GIS 9

PATHOLOGY

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LIVER PATHOLOGY

Diseases of the liver are related to loss of its functions.

Functions of the liver:

1-Metabolic: **metabolism** of different substances.

2-Synthetic: Albumin, clotting factors…
If there is a Liver dysfunction, **less albumin will be synthesized**, and as you know **albumin is the main plasma protein** that generates the oncotic pressure causing fluid to go back from the interstitial fluid to the blood, decreasing the amount of albumin will cause edema.

3-Detoxification: **Drugs, hormones, NH3.**
Most of drugs are detoxified in the liver, some of them exhibit side effects on it. **(You should always ask the patients about their history regarding drugs).**

4-Storage: Glycogen, TG—Triacylglycerides (fat), Fe, Cu, vitamins.

5-Excretory: Bile (which contains bilirubin from the metabolism of the heme).

❖ Features of the liver

- ✓ Normal weight of the liver is about **1.5 kg (2.5% of body weight).**
  Increased liver weight is associated with many diseases.
- ✓ **Blood supply of the liver:**

1-Portal vein: 60 - 70%.
2-Hepatic artery: 30- 40%.

Blood that is coming from the portal vein is not oxygenated but is filled with nutrients and other stuff coming from the gut in which hepatocytes are required to metabolize. On the other hand, blood that is coming from the hepatic artery is oxygenated. They both get mixed in the sinusoidal system of the liver; the hepatocytes do their action on the blood in the sinusoids, after that, blood is discharged to the three hepatic veins draining in the inferior vena cava.

NOTE: **Some diseases of the liver may affect both vessels supplying the liver (the hepatic artery and portal vein) and cause obstruction.**

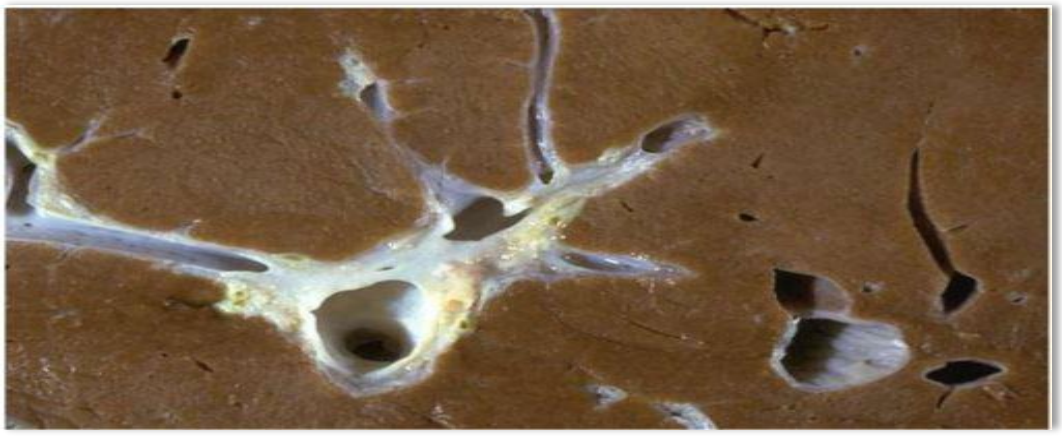
Microstructure of the liver:

- We know that the liver consists of hexagonal lobules, and the angles of each hexagonal lobule are formed by **portal triads or tracts** (bile ductule, hepatic artery, and hepatic portal vein). At the centre of the hexagonal lobule, there is a central vein.

The thickness of the sinusoid system that distributes blood to other hepatocytes is 1-2 cell thickness (Explanation: each sinusoid is surrounded by one or two lines of hepatocytes, If thicker lines present (more than two lines), this means that there is disarrangement or abnormal condition such as tumor or else..).

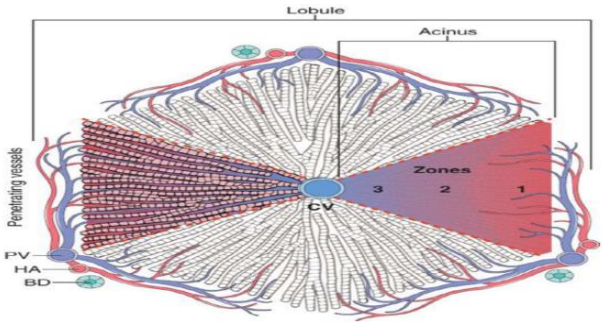
- Hepatocytes surround the **vascular sinusoids** and are in close contact with the blood to uptake **drugs and other substances** for detoxification and secretion of synthesized substances.
- The normal liver has a nice brownish color and its surface is smooth.

