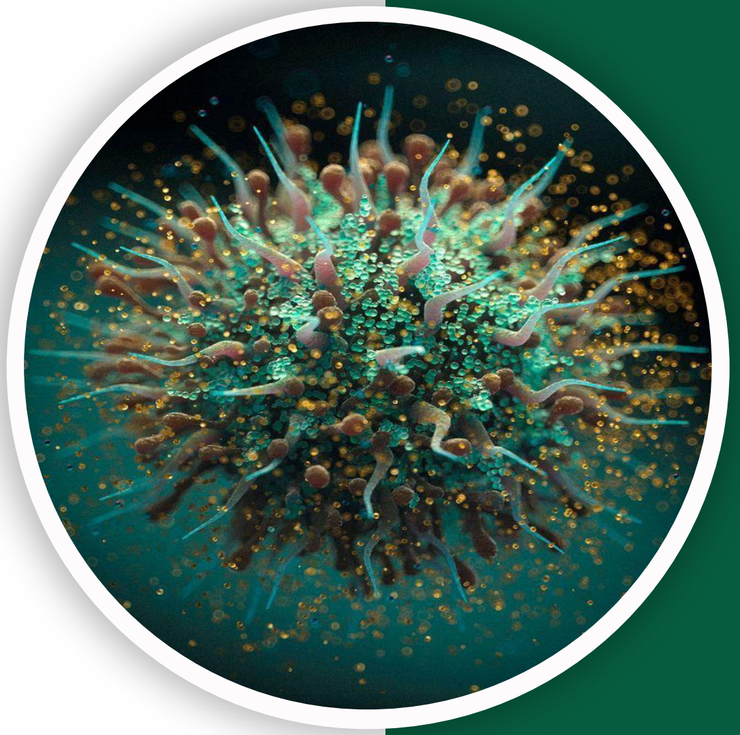
بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

GIS Pathology | FINAL 3

Cirrhosis



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Cirrhosis

- **It is a diffuse process characterized by irreversible fibrosis & the conversion of liver parenchyma into nodules .**

- Cirrhosis represents the end stage of many chronic liver diseases and leads to distortion of the normal hepatic architecture.
- The pathological process results in impaired hepatic blood flow and progressive loss of liver function.
- Structural and functional hepatic impairment eventually leads to multiple clinical complications.

Main characteristics

1. **Bridging fibrous septae;** the development of fibrous septa between portal tracts and central veins leads to bridging fibrosis and progressive distortion of the normal hepatic architecture.

2. **Parenchymal nodules encircled by fibrotic bands**

Regenerating hepatocytes form parenchymal nodules that become completely surrounded by fibrotic connective tissue bands as a result of continuous fibrosis and regeneration.

3. Diffuse architecture disruption

- The normal arrangement of hepatocytes, sinusoids, and vascular channels becomes diffusely disrupted, leading to impaired blood flow, defective exchange functions, and progressive loss of liver function.

- **Types :**

Regardless of the underlying etiology, the pathological features, pathogenesis, complications, and overall outcome of cirrhosis are generally similar. Nevertheless, the pattern of nodularity may occasionally provide clues about the original cause of liver injury.

Micronodules < 3mm in diameter

Macronodules > 3 mm in diameter

Despite these morphological differences, both forms ultimately progress to persistent fibrosis, architectural distortion, and chronic liver dysfunction.

