Pathology

Doctor 2017 | Medicine | JU | GI

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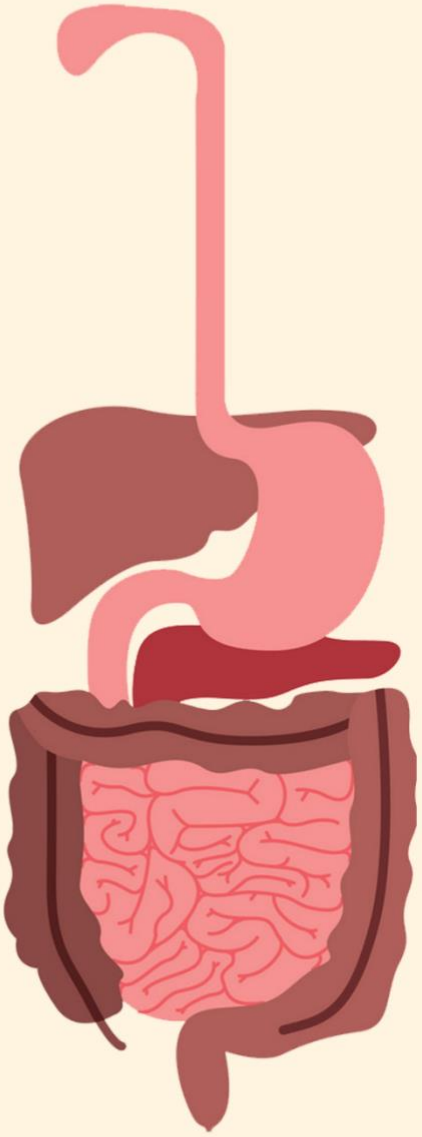


2nd system - GI

In the last lecture we started talking about alcoholic liver disease, which has 3 manifestations:

Hepatic steatosis (90-100% of drinkers), Alcoholic hepatitis (1- 35% of drinkers), Cirrhosis (14% of drinkers).

In this sheet, we will talk about:

- Ethanol metabolism -Pathologic changes related to alcoholic liver disease
- Alcoholic hepatitis -Cirrhosis

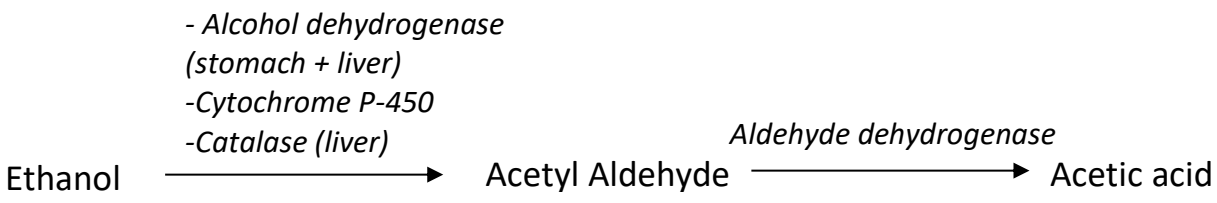
Ethanol metabolism

1) Ethanol in the liver is transformed into acetyl aldehyde by alcohol dehydrogenase. The enzyme's not only present in the liver, it is also found in the stomach, therefore ethanol metabolism actually starts in the stomach.
2) After absorption of ethanol, it's distributed in the tissues in the form of acetic acid.
3) The level of acetic acid in blood is proportional to that in the tissue.
4) A small amount (less than 10%) of the ingested ethanol is excreted unchanged in urine, sweat and breath.

⇨ The outcome and duration of alcohol metabolism depends on the activity of alcohol dehydrogenase, aldehyde Dehydrogenase, and other enzymes.

⇨ Females are more prone to having a higher blood level of acetic acid (higher toxicity) than males for the same amount of ethanol due to the fact that they have a lower level gastric alcohol dehydrogenase.

