الجهاز الهضمي

علم الأمراض

رقم المحاضرة :

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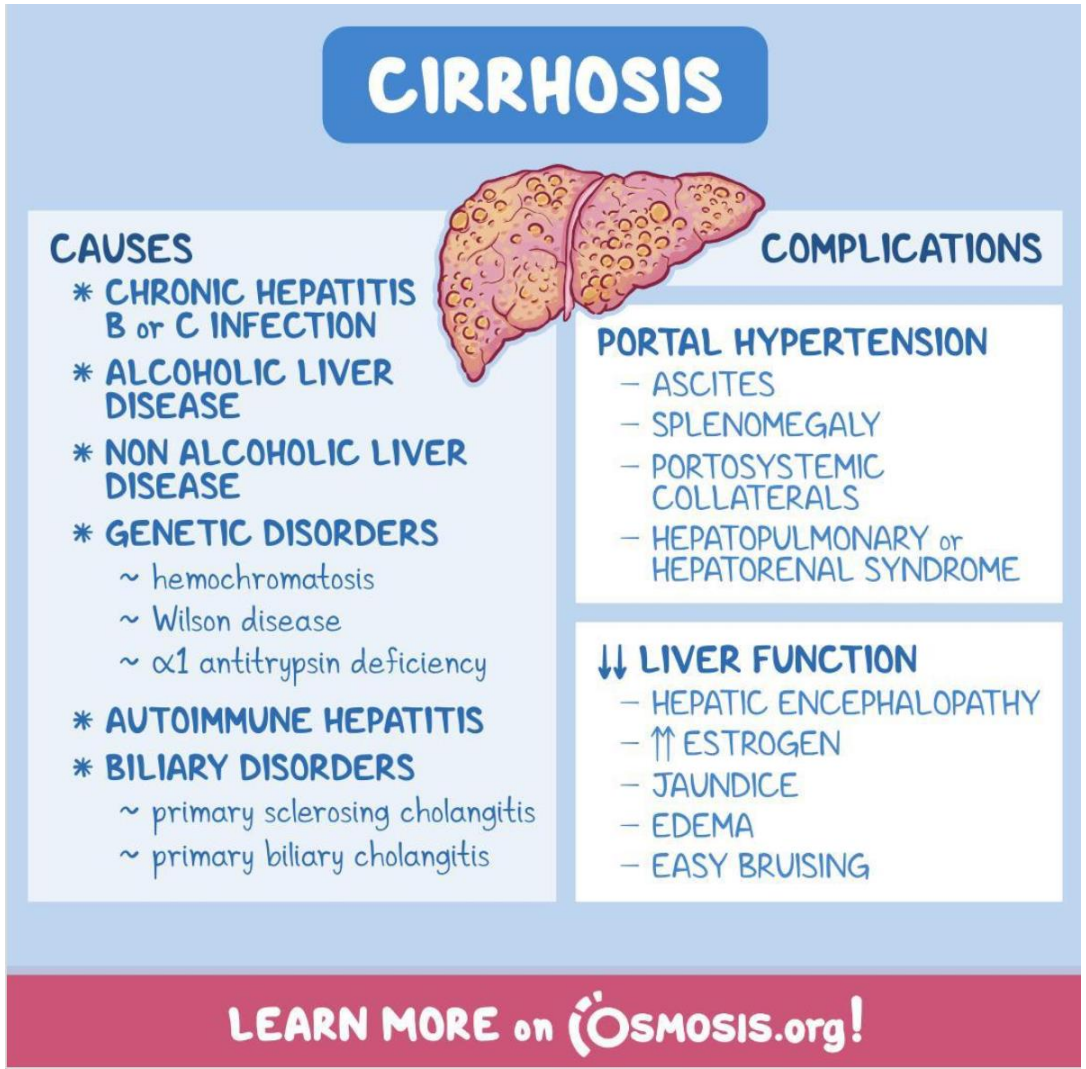
Liver cirrhosis , portal hypertension

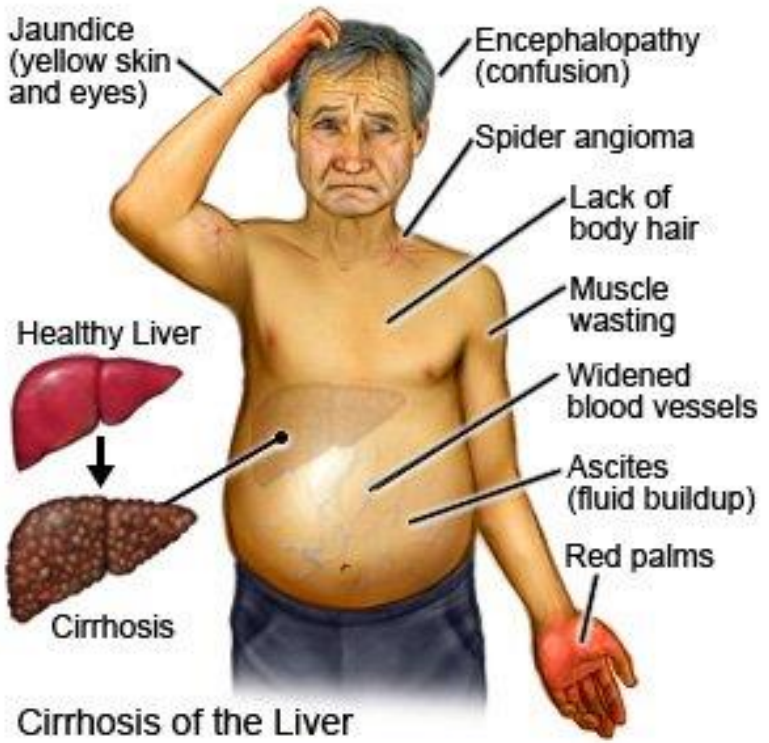
اللون الأزرق معلومات إضافية
اللون البنفسجي معلومة مهمة
اللون الأحمر كلام الدكتورة
ما أسفله خط الكلام الذي ذكرته الدكتورة من المكتوب

بسم الله ، هيّا لنبدأ 💪

Liver Cirrhosis

خذوا فكرة سريعة ثم خوضوا في التفاصيل 🌱





Cirrhosis

Involves the whole liver

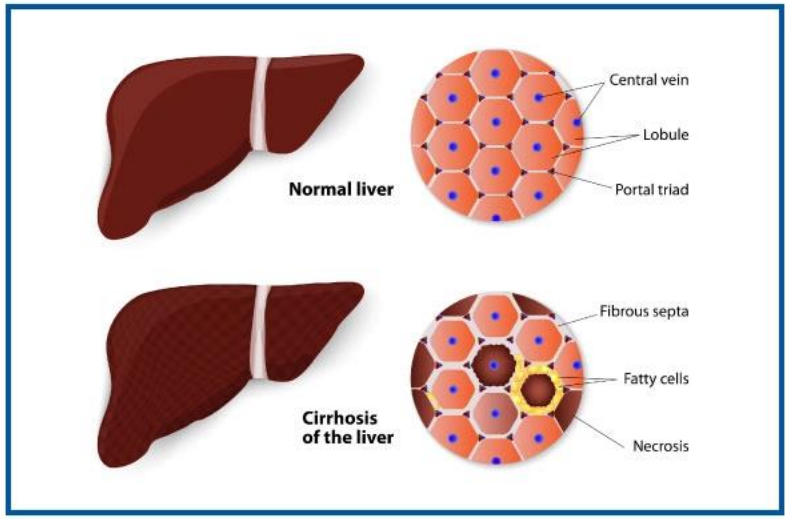
- **It is a diffuse process characterized by fibrosis & the conversion of liver parenchyma into nodules .**

