GIS

Pathology

|Modified slides

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Cirrhosis

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

- **Main characteristics**

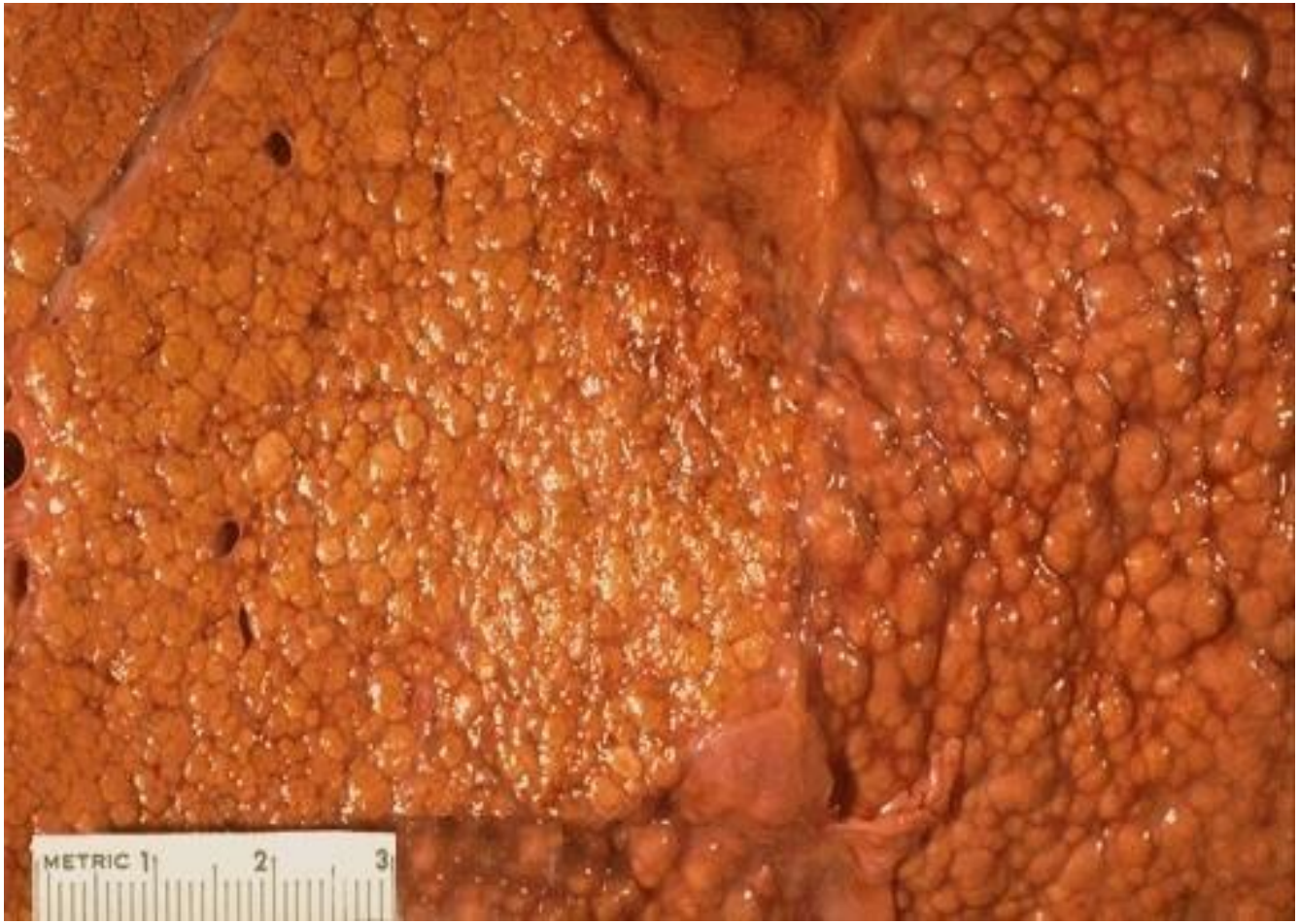
1. Bridging fibrous septae
2. Parenchymal nodules encircled by fibrotic bands
3. Diffuse architecture disruption