⇨ Alcohol metabolism is also affected by the genetic makeup of the individual due to genetic polymorphism in aldehyde 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.



Pathological changes related to Ethanol

A) Ethanol leads to ***Fat infiltration***, which happens due to:

- *Alteration in metabolism of fatty acids in many pathways. All of them end up with increasing free fatty acids availability in the blood. Fatty acids start to infiltrate to different organs, primarily the liver.*
- *Shunting toward free fatty acids synthesis and decreasing lipoprotein level in the blood (liver injury leads to less excretion of fat from liver > leads to accumulation of fat in liver > more steatosis).*
- *Releasing of free fatty acids into the circulation from peripheral storage sites, because they are activated.*
- *Decreasing the utilization of free fatty acids in the tissues, due to mitochondria malfunction.*

B) ***Inflammation***, which involves:

- *Inflammatory cells infiltration*
- *Releasing of mediators and reactive oxygen species (ROS)*
- *More damage to hepatocytes and causing injury.*
- *Changes in the antigenicity of hepatocytes due to chronic exposure to toxic substances;* OUR CELLS NORMALLY DON'T HAVE ANTIGENS THAT CAN BE RECOGNIZED BY IMMUNE CELLS TO BE DESTROYED. ONCE THE ANTIGENECITY OF HEPATOCYTES IS CHANGED, THE IMMUNE CELLS ARE ACTIVATED TO ATTACK THEM.

C) ***Alterations in drugs detoxification*** due to ethanol requiring the same enzymes as the drugs. Therefore, the higher the amount of ethanol or drug, the less the other is metabolized/detoxified.

D) ***Hypoxia*** at the cellular level, so *increasing the* ***damage***.

E) ***Non-specific manifestations*** such as *malaise, chronic fatigue and weight loss.*

F) ***Increasing*** *the release of* ***hepatic enzymes*** (transaminases) so alcoholic liver disease can be detected by liver function test.

G) ***Increased size*** *of liver and spleen*.

H) *Increasing the probability of* ***Superinfection*** *with hepatitis C virus.*

I) ***Developing cirrhosis*** which will leads to portal hypertension.

J) ***Decreasing in liver size in very late stage of the disease***, because the diffuse fibrous tissue in the liver will shrink.

Causes of death in Alcoholic Liver disease:

- Hepatic Failure
- Massive GI bleeding due to clotting factors deficiency. A classical presentation in cirrhosis patients is upper GI bleeding.
- Infection
- Hepatorenal syndrome: organ failure in other places, kidney for instance.
- Hepatocellular carcinoma: in 3-6% of cases. Mostly happens due to cirrhosis, and it might cause liver failure.

Clinical features for alcoholic liver disease:

a- Hepatic steatosis (reversible):
Increased Liver size and liver enzymes, severe hepatic dysfunction is unusual.

b- Alcoholic hepatitis:
- Happens after 15-20 years of excessive drinking.
- Non-specific symptoms such as malaise, anorexia, weight loss, increased Liver & spleen size, high LFT (liver function test).
- 10-20% of patients are at risk of death, 1/3 of patients develop cirrhosis in few years.

c- Cirrhosis:
Portal hypertension.