A section in the liver Shows the homogeneous parenchyma. You can't see sinusoids in gross section, they are only seen under the microscope.



- The area between the central vein and the portal triad is divided into three zones, diseases can develop in each of these three zones:

1-Periportal area: closest to the vascular supply.
2- Intermediate area: between zone 1 and zone 3.
3- Pericentral area: closest to the central vein.
NOTE: when disease severity increases, all zones will be affected.



❖ Hepatic injury

There are certain features and changes that might point to some underlining causes, but these changes are not specific:

1-Inflammation (Hepatitis): infiltration of the liver by inflammatory cells. This infiltration starts in the portal vein **(early and mild inflammation)** and may extend to the parenchyma **(severe inflammation**).

2-Ballooning degeneration: Caused by disturbances in the **permeability of the cell membrane** of hepatocytes via certain injury sources. This causes the hepatocytes to increase in size, and large amounts of water accumulate inside the cytoplasm which in turn causes rupture of the hepatocytes. Also, substances may accumulate in hepatocytes, including fat (fatty liver), iron (hemochromatosis), copper (Wilson's disease), and retained biliary material.

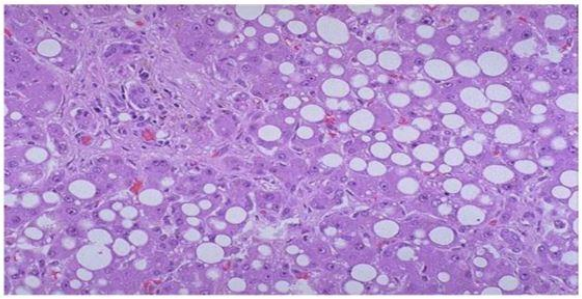
3-Steatosis (fatty change): Normally, there is no fat tissue in the liver. So, any small amount of fat inside the liver indicates a pathological condition. Previously, this fatty change was thought to be reversible and harmless, but now it is considered as a disease which may be chronic and liver damaging.

NOTE: It's totally nonspecific and can be seen in many diseases. This picture shows enlarged liver with severe fatty change (yellowish color).

1-microvesicular steatosis: is characterized by intracytoplasmic fat vacuoles that accumulate in the cell, examples of: ALD, Reye syndrome, acute fatty change of pregnancy.

2- macrovesicular steatosis: is the more common form of fatty degeneration and is caused by oversupply of fat in obese people and diabetic people as well.

Microscopically Fat appears as empty spaces (vacuoles) within the cytoplasm of the cells. Fat that's been accumulated in the cytoplasm affects the integrity of the hepatocytes and their functions.



4-Necrosis: The presence of necrosis is very important because it means total loss of cells and loss of function. Necrosis evaluates the severity of the condition. If a disease causes necrosis, it is a very severe disease. Necrosis is divided into several types to predict what is the underlying cause (It is not specific but can help):

- ✓ Coagulative necrosis: takes place around the central vein, and It's related to ischemia.
- ✓ Councilman bodies (apoptotic body): Eosinophilic globule of cells that represents a dying hepatocyte often surrounded by normal parenchyma. It represents a hepatocyte that is undergoing necrosis or apoptosis. If we look at a liver tissue specimen from a patient **without an active disease** and we found councilman bodies, we should know that this liver **was previously exposed to** injury leaving these globules of cells that are surrounded by parenchymal cells scattered in between hepatocytes. They are **shrunken cells** with very eosinophilic cytoplasm and the nucleus is dark. This indicates that the patient is in long term drug use causing this type of injury.
- ✓ Lytic necrosis: can be related to infections. **Parasitic infections** can be related to lytic necrosis.

❖ Necrosis can also be classified depending on the cause:

1-Ischemic: obstructions in the blood vessels that supply the liver.

2-Toxic: exposure to toxic substances like drugs or toxins in mushrooms.

❖ Depending on the location:

1-Centrilobular necrosis: around the central vein.
2-Mid zonal necrosis: between the central vein and the portal triad.
3-Periportal necrosis: around the portal tract (triad), previously called the Piece meal necrosis, now it's called interface hepatitis, because it's most commonly caused by viral hepatitis.

❖ Depending on the scatter of the inflammation:

1-Focal: necrosis affecting small group of cells like the piece meal necrosis and bridging necrosis which leaves bridging fibrosis. Fibrosis is irreversible and it indicates chronic liver disease.
2-Diffuse: massive necrosis (is characterized by extensive panlobular and multilobular hepatocyte **necrosis** and is the morphological counterpart of acute fulminant **liver** failure, involves more than 75% of liver parenchyma) & submassive necrosis (involving 26%-75% of the parenchymal volume).