-One of many diseases that is characterized by the damage of the liver
- It is a chronic process & irreversible , it develops over time (needs years to develop) but once it is developed it becomes irreversible , so the patient should live with cirrhosis or with the complications of cirrhosis for the rest of his life

- Cirrhosis is important because of the change in the liver's consistency or arrangement of cells and loss of the function of hepatocytes
- Actually the presentation and clinical manifestation of liver disease or cirrhosis is due to hepatocytes misfunction(they are injured) so the liver's normal arrangement is lost

There is some other conditions that show similarity to cirrhosis but it is FOCAL not diffused

Additional picture



- **Main characteristics**

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

In order to diagnose cirrhosis we need to see fibrosis , fibrous tissue forming nodules of regenerative liver parenchyma that is surrounded by fibrous tissue and separated by fibrous septa

If we took small biopsy , we need to be informed whether the disruption is a diffuesd or localized , because it is small , we will not know if the whole liver is disrupted , it can't tell us how diffused the disruption is

Depending on the size of the nodules , we can divide the nodules into :

- **Types :**

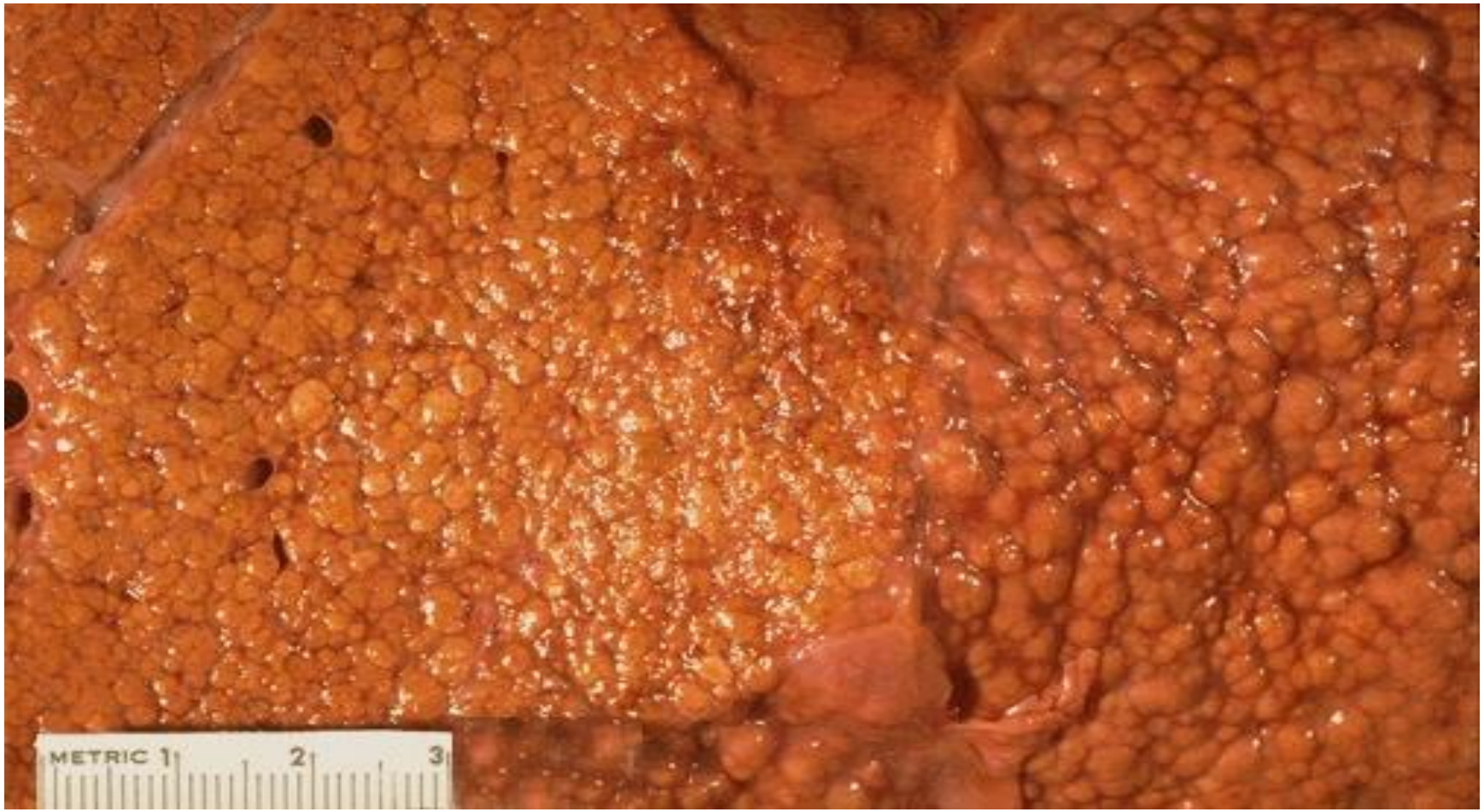
Micronodules < 3mm in diameter

Macronodules > 3 mm in diameter

Sometimes micronodules become macronodules when there is more formation of fibrous tissue