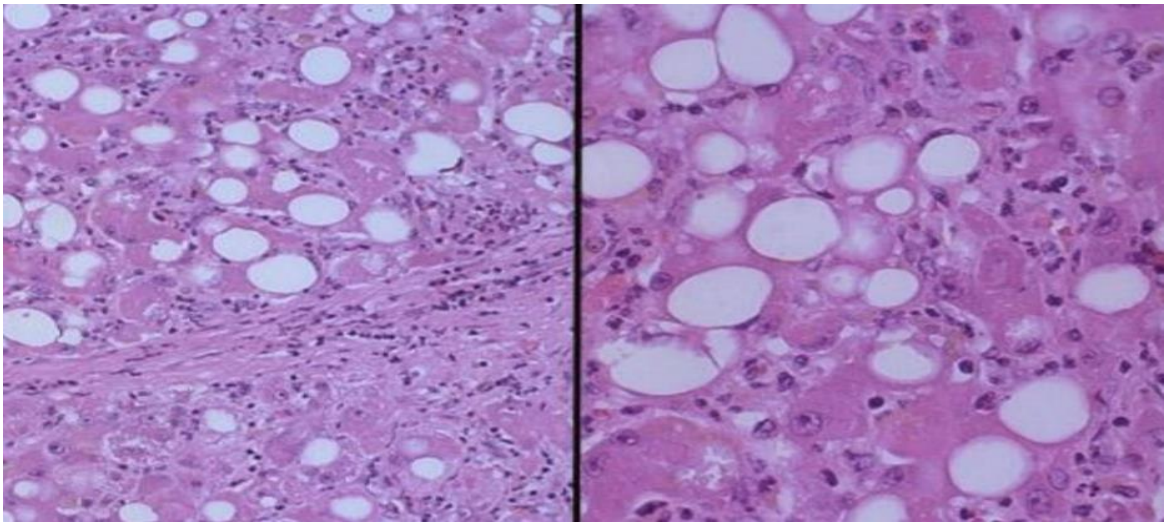
Alcoholic hepatitis

Damage of the hepatocytes due to an ethanol-induced injury.

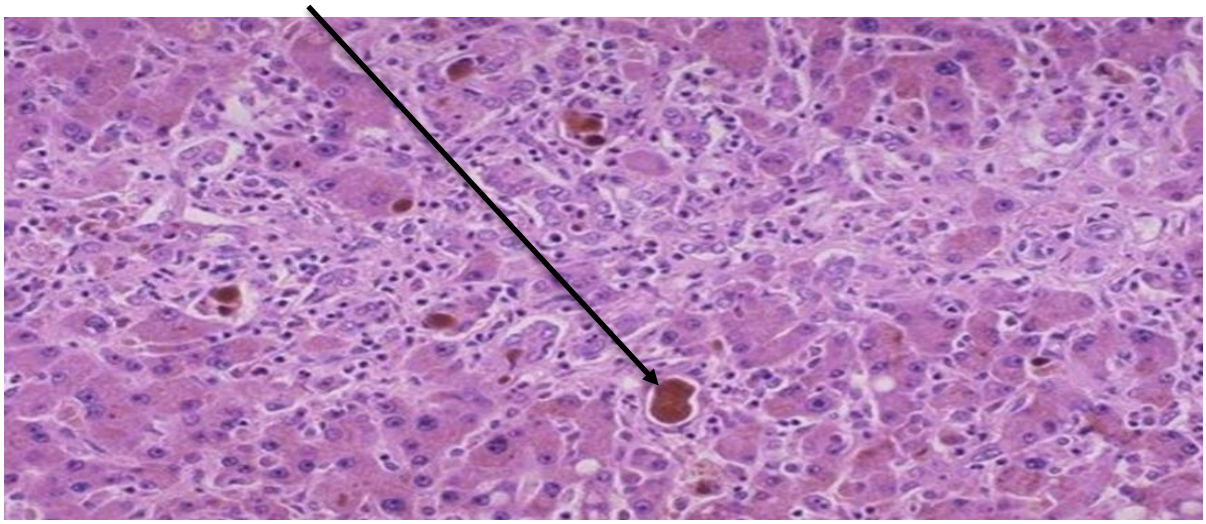
Characteristic findings :

1) Hepatocyte swelling & necrosis

- Infiltration of inflammatory cells (neutrophils which cause further damage to hepatocytes) .
- Accumulation of fat (steatosis), water, and proteins.
- Hemosiderin deposition (Iron storage complex) in hepatocytes and Kupffer cells.