5-Regeneration: Liver regeneration is the process by which the liver is able to replace lost liver tissue by growth of the remaining tissue. There are two events in which the liver has the capability to regenerate, one being a partial hepatectomy and the other being damage to the liver by toxins or infection.

- ✓ It is evidenced by increased mitosis or cell cycle markers.
- ✓ The cells of the canal of Hering are the progenitor for hepatocytes & bile duct cells (oval cells).

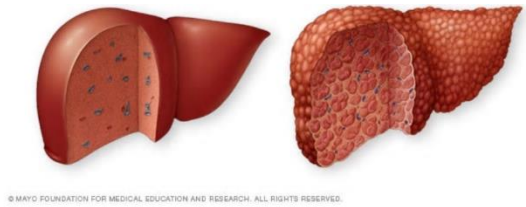
6-Fibrosis:

- ✓ Liver fibrosis occurs when repetitive or long-lasting injury or inflammation causes excessive amounts of scar tissue to build up in the organ. Most types of chronic liver disease can eventually cause fibrosis.
- ✓ Advanced fibrosis tends to cause widespread, irreversible damage that eventually leads to cirrhosis.

❖ Terms related to fibrosis:

portal fibrosis	Fibrosis within a portal tract.
periportal fibrosis	fibrosis of the parenchyma adjacent to a portal tract.
pericellular fibrosis	Fibrous tissue strands that extend along the sinusoids to surround single or small groups of hepatocytes.
Pericentral fibrosis	Fibrous tissue around a central vein.
bridging fibrosis	Central-central. Connects central veins with central veins. Porto-central: connecting central vein to a portal area. Porto-portal: connecting portal areas.

7-Cirrhosis: Cirrhosis is a late stage of scarring (fibrosis) of the liver caused by many forms of liver diseases and conditions. It refers to the diffuse transformation of the liver into regenerative parenchymal nodules surrounded by fibrous bands.



Normal liver vs. liver cirrhosis

A normal liver (left) shows no signs of scarring. In cirrhosis (right), scar tissue replaces normal liver tissue.

✓ EXTRA: In the micronodular form, regenerating nodules are under 3 mm. In macronodular cirrhosis, the nodules are larger than 3 mm.

8-Ductular proliferation: the appearance of biliary epithelial cells in the portal tracts of diseased livers.

❖ Liver failure:

✓ The most severe clinical consequence of liver disease, it results when the hepatic functional capacity is almost totally lost (80 – 90%).

❖ Causes:

1. Massive hepatic necrosis: diffused necrosis with most of the liver is involved, commonly:
   - Fulminant viral hepatitis: hepatitis B, hepatitis B-D, hepatitis C, and sometimes hepatitis A.

- Drugs & chemicals: acetaminophen (paracetamol), halothane (anesthetic agent), anti TB drugs, CCL4 poisoning, Mushroom poisoning.

2. Chronic liver disease: like in cirrhosis
3. Hepatic dysfunction without overt cirrhosis: there is no obvious necrosis and hepatocytes are normal. Failure is due to loss of function

✓ Examples:

- Reye's syndrome.
- Tetracyline toxicity.
- Acute fatty liver of pregnancy. It occurs suddenly in a pregnant woman and represents severe acute fat infiltration in the liver leading to acute sudden liver failure.

❖ Clinical features of liver failure:

1. Jaundice: yellow discoloration of the skin and sclera due to retention of bilirubin.
2. Hypoalbuminemia →edema the level of albumin in the blood is low, due to decreased production in the liver.
   Clarification: hypoalbuminemia decreases the total protein concentration in blood plasma, also known as the colloid osmotic pressure, which causes fluid to exit the blood vessels into tissues to equalize the concentrations. This leads to fluid induced swelling of the extremities known as edema.
3. Hyperammonemia: excess of ammonia in the blood, due to impaired urea cycle in the liver.
4. Fetor hepaticus (musty or sweet & sour).
5. Hyperestrogenemia: due to impaired estrogen metabolism in male patients with chronic liver failure can give rise to palmar erythema (local vasodilation).
6. Spider angiomas.
7. Hypogonadism (diminished functional activity of the gonads, the testes or the ovaries) & gynecomastia (Hypogonadism & gynecomastia).

❖ Consequences:

- Multiple organ failures (kidneys and lungs), the body can't deal with the toxic substances.
- Coagulopathy a condition in which the blood's ability to coagulate (form clots) is impaired, defect synthesis of clotting factors II, VII, IX, X.
- Hepatic encephalopathy: liver failure affects the brain (e.g. hyperammonemia) which causes neurological manifestations:
  - decreased level of consciousness
  - Rigidity.
  - Hyperreflexia.
  - EEG changes.
  - Seizures.
  - Asterixis.

