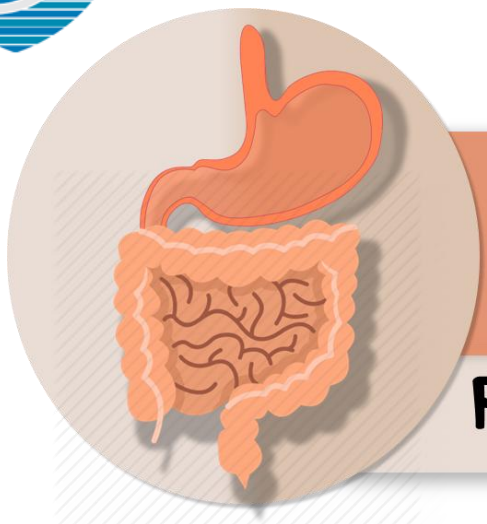

# GI system

## Pathology

◉ Sheet ○ Slide

| | |
|---|---|
| Number: | 2 |
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Note: It's preferable to study the slides in my opinion since the doctor mostly reads them and doesn't add any new information, you'll notice similarity in this sheet between the slides and the things written, this is due to the doctor skipping some slides and reading some points instead of the others (I think everything is required even if she doesn't mention it)

## Alcoholic Liver Cirrhosis

Alcoholic liver cirrhosis is a slowly developing disease which takes time to occur in people who ingest alcohol. However, It may develop rapidly if the person ingesting alcohol already has a present condition of alcoholic hepatitis (Occurs within 1-2 years).

This is a liver which shows the difference between a normal and a cirrhotic liver, each nodule is formed by parenchyma (the surface) surrounded by fibrous tissue.

Ethanol in the liver is transformed into acetyl aldehyde by an enzyme. The outcome and duration of the metabolism depends on the activity of

those enzymes, these enzymes , Acetyl Dehydrogenase, are not only present in the liver, they're also found in the stomach, that’s why ethanol metabolism starts in the stomach, other enzymes are also involved in diagnosis .

After absorption of ethanol, it's distributed in the tissues in the form of Acetic acid by the action of Aldehyde dehydrogenase , the level of acetic acid in blood is the same as that in the tissue.

Women are more prone to having a higher blood level of acetic acid due to the fact that they have a lower level of alcohol dehydrogenase activity.

A small amount (less than 10%) of the ingested ethanol is excreted unchanged in urine, sweat and breath.

Alcohol metabolism is also affected by the genetic makeup of the individual due to genetic polymorphism in alcohol dehydrogenase enzyme genes, for instance, Asians have a lowered enzyme activity due to a point mutation to the enzyme's genes, that’s why they're more likely to show signs of hyperventilation, tachycardia and facial flushing after ethanol ingestion.

- Clinical features of Alcoholic cirrhosis:

The manifestations of this disease are non-specific, such as malaise and weakness. However, if we do a liver function test, for bilirubin and enzymes, we will notice an increase in hepatic enzymes in the blood due to increased hepatic toxicity and hepatic enzyme release.

Patients might also have increased liver and spleen size due to this disease, also they might manifest with cirrhosis which will eventually lead to portal hypertension.