- **Types :**

Micronodules < 3mm in diameter

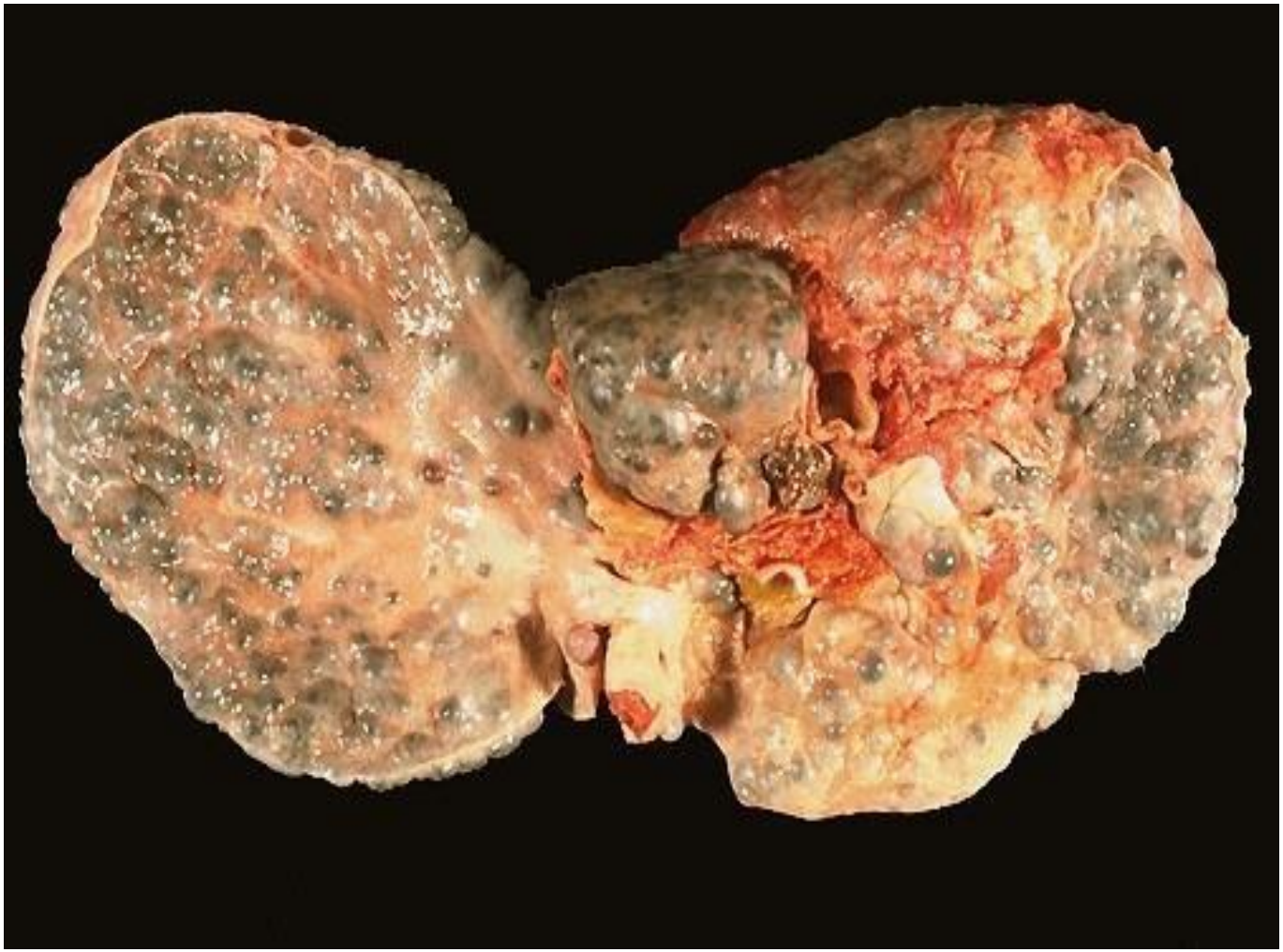
Macronodules > 3 mm in diameter

Micronodular cirrhosis



Gross appearance.
The surface which is normally smooth changed into nodules (diffuse process)