Micronodular cirrhosis

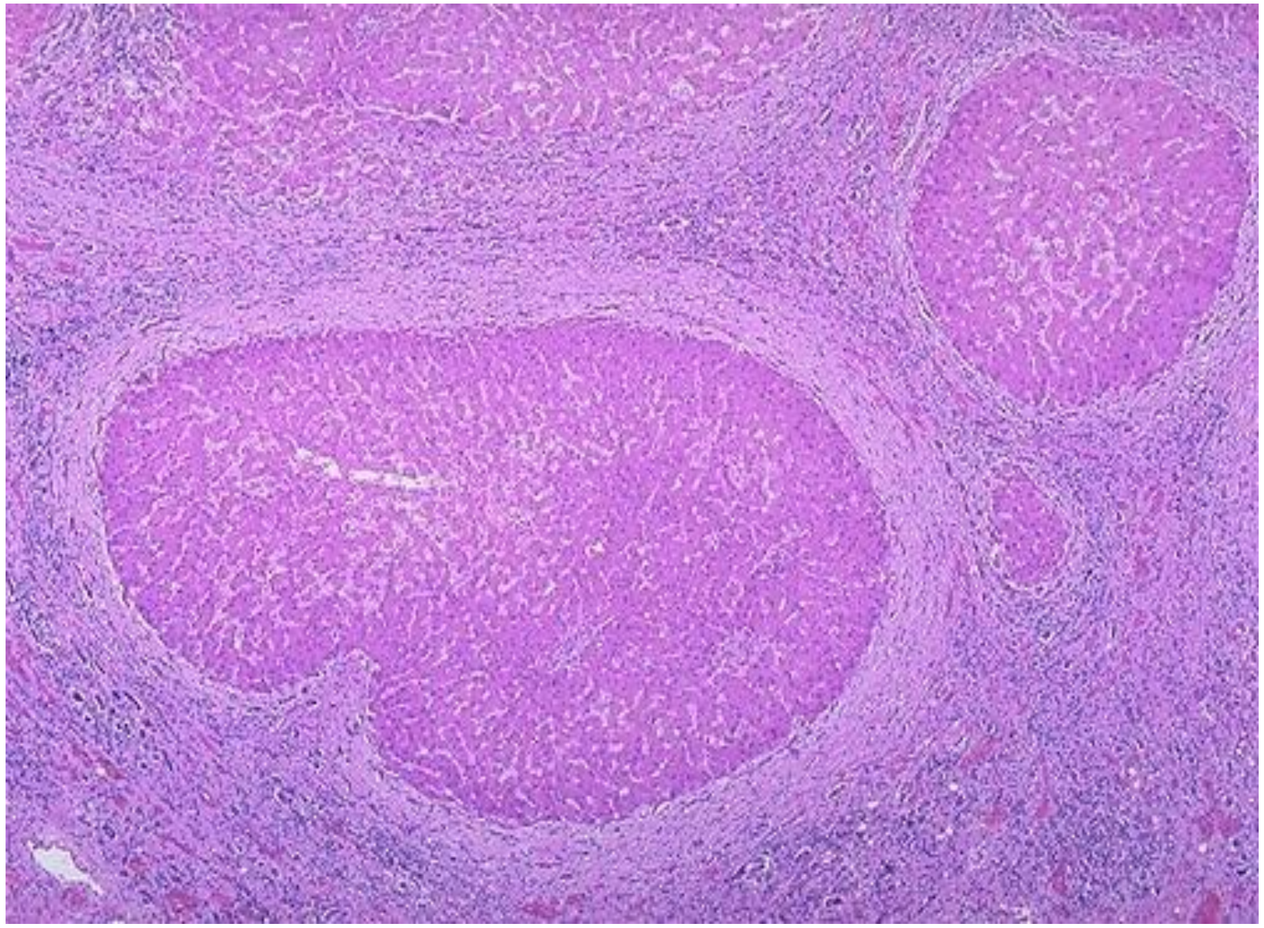
The image represents **micronodular cirrhosis**, which is characterized by the presence of numerous small and relatively uniform regenerative nodules distributed throughout the liver surface. These nodules are separated by thin fibrous septa and produce diffuse distortion of the hepatic architecture.

Macronodular cirrhosis

The image demonstrates **macronodular cirrhosis**. In this form, the liver surface is transformed into irregular nodular structures of varying sizes. Some nodules may involve large portions of the hepatic parenchyma and are separated by broad fibrous bands. The entire liver architecture becomes markedly distorted because of extensive nodular regeneration and fibrosis.

Macronodular cirrhosis may initially develop as a consequence of chronic hepatic injury followed by continuous deposition of fibrous tissue. With disease progression, persistent fibrosis and repeated cycles of hepatocyte injury and regeneration lead to severe architectural distortion of the liver parenchyma. Grossly, the liver eventually acquires an irregular, firm, and scarred appearance due to the extensive fibrotic transformation.

Cirrhosis



This image demonstrates the characteristic histopathological features of cirrhosis. At the center, a regenerative nodule can be observed, which is formed as a result of continuous regeneration of surviving hepatocytes following chronic liver injury.
The regenerative hepatocellular islands are completely surrounded by fibrous septa, indicating extensive fibrosis and architectural distortion of the liver parenchyma. These fibrous bands separate the hepatic tissue into abnormal nodular units and disrupt the normal vascular and functional organization of the liver.
Therefore, the two major pathological features of cirrhosis are:
1. **Regenerative nodules** formed by proliferating hepatocytes.
2. **Diffuse fibrosis** surrounding and separating these nodules.

