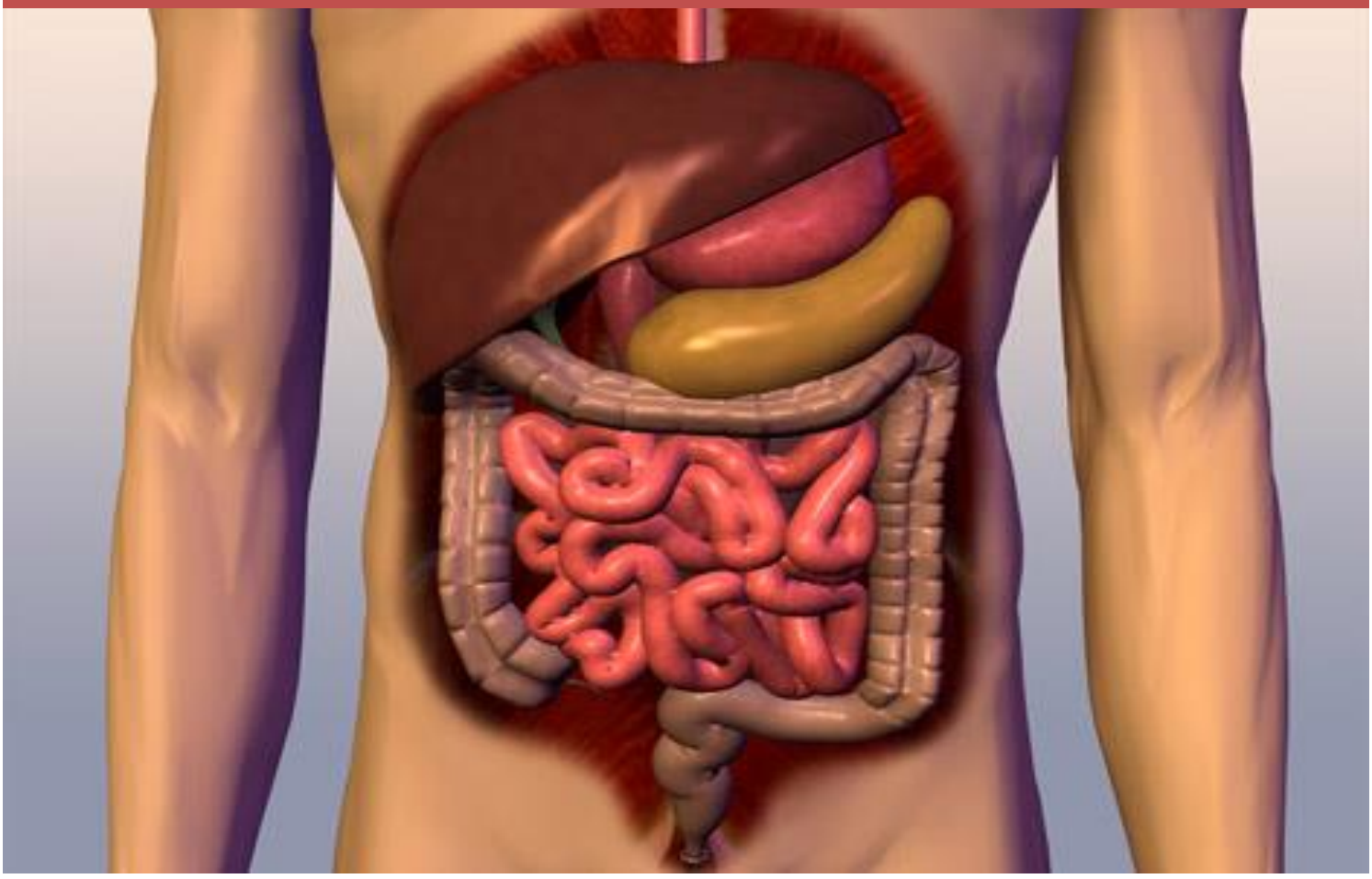


Lecture 10 & 11:

Liver Cirrhosis & Its Complications

432 ***Pathology*** *Team*

Done By: Abdulrahman *Al-Akeel &* ***Abdullah*** *Al-Zahrani*

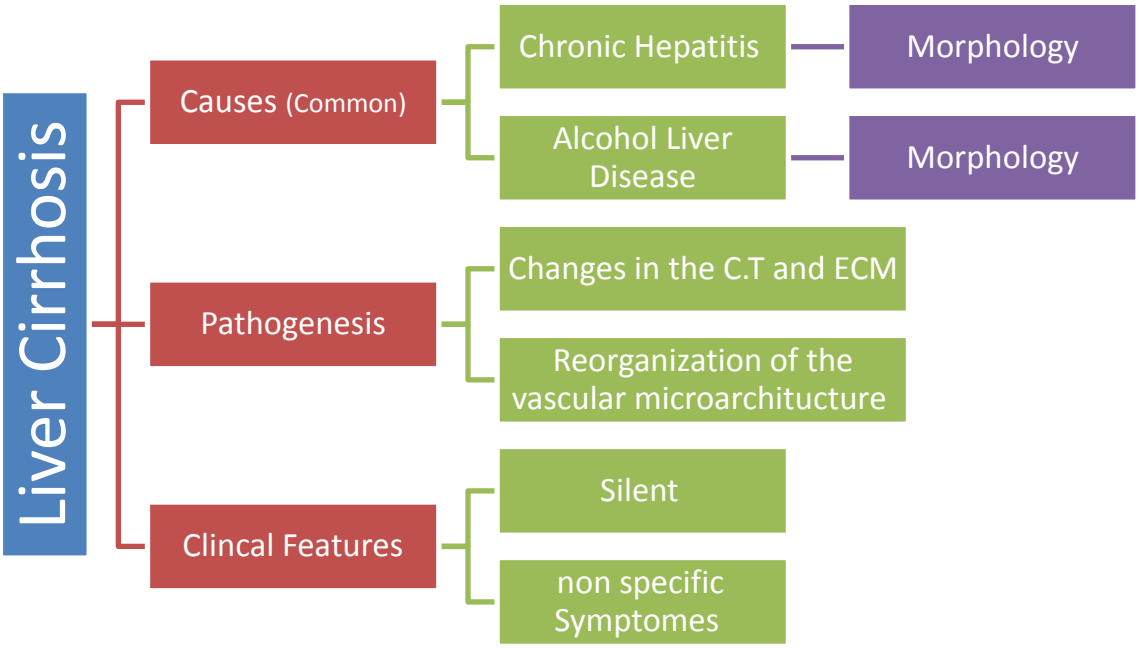
Reviewed By: Dana *Al-Dubaib &* ***Amal*** *Al-Sinan*