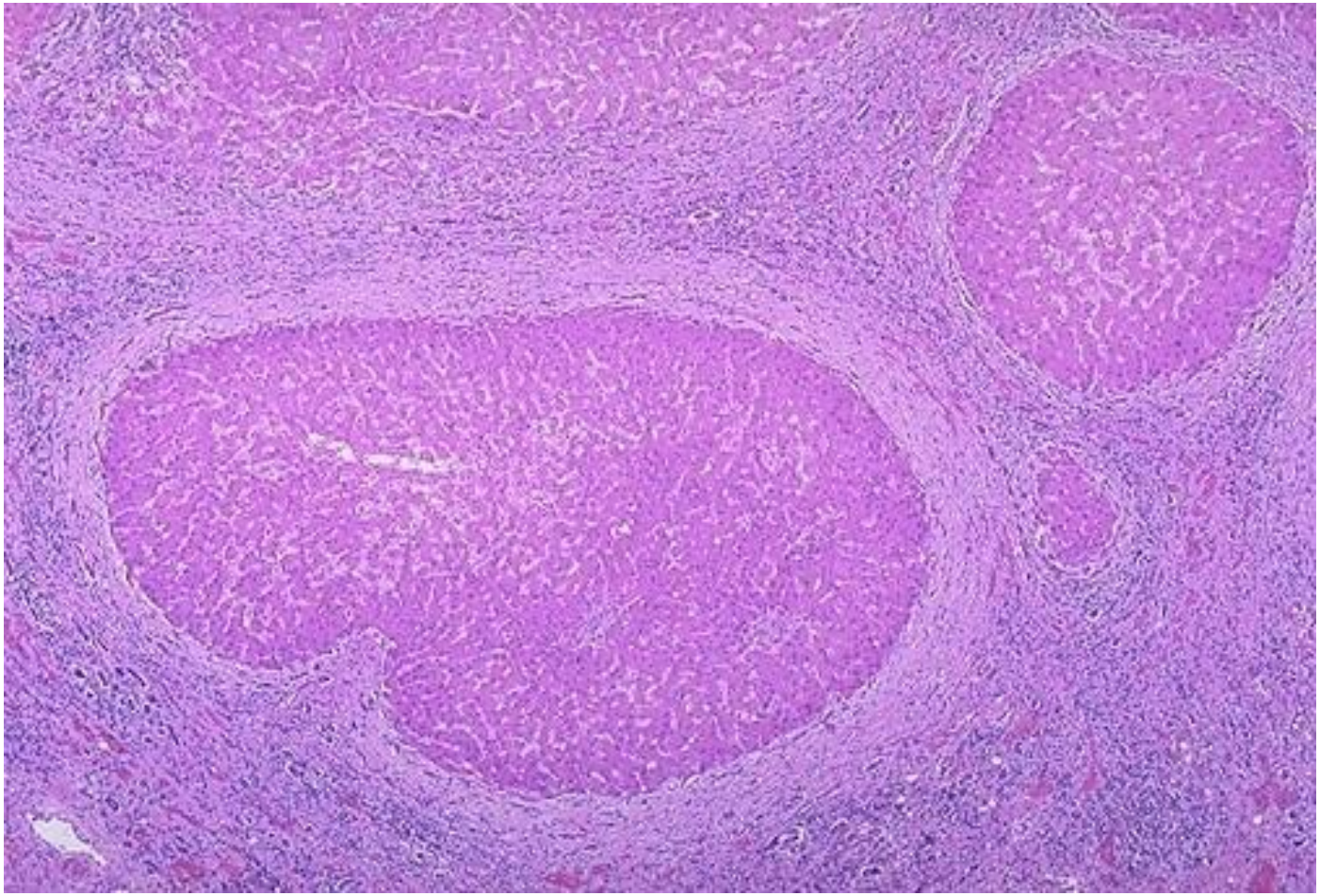
Macronodular cirrhosis



There are small nodules that cumulated to form large nodules.