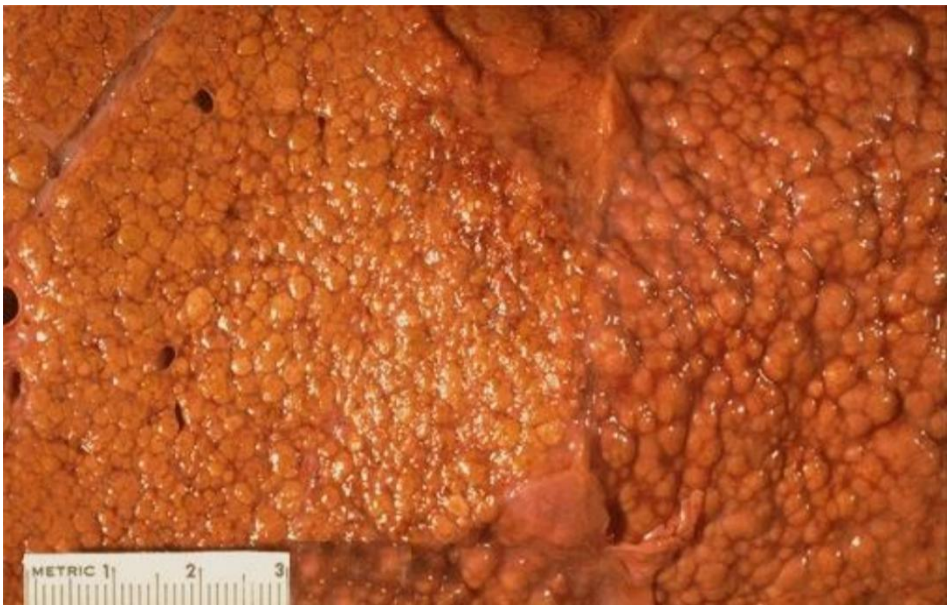
- Causes of death in Alcoholic Liver disease:
  1- Hepatic Failure
  2- Massive GI bleeding due to portal hypertension
  3- Infection
  4- Hepatorenal syndrome: organ failure in other places, kidney for instance.

5- Hepatocellular carcinoma

**Cirrhosis:**

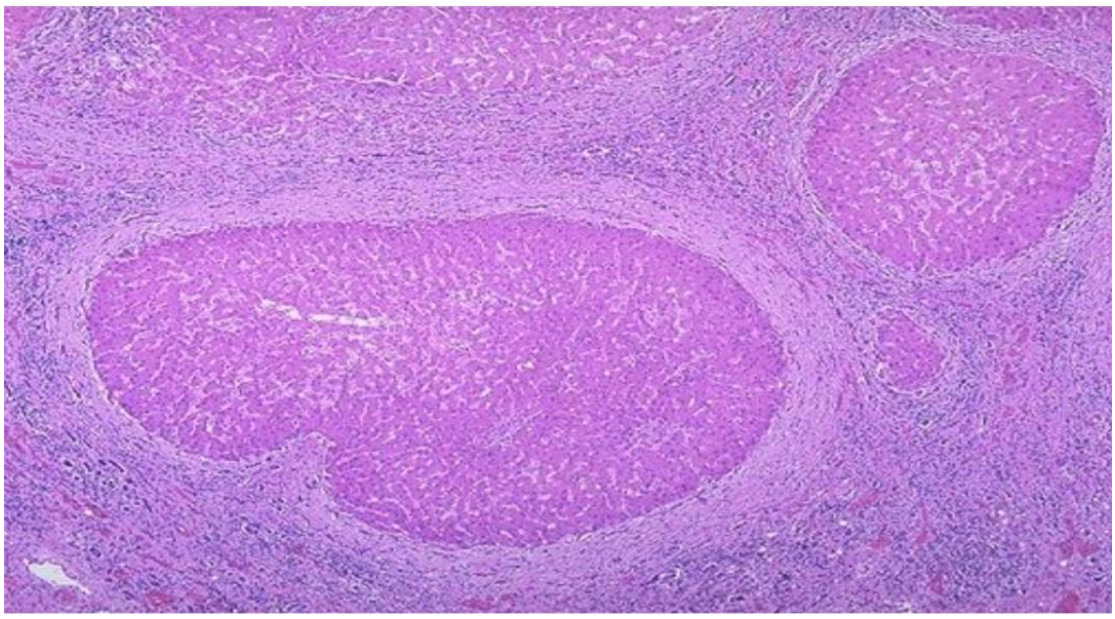
A very important disease in the liver, usually is the end result of many liver diseases, it's described as a diffuse process, cirrhosis can't involve only a part of the liver, it must involve the entire liver to be diagnosed as cirrhosis, also fibrosis must encircle the entire nodules, partially encircled and not diffused nodules mean that this is a *pre-cirrhotic* stage.