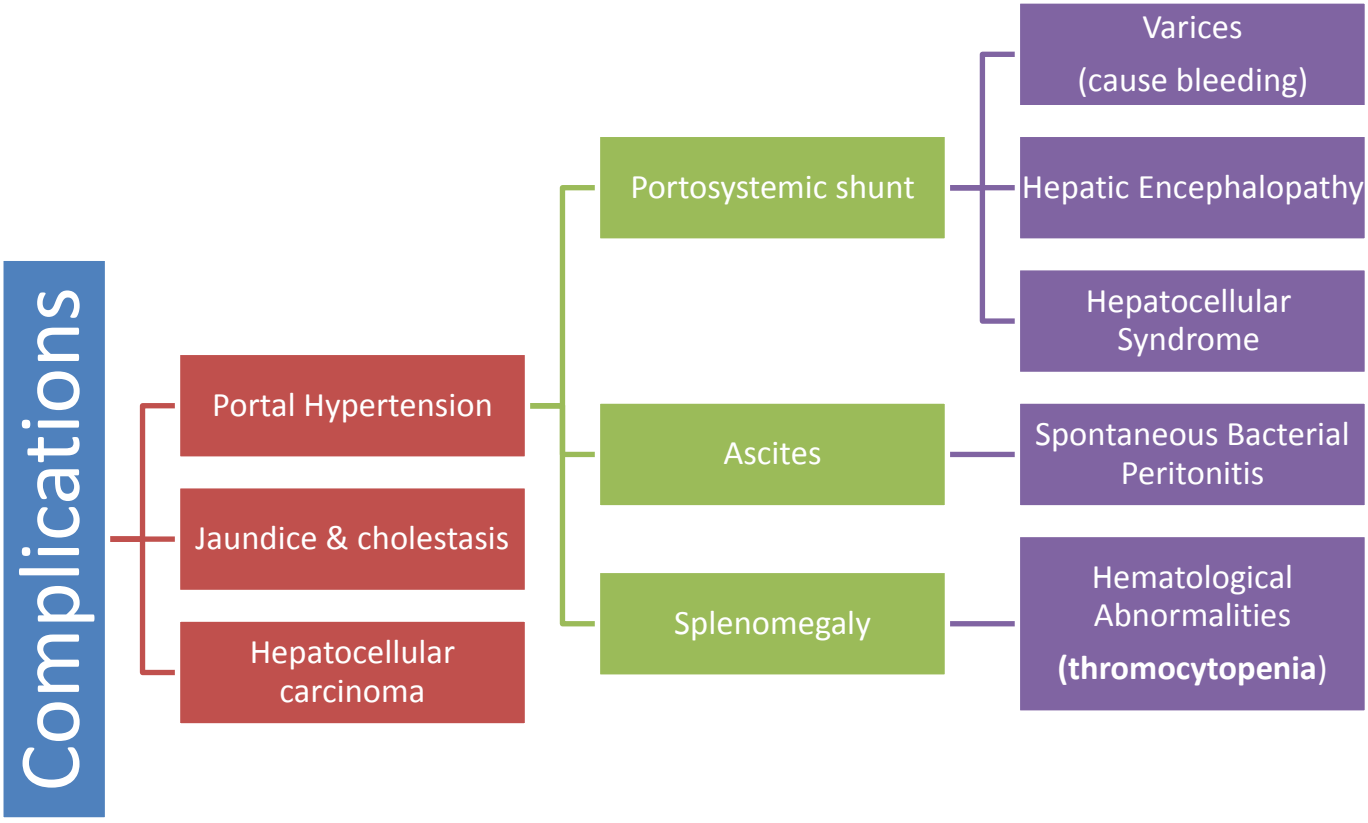
GIT Block

Color Index: Female notes are in Green. Male notes are in Blue. Red is important. Orange is explanation.

Liver Cirrhosis & Its complications

Mind Map:





Liver Cirrhosis

Cirrhosis is among the top 10 causes of death in the Western world. The chief worldwide contributors are alcohol abuse and viral hepatitis. Other causes include biliary disease, and iron overload.

- Cirrhosis is the end-stage of chronic liver disease.
- 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). (diffuse nodules, if it only one or two close to gallbladder it is inflammation of gallbladder not cirrhosis).
  3. **Disruption of the architecture** of the entire liver (Irreversible).

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 (shunting of blood by collateral and abnormal anastomosis).
- Fibrosis is the key feature of progressive damage to the liver. Once cirrhosis has developed, reversal is thought to be rare.

Classifications of cirrhosis: Base on the underlying etiology

Classification of cirrhosis based on causes:	Percentage %
Alcoholic liver disease (most common worldwide) **Micro nodules in the beginning then it becomes larger**	60% to 70%
Viral hepatitis (most common in Saudi Arabia)	10%
Biliary diseases **1) Ductular proliferation 2) Obstruction by stone**	5% to 10%
Primary hemochromatosis (iron Precipitation)	5%
Wilson disease (copper Precipitation) **The patient have kayser fleischer ring in the eye**	Rare
α1-Antitrypsin deficiency	Rare
Cryptogenic cirrhosis (unknown cause) idiopathic	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 and tyrosinosis. (The only chance to survive in children is liver transplantation).
- Drug-induced cirrhosis. (Paracetamol on the long run)
- Severe fibrosis can occur in the setting of cardiac disease (sometimes called "cardiac cirrhosis"). (Stasis in the blood for long time will cause stimulation of fibroblast).
- In some cases there is no cause and these are referred to as cryptogenic cirrhosis.
- Once cirrhosis is established, it is usually impossible to establish an etiologic diagnosis on morphologic grounds alone.

Pathogenesis of cirrhosis:

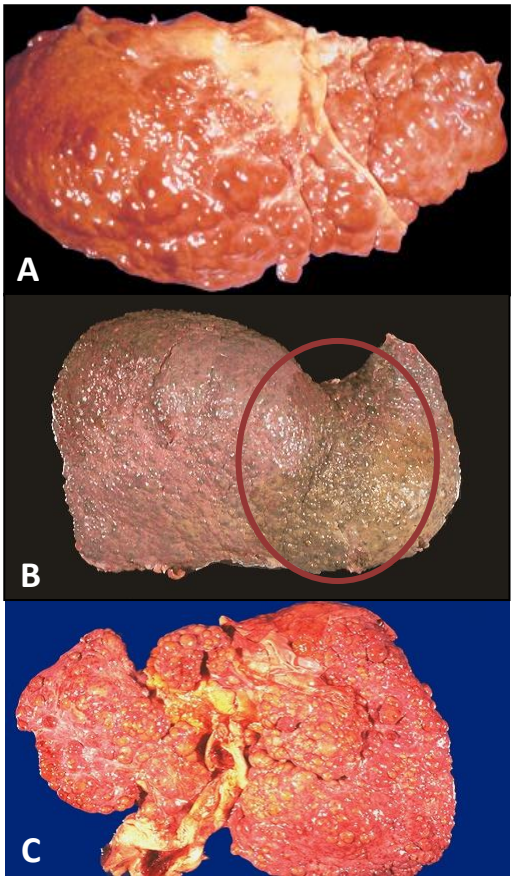
- The pathogenetic processes in cirrhosis are progressive fibrosis and reorganization of the vascular microarchitecture of the liver.
- In the normal liver, interstitial collagens (types I and III) are concentrated in portal tracts and around central veins. The type IV collagen (reticulin) is in the space of Disse.
- In cirrhosis, types I and III collagen are deposited in the lobule, creating delicate or broad septal tracts.
- The major source of excess collagen in cirrhosis is the perisinusoidal stellate cells (Ito cells), which lie in the space of Disse. Although normally functioning as vitamin A fat-storing cells, during the development of cirrhosis they become activated and transform into myofibroblast-like cells.
- Collagen synthesis is stimulated by:
  - Chronic inflammation, with production of inflammatory cytokines.
  - Cytokine production by activated endogenous cells (Kupffer cells, endothelial cells, hepatocytes, and bile duct epithelial cells).
- Disruption of the normal extracellular matrix.
- There is loss of fenestrations in the sinusoidal endothelial cells (capillarization of sinusoids that is the sinusoidal space comes to resemble a capillary rather than a channel for exchange of solutes between hepatocytes and plasma).