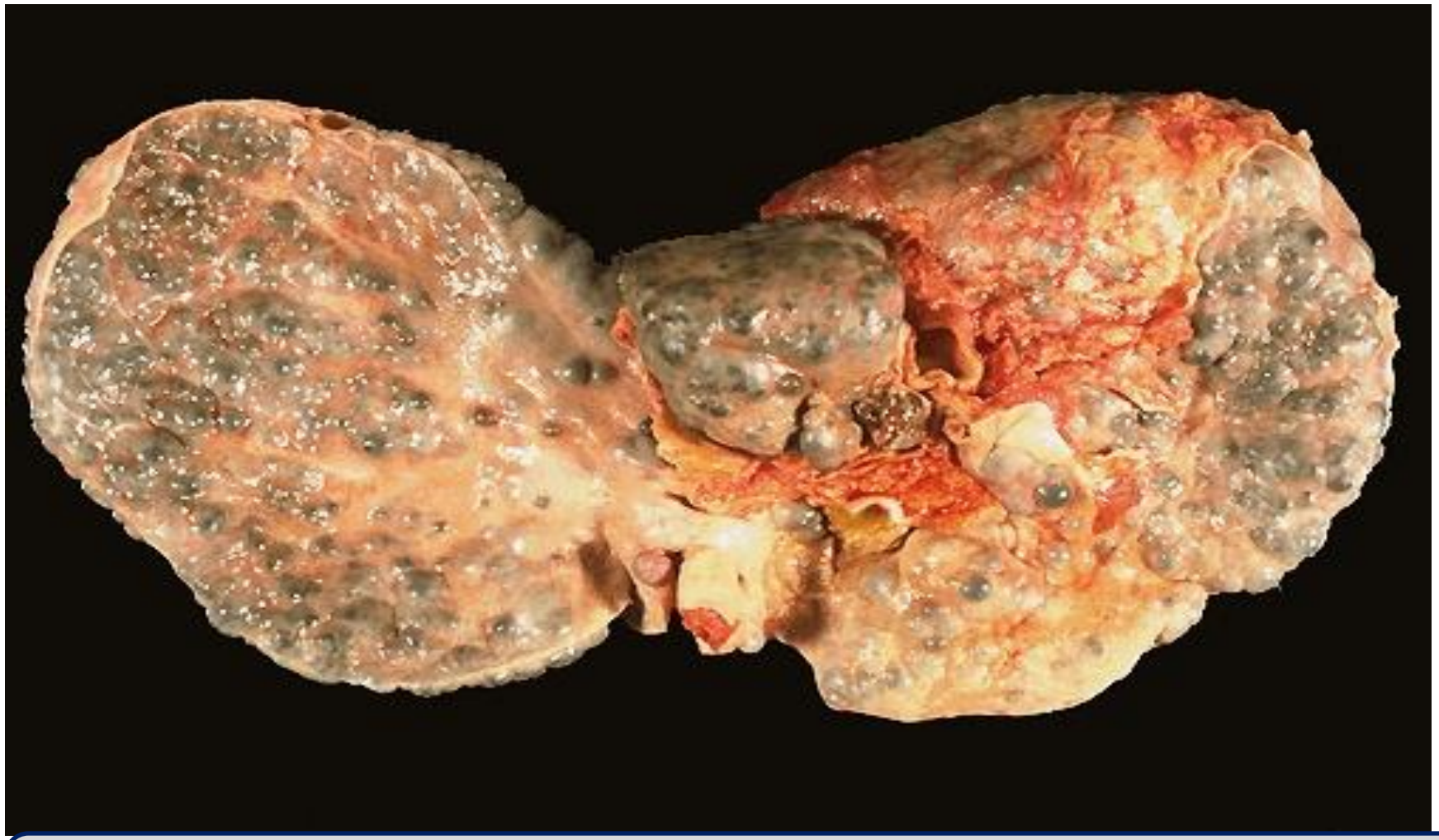
اللهمّ صلّ على سيدنا محمد وعلى آله وصحبه أجمعين

Micronodular cirrhosis



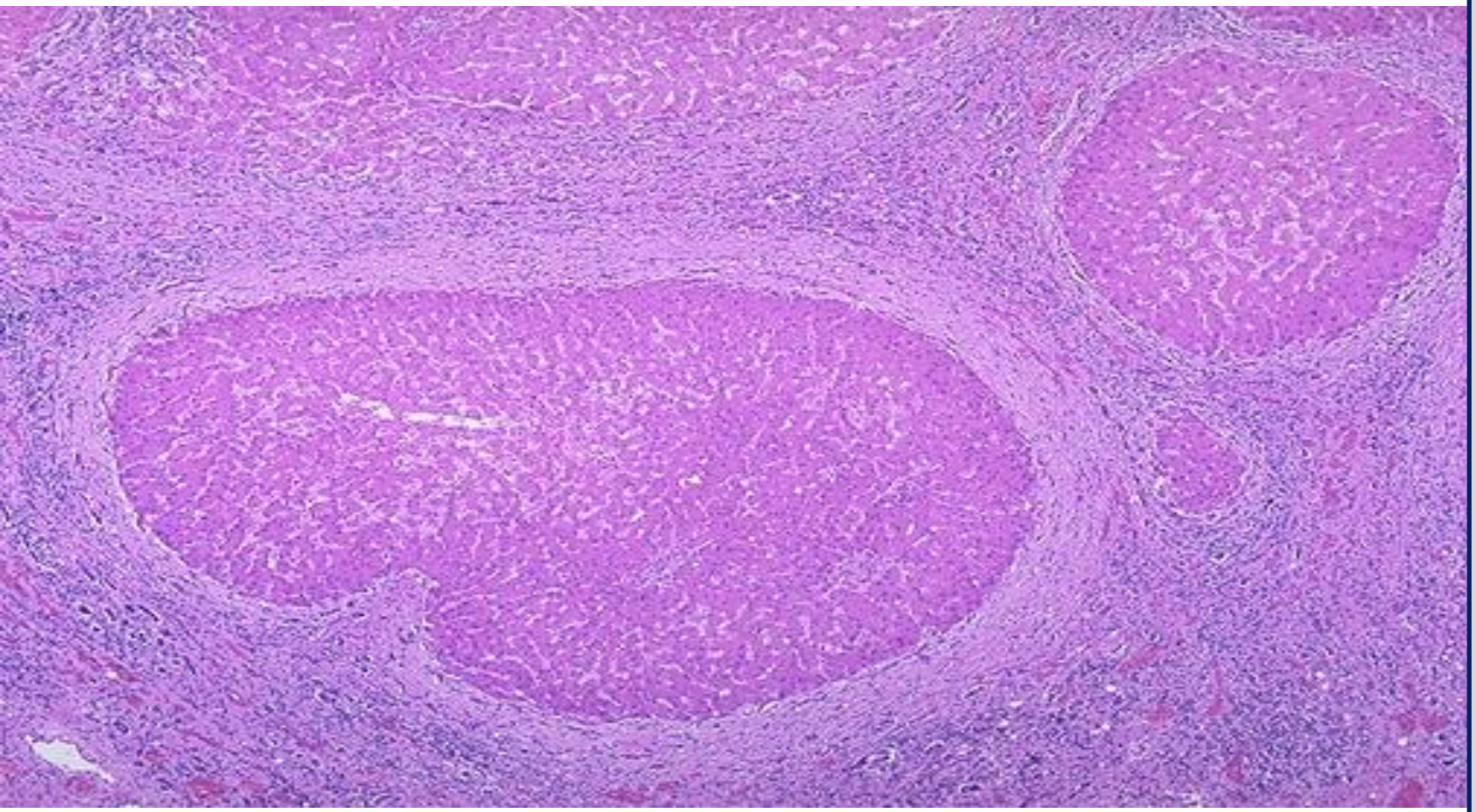
This is a gross appearance to the surface of the liver which shows small diffuesd nodules(INVOLVE ALL THE LIVER)

Macronodular cirrhosis



Macronodular cirrhosis create scarred distorted tissue because of the retraction of fibrous tissue which makes disformity of the liver

Cirrhosis



This is a microscopic appearance of cirrhosis , we have nodules of variable size , composed of regenerative hepatocytes (parenchyma) that is surrounded by fibrous tissue

