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Pathology GIS

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LECTURE 2

Alcoholic liver disease

-Alcohol is most widely abused agent

-It is the 5th leading cause of death in USA due to :

1. Accidents
2. Cirrhosis

-80 – 100 mg/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

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- In occasional drinkers, bl. Level of 200 mg/dl produces coma & death & resp. failure at 300-400 mg/dl

-Habitual drinkers can tolerate levels up to 700 mg/dl without clinical effect due to metabolic tolerance (To ethanol) explained by 5-10X induction of cytochrome P-450 system (which is responsible for the elimination of ethanol from the blood) that includes enzyme CYP2E1 which increases the metabolism of ethanol as well as other drugs as cocaine & acetominophen

- **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 & should be considered as an early indication for Chirrhosis development in the future.

Hepatic steatosis

-Can occur following even moderate intake of alcohol in form of microvesicular steatosis

-Chronic intake (of ethanol/ Alcohol) → diffuse steatosis

-Liver is large (4 – 6 kg) soft yellow & greasy

-Continued intake →fibrosis (which is irreversible)

-Fatty change is reversible with complete absention from further intake of alcohol (But if the patient continues to drink the progression into fibrosis or steatosis are inevitable)

Alcoholic hepatitis

Characteristic findings :

1-Hepatocyte swelling & necrosis

-Accumulation of fat & water & proteins

-Cholestasis (Bile salts accumulation within small bile ducts in the liver)

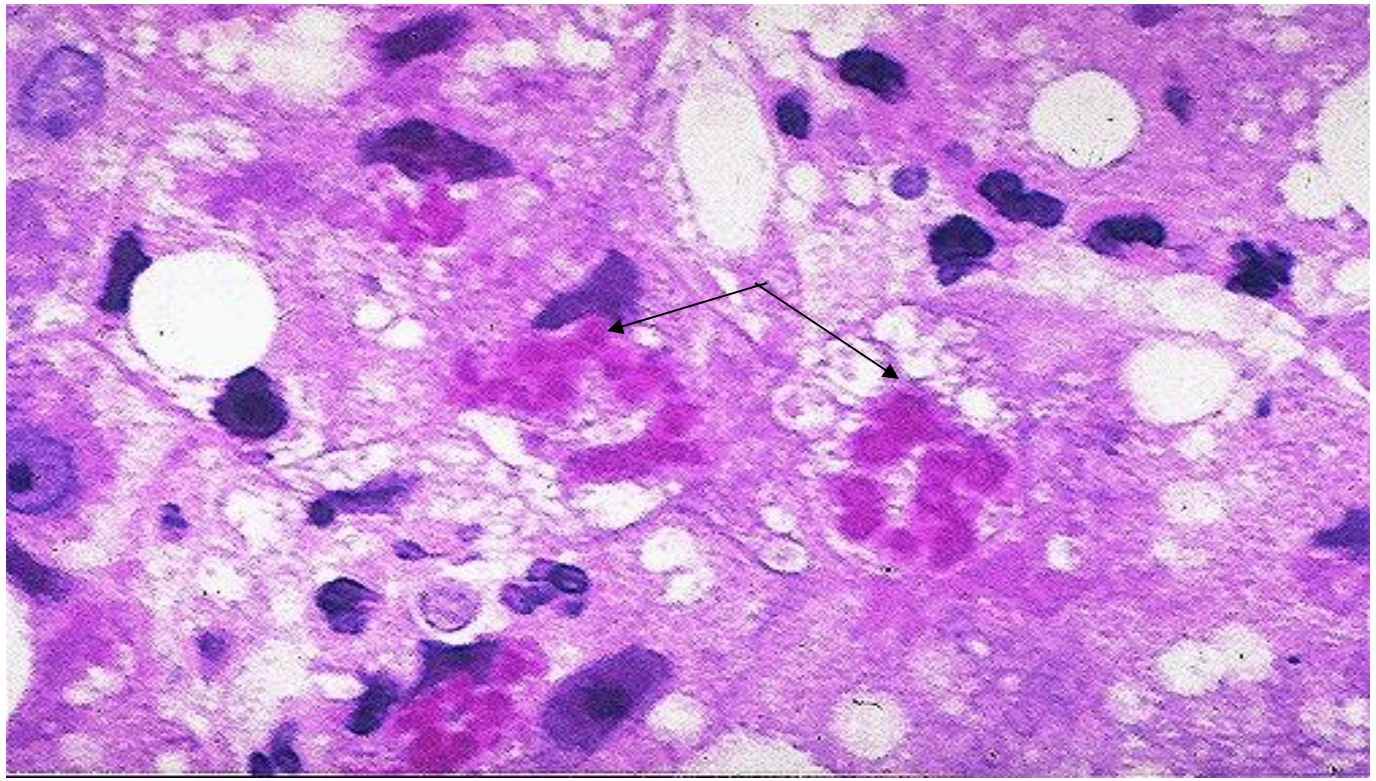
-Hemosiderin deposition in hepatocytes & Kupffer cells