Clinical Features:

- All forms of cirrhosis may be clinically silent.
- When symptomatic they lead to nonspecific clinical manifestations: anorexia, weight loss very skinny, ascites, tremor, weakness, osteoporosis, and, in advanced disease, frank debilitation (الضعف العام). Can't get up from the bed!
- Jaundice.
- Incipient or overt hepatic failure may develop.
- The ultimate mechanism of most cirrhotic deaths is:
  1. Progressive liver failure, short life span.
  2. A complication related to portal hypertension (like esophageal varices), or
  3. The development of hepatocellular carcinoma (less common).

Gross feature:

A. Very firm liver, very nodular surface.

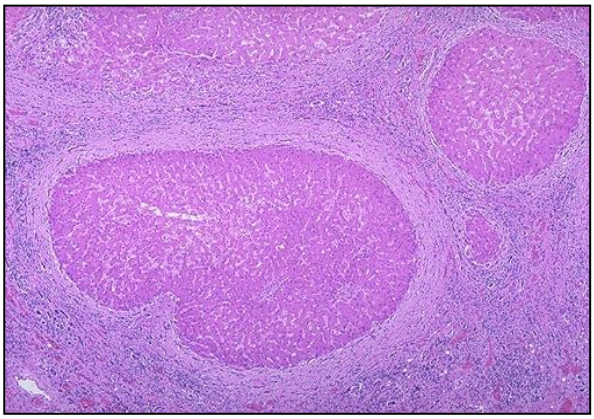


B. Micronodular cirrhosis: The regenerative nodules are quite small, averaging less than 3 mm in size; Chronic alcoholism. (Greenish color from bile stasis; there is disruption of biliary metabolism).

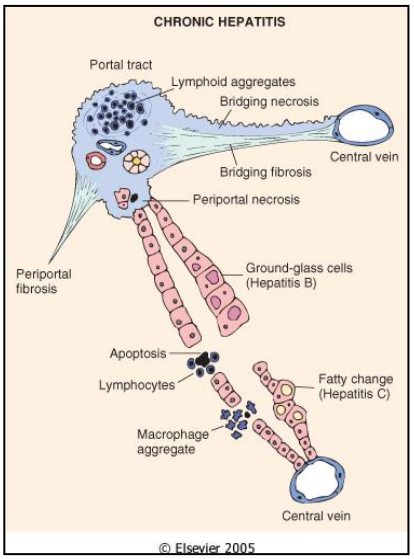
C. The nodules seen here are larger than 3 mm and, hence, this is an example of "macronodular" cirrhosis. Over 1 cm

Histological feature:

- Regenerative nodules of hepatocytes, which vary in size, are surrounded by fibrous connective tissue (fibrous septum) that bridges between portal tracts.
- Collagenous tissue, lymphocytes as well as a proliferation of bile ducts and blood vessels (abnormal anastomosis).



Chronic Hepatitis:



Morphology:

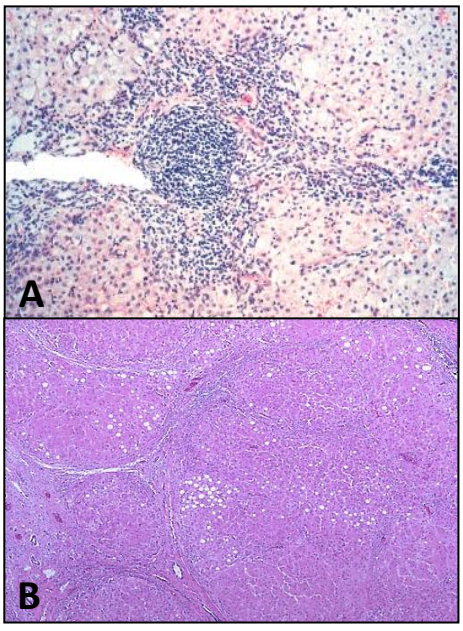
- Hepatocyte injury, necrosis, and regeneration.
- Sinusoidal cell reactive changes.
- Portal tract Inflammation (grading):
  - Confined to portal tracts (grade I), or
  - Spillover into adjacent parenchyma, with necrosis of hepatocytes ("interface hepatitis") (grade II), or
  - Inflammation in the lobules with hepatocytes necrosis and injury (grade III).
  - Bridging inflammation and necrosis (higher grade)