- Macronodules > 3mm in diameter
- Micronodules < 3mm in diameter




As we can notice in the picture the nodules are diffuse in the entire liver, and the fibrous tissue is diffused and completely surrounding the nodules=*cirrhosis*

Initially the liver is enlarged in cirrhosis, but with expansion of fibrous tissue it will shink, causing shrinkage of the liver as we can notice in the histological picture below (presence of fibrous tissue)



## Causes of cirrhosis

1.Chronic alcoholism

2.Chronic viral infection HBV & HCV

3.Biliary disease

4.Hemochromatosis (increase deposition of iron)

5.Autoimmune hepatitis

6.Wilson disease (increase deposition of copper)

7.α-1- antitrypsin deficiency

8. Rare causes: (Metabolic diseases)

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

9. Cryptogenic cirrhosis 10%

## Pathogenesis of liver Cirrhosis:

First manifestation of liver cirrhosis is the occurrence of hepatocellular damage, this could be caused by toxicity or any other cause of the ones mentioned earlier, which will trigger the repair mechanism in the liver and with recurrent hepatocellular damage, fibrosis will occur and this

will eventually lead to liver cirrhosis, because of increased collagen production, with vascular changes included.

Liver damage is associated with production of fibrous tissue, fibrous tissue in the liver is present in different forms, like type 1, 3 and 5 collagen, it's mainly present in the basement membrane, portal areas, and surrounding central veins. The parenchyma itself is present within the basement membrane where the hepatocytes rest.

Type 4 collagen is very important, it's mainly present in the basement membrane, it's reduced in the space of disse, this space is very important, the basement membrane itself should be fit to allow the space of disse to exist. However, increased amount of collagen in the basement membrane this will cause the decrease of space in the space of disse, which will lead to negative effects on the function on hepatocytes, like making the exchange of materials between blood and hepatocytes more difficult.

Ischaemia is associated with death of cells, if this death of cells is followed by the infiltration of inflammatory mediators, such as growth factors, if fibrogenic growth factor is present among those mediators, it will stimulate the cells which are normally present, to activate them to start fibrous tissue formation. Normally those Fibrous tissue producing cells are used for storage of Vitamin A and fat, but in incidence of liver damage they're stimulated by growth factors ( Fibrogenic growth factors) to produce fibrous tissue in the liver.

**-Factors that influence fibrous tissue production:**

1- Reactive oxygen species

2- Growth factors

3- Cytokines and Inflammatory mediators.

Other changes associated with liver cirrhosis, is vascular changes, since fibrous tissue is being deposited around blood vessels, this will decrease the elasticity of the blood vessels, elasticity is needed to allow the circulation of blood to leave the sinusoids, so this will cause a decrease of blood flow in the liver. This will cause the development of shunts (opening of connection between the portal vein with hepatic vein or

hepatic artery with portal vein) to allowed the fluids to find a less resistant pathway and avoid resistance.

This is very important since bold vessels are important for the function.

The connection between the arteries and veins is very bad and this is because of the much higher pressure in arteries and veins , this wil create portal hyprtension.

Also, because the hepatocytes mainly exchange materials with blood through their surface micro-villi, and the decreased elasticity and increased pressure will cause destruction of those micro-villi, which causes a decreased ability in the exchange of materials between the blood and hepatocytes.

**-Clinical features of cirrhosis :**

-Silent: A patient might live for years without knowing of their cirrhosis because of the non-specific symptoms

-Anorexia, wt loss, weakness

**-Complications :**

1-Progressive hepatic failure

2-Portal hypertension: This will cause the suffering of blood vessels and resistance of blood vessels. And the flow starts going against resistance which will also assist the creation of anastomosis in the blood vessels.