-Within the fibrous tissue we find blood vessels and inflammatory cells

-If we look at the parenchyma itself , it is regenerative hepatocytes which can carry out some functional hepatocytes , that is why patients with cirrhosis can survive years with normal like function of the liver and they might be asymptomatic because of the function of these nodules

Causes of cirrhosis

If we have seen one of these conditions in the patient we should follow him up

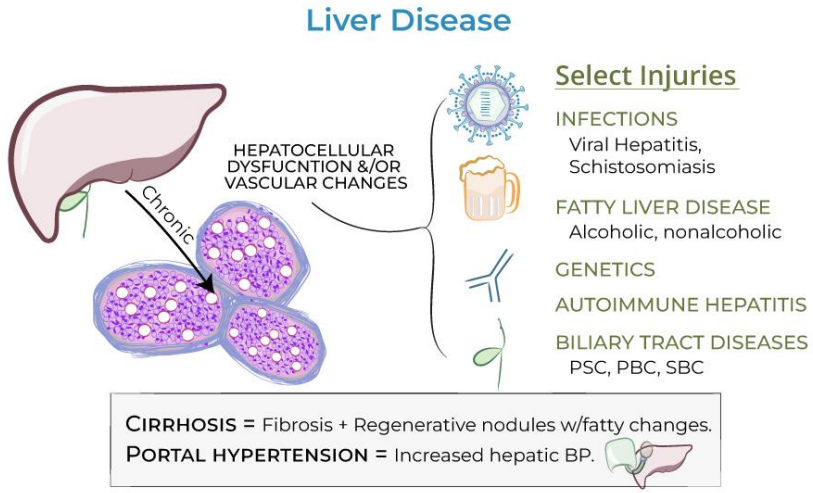
1. **Chronic alcoholism** — The most common cause

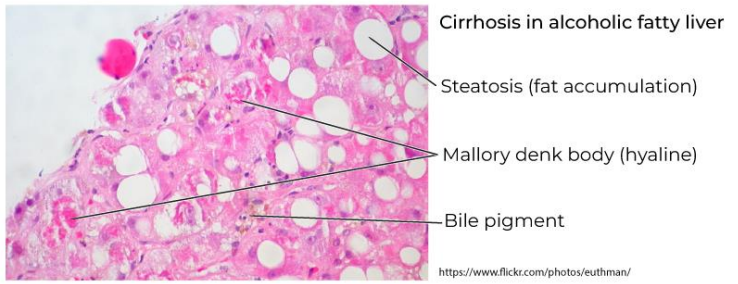
2. **Chronic viral infection HBV & HCV**

3. **Biliary disease** — -When we exclude the first two causes we should think of biliary diseases , certain diseases of the liver primary target biliary system , loss and construction can happen
- Chronic base can produce liver fibrosis because obstruction of biliary system can lead to the damage of surrounding hepatocytes in parenchyma

4. **Hemochromatosis** — Then If we excluded biliary disease , we think of metabolic diseases , and the most common cause here is Hemochromatosis which is characterized by deposition of iron in hepatocytes

Additional picture





5.Autoimmune hepatitis

Autoimmune hepatitis causes changes similar to that in hepatitis (damaging the liver parenchyma) , it is a chronic illness that can progress and give fibrosis

6.Wilson disease

It is also a metabolic disease which is characterized by deposition of copper in hepatocytes

7.α-1- antitrypsin deficiency

Due to enzyme deficiency, even though it is a rare cause but we should consider it if we have cirrhosis

Patients with cirrhosis (fully developed cirrhosis) might show features of cirrhosis not necessarily showing the features of original disease , that is why if the patient was diagnosed by cirrhosis we may not always be able to detect what was the underlaying cause , so for that we should think of these diseases (in previous and coming slides) depending on the patient’s profile ,because some diseases present in early stages while others in older patients

8. Rare causes
   Galactosemia
   Tyrosinosis
Glycogen storage disease III &IV
   Lipid storage disease
   Hereditary fructose intolerance
   Drug induced e.g methyldopa

9. Cryptogenic cirrhosis 10%

-We consider them when all the other causes are excluded
- They are metabolic diseases , inherited ,due to enzyme deficiencies and characterized by deposition of substances within hepatocytes
- Remember any substance(even it is normally stored in the liver) increases in amount of deposition will stimulate cells regeneration and fibrosis

It is important when the patient is presented with manifestations related to certain organs to check the liver , take biopsy and see if the liver is involved

More details in the next slides —>

8. Rare causes

Galactosemia & Hereditary fructose intolerance

Galactose and fructose are disaccharides and there is an enzyme deficiencies (which is responsible for breaking them down) so these disaccharides can't be metabolized , this result in deposition of these materials in hepatocytes

Tyrosinosis

Tyrosine is an amino acid , when it is accumulated due to metabolic problems it will cause damage. Patients with tyrosinosis have increased risk of malignancy even if the disease was controlled

Glycogen storage disease III &IV / Lipid storage disease

These are disease that present early in life , so they are pediatric diseases , they are inherited , characterized by enzyme deficiencies leading to accumulation of glycogen and lipids in different organs

8.Rare causes

Drug induced e.g :methyldopa(drug used in the treatment of hypertension)

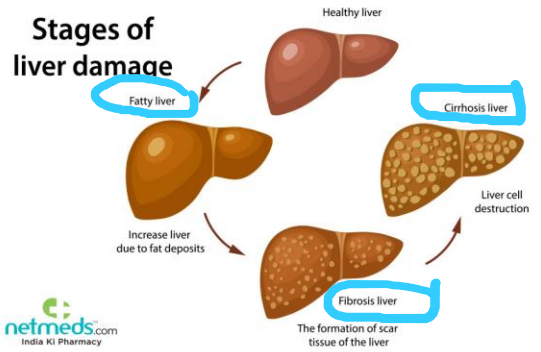
Don’t forget drugs !! Always consider drugs as underlaying cause of liver cirrhosis ,for example --> the chronic use of methyldopa

9. Cryptogenic cirrhosis 10%

When it is difficult to differentiate and know the underlying cause of cirrhosis, then it is cryptogrnic cirrhosis

One of the conditions that later on is recognized as a cause of cirrhosis is non-alcoholic fatty liver disease , related to metabolic problem , in the past we didn’t consider it a cause of cirrhosis because we thought fatty changes and fatty infiltration are harmless and reversible , but now we recognizes that NAFD and fatty changes/infiltration in the liver can induce fibrosis

Additional picture



Pathogenesis of cirrhosis

-The mechanism of cirrhosis involves:

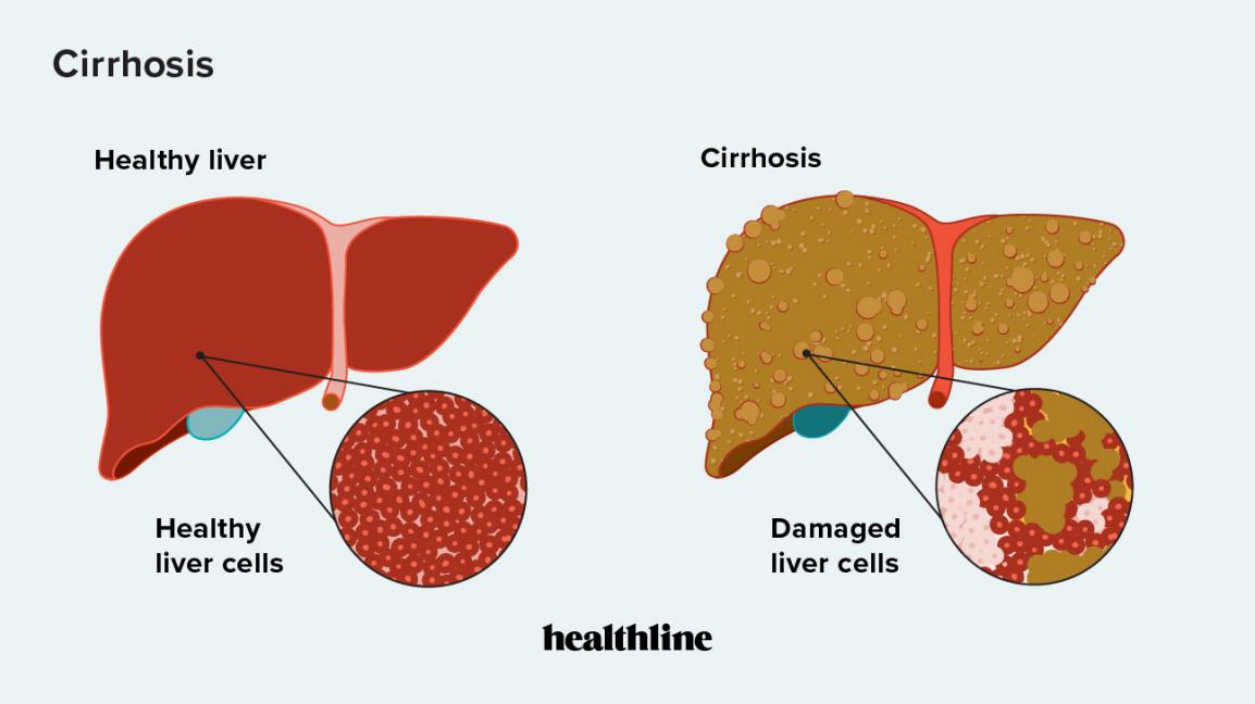
1-Hepatocellular death

2-Regeneration

3-Progressive fibrosis

4-Vascular changes

Additional picture



For details please go to the next slide

In order to have cirrhosis ,we have four requirements :

- Firstly hepatocellular death(or cell damage) , as you would imagine that different diseases which affect the liver can cause hepatocellular damage and cell damage associated with malfunction of hepatocytes and possibility in long term induction of fibrosis
- Secondly Regeneration of hepatocytes " cell damage is followed by cells regeneration " because hepatocytes are regenerative cells and their regeneration capacity is high
- Thirdly ,the regeneration is associated with progressive synthesis of collagen which is part of fibrous tissue , as we said fibrosis in the liver is minimal and can be induced by cells damage .Fibrosis must be in cirrhosis because the nodules are formed by fibrous tissue
- Fourthly , this process of fibrosis is associated with vascular changes and actually the complications of cirrhosis are very related to the development of 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

The Capsule itself is fibrous , it is not related to the function of the liver

Normally in parenchyma there is no fibrous tissue , that is why presentation of collagen in any degree in the parenchyma means always there is problem /cell death

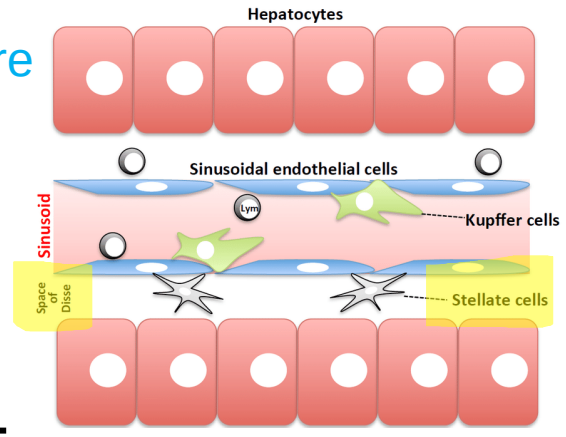
- Actually in the parenchyma there is very thin layer in the basement membrane of collagen type 4 (IV) which is important to hold the cells in the basement membrane . If there is cirrhosis all types of collagen will be everywhere

-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

Space of Disse is the space that connect hepatocytes and sinusoids (which have blood) , hepatocytes should be close to the sinusoids in order to carry it's function so the exchange can occur (the substances that are absorbed from intestines in portal blood should be absorbed by hepatocytes in order to deal with it) or the toxin substance that is resulted from metabolism in hepatocytes should be excreted to the blood .But in cirrhosis when the space of Disse and basement membrane are filled with fibrous tissue these processes will be affected and hepatocytes will be far away from sinsusoids(blood)

Additional picture



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)

Upon disease process they change their function to become cells that produce collagen and start to fill spaces of Disse

Which stimulate the cells to produce fibrous tissue

Any damage effect or inflammatory process in the liver can induce the stimulation of ito cells to become cells that produce collagen

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

1-reactive oxygen species

Which can affect the cells in DNA and protein synthesis , causing damage to hepatocytes

2-Growth factors

Include fibrinogen growth factor

3-cytokines TNF, IL-I, lymphotoxins

So when we have disease process we have injury followed by the releasing of these factors to increase synthesis of fibrous tissue leading to the change in agriculture

Fibrosis(bridging fibrosis) ->increase amount of laying down collagen in the parenchyma -> forming nodules

-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

It will reduce the surface area and lower the efficiency of exchange

Important consequence of laying down the fibrous tissue is vascular problems, when the fibrous tissue start to surround the vessels and it is hard tissue not elastic and produce some pressure and rigidity on the vessel's wall , that will create some difficulty in blood flow so the vessels will try to compensate for these difficulties (slowing blood flow)by creating shunts that connect the arterial and venous circulation so :

Portal vein –hepatic vein shunt and hepatic artery –portal vein shunt

This means that the circulation and flow of blood in the liver is altered and the function is affected (the normal =blood come through sinuses ,exchange and interact with hepatocytes and then leave the liver through central vein and hepatic vein)

- 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.