✓ Hepatorenal syndrome: renal failure in patients with severe liver disease with no morphologic or functional causes for renal failure. (treating the liver disease cures the kidneys).

❖ Massive hepatic necrosis:

✓ Fulminant hepatic failure from the onset of symptoms to hepatic encephalopathy (within 2 -3 weeks).

✓ Subfulminant (within 3 months).

❖ Causes:

✓ Viral hepatitis 50 – 65% (B, B-D, A, C hepatitis), it's the most common cause.

✓ Drugs & chemicals 20 – 30%

✓ Other causes that are not common:

- Heat stroke.
- Hepatic vein obstruction.
- Wilson disease.
- Acute fatty liver of pregnancy.
- Massive malignant infiltration.
- Reactivation of chronic HBV hepatitis on HDV. superimposed infection.
- Autoimmune hepatitis.

❖ Alcoholic liver disease:

✓ Alcohol is most widely abused agent, and the most common toxin affecting the liver

- ✓ It is the 5th leading cause of death in USA due to:
    1. accidents
    2. Cirrhosis, most common cause of cirrhosis in western countries is alcoholism.
- ✓ **80-100mg/dl** is the legal definition for driving under the influence of alcohol, **44 ml** of ethanol is required to produce this level in 70kg person. Short term ingestion of 80 gms/d of ethanol is associated with fatty change in liver.
- ✓ Effect of ethanol varies between people and between males and females.
- ✓ In occasional drinkers, blood Level of 200 mg/dl produces coma & death, and respiratory failure at 300-400 mg/dl.
- ✓ Habitual drinkers can tolerate levels up to 700 mg/dl without clinical effect. This is due to metabolic tolerance explained by 5-10X induction of cytochrome P-450 system that includes enzyme CYP2E1 which increases the metabolism of ethanol as well as other drugs as cocaine & acetaminophen.

❖ Forms of alcoholic liver disease:

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

- Steatosis & hepatitis may develop independently.

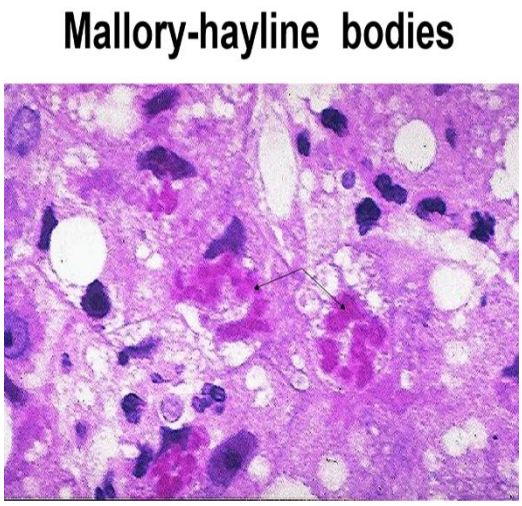
❖ Hepatic steatosis:

- ✓ Ethanol can affect all the aspects and pathways of fat metabolism; it can increase fatty acids release from adipose tissue or increase its de novo synthesis. Thus, uptake of ethanol leads to increase in the amount of free fatty acids in the blood. These free fatty acids accumulate in the liver and cause steatosis.
- ✓ Can occur following even moderate intake of alcohol in form of microvesicular steatosis.
- ✓ Chronic intake → diffuse steatosis.
- ✓ Liver is large (hepatomegaly, 4 – 6 kg) soft yellow & greasy.
- ✓ Continued intake →fibrosis.
- ✓ Fatty change is reversible with complete abstention from further intake of alcohol.