3-Hepatocellular carcinoma

## Portal Hypertension:

Normally the portal blood pressure is very low. However, when the fibrosis develops and when the vessels are surrounded by fibrous tissue, it becomes non-elastic, so the only way to adapt to these changes is by increasing the blood pressure, and also anastomosis will occur between

the arteries and veins which will also increase the blood pressure in the veins.

Portal hypertension is a condition which may be cause mainly by liver cirrhosis, but there are also other reasons which are extra-hepatic and are not related to it. The most common cause is Cirrhosis.

**Outcomes of portal hypertension:**

**1- Ascitis**

**2- Porto-systemic shunts**

**3- Hepatic encephalopathy**

**4- Splenomegaly**

## Ascitis:

Presence of fluid in the peritoneal cavity. Normally, there is a little amount of fluid in the peritoneal cavity but with ascitis it's increased.

It becomes clinically detectable when at least 500 ml have accumulated, but most patients attend clinics when there are litres of fluids in the peritoneal cavity

**Characteristics of the fluid:**

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 & lymphocytes

5-Neutrophils = infection

6-RBCs = DISSEMINATED CANCR

**Pathogenesis:**

1-Sinusoidal ↑ Bp

2-Hypoalbuminemia: which causes fluid edema, so the fluid is pushed out of the blood vessels into the abdominal cavity

3-Leakage of hepatic lymph into the peritoneal cavity Normal thoracic duct lymph flow is 800- 1000 ml/d in cirrhosis is 20L /d

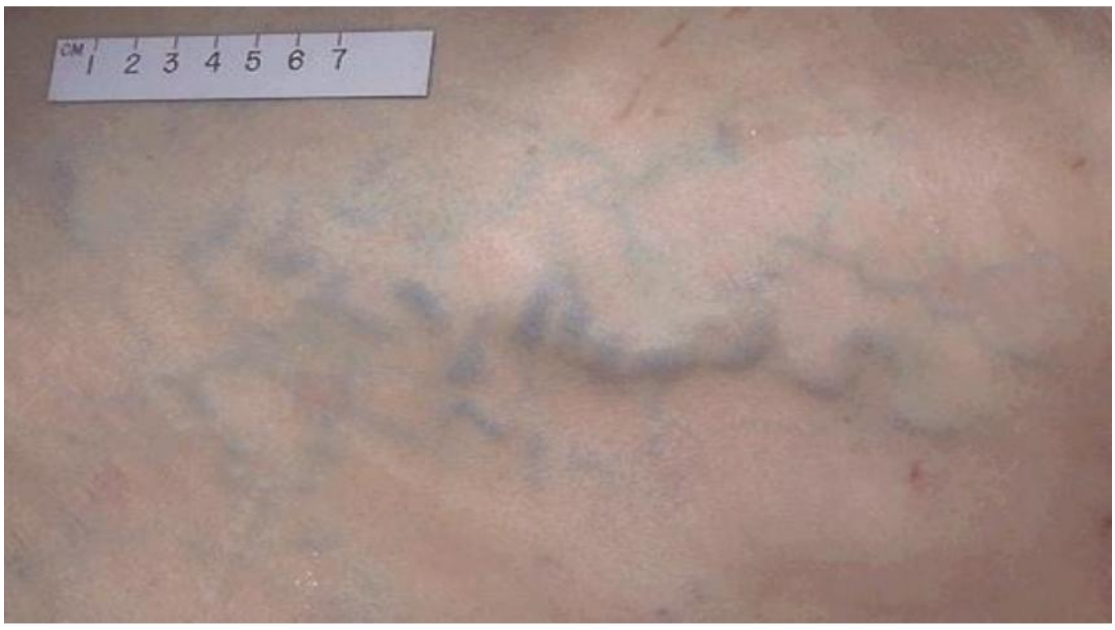
4-Renal retention of Na+ & water due to hyperaldosteronism