(Macronodular cirrhosis)

Cirrhosis



Fibrous septa: Thick bands of collagen separate rounded cirrhotic nodules.

Microscopic appearance of cirrhotic liver. The parenchyma is replaced by nodules

(Nodules = parenchyma encircled by fibrous tissue)

Nodules of variable size & there is infiltrating by inflammatory cells

Causes of cirrhosis

1. **Chronic alcoholism** (most common in western countries)
2. **Chronic viral infection HBV & HCV** (mainly in countries where hepatitis viral infections are common)
3. **Biliary disease**
4. **Hemochromatosis** (excessive deposition of iron within liver)
5. **Autoimmune hepatitis** (we can see antinuclear antibodies in the blood)
6. **Wilson disease** (excessive predisposition of copper, usually will be child at the age of 10)

7. **a-1- antitrypsin deficiency**

8. Rare causes

(should be considered when other common causes are excluded)

The incidence of these diseases is low , not their ability to cause cirrhosis.

Galactosemia

Tyrosinosis (causes cirrhosis rapidly, in young age)

Glycogen storage disease III &IV Lipid storage disease

Hereditary fructose intolerance Drug induced e.g methyldopa

9. Cryptogenic cirrhosis 10%

(when the underlying causes are not identified)

Pathogenesis of cirrhosis

-The mechanism of cirrhosis involves:

1-Hepatocellular death (regardless of the cause)

2 Regeneration

3Progressive fibrosis

4-Vascular changes

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

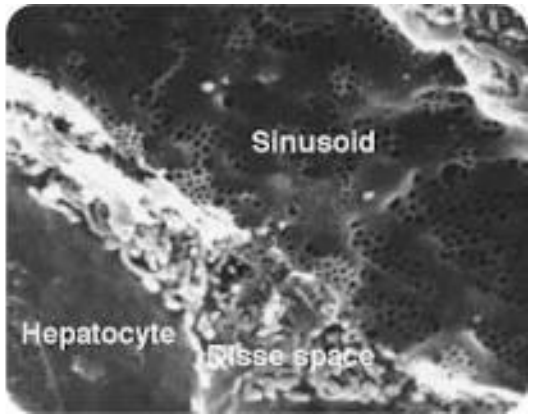
Portal tracts

Around central vein

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

Remember:

The perisinusoidal space (or space of Disse) is **a location in the liver between a hepatocyte and a sinusoid**. It contains the blood plasma. Microvilli of hepatocytes extend into this space, allowing proteins and other plasma components from the sinusoids to be absorbed by the hepatocytes.



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

-The major source of collagen in cirrhosis is the perisinusoidal stellate cells (Ito cells) which lie in space of Disse

-Perisinusoidal stellate cells act normally as storage cells for vit A & fat

-Upon stimulation myofibroblast- like cells

↓

transforming growth factor β

(TGF-β)

➢ *Effect of Cirrhosis on ECM components and stellate cells:*

	Normal	Cirrhosis
ECM **Collagen (types I, III, V& XI)**	Are present **only** in: 1. **Liver capsule** 2. **Portal tracts** 3. **Around the central vein**	Are deposited in the space of Disse → **This interferes with the exchange function of hepatocytes**
Delicate framework **of type IV collagen** & other proteins:	Lie in the space of Disse.	
Perisinusoidal stellate cells **(Ito cells)**	They act as storage cells for: 1. **Vitamin A** 2. **Fat**	-They are the main source of collagen in cirrhosis. -They lie in the space of Disse. How? -When these stellate cells are **stimulated by TGF-Beta** (A common mediator released during the inflammatory process), they start to **produce collagen**

018 sheet

-The stimuli for the activation of stellate cells & production of collagen (can be variable)are :

1-Reactive oxygen species (are generated during inflammatory process)

2 Growth factors

3 Cytokines TNF, IL-I, lymphotoxins

-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 (in exchange of substances between the blood and hepatocytes)

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

- 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) (which are synthesized by hepatocytes) 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 (and the deterioration of liver function gets of cirrhosis).