-Clinical features of cirrhosis :

-Silent

-Anorexia, wt loss, weakness

-Complications :

1-Progressive hepatic failure

2-Portal hypertension

3-Hepatocellular carcinoma

The nodules (regenerative hepatocytes) for some time it will carry the function so patients can have a period without serious manifestations until the hepatocytes overloaded and can't stand the conditions and can't increase the functional capacity , in this stage the patient will start to have non specific clinical manifestations ,later on the patient will develop significant clinical manifestation related to progressive hepatic failure (liver failure) & portal hypertension and increase in the blood pressure of the veins (leading to shunts) ,the heigh BP of arterial circulation will be reflected in low pressure in portal circulation &increase the risk of developing malignancy in parenchyma , the patient who don't suffer from anything , once he develop tumors he will start to have manifestations of malignancy and the health will be lower than normal

Portal hypertension

What is portal hypertension?
It is increase in portal tension due to

- ↑ increase resistance to portal blood flow at the level of sinusoids & compression of central veins by perivenular fibrosis & parenchymal nodules

This will lead to open channels (Anastomosis) between portal and arterial system, in the fibrous bands, to direct blood in to less resistance pathways, However it is not enough, and the pressusre will increase and result in manifestation

- 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

The common cause of portal hypertension is liver cirrhosis. However it could result from other less common causes devided in three categories:

I.Prehepatic

1-Portal vein thrombosis
2-Massive splenomegaly

Related to portal vein.
Recall there is a blood circulation between spleen the portal vein any problem in spleen could affect the portal vein

II. Post hepatic

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

Related to liver venous drainage.
In right-sided heart failure, the pump's right side weakens, causing blood to back up into the liver through IVC → Central vein → portal vein causing blood congestion.

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

Related to the liver structure , architecture and consistency
Schistosomiasis (bilharzia) which will cause severe fibrosis

Clinical consequence of portal hypertension

1-Ascitis

2-Portosystemic shunts

3-Hepatic encephalopathy

4-Splenomegaly

Neurological manifestion

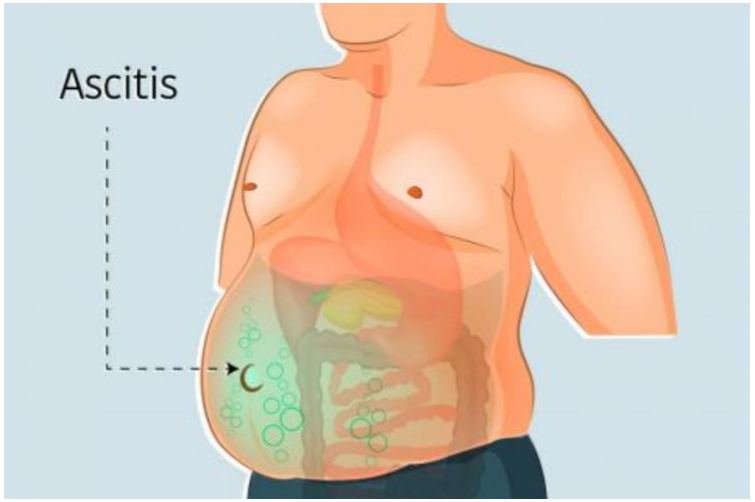
Hepatic encephalopathy is a condition where the liver, which usually filters toxins from the blood, can’t work properly. As a result, harmful substances build up in the blood and affect the brain, leading to problems with thinking, behavior, and consciousness.

Ascitis

-Collection of excess fluid in peritoneal(abdominal)cavity

-It becomes clinically detectable when at least 500 ml have accumulated

The accumulation of fluids in abdominal cavity will cause abdominal destintion in real life patients come with liters of fluids have been accumulated additional image
This accumulation of fluids will lead to pressure on the organs , so it should be aspirated to relief and avoid the complications



Ascitis

-**Features**

-Features of the accumulated fluid(examination of the aspirated fluid

1-Serous fluid

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

Low in the protien

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

4-Mesothelial cells & lymphocytes

Mesothelial cells are normally lining the cavity

5-Neutrophils = infection

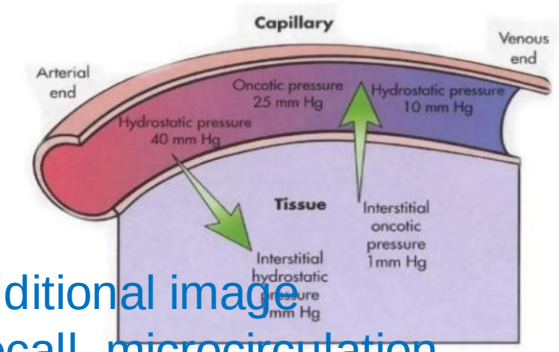
The presence of PMN indicates an infection

6-RBCs = DISSEMINATED CANCR

The presence of RBC indicates the possibility of tumours

Pathogenesis

How ascitis happens(mechanism)?



Additional image
Recall microcirculation

1-Sinusoidal ↑ Bp

The high pressure will push the fluids outside the the vessels causing leakage of fluids to the surface of the liver accumulated in the abdomenal cavity

2-Hypoalbuminemia

Major mechanism : patient already has Low albumin concentration in blood and liver leading to fluid leakage

3-Leakage of hepatic lymph into the peritoneal cavity

Normal thoracic duct lymph flow is 800-1000 ml/d in cirrhosis is 20L /d

leakage could happen in the lymphatic not only in the vesicular, thoracic duct shunt from the liver and pass through the abdomin. the flow of thoracic duct is high however when it decreases the fluid accumulates

Additional :The thoracic duct plays a significant role in draining excess fluid and proteins from tissues, including the abdominal cavity, back into the bloodstream.

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

This will increase the hydrostatic pressure pushing the fluids out of the vesseles

aldoessterone→ re-absorption of Na+ → water follows salt → increase the hydrostatic pressure

Clinical consequence of portal hypertension 2

Portosystemic shunt

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

-Sites: Where these shunts could occur:

1-Around & within the rectum (Hemorrhoids)

These shunts starts to dilate and get tortuous .Not all patients who have hemorroids have cirrhosis, however Pts who have cirrhosis ,develop hemorrhoids. NO serious bleeding

2-Gastroesophageal junction (varicies)

Dilated vesseles in the mucosa of the proximal part of the stomach , and it is very important site which can bleed easily , life threatening

3-Retroperitoneum

Not easily bleeding and we can't see it because it's site

4-Falciform ligament of the liver (periumbilical & abdominal wall collaterals) → caput medusae