## Porto-systemic Shunts:

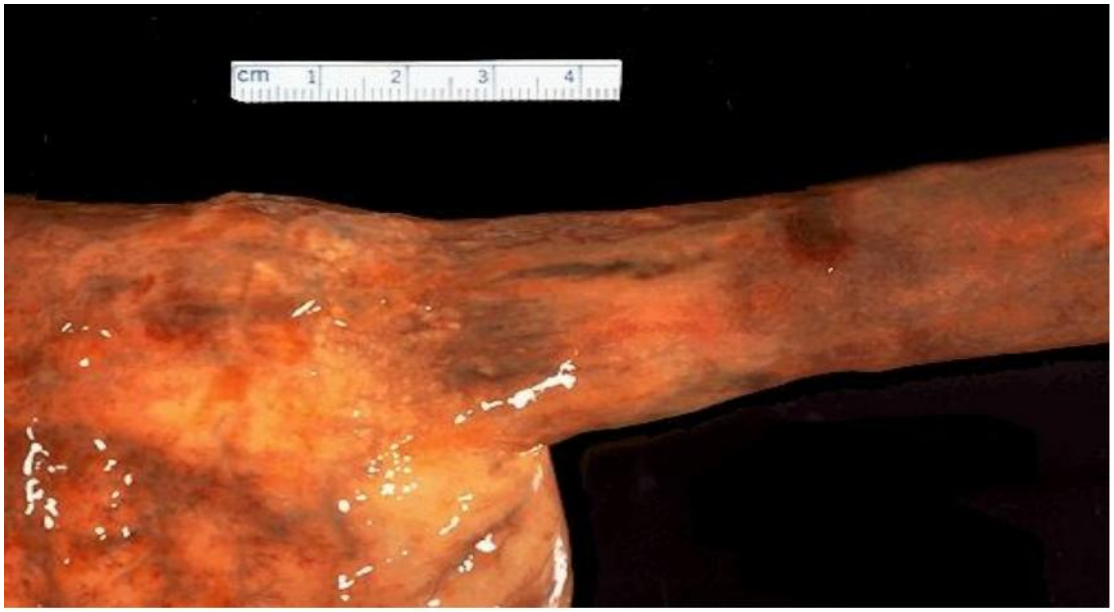
These shunts in certain sides of the body are very important, classically around rectum, but dilation of these shunts cause haemorrhoids, another important site is around the fundus of the stomach, and these cause gastroesophegeal varices, also around the umbilicus and they're evident around the anterior abdominal wall as caput medosum.

Varices appear as tortious dilated blood vessels, which can rupture easily.

Patients with liver cirrhosis mainly develop upper gastrointestinal varices which is the main cause of their death.




This picture shows Caput medusae, which is the varices of umbilical veins, medusae as in reference to medusa's head (a mythological creature)




This picture shows Esophageal varices in the upper Gastrointestinal tract.

**Splenomegaly:**

Spleen is connected to the liver through venous drainage, the spleen weight is normally less than 300grams, but in these patients it's enlarged to become 500-1000grams in weight. This makes it an easily ruptured organ, it also contains red blood cells, which causes severe bleeding.

It also may cause Hypersplenisim, what does this mean, the main function of the spleen is to remove damaged blood cells from the circulation. However, because blood is stagnant in the spleen this function is lost. It will cause anaemia leukopenia and other conditions.

## Hepatic Encephalopathy:

It's the exposure of the brain to toxic substances such as ammonia, because it's capable of crossing the blood brain barrier, and it can affect the brain and cause damage to the neurons, which will correspond as behavioural changes in the patient.

**Neurological manifestations:**

Totally the brain is normal, there aren't any signs of inflammation or any other microscopic changes, the only thing that induces these manifestations is the edema, which causes pressure on the neurons which will induce loss of normal functions.

## Drug – Induced liver disease:

Drugs affect the liver because they're metabolised in the liver, the effect of the drug on the liver is one of two:

1- Predictable: we predict the effect of the drug on the liver will cause damage over the long term use. (Dose-dependent)

2- Unpredictable: Patient respond to the drug with drug damage even if it's the first dose. (Dose-independent)

The injury depends on the type of the drug, it might take a long time to occur or it may be immediate.