Together, these features represent the hallmark microscopic appearance of cirrhosis and explain the progressive loss of normal liver structure and function

Causes of cirrhosis

Regardless of the underlying etiology, advanced cirrhosis usually demonstrates similar morphological and pathological changes. Therefore, when a patient presents with fully developed cirrhosis, the original cause may no longer be easily identifiable because the architectural distortion and fibrosis become common end-stage features shared by most chronic liver diseases.
For this reason, early identification and treatment of the underlying liver disease are essential to prevent or delay the progression to cirrhosis.

1. **Chronic alcoholism;** most common in western countries

2. **Chronic viral infection HBV & HCV;** One of the most common causes of cirrhosis worldwide, particularly in regions where viral hepatitis is endemic. Chronic infection with the Hepatitis B virus and Hepatitis C virus is strongly associated with chronic hepatitis that may eventually progress to cirrhosis.

3. **Biliary disease;** may also lead to cirrhosis. Chronic cholestatic can produce progressive fibrosis and hepatic architectural distortion, a condition historically referred to as Primary Biliary Cholangitis.

4. **.Hemochromatosis;** a metabolic disorder characterized by excessive iron accumulation within hepatocytes. Progressive iron deposition causes hepatocellular injury, fibrosis, and ultimately cirrhosis. It is considered one of the most common inherited metabolic causes of chronic liver disease.

5. Autoimmune hepatitis; this condition may clinically and histologically resemble chronic viral hepatitis because both produce inflammatory changes and abnormal liver function tests. Therefore, differentiation between these conditions is important for accurate diagnosis and management.

6. Wilson disease; is an inherited metabolic disorder. which results from abnormal copper accumulation in hepatocytes. Excess copper causes chronic liver injury and may progress to cirrhosis if untreated.

7. α-1- antitrypsin deficiency;

It is due to antitrypsin enzyme deficiency, which is a primary liver disease. This enzyme is synthesized in the liver, and the liver can also be involved in fibrosis. It is important in the differential diagnosis of neonatal hepatitis. It can produce changes similar to other conditions, so it should be kept in mind, although it is not frequent.

Rare Metabolic and Inherited Causes of Cirrhosis

the common causes of cirrhosis are excluded, rare inherited metabolic disorders should be considered. These conditions are usually caused by specific enzyme deficiencies that lead to abnormal accumulation of metabolic substances within hepatocytes and progressive liver injury.

8.Rare causes

Galactosemia; which results from deficiency of enzymes involved in galactose metabolism.

Tyrosinosis; an inherited abnormality of tyrosine metabolism

Glycogen storage disease III &IV: These disorders are characterized by excessive deposition of glycogen in various tissues and organs. Among the different subtypes, glycogen storage disease types III and IV particularly involve the liver. Since the liver normally functions as the major storage site for glycogen, excessive intracellular glycogen accumulation leads to hepatocellular injury, fibrosis, and eventually cirrhosis

Similarly, Lipid storage disease occur due to enzyme deficiencies that impair lipid metabolism. Because lipids cannot be properly metabolized, they accumulate within hepatocytes, producing steatosis, fibrosis, and progressive cirrhosis.

Hereditary fructose intolerance is another metabolic disease caused by enzyme deficiency .

Drug induced: Certain drugs may also induce chronic liver injury and cirrhosis after prolonged use e.g methyldopa which may produce chronic hepatic injury and fibrosis in susceptible individuals.

9. Previously, many cirrhosis cases without an identifiable cause were classified as **Cryptogenic cirrhosis 10%.**
However, current evidence suggests that a large proportion of these cases are actually related to Nonalcoholic Fatty Liver Disease associated with metabolic abnormalities.
In the past, fatty infiltration of the liver was considered a reversible and relatively harmless condition. It is now recognized that persistent fatty liver disease may progress to chronic inflammation, fibrosis, and eventually cirrhosis.

Pathogenesis of cirrhosis

-The mechanism of cirrhosis involves:

1-Hepatocellular death

2 Regeneration

3 Progressive fibrosis

4-Vascular changes

The development of hepatic fibrosis and cirrhosis occurs through a progressive pathological process initiated by chronic liver injury, whether inflammatory or non-inflammatory in origin. Persistent hepatic injury stimulates both hepatocellular regeneration and fibrogenesis simultaneously.
Hepatocytes possess a high regenerative capacity. Following liver injury, surviving hepatocytes proliferate to restore the damaged hepatic tissue. However, regeneration alone is insufficient to restore normal architecture because it occurs in association with continuous deposition of fibrous connective tissue. As a result, regenerative hepatocellular nodules become surrounded by fibrous septa, producing the characteristic nodular appearance of cirrhosis.