2-Mallory-hayline bodies

-eosinophilic cytoplasmic inclusions in degenerating hepatocytes formed of cytokeratin intermediate filaments & other proteins.

Mallory-hayline bodies

This figure shows the resemblance of cytoplasmic granules in an alcoholic hepatitis patient(Marked by the arrows)



-Mallory-hayline inclusions are characteristic but 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

: Characteristic findings

3-Neutrophilic reaction

4-Fibrosis (depending of the duration of ethanol intake)

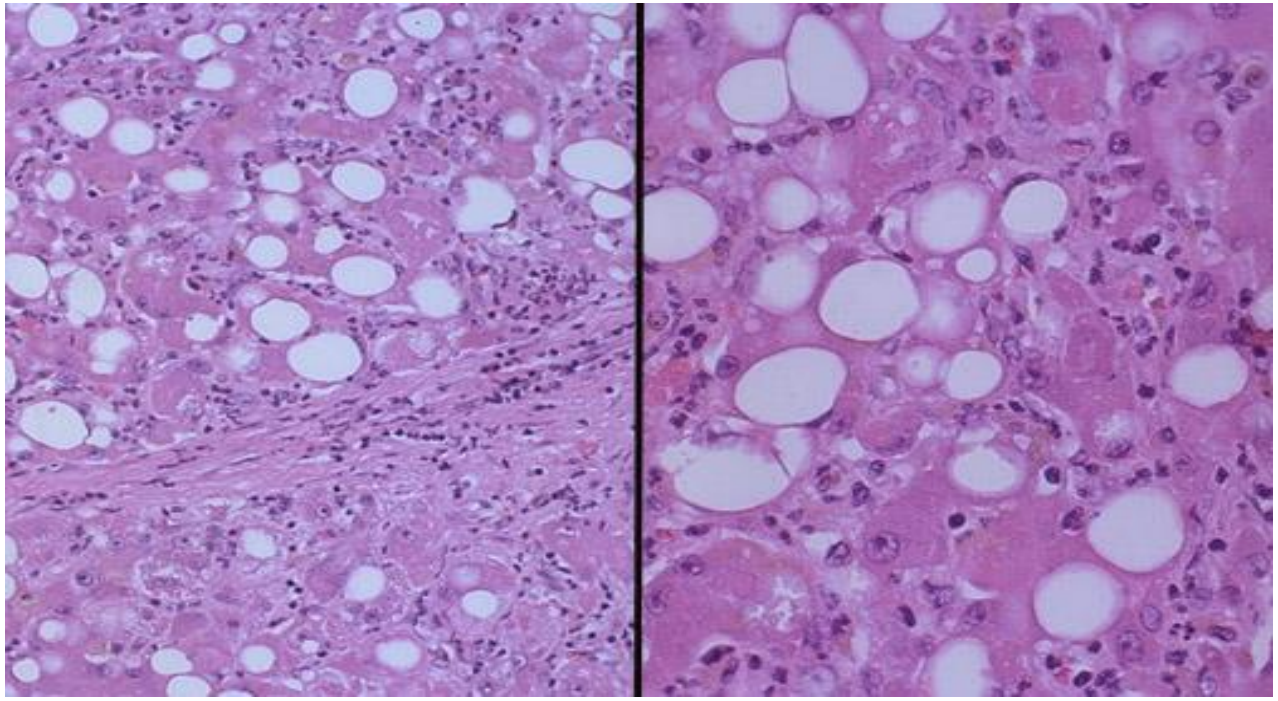
-Sinusoidal & perivenular fibrosis

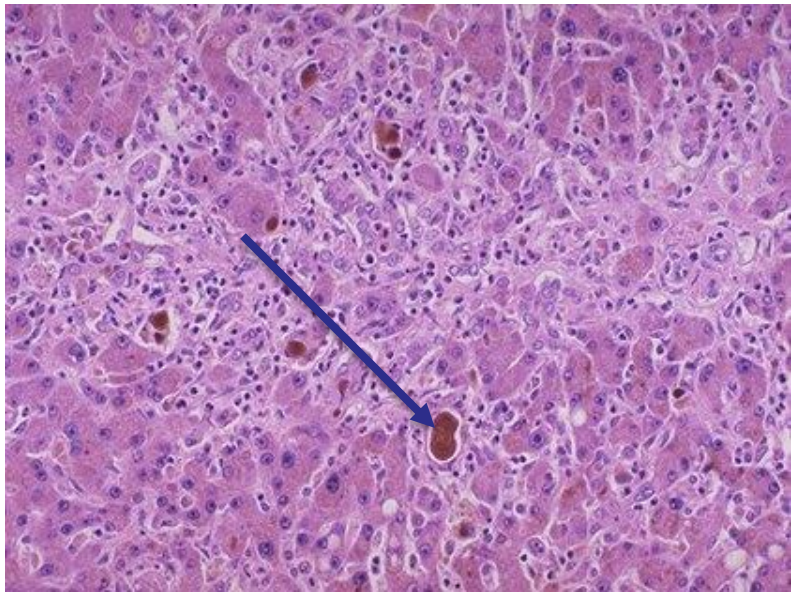
-Periportal fibrosis

5-Cholestasis within the cytoplasm of hepatocytes and the bile duct

6-Mild deposition of hemosiderin in hepatocytes & Kupffer cells

This is the liver parenchyma of an alcoholic hepatitis patient, we can see 1-Inflammatory infiltration. Figure 1
2- Cholestasis (accumulation of bile in the cytoplasm of hypatocytes and small bile ducts/ ductules) Figure 2





Alcoholic cirrhosis

-Usually it develops slowly

Cirrhosis due to alcoholism is similar to cirrhosis due to any other cause however in alcoholic cirrhosis, Initially the liver is enlarged yellow **but over years** it becomes brown shrunken non-fatty organ s.t < l kg in weight

-Micronodular → OR mixed micro & macronodular

-Laennec cirrhosis = scar tissue (sever liver fibrosis)

-Bile stasis

-Mallory bodies are only rarely evident at this stage

-Irreversible

-It can devolop rapidly in the presence of alcoholic hepatitis (within 1-2 yrs).

Macroscopic appearance of a liver with Alcoholic Cirrhosis.
With micronodules appearnce on the surface of the liver ((one of the hallmarks of alcoholic cirrhosis))

Ethanol metabolism

Ethanol → acetaldehyde

CH_3CH_2OH $CH_3C(=O)H$

↑