-Clinical features of cirrhosis :

-Silent (asymptomatic)

-Anorexia, wt loss, weakness (minimal nonspecific manifestations)

-Complications : (clinical manifestations of cirrhosis is mainly related to them)

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 (which are characteristic of cirrhotic lesions)
- Arterial – portal anastomosis develops in the fibrous bands →increase in the blood pressure in portal venous system

- **Anastomoses between the arterial and portal systems in the fibrous bands also contribute to portal hypertension by imposing arterial pressure on the normally low-pressure portal venous system.**

Causes of portal hypertension

Can be due to different diseases some are hepatic & some are extra hepatic.

I.Prehepatic

1 Portal vein thrombosis
2 Massive splenomegaly

II. Post hepatic

1 Severe Rt.- sided heart failure
2 Constrictive pericarditis
3 Hepatic vein out flow obstruction

III. Hepatic

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

Clinical consequence of portal hypertension

1 Ascitis

2Portosystemic shunts

3Hepatic encephalopathy

4-Splenomegaly

Ascitis

-Collection of excess fluid in peritoneal cavity

-It becomes clinically detectable when at least 500 ml have accumulated in the abdomen.

-**Features**

1 Serous fluid

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

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

4Mesothelial cells & lymphocytes 5-

Neutrophils = infection (presence of neutrophils indicates the development of inflammation)

$_6$6$_4$-RBCs = DISSEMINATED CANCER (presence of RBCs raise the suspicion of development of cancer)

Pathogenesis

(the causes of fluid accumulation in abdominal cavity)

1 Sinusoidal ↑Bp

2 Hypoalbuminemia

3 Leakage of hepatic lymph into the peritoneal cavity (due to increase in the lymph flow)
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

Clarifying

First cause: (leads to releasing of fluid into the surface of bladder which is in the abdomen)

Second cause: (happens due to decrease in liver function “blood protein synthesis” which leads to decreasing osmotic pressure in vascular circulation which leads to leakage of fluid into the surrounding)

Fourth cause: (leads to increase in the total vascular fluid volume leading to increase hydrostatic pressure & leakage of fluid into extravascular space)

Portosystemic shunt

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

(because the flow tries to shift to other circulation that have less resistance)

-Sites:

1 Around & within the rectum (Hemorrhoids)

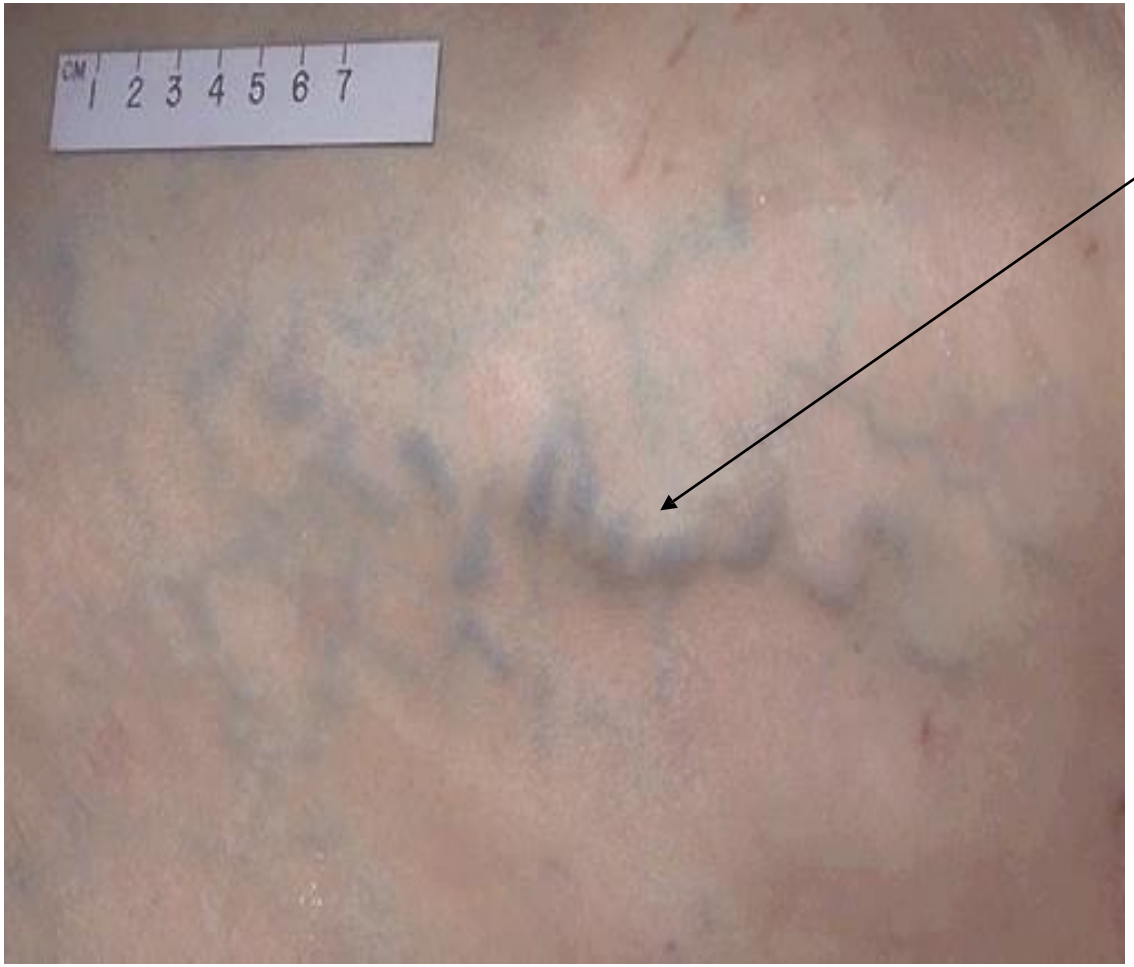
2 Gastroesophageal junction (varicies)