- Fibrosis (staging):
  Continued loss of hepatocytes results in fibrous septa formation which ultimately leads to cirrhosis
  - Begin at portal tracts (stage I)
  - Begin to spread (stage II)
  - Bridging fibrosis (stage III)
  - Nodules formation (stage IV)

  HBV: "ground-glass" hepatocytes, "sanded" nuclei
  HCV: bile duct damage, lymphoid aggregate formation
- **Cirrhosis: The end-stage outcome**
- Staging and grading help to know the prognosis and severity of the disease; so they help in treating the patient.
- Fat change, which is feature of hepatitis C, may found in little amount in normal population; especially obese people.

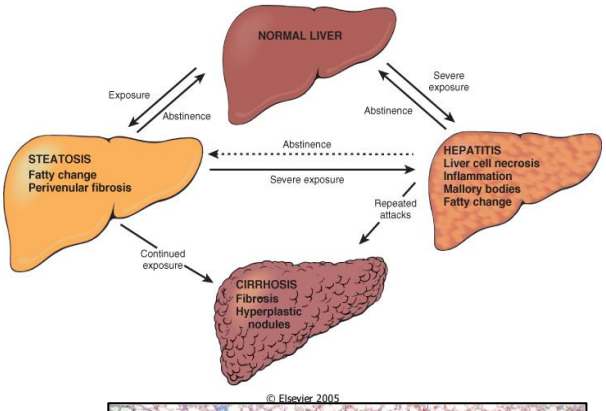
Histological feature:

A. Lymphocyte aggregation in the portal tract, it is one of chronic hepatitis C features.
B. 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.



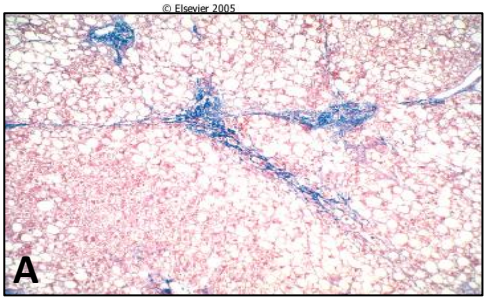
Alcoholic liver disease:

- Liver injuries caused by alcohol depend on the amount and duration of alcoholic intake.
- First changes seen are liver steatosis with mild venular fibrosis (reversible).
- Continues exposure of alcohol may end-up with cirrhosis.
- Sever exposure of alcohol it may leads to hepatitis, with repeat attaches of hepatitis it will cause liver cirrhosis.

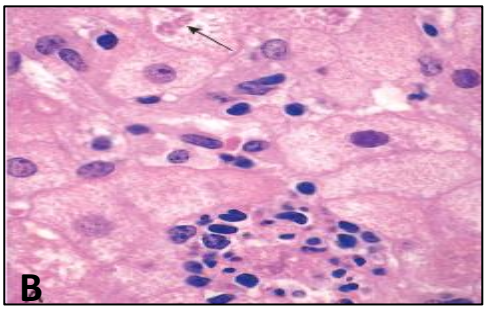


Gross and Histological features:

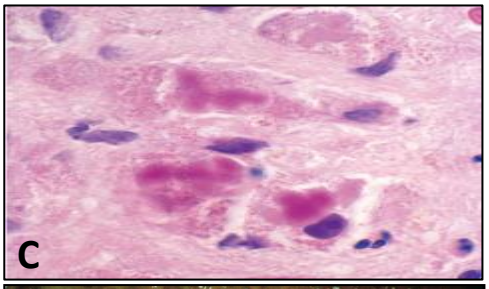
A. Macrovesicular steatosis, involving most regions of the hepatic lobule. The intracytoplasmic fat is seen as clear vacuoles (classical feature of alcoholism). Some early fibrosis (stained blue) is present (Masson trichrome stain).



B. Alcoholic hepatitis. The cluster of inflammatory cells marks the site of a necrotic hepatocyte. A Mallory body is present in a second hepatocyte (arrow).



C. Eosinophilic Mallory bodies are seen in hepatocytes, which are surrounded by fibrous tissue (H&E).



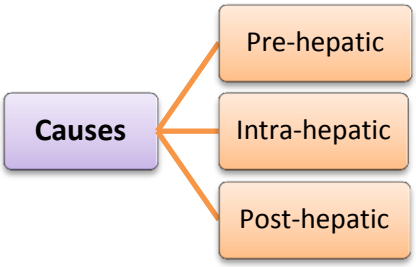
D. Alcoholic cirrhosis. The characteristic diffuse nodularity of the surface reflects the interplay between nodular regeneration and scarring. The greenish tint of some nodules is due to bile stasis. A hepatocellular carcinoma is present as a budding mass at the lower edge of the right lobe (lower left of figure).