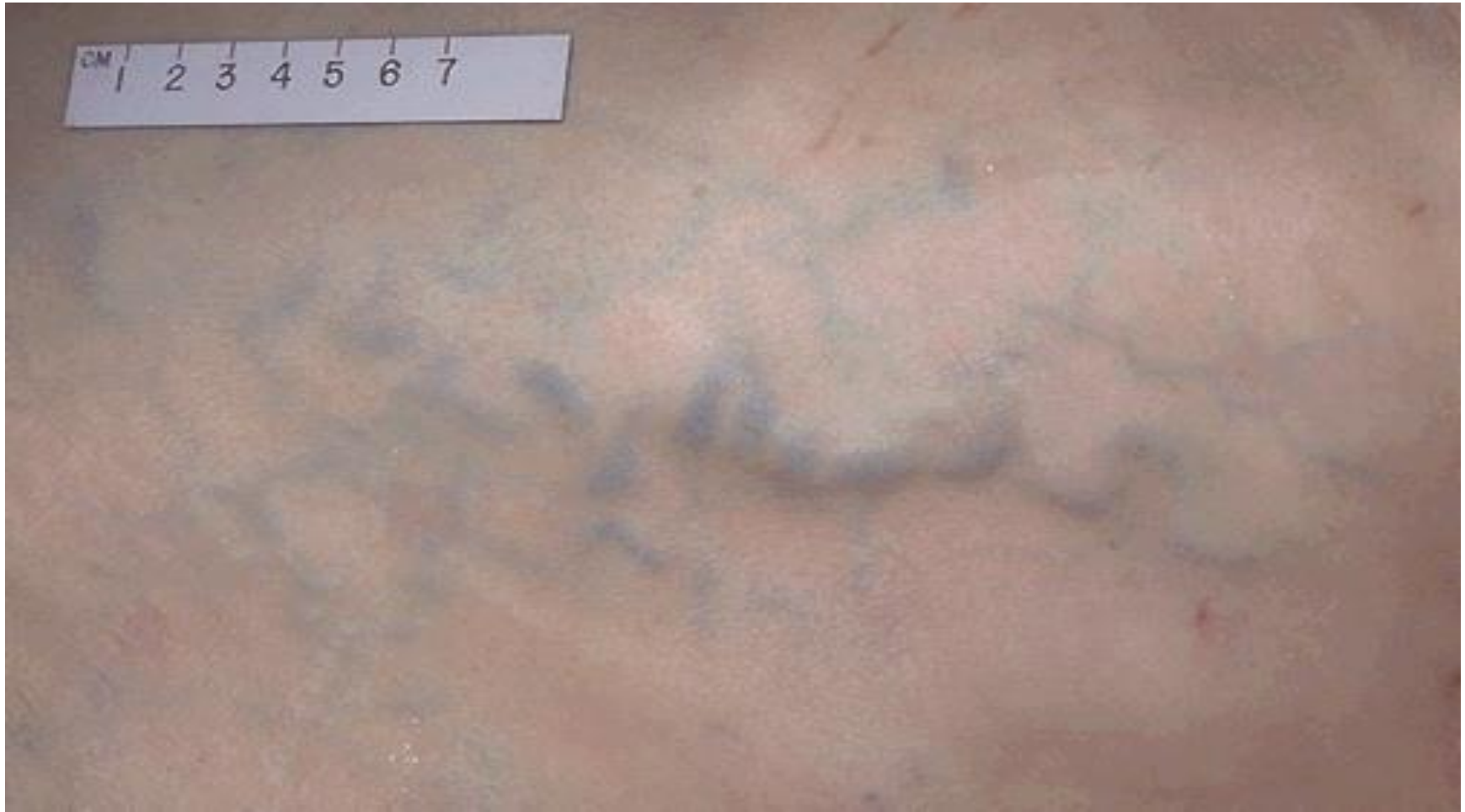
Carput medusaeis dilated tortuous vessels aroud the umbilicus

- Gastroesophageal varicies appear in 65% of pts. with advanced cirrhosis & cause death in 50% of then due to UG1 bleeding

caput medusae

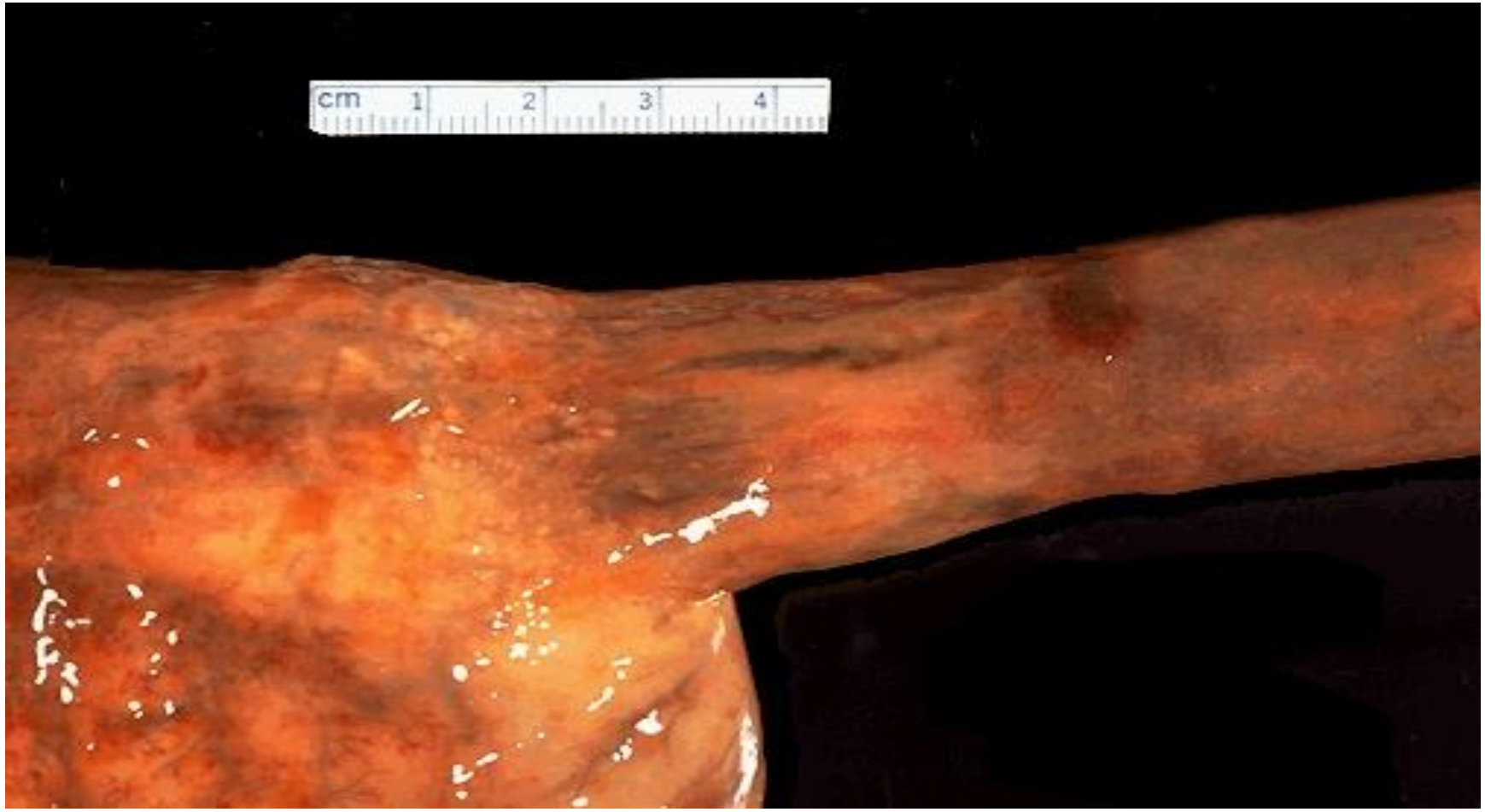
In the anterior abdominal wall

Veins here like veins in varicose disease



Esophageal varicies

- It can cause liver failure



Clinical consequence of portal hypertension 3

Splenomegaly

Increasing in the size of the spleen , due the redirection of circulation into spleen , increasing in the blood flow to spleen , so the spleen get inlarged and fill with blood ,