3 Retroperitoneum

4 Falciform ligament of the liver (periumbilical & abdominal wall collaterals) → caput medusae (which happens because of dilatation & tortuosity of Antero abdominal veins that radiate from the umbilicus)

- Gastroesophageal varicies appear in 65% of patients with advanced cirrhosis & cause death in 50% of them due to upper GI bleeding

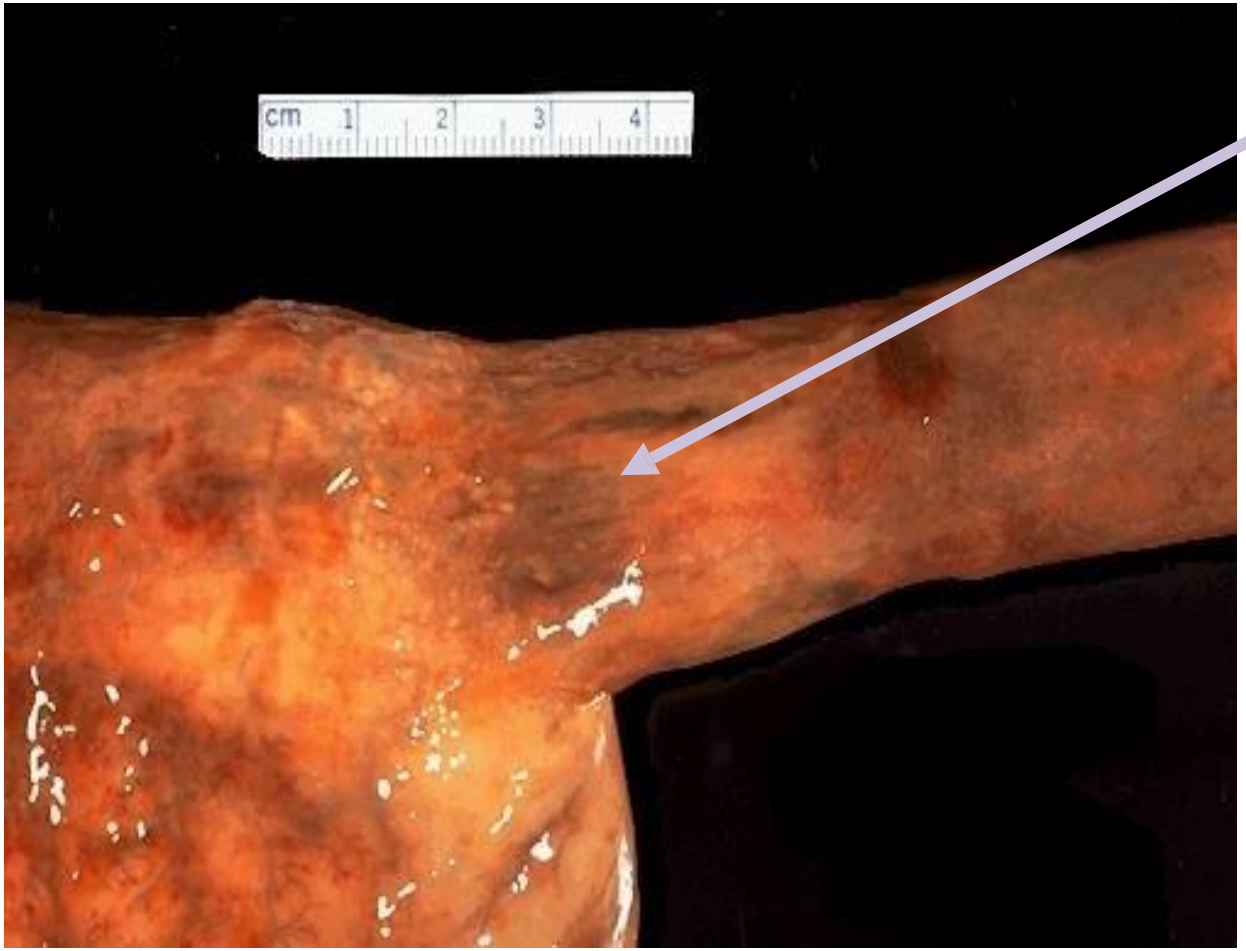
caput medusae



Anterior abdominal
wall of a cirrhosis patient.

The dilated tortuous veins are so clear and indicates the development of shunts

Esophageal varicies



The dark linear area on the esophageal mucosa indicates the presence of esophageal varices

Splenomegaly

-Usu. 500-1000 gms

(Normal weight <300gms)

-Not necessarily correlated with other features of portal ↑Bp

-May result in hypersplenism (most important)

(which associated with excessive restriction of RBCs in the spleen “which is normally filled with blood” this leads to peripheral pancytopenia and other complications)

splenomegaly

Gross appearance of spleen which is large ,gorged and filled with blood.

Hepatic encephalopthy

-It is a complication of (cirrhosis)
acute & chronic hepatic failure

(the liver is unable adequately remove toxins from the blood)

-Disturbance in brain function ranging from behavioural changes to marked confusion & sutpor to deep coma & death