Thus, cirrhosis develops due to the combined effects of:
1.Regeneration of hepatocytes.
2.Progressive deposition of fibrous tissue.
The excessive accumulation of fibrous tissue within the liver parenchyma leads to entrapment of regenerating hepatocytes and distortion of the normal hepatic architecture. These fibrotic changes are clinically significant because they interfere with hepatic blood flow and impair the normal exchange of substances between blood and hepatocytes.

Cell death should occur over a long period of time & accompanied by fibrosis

-In normal liver the ECM collagen (types I, III,V& XI) is present only in :

Liver capsule Portal tracts

Around central vein

-delicate framework of type IV collagen & other proteins lies in space of Disse

-In cirrhosis types I & III collagen & others are deposited in the space of Disse

Normally, fibrous tissue within the liver is minimal and is mainly localized in:
·The portal tracts,
·Around the central veins,
·The liver capsule.
The normal extracellular matrix of hepatic connective tissue consists primarily of:
·Collagen types I, III, XI , and V,
Any excessive deposition of collagen within the liver parenchyma is considered abnormal and represents fibrosis.

In addition, collagen type IV is a major component of the basement membrane. The basement membrane is an essential delicate structure that facilitates exchange between sinusoidal blood and hepatocytes. Under normal conditions, this specialized structure supports efficient metabolic exchange and hepatocellular function.
During cirrhosis, abnormal deposition of fibrillar collagens, mainly collagen types I and III, disrupts the normal sinusoidal architecture and interferes with exchange between blood and hepatocytes, leading to progressive impairment of liver function.

The major source of collagen in cirrhosis is the perisinusoidal (between hepatocytes and sinusoidal endothelial cells) stellate cells (Ito cells) which lie in space of Disse

-Perisinusoidal stellate cells act normally as storage cells for vit A & fat; In the healthy liver, these cells remain quiescent and produce only minimal amounts of extracellular matrix components

Upon stimulation myofibroblast- like cells

↓

EXPLANATION NEXT SLIDE

transforming growth factor β

(TGF-β)

Upon stimulation myofibroblast- like cells

↓

transforming growth factor β
(TGF-β)

Following chronic liver injury or inflammation, stellate cells become activated and transform into myofibroblast-like cells. This transformation is stimulated particularly by Transforming Growth Factor Beta, which is one of the most important fibrogenic cytokines in hepatic fibrosis.

Activated stellate cells acquire the ability to:

·Proliferate,

·Produce large amounts of collagen,

·Synthesize extracellular matrix proteins,

·Promote hepatic fibrosis and architectural distortion.

As fibrosis progresses, excessive collagen deposition disrupts the normal sinusoidal structure and contributes to the development of cirrhosis.

The stimuli for the activation of stellate cells & production of collagen are :

1.reactive oxygen species; which are generated during inflammation, ischemia, metabolic injury, and exposure to toxic substances. Reactive oxygen species induce oxidative stress and directly damage hepatocytes, leading to cell injury and death.

In addition, multiple cytokines and growth factors released from injured hepatocytes, inflammatory cells, and Kupffer cells contribute to stellate cell activation. These mediators include:

2. Growth factors

3. cytokines TNF, IL-I, lymphotoxins

These mediators stimulate stellate cells to transform into collagen-producing myofibroblast-like cells. Consequently, activated stellate cells synthesize excessive extracellular matrix proteins, especially collagen, leading to progressive hepatic fibrosis. Therefore, chronic inflammation, oxidative stress, and cytokine-mediated activation of stellate cells represent the central mechanisms responsible for collagen deposition and the development of cirrhosis.