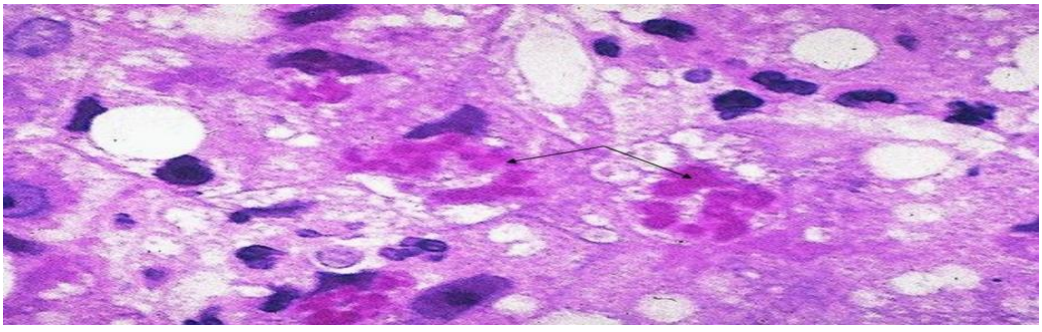


Dr. said this bile due to cholestasis.



2) Mallory-Hayline bodies

- Eosinophilic cytoplasmic inclusions in degenerating hepatocytes formed of cytokeratin intermediate filaments & other proteins.
- Mallory-Hyaline inclusions are characteristic but not pathognomonic of alcoholic liver disease. They are also seen in: Primary biliary cirrhosis, Wilson disease, chronic cholestatic syndromes, and Hepatocellular carcinoma .



3) Fibrosis associated with long term damage of hepatocytes:

Sinusoidal, perivenular and Periportal fibrosis.

4) *Neutrophilic reaction*
5) *Cholestasis:* is a decreased flow of bile from the hepatocytes due to malfunction of hepatocytes with continuous damage. We can notice them intracellular or intercellular in the cross section

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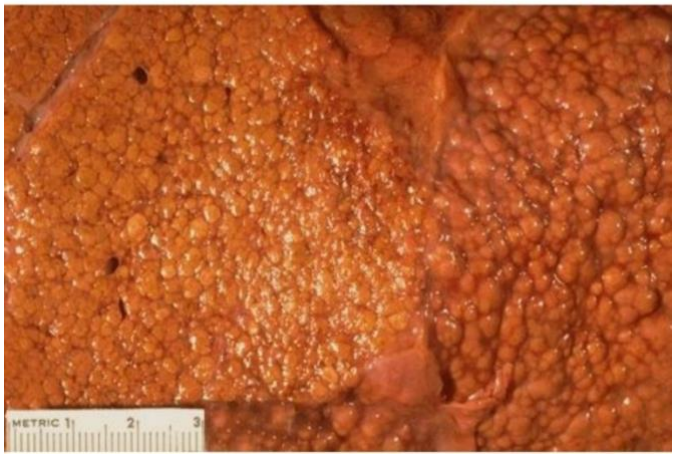
Alcoholic Liver Cirrhosis