E. The microscopic view shows nodules of varying sizes entrapped in blue-staining fibrous tissue (bridging fibrosis). The liver capsule is at the top (Masson trichrome).

Portal hypertension

Definition:

Increased resistance to portal blood flow that leads to increase in portal venous pressure



- *The **dominant intrahepatic** cause is **cirrhosis**, accounting for most cases of portal hypertension*
  Portal hpertension could induce splenomegaly

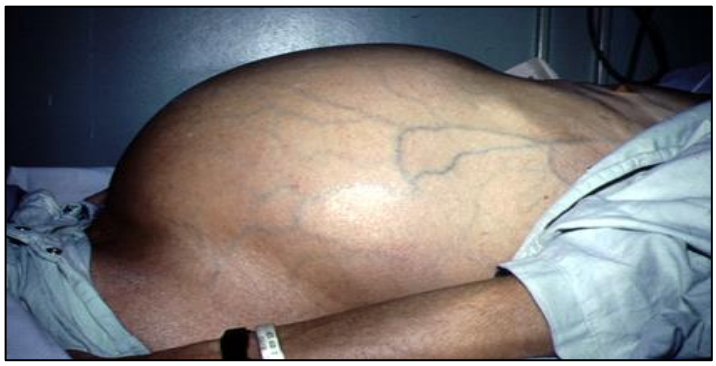
Robbins: Portal hypertension in **cirrhosis** results from increased resistance to portal flow at the level of the sinusoids and compression of central veins mainly by:
1- Peri-venular fibrosis **2- Expanding parenchymal nodules**

Ascites:

- It is the **accumulation of excess fluid** in the peritoneal cavity.
- In 85% of cases, ascites is caused by **cirrhosis.**
- Serous type of fluid, having less than 3 gm/dL of protein.
- It causes: shortness of breath.

Result from:

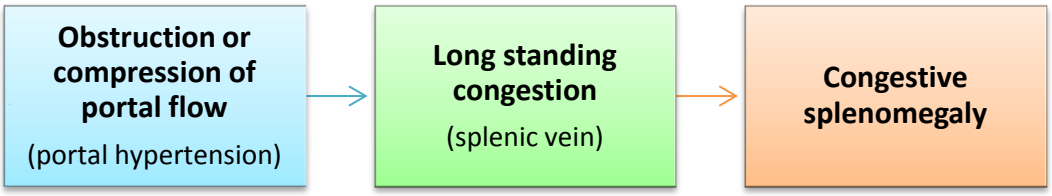
1- **Increase hydrostatic pressure** (Portal hypertension).
2- **Decrease osmotic pressure** (hypoalbuminemia).
3- **Renal retention of Na & water** secondary to hyperaldosteronism.
4- **Leakage of fluid** from hepatic interstitium into peritoneal cavity (due to increase hepatic lymphatic flow that exceeding thoracic duct capacity).
In ascites we take a sample of the fluid accumulated and send it to serology, and this important to check if there is bacteria (infection) or malignant cells (hepatocellular carcinoma).



NOTE: In patients with ascites related to portal hypertension, bacteria from the gut may spontaneously invade the peritoneal fluid (ascites) and cause an infection. This is called **spontaneous bacterial peritonitis** (life-threatening) (cannot be treated)

Splenomegaly:

- **Defined as Abnormal increase in the size of spleen**

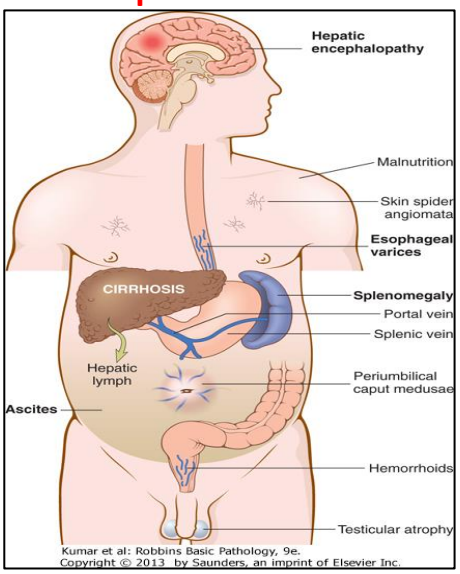


- Long-standing congestion may cause congestive splenomegaly.
- The degree of enlargement varies widely (usually 1000g or less).
- Not necessarily correlated with other features of portal hypertension.
- **Massive splenomegaly** can cause **(secondarily)**: Hematologic abnormalities attributable to hypersplenism, such as pancytopenia especially **thrombocytopenia** (due to destruction of the cells esp. thrombocytes by spleen).