-The vascular changes include :

1-Loss of sinusoidal endothelial cell fenestration

2-development of vascular shunts as

Portal v- hepatic v

Hepatic a - portal v

→defect in liver function

-Loss of microvilli from hepatocytes →↓ transport capacity of the cells

-The vascular changes

The vascular changes in cirrhosis are very important because hepatic function depends greatly on normal blood flow and the exchange process within the liver.
The process of fibrosis and deposition of collagen in the Space of Disse is associated with loss of the fenestrations of sinusoidal endothelial cells. These fenestrations are essential for normal exchange between sinusoidal blood and hepatocytes. Once collagen is deposited, these fenestrations are lost from the sinusoidal walls, creating the initial obstacle to normal exchange.
In addition, blood flow becomes subjected to increased resistance because blood vessels become entrapped within fibrous tissue, and the sinusoids become surrounded by excessive collagen deposition. This leads to the formation of vascular shunts.
These shunts may connect:
•Portal vein to hepatic vein,
•Hepatic artery to portal vein,
•Other abnormal vascular channels.
As a result, blood flow deviates from its normal pathway, further impairing the exchange process. Some blood may bypass hepatocytes without receiving synthetic products or without delivering toxic substances for detoxification, leading to progressive liver failure.
Furthermore, the microvilli of hepatocytes are lost, reducing the available surface area necessary for efficient exchange and metabolic activity. Loss of microvilli further contributes to hepatocellular malfunction and impairment of normal liver function.

- Collagen deposition converts sinusoids with fenestrated endothelial channels that allow free exchange of solutes between plasma and hepatocytes to higher pressure, fast-flowing vascular channels without such solute exchange.
- the movement of proteins (e.g., albumin, clotting factors, lipoproteins) between hepatocytes and the plasma is markedly impaired.
- These functional changes are aggravated by the loss of microvilli from the hepatocyte surface, which diminishes the transport capacity of the cell.

Effect of Cirrhosis on Exchange Functions and Hepatic Metabolism

The deposition of collagen, loss of endothelial fenestrations, and impairment of the exchange process significantly affect liver function in cirrhosis.
The normal movement and exchange of substances synthesized by hepatocytes become impaired. These substances include:
•Albumin,
•Lipoproteins,
•Clotting factors,
•Other plasma proteins.
As liver function progressively declines, synthesis and release of clotting factors into the circulation become impaired, leading to increased bleeding tendency and coagulation abnormalities.
Lipoproteins synthesized by the liver are important for transport of free fatty acids from the liver into the circulation for utilization by peripheral tissues. When this process is impaired, lipids accumulate within hepatocytes and contribute to fatty change in the liver.
In addition, detoxification functions of the liver become markedly reduced. Because hepatocytes lose functional surface area and normal exchange mechanisms are disrupted, toxic substances cannot be adequately removed from the blood. Consequently, toxic metabolites accumulate within the circulation.
Thus, impairment of exchange, decreased hepatocellular function, and loss of normal vascular architecture collectively lead to progressive liver dysfunction and the clinical manifestations of hepatic failure.

-Clinical features of cirrhosis :

-Silent; for a prolonged period due to preserved hepatic functional reserve.
A patient may appear clinically stable under normal conditions; however, any additional physiological stress can precipitate hepatic decompensation. Such precipitating factors include: Gastrointestinal bleeding, Infections, Renal dysfunction, Surgery or trauma, Metabolic stress, Alcohol or drug toxicity.
Under these stressful conditions, the diseased liver is unable to increase its functional capacity adequately, unlike a normal liver. Consequently, hepatic insufficiency becomes clinically evident.

-Common nonspecific manifestations Anorexia(loss of appetite experienced by patients with chronic liver disease), wt loss, weakness

-Complications :

1-Progressive hepatic failure

2-Portal hypertension

3-Hepatocellular carcinoma

Portal hypertension

- ↑ resistance to portal blood flow at the level of sinusoids & compression of central veins by perivenular fibrosis & parenchymal nodules
- Arterial - portal anastomosis develops in the fibrous bands →increase in the blood pressure in portal venous system

Portal Hypertension

Portal Hypertension is a pathological condition characterized by elevation of pressure within the portal venous system. It develops mainly as a consequence of cirrhosis, where fibrosis and architectural distortion of the liver increase resistance to portal blood flow.

Normally, portal venous pressure is relatively low, allowing blood from the gastrointestinal tract and spleen to pass smoothly through the liver sinusoids. However, in cirrhosis, fibrous septa and regenerative nodules compress and distort the intrahepatic vascular channels, markedly increasing vascular resistance.

As resistance to blood flow rises, portal venous pressure progressively increases. In order to overcome this elevated resistance, the body attempts to divert blood through alternative vascular pathways known as portosystemic shunts

These collateral shunts develop to decompress the portal circulation and maintain venous blood flow despite the increased intrahepatic resistance. Blood is therefore redirected from the high-pressure portal venous system into lower-pressure systemic veins.