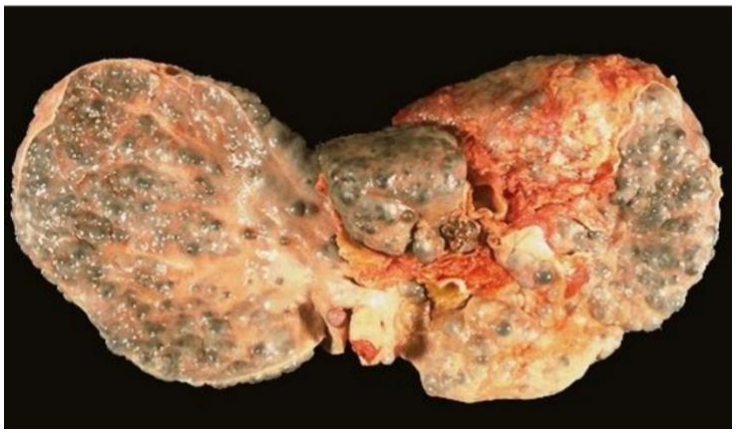
- *Usually, cirrhosis is the end result of many liver diseases.*
- *It's the conversion of liver parenchyma into nodules, each nodule is surrounded by fibrous tissue. Any condition that doesn't have these two features "nodule formation and fibrosis" in a diffused form isn't cirrhosis.*
- *It is a diffuse process and can't involve only a specific part of the liver, it must involve the entire liver to be diagnosed as cirrhosis.*
- *It's 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).*
- *Morphologic differences are obvious between a normal and a cirrhotic liver, each nodule is formed by parenchyma (the surface) surrounded by fibrous tissue. ➔ Rough nodular surface and liver shrinkage.*
- *Parenchyma cells in nodules still can function, therefore the patient can maintain normal liver function for a long period of time. Cirrhosis usually presents when the patient is involved in new condition (e.g. drug) that needs high liver function.*
- *Septa can show inflammatory cells.*
- Nodules are classified according to their diameter into:

Macro-nodules > 3 mm in diameter
Micro-nodules < 3 mm in diameter
"No difference between them in manifestations or pathogenesis, it is only the diameter"

Micronodular cirrhosis



Macronodular cirrhosis



Causes of cirrhosis:

a) Alcoholism: common in western countries
b) Viral Hepatitis: usually due to B and C virus infection, common in eastern countries
c) Hemochromatosis:
d) Wilson disease: a metabolic disease is characterized by copper deposition in hepatocytes. Cirrhosis in young patients (10-12 years old) is usually caused by metabolic disease.

How to exclude hepatitis as a cause of cirrhosis?

Blood test for antigens and antibodies of hepatitis B and C virus

Antibodies aren't enough to diagnose viral hepatitis.

e) Autoimmune hepatitis: can be very similar to viral hepatitis, so diagnosis needs laboratory tests.
f) α-1- antitrypsin deficiency: it's uncommon disease.
g) Other rare causes especially in young patients: most of them is due to enzyme deficiency, such as:

- ✓ Galactosemia (galactase deficiency)
- ✓ Abnormalities in amino acids metabolism: such as Tyrosinosis.
- ✓ Storage diseases: including lot of abnormalities in fat and glycogen storage.
- ✓ Glycogen disease type III and type IV are characterized by increased deposition of glycogen in hepatocytes.
- ✓ Hereditary fructose intolerance
- ✓ Drugs: like methyldopa

h) Cryptogenic cirrhosis: 10% of patients to obvious cause for cirrhosis.

**Whatever the cause is, cirrhosis is irreversible, so patients receive supportive care to prevent complications of cirrhosis by removing the cause of hepatocellular damage.

Pathogenesis of liver Cirrhosis:

Summary:

Liver cirrhosis starts with occurrence of continuous hepatocellular damage, due to toxicity or any other type of injury, which triggers the regeneration in the liver and with recurrent hepatocellular damage and repair, fibrosis occurs which eventually leads to liver cirrhosis, due to increased collagen production with obvious vascular changes.

1- Cell death

Cell death happens as a result of inflammation, toxicity, deposition or increased deposition of certain substances, or metabolic disease.

2- Regeneration

Regeneration happens after cell death, which is associated with production of fibrous tissue.

3- Progressive Fibrosis

Fibrous tissue in normal liver:

- Collagen (types I, III,V& XI) is present only in : Liver capsule, Portal tracts, and around central veins.
- Delicate framework of type IV collagen & other proteins lies in space of Disse. So the normal basement membrane is fit to allow the space of Disse to exist.

