic reaction.
- Reversible if the underlying hepatic condition can be **corrected**.

4. Hepatorenal syndrome:

- Appearance of **renal failure** in individuals with severe chronic liver disease.
- There will be no intrinsic morphologic or functional causes for the renal failure (this is mean that the patient kidney will be **normal** under the microscope and if we transplant it in other patient it will work perfectly).
- The cause of failure is decreased renal perfusion pressure due to **systemic vasodilation** and activation of the renal **sympathetic nervous** system with vasoconstriction of the afferent renal arterioles (systemic vasodilatation and renal vasoconstriction).
- Increased synthesis of **renal vasoactive mediators** will **decrease glomerular filtration**.
- The incidence of this syndrome is about 8% per year among patients who have cirrhosis and ascites.

C. Hepatocellular carcinoma.

Will be discussed next lecture.

[9] Presence of jaundice seen in the sclera.

Summary

Cirrhosis	
Characteristics	Fibrosis, nodules and disruption of the architecture of the **entire liver.**
Features	- Vascular architecture is reorganized by the parenchymal damage and scarring, with the formation of abnormal interconnections between **vascular inflow** and **hepatic vein outflow** channels.
Classifications	**1- Alcoholic liver disease.** **2- Viral hepatitis.** **3- Biliary diseases.**
Pathogenesis	Excess collagen due to: - Chronic inflammation, with production of inflammatory cytokines. - Cytokine production by activated endogenous cells (Kupffer cells, endothelial cells, hepatocytes, and bile duct epithelial cells).
Clinical Features	- Jaundice and even hepatic failure. - When symptomatic they lead to nonspecific clinical manifestations: anorexia, weight loss, weakness, osteoporosis, and, in advanced disease, frank debilitation.

Complications	Features
A- Portal Hypertension:	- Resistance to blood flow.
1- Ascites	- Is the accumulation of excess fluid in the peritoneal cavity: 85%.
2- Portosystemic venous shunts	- **Esophageal Varices:** Diseases that impede this flow cause portal hypertension and can lead to the development of esophageal varices, an important cause of esophageal bleeding. - **Hepatic Encephalopathy:** Appears to be associated with elevated blood ammonia levels, which impair neuronal function and promote generalized brain edema. - **Hepatorenal Syndrome:** Appearance of **renal failure** in individuals with severe chronic liver disease.
3- Splenomegaly:	- Hematologic abnormalities.
B- Liver failure	- **Jaundice & Cholestasis.**
C- Hepatocellular Carcinoma	-

MCQs

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 flapping 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. Hypoalbuminemia.
   D. Increased portal hydrostatic pressure.

3. **Which of the following statements describes functional renal failure in cirrhosis?**
   A. Renal failure where there is no structural damage in the kidneys. *
   B. Diagnosed when the serum creatinine is >2 mg/dL.
   C. Acute renal failure that occurs in patients with cirrhosis.
   D. The same as hepatorenal syndrome.

4. **The end stage of many forms of liver disease. It is defined pathologically as extensive fibrosis with regenerative nodules.**
   A. Cirrhosis.
   B. Hepatocellular carcinoma.
   C. Portal hypertension.
   D. Hepatocellular disease.
   E. Chronic bile duct obstruction.

5. **Precipitated by gastrointestinal haemorrhage, sepsis, sedatives, renal failure or electrolyte imbalance. Infants present with irritability and sleepiness, while older children present with abnormalities in mood, sleep rhythm, intellectual performance and behaviour. EEG is always abnormal.**
   A. Oesophageal varices
   B. Spontaneous bacterial peritonitis
   C. Encephalopathy.
   D. Ascites
   E. Renal failure

6. Which of the following results in impaired coagulation and consequent bleeding?

A. Vitamin K deficiency.
B. Vitamin D deficiency.
C. Vitamin C deficiency.
D. Vitamin E deficiency.
E. Vitamin A deficiency.

Answers: 1-C , 2-D , 3-A , 4-A , 5-C ,6-A

SAQs

A 62-year-old man is brought to the emergency room in a disoriented state. Physical examination reveals jaundice, splenomegaly, and ascites. The patient has a coarse flapping 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.

A. **what is the diagnosis ?**
   - Liver cirrhosis.

B. **what are the most common etiologies of this disorder?**
   - Alcohol abuse and viral hepatitis. Other causes include biliary disease, and iron overload.

C. **Other appropriate tests?**
   - Liver biopsy

D. **what are the possible complications of liver cirrhosis?**
   1. Portal Hypertension :Ascites,Portosystemic venous shunts and Splenomegaly.
   2. Liver failure.
   3. Hepatocellular Carcinoma.

For any suggestions or questions please don't hesitate to contact us on: Pathology434@gmail.com
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GOOD LUCK !!

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