Although these shunts partially reduce portal pressure, they also produce important pathological consequences because portal blood bypasses the liver without undergoing normal metabolic processing and detoxification.

Thus, portal hypertension results primarily from:

1.Increased resistance to portal blood flow caused by fibrosis and vascular distortion.

2.Altered hemodynamics and formation of collateral vascular shunts.

The increased portal pressure and abnormal blood flow contribute significantly to the major complications of cirrhosis, including ascites, splenomegaly, varices, and hepatic encephalopathy.

- **Once these shunts develop Anastomoses between the arterial and portal systems in the fibrous bands also contribute to portal hypertension** (Because these channels occur between vessels within the fibrous tissue, resistance to blood flow increases, leading to increased portal venous pressure. Consequently, arterial pressure is transmitted to the normally low-pressure portal venous system) **by imposing arterial pressure on the normally low-pressure portal venous system.**

Causes of portal hypertension

Portal Hypertension is a characteristic and common complication of cirrhosis. However, when portal hypertension occurs in the absence of cirrhosis, other causes must be considered.
These causes may be classified into pre-hepatic, intrahepatic, and post-hepatic causes depending on the site of obstruction to portal blood flow.

I.Prehepatic: results from obstruction of blood flow before it reaches the liver

1 Portal vein thrombosis
2 Massive splenomegaly; causing increased vascular pressure and impaired portal flow.
In these conditions, blood flow toward the liver becomes obstructed, resulting in congestion and increased portal venous pressure.

II. Post hepatic: occurs when blood flow leaving the liver becomes obstructed

1-Severe Rt.- sided heart failure; venous blood becomes stagnant because the heart cannot pump blood effectively. This causes hepatic venous congestion and elevation of portal venous pressure.
2-Constrictive pericarditis
3-Hepatic vein out flow obstruction

III. Hepatic:

The most common intrahepatic cause is cirrhosis. Loss of normal hepatic architecture due to fibrosis, fatty infiltration, or chronic liver disease increases resistance to portal blood flow and produces portal hypertension

1 Cirrhosis
2 Schistosomiasis
3 Massive fatty change
4 Diffuse granulomatosis as sarcoidosis, TB
5 Disease of portal microcirculation as nodular regenerative hyperplasia

Therefore, although portal hypertension is classically associated with cirrhosis, it may also occur in other conditions that obstruct portal circulation or alter the normal hepatic vascular architecture. Nevertheless, cirrhosis remains the most common cause.

Clinical consequence of portal hypertension

1 Ascitis

2 Portosystemic shunts

3 Hepatic encephalopathy

4-Splenomegaly

Ascitis

-Collection of excess fluid in peritoneal cavity; Under normal conditions, only a small amount of peritoneal fluid is present to lubricate the abdominal surfaces and facilitate movement between abdominal organs.

-It becomes clinically detectable when at least 500 ml have accumulated, In advanced cases, several liters of fluid may collect, leading to marked abdominal distension.

Because large volumes of fluid may accumulate and produce significant pressure effects, patients frequently undergo abdominal aspiration (paracentesis) to relieve symptoms and reduce intra-abdominal pressure.
Analysis of ascitic fluid is clinically important in evaluating patients with cirrhosis and portal hypertension.

-**Features**

1 Serous fluid

2 Contains as much as 3g/ml of protein (albumin)

3 It has the same concentration as blood of glucose, Na^+, & K^+

4 Mesothelial cells **derived from the peritoneal lining** & lymphocytes

5-Neutrophils = **superimposed** infection

6-RBCs = DISSEMINATED CANCR **since tumors tend to bleed**

This is particularly important because Hepatocellular Carcinoma commonly develops on a background of cirrhosis. Therefore, patients with cirrhosis and ascites require regular follow-up and careful evaluation for possible malignant transformation.

Pathogenesis

1-Sinusoidal ↑ Bp

2-Hypoalbuminemia

3-Leakage of hepatic lymph into the peritoneal cavity

Normal thoracic duct lymph flow is 800-1000 ml/d

in cirrhosis is 20L /d

4-Renal retention of Na^+ & water due to 2ry hyperaldosteronism

Pathogenesis of Ascites

Ascites develops when the mechanisms that normally regulate fluid balance within the peritoneal cavity become disturbed. In cirrhosis, several mechanisms act together and lead to progressive accumulation of fluid.