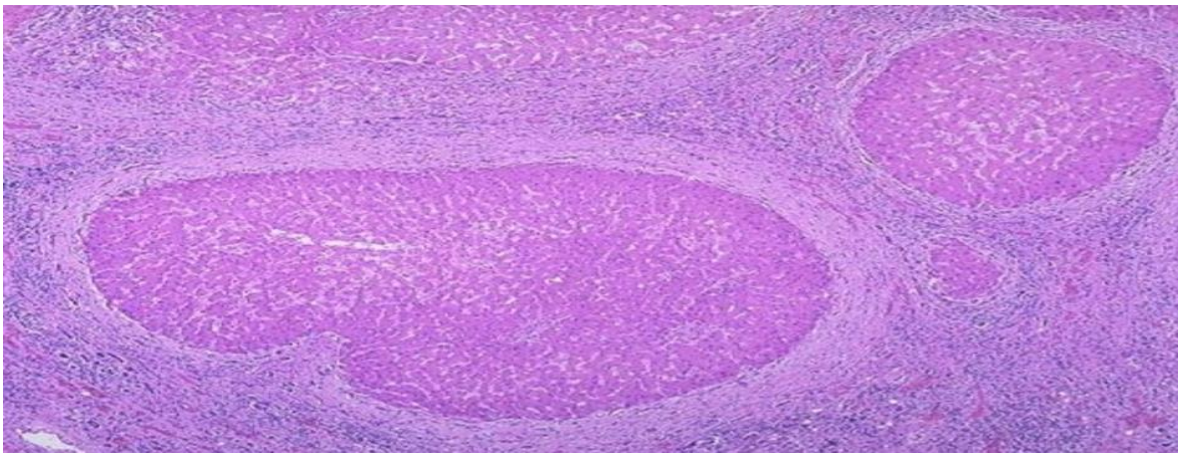
In cirrhosis

- Types I & III collagen & others are deposited in the space of Disse (and basement membrane) in Increased amounts, which leads to negative effects on the function on hepatocytes, such as reducing the exchange of materials between blood and hepatocytes.
- The continuous hepatic regeneration (due to any type of injury) causes the conversion of Ito cells into myofibroblasts.
- Ito cell is the major cell type involved in liver fibrosis in response to liver damage, they are stimulated by mediators of inflammation, fibrogenic growth factors, TGF-β. By this activation they start synthesis of large amount of ECM including collagen due to their transformation into myofibroblast- like cells.

Hepatic Stellate Cells (HSCs): are vitamin A- and fat-storing cells, also known as Ito cells or perisinusoidal cells. They are normally found in the space of Disse in the liver.

- Factors that influence fibrous tissue production:

- Reactive oxygen species
- Growth factors, such as transforming growth factor β (TGF-β).
- Cytokines and Inflammatory mediators, such as: TNF, IL-I, lymphotoxins.



4- Vascular changes

Since fibrous tissue is being deposited around blood vessels, this results in:

- ✓ Loss of sinusoidal endothelial cell fenestration
- ✓ Decreasing the elasticity of the blood vessels. (Elasticity is needed to allow the circulation of blood leave the sinusoids, so this will cause a decrease of blood flow in the liver).
- ✓ Increasing the resistance of vessels wall in the liver.
- ✓ Development of shunts (opening of channels between the portal vein and a hepatic vein or a, hepatic artery) to allow the fluids to find a less resistant pathway.
- ✓ Destruction of micro-villi which are found in the surface of hepatocytes due to high pressure. This causes a decreased ability in the exchange of materials between the blood and hepatocytes.
- ✓ The connection between the arteries and veins is very bad and this is because of the much higher pressure in arteries and veins, this creates portal hypertension.

Clinical features of cirrhosis

-Silent: A patient might live for years without knowing of their cirrhosis because of the non-specific symptoms, *such as Anorexia, weight loss, weakness*

-***Complications***: they happen due to a sudden condition that needs a high liver function

I. Progressive hepatic failure: can occur at any time during cirrhosis.
II. Portal hypertension: which causes the higher resistance blood vessels. So the blood flow starts going against resistance which will assist the formation of anastomosis in the blood vessels.
III. Hepatocellular carcinoma (HCC).