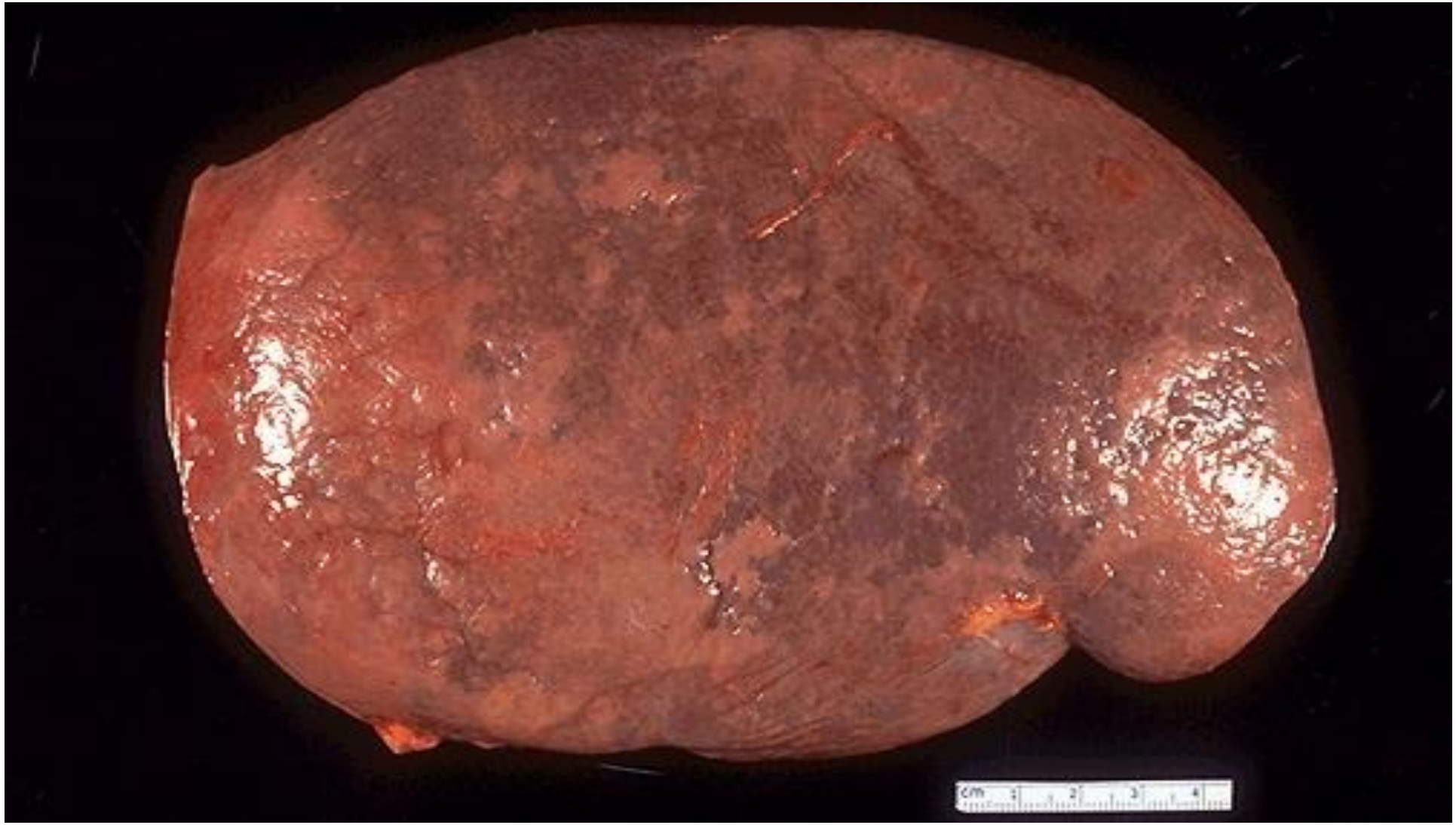
-Usually 500-1000 gms (N <300gms)

-Not necessarily correlated with other features of portal ↑Bp

-May result in hypersplenism

Very important outcome of splenomegaly developping of hypersplenism,
The normal function of spleen is to destruct abnormal and aged blood cells and remove them from the circulation, hypersplenism will accelerate that function, so the patient will suffer from decline in cellular blood components (WBC ,RBC ,platelets) which is termed as "pancytopenia", increasing bleeding tendency , infections and developing anemia

Splenomegaly



Clinical consequence of portal hypertension 4

Hepatic encephalopthy

In advanced stages patient would develop neurological manifestations due to the increase of ammonia concentration in the blood which can cross BBB affecting brain causing edema which increases the pressure on the brain leading to decrease of consciousness, coma .... Depending on the site of pressure

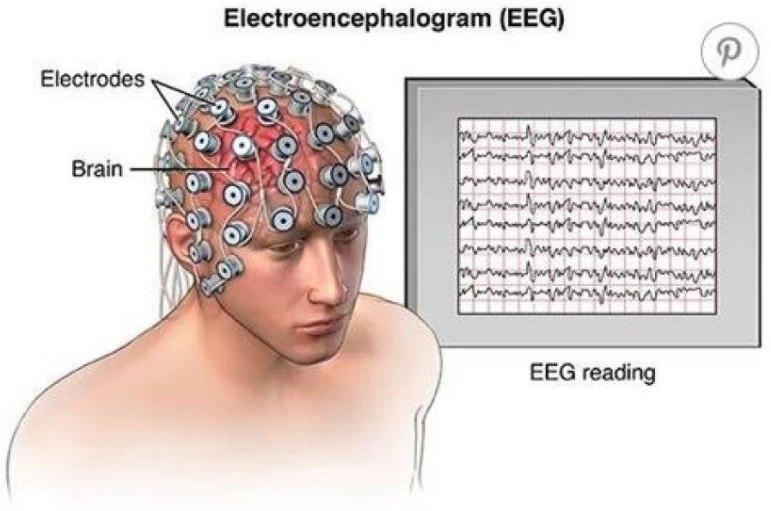
-It is a complication of acute & chronic hepatic failure

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

-The changes may progress over hrs. or days

It is serious condition may indicate late stages of liver cirrhosis

Neurological signs:



Rigidity

Hyper-reflexia

Non – specific EEG

Seizures

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

-Brain shows edema & 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

- **↑ NH3 level in blood → generalized brain edema impaired neuronal function**
- **alteration in central nervous system AA metabolism**

وكما قالوا «النَّعيم لا يُدرَك بالنَّعيم» .. وقال ابن القيّم «الكمالات كلها لا تُنال إلا بحظٍ من المشقة، ولا يُعبَر إليها إلا على جسرٍ من التّعب» لذلك يا رِفاق، هي حياة واحدة، ولحظاتها معدودة، وإنّما يمتَدّ عُمر الإنسان بإحسانه، و عُمر الواحد منّا عَمَلُه، فأحسنوا