**Example of drugs the affect the liver:**

**Predictable drugs:**

Acetaminophen

Tetracycline

Antineoplastic agents

CCL4 / Alcohol

**Unpredictable drugs:**

Chlorpromazine

Halothane: the doctor said she had spoken about these drugs earlier and that they cause damaging effect on the first occurrence of drug intake.

Sulfonamides

Methyldopa

Allopurinol

**-Mechanism of drug injury :**

**1-Direct toxic damage**

e.g acetaminophen, CCl4, mushroom toxins

**2-Immune-mediated damage:** Drugs are known to cause antigenic changes, certain drugs can attach themselves to the a protein present on the surface changing the antigenicity of the cell this will stimulate the immune response, which will attack the hepatocytes causing their damage. (These drugs are called Hapters)

-Patterns of injury

1-Hepatocellular necrosis

2-Cholestasis

3-Steatosis

4-Steatohepatitis

5-Fibrosis

6-Vascular lesions

7-Granuloma

8-Neoplasms benign & malignant

**Drugs that may cause acute liver failure**

1-acetaminophen most common

2-Halothane

3-antituberculosis drugs (rifampin, isoniazid)

4-antidepressant monoamine oxidase inhibitors

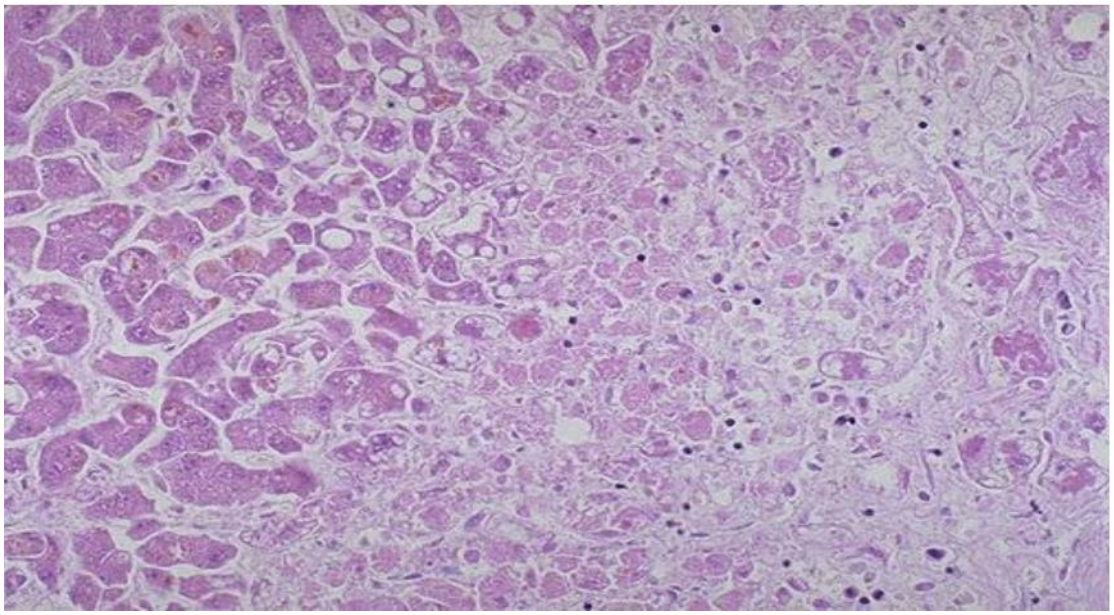
5-toxins as CCL4 & mushroom poisoning

**Morpholagy:**

Massive necrosis → 500 – 700 gm liver

Submassive necrosis

Patchy necrosis



This is  a cross section containing necrotic and normal hepatocytes, the necrotic cells are on the right side of the picture ( the transparent cells )

“Let’s practice some Medicine :)” - The medic (T.F.2)