The first important mechanism is **portal hypertension**. Increased pressure within the portal venous system raises the hydrostatic pressure inside the hepatic and splanchnic vessels. As a result, fluid is pushed out of the vascular compartment into the peritoneal cavity.

Normally, this excess fluid can be drained by the lymphatic system. However, in cirrhosis, lymph production increases markedly and eventually exceeds the absorptive capacity of lymphatic drainage. Therefore, the fluid can no longer be adequately removed, leading to its accumulation as ascites.

Another important mechanism is **hypoalbuminemia**. Because the cirrhotic liver cannot synthesize sufficient albumin, plasma oncotic pressure decreases. This reduces the ability of blood vessels to retain fluid within the circulation, allowing more fluid to escape into the abdominal cavity.

In addition, cirrhosis causes renal retention of sodium and water. This occurs due to altered circulatory regulation and activation of fluid-retaining hormonal systems. Retention of sodium and water expands the total body fluid volume and further contributes to ascites formation.

Therefore, ascites results from the combined effects of:

- Increased portal venous hydrostatic pressure.
- Increased hepatic lymph production with impaired drainage.
- Decreased plasma oncotic pressure due to hypoalbuminemia.
- Renal sodium and water retention.

Together, these mechanisms lead to persistent accumulation of fluid within the peritoneal cavity.

Portosystemic shunt

-Because of ↑portal venous pressure bypasses develop wherever the systemic & portal circulation share capillary beds

-Sites:

1-Around & within the rectum (Hemorrhoids) ; dilatation and tortuosity of rectal veins may occur, producing hemorrhoids. Although patients with cirrhosis can develop hemorrhoids due to portal hypertension, hemorrhoids are far more commonly caused by non-cirrhotic conditions. Therefore, not all hemorrhoids are caused by cirrhosis, although portal hypertension may contribute to their development.

2-Gastroesophageal junction (varicies); this is the most clinically important site of collateral formation. Dilated veins develop within the lower esophageal mucosa, producing Esophageal Varices. These fragile vessels are highly susceptible to rupture and may cause severe upper gastrointestinal bleeding.

3-Retroperitoneum
4-Falciform ligament of the liver (periumbilical & abdominal wall collaterals) → may become visible over the anterior abdominal wall. These tortuous radiating veins produce the classical appearance known as **caput medusae** named after the snake-haired figure in Greek mythology.

- Gastroesophageal varicies appear in 65% of pts. with advanced cirrhosis & cause death in 50% of then due to UGT bleeding; Importantly, if a patient survives the initial episode of variceal bleeding, the risk of recurrent bleeding episodes remains significantly increased.
Therefore, development of portosystemic collateral circulation represents a major pathological and clinical consequence of portal hypertension in cirrhosis.

caput medusae

The varices that develop in portal hypertension, whether caused by cirrhosis or other conditions, are essentially dilated and tortuous superficial veins formed as a result of increased venous pressure and collateral circulation.

In patients with Portal Hypertension, collateral veins may become visible on the anterior abdominal wall. These superficial dilated veins develop because blood is diverted through alternative venous pathways in an attempt to bypass the increased resistance within the portal venous system.

Since these veins are located superficially beneath the skin, they can often be observed during physical examination as prominent tortuous venous channels over the abdomen. Therefore, in patients with cirrhosis, examination of the abdomen is clinically important, as visible abdominal wall varices may indicate significant portal hypertension and the presence of collateral venous circulation.

Esophageal varicies

This image demonstrates Esophageal Varices at the gastroesophageal junction. The mucosal surface shown includes the stomach on the left side and the lower esophagus on the right side.
The dark longitudinal elevations visible within the lower esophageal mucosa represent dilated submucosal veins, known as esophageal varices. These varices develop as a consequence of Portal Hypertension, where portal blood is diverted through collateral venous channels connecting the portal and systemic circulations.

Esophageal varices are clinically important because they are fragile and highly susceptible to rupture. Bleeding from ruptured varices can result in severe upper gastrointestinal hemorrhage, which represents one of the most serious and life-threatening complications of cirrhosis and portal hypertension.

Splenomegaly

a common complication of Portal Hypertension and is associated with characteristic gross and microscopic pathological changes.
Portal hypertension causes congestion of splenic venous blood due to impaired venous drainage through the portal circulation. As blood flow becomes stagnant within the spleen, the spleen progressively enlarges.