-The changes may progress over hours or days

(It's a terminal stage of portal hypertension and may lead to the death of the patient)

Neurological signs:

Rigidity

Hyper-reflexia

Non – specific EEG

Seizures

Asterixis (non-rhythmic rapid extension flexision movements of head & extremities).

-Brain shows edem a & astrocytic reaction.

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

(the toxins passed blood brain barrier)

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

alteration in central nervous system Amino Acids metabolism

I think this will be helpful

SUMMARY

LIVER FAILURE

- Liver failure may follow acute injury or chronic injury, or it may occur as an acute insult superimposed on otherwise well-compensated chronic liver disease.
- The mnemonic for causes of acute liver failure are as follows:
  - A: acetaminophen, hepatitis A, autoimmune hepatitis
  - B: hepatitis B
  - C: cryptogenic, hepatitis C
  - D: drugs/toxins, hepatitis D
  - E: hepatitis E, esoteric causes (Wilson disease, Budd-Chiari syndrome)
  - F: fatty change of the microvesicular type (fatty liver of pregnancy, valproate, tetracycline, Reye syndrome)
- Potentially fatal sequelae of liver failure include coagulopathy, encephalopathy, portal hypertension and ascites, hepatorenal syndrome, and portopulmonary hypertension.

تذكرونا بدعوة في ظهر الغيب