NOTE: **pancytopenia** is abnormal reduction of all the cellular elements of the blood.

Portosystemic Shunt

With the rise in portal venous pressure, shunts develop wherever portal and caval systems communicate (collaterals).



From Robbins: Principal sites:
1- **Rectum** (manefist as hemorrhoids)
2- **Cardioesophageal junction** (esophagogastric varices)
3- **The retroperitoneum, and the falciform ligament** of the liver (involving periumbilical and abdominal wall collaterals)

Lead to:

1- Hepatic encephalopathy:

Portosystemic shunt → Allow toxins to systemic circulation **(mainly ammonia)** → **Ammonia** go to brain → Hepatic encephalopathy

Symptoms:
Ranging from subtle behavioral abnormalities to marked confusion and stupor, to deep coma and death.

2- Esophageal varices:

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

Pathogenesis:

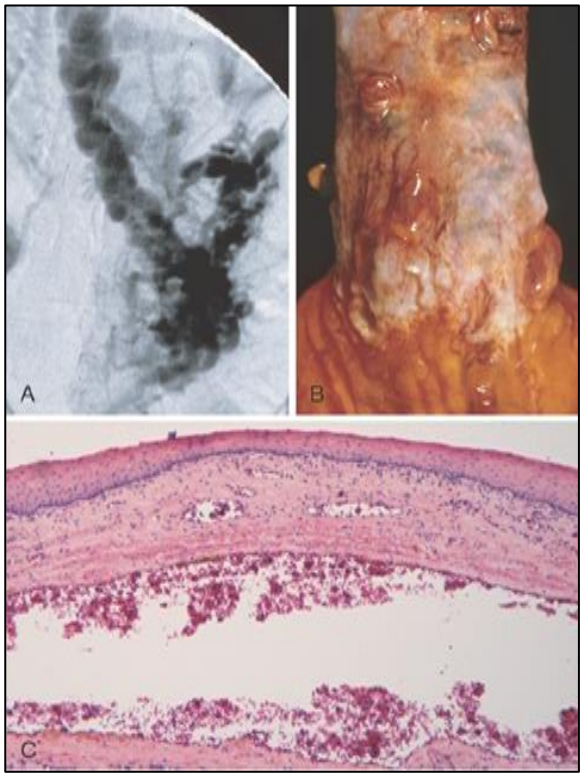
- Portal hypertension results in the development of collateral channels at sites where the portal and caval systems communicate (Portosystemic shunt).
- Although these collateral veins allow some drainage to occur, they lead to development of a congested sub-epithelial and sub-mucosal venous plexus within the distal esophagus.
- 90% of cirrhotic patients will develop varices, most commonly in association with alcoholic liver disease.
- Worldwide, hepatic schistosomiasis is the second most common cause of varices.

Morphology:

- Varices can be detected by **venogram** (Fig. A) and appear as 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 (Fig. B)

- When they are not ruptured, the overlying mucosa is intact (Fig. C).



Factors that lead to rupture of the varices:

- Inflammatory erosion of thinned overlying mucosa (appears ulcerated and necrotic).
- Increased tension in progressively dilated veins.
- Increased vascular hydrostatic pressure associated with coughing & vomiting.
- If rupture has occurred in the past, venous thrombosis, inflammation, and evidence of prior therapy may also be present.

Hemorrhage due to variceal rupture is a medical emergency that is treated by any of several methods:

- **Sclerotherapy**: by endoscopic injection of thrombotic agents that stop the bleeding.
- **Endoscopic balloon tamponade:** by inserting a balloon to the lumen of esophagus & inflate it against the wall of esophagus to stop the bleeding.
- **Endoscopic rubber band ligation.**

- **Half** of patients die from the first bleeding episode either as a direct consequence of hemorrhage or following hepatic coma triggered by hypovolemic shock.
- Additional 50% within 1 year.
- Each episode has a similar rate of mortality.
- Over half of deaths among individuals with advanced cirrhosis result from variceal rupture.

3- Hepatorenal syndrome

Appearance of renal failure in individuals with severe chronic liver disease such as cirrhosis no intrinsic morphologic or functional causes for the renal failure.