- -Usu. 500-1000 gms (N <300gms)
- -Not necessarily correlated with other features of portal ↑Bp
- -May result in hypersplenism; in which the enlarged congested spleen sequesters and destroys blood cells excessively.

Normally, the spleen participates in filtration and removal of aged blood cells. However, in hypersplenism, increased splenic activity accelerates destruction of:

- Red blood cells,
- White blood cells,
- Platelets.

As a result, patients may develop:

- Anemia due to loss of red blood cells,
- Leukopenia with increased susceptibility to infections,
- Thrombocytopenia due to decreased platelet count.

Thrombocytopenia is particularly important because it increases the risk of bleeding. Reduced platelet numbers impair normal hemostasis and contribute to bleeding tendencies commonly seen in advanced cirrhosis and portal hypertension.

Therefore, splenomegaly and hypersplenism represent important hematological complications of portal hypertension and significantly contribute to the clinical manifestations of chronic liver disease.

splenomegaly

This image demonstrates congestive enlargement of the spleen, a common finding in patients with Portal Hypertension associated with cirrhosis.
In portal hypertension, impaired venous drainage causes stagnation and congestion of blood within the splenic circulation. As a result, the spleen becomes enlarged and congested with blood, a condition referred to as congestive splenomegaly.
Grossly, the spleen appears enlarged, dark, and congested due to excessive accumulation of venous blood. This condition is frequently observed in patients with advanced cirrhosis and contributes to the development of hypersplenism and associated hematological abnormalities.

Hepatic encephalopthy

- -It is a **serious neuropsychiatric** complication of acute & chronic hepatic failure
- -Disturbance in brain function ranging from behavioural changes to marked confusion & sutpor to deep coma & death
- -The changes may progress over hrs. or days

The condition results mainly from accumulation of toxic substances in the blood, particularly ammonia. Normally, ammonia produced in the intestine from protein metabolism and bacterial activity is transported to the liver, where it is converted into urea and detoxified.

In cirrhosis and severe liver dysfunction, the damaged liver is unable to adequately remove ammonia from the circulation. In addition, portosystemic shunting allows portal blood to bypass the liver without detoxification. Consequently, ammonia and other toxic metabolites accumulate in the bloodstream and reach the brain.

Hepatic encephalopathy may develop:
·Acutely over a short period of time,
·Or gradually over several years in chronic liver disease.

Clinical manifestations may range from mild cognitive impairment and behavioral changes to severe neurological dysfunction, confusion, coma, and death.
This condition represents a very serious complication of cirrhosis and advanced liver disease. Without appropriate management and treatment of the underlying hepatic dysfunction, hepatic encephalopathy may progress to irreversible neurological damage and fatal outcome.

Neurological signs:

Rigidity
Hyper-reflexia
Tremors,
Abnormal involuntary movements,
Non - specific EEG
Seizures
Asterixis (non-rhythmic rapid extension flexision movements of head & extremities .

-Brain shows edema & astrocytic reaction

In severe cases, patients may progress to coma and death if the underlying liver failure is not adequately managed.
Pathologically, the brain in these patients commonly demonstrates cerebral edema resulting from accumulation of fluid within the brain tissue. This edema is generally non-inflammatory in nature and is related to metabolic and toxic disturbances associated with liver failure. Some degree of astrocytic reaction may also occur as part of the pathological process.
Cerebral edema is particularly dangerous because the brain is enclosed within the rigid bony cranial cavity, which cannot expand. Consequently, swelling of brain tissue increases intracranial pressure and leads to compression of neural structures.
The neurological manifestations observed in these patients depend largely on the anatomical sites most affected by compression and increased intracranial pressure. Progressive cerebral compression may ultimately result in severe neurological deterioration, coma, and fatal outcome.

Pathogenesis

-Physiologic factors important in development of hepatic encephalopathy :-

1 Severe loss of hepatocellular function

2 Shunting of blood around damaged liver

↓↓

Exposure of Brain to toxic metabolic products

↑ NH3 level in blood → generalized brain edema impaired neuronal function

alteration in central nervous system AA metabolism

رسالة من الفريق العلمي:

فضل أيام عشر ذي الحجة

قال رسول الله صل الله عليه وسلم :

«مامن أيّام أعظم عند الله سبحانه
ولا أحب إليه العمل فيهن من هذه الأيام العشر
فأكثروا فيهن من التهليل والتكبير والتحميد»

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