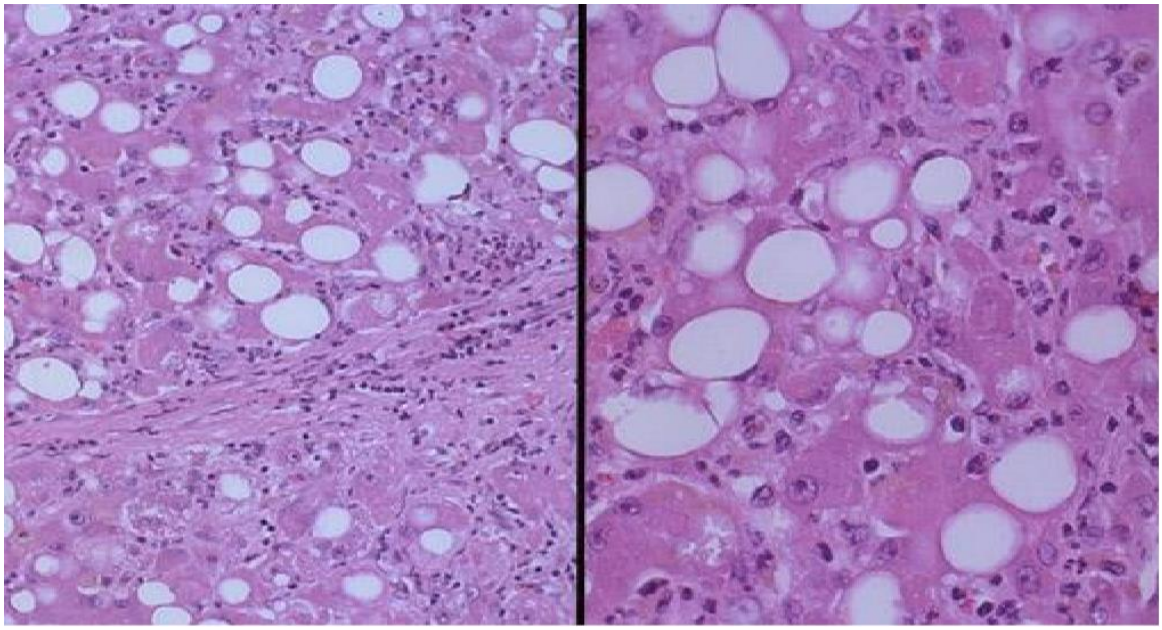
❖ Alcoholic hepatitis:

✓ Characteristic findings:

- Hepatocyte swelling (hepatomegaly) & necrosis:
- Accumulation of fat, water & proteins
- Cholestasis.
- Hemosiderin deposition in hepatocytes & Kupffer cells.
- Mallory-hyaline bodies:
- an inclusion found in the cytoplasm of liver cells. Mallory bodies are damaged intermediate filaments within the hepatocytes.
  - Eosinophilic cytoplasmic inclusions in degenerating hepatocytes formed of cytokeratin intermediate filaments & other proteins.
- Mallory bodies are classically found in the livers of people suffering from alcoholic liver disease but are not pathognomonic of alcoholic liver disease.

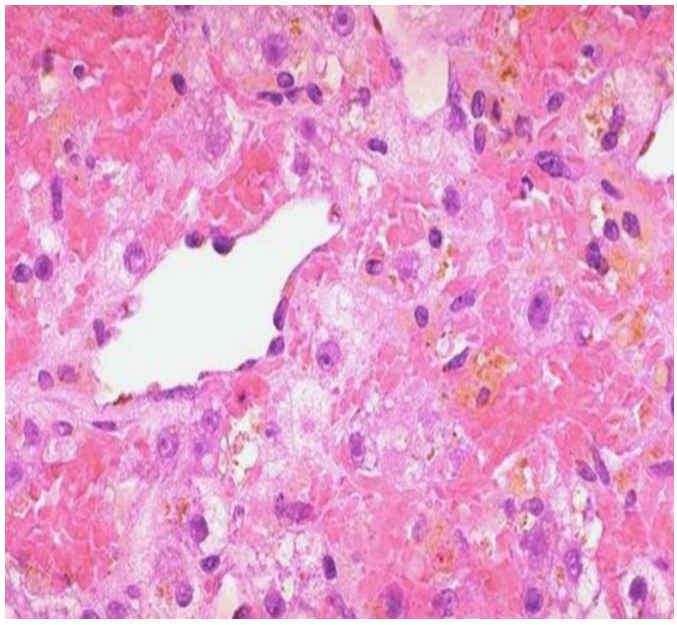


- they are also seen in:
  1. Primary biliary cirrhosis.
  2. Wilson disease.
  3. Chronic cholestatic syndromes.
  4. Hepatocellular carcinoma.
- Neutrophilic reaction, infiltration of inflammatory cells (neutrophils which cause further damage (necrosis) to hepatocytes).
- Fibrosis.
- Sinusoidal & perivenular fibrosis.
- Periportal fibrosis.
- Cholestasis: decreased flow or secretion of bile from hepatocytes.
- Mild deposition of hemosiderin in hepatocytes & Kupffer cells.



- ✓ Morphologic features of hepatocyte injury in fatty liver disease associated with chronic alcohol use.
  - › Inflammatory infiltration.
  - › Cholestasis, characteristic accumulation of bile pigments in the cytoplasm.

- ✓ The specimen shows unusual color (pigments) within the hepatocytes. These pigments mean accumulation of certain substances (e.g. Bile or iron) within the cells.



Good Luck