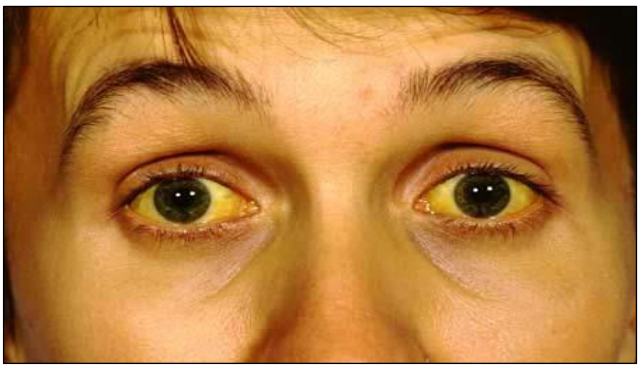
Means: patient who developed liver failure (from cirrhosis) he will develop renal failure without primary abnormalities of the kidneys themselves

- Characterized by **immediate improve** of kidneys if hepatic failure is reversed
- The incidence of this syndrome is about 8% per year among patients who have cirrhosis and ascites.
- 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** that decrease glomerular filtration.
- **In biopsy sample we see no abnormalities.**

Jaundice & Cholestasis

Jaundice: result from retention of bile

Ictrus: yellowish sclera



Cholestasis: systemic retention of not only bilirubin but also other solutes eliminated in bile characterized mainly by pruritus.

- The common causes of jaundice are: **bilirubin overproduction, hepatitis, and obstruction of the flow of bile.**
- **Present commonly at late stages of cirrhosis.**
- **Reduced uptake of unconjugated bilirubin is the major cause of jaundice in cirrhosis.**

Main causes of Jaundice
Predominantly unconjugated hyperbilirubinemia
Excess production of bilirubin
Hematolytic anemias Resorption of blood from intestinal hemorrhage Ineffective erythropoiesis syndrome
Reduced hepatic uptake
Drug interfere with membrane carrier system Diffuse hepatocellular disease**(e.g. cirrhosis)**
Impaired bilirubin conjugation
Physiological jaundice of the newborn
Predominantly conjugated hyperbilirubinemia
Decreased hepatocellular excereton
Deficiency in canalicular membrane transporters Drud-induced canalicular membrane dysfunction Hepatocellular damage or toxicity
Impaired intr- or extrahepatic bile flow
Inflammatory destruction ofintrahepatic bile duct

Hepatic bile serves two major functions:

1- **Emulsification** of dietary fat in the lumen of the gut through the detergent action of bile salts

2- **Elimination** of bilirubin, excess cholesterol, xenobiotics, and other waste products that are insufficiently water-soluble to be excreted into urine

- Pathophysiology of jaundice it is important first to become familiar with the major aspects of bile formation and metabolism.
- The metabolism of bilirubin by the liver consists of **four** separate but interrelated events: **uptake from the circulation; intracellular storage; conjugation with glucoronic acid; and biliary excretion**.

Hepatocellular Carcinoma

Caused:

- **Directly:** by cirrhosis
- **Indirectly:** by portal hypertension

Summary (from Robbins Basic Pathology)

Cirrhosis

The three main characteristics of cirrhosis are:
(1) bridging fibrous septa.
(2) parenchymal nodules containing replicating hepatocytes.
(3) disruption of the architecture of the entire liver.
It is an end-stage liver disease that may have multiple causes. The most frequent are chronic hepatitis B and C and chronic alcoholism. Less frequent causes are autoimmune and biliary diseases and metabolic conditions such as hemochromatosis. The morphologic features of advanced cirrhosis are similar, regardless of the cause of the disease. Nonalcoholic fatty liver disease is a newly recognized cause of cirrhosis. The main complications of cirrhosis are related to decreased liver function, portal hypertension, and increased risk of hepatocellular carcinoma.

Alcoholic Liver Disease

• Alcoholic liver disease has three main manifestations: hepatic steatosis, alcoholic hepatitis, and cirrhosis, which may occur alone or in combination.
• Consumption of 50 to 60 g/day of alcohol is considered to be the threshold for the development of alcoholic liver disease.
• Cirrhosis typically develops after 10 to 15 years of drinking or more, but only occurs in a small proportion of chronic alcoholics; alcoholic cirrhosis has the same morphologic and clinical features as cirrhosis caused by viral hepatitis.
• The multiple pathologic effects of alcohol include changes in lipid metabolism, decreased export of lipoproteins, and cell injury caused by reactive oxygen species and cytokines.

Questions

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) Hyperalbuminemia
(D) Increased portal hydrostatic pressure

3/ A liver biopsy in the patient with alcoholic liver cirrhosis would **definitely** show which of the following pathologic changes?

(A) Dilated bile ducts and portal inflammation
(B) Fatty liver
(C) Nodular regeneration and scarring
(D) Periportal necrosis and peripheral cholestasis

4/ 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 and a high serum level of alkaline phosphatase. Shortly after admission, the patient develops coma, adult respiratory distress syndrome, and renal failure, leading to death within 3 days. Histologic examination of the patient's kidney at autopsy would most likely show which of the following?

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

Answers:

- 1- C
- 2- D
- 3- C
- 4- C

اللهم إني استودعك ما قرأت و ما حفظت و ما تعلمت فرده عليَ عند حاجتي إليه انك على كل شيء قدير

If there is any mistake or feedback please contact us: 432PathologyTeam@gmail.com