-Alcohol dehydrogenase
(stomach + liver)
-Cytochrome P-450
-Catalase (liver)

Ethanol metabolism occurs in the liver so it's exposed to ethanol toxicity.

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Acetaldehyde → Acetic acid

↑

Aldehyde dehydrogenase

- After absorption ethanol is distributed as Acetic acid in all tissues & fluid in direct proportion to blood level

- Women have lower levels of gastric alcohol dehydrogenase activity than men & they may develop higher blood Levels than men after drinking the same quantity of ethanol.

- less than 10% of absorbed ethanol is excreted unchanged in urine sweat & breathe

-There is genetic polymorphism in aldehyde dehydrogenase that affect ethanol metabolism

e.g 50% of chinese , vietnamase & Japanese have lowered enzyme activity due to point mutation of the enzyme. → accumulation of acetaldehyde → facial flushing, tachycardia & hyperventilation. ((after exposure to ethanol))

Pathogenesis of alcoholic liver disease

**Ethanol toxicity is dose dependant.

Short term ingestion of 80gm of ethanol/day (8bears) → mild reversible hepatic changes (fatty liver)

- Long term ingestion (10-20yrs) of 160gm of ethanol per day → severe hepatic injury
- 50 – 60gm/day → borderline effect
- Women are more susceptible to hepatic injury due to ↓gastric metabolism of ethanol . ((Lower level of ethanol metabolism ezymes))
- Only 8 – 20% of alcoholics develop cirrhosis

Mechanism of ethanol toxicity

1-Fatty change

a-Shunting of lipid catabolism toward lipid bio-synthesis due to excess production of NADH over NAD in cytosol & mitochondria

b-Acetaldehyde forms adducts with tubulin & ↓ function of microtubules → ↓ in lipoprotein transport from liver

c- ↑ peripheral catabolism of fat → ↑ FFA (Free fatty acids) delivery to the liver

d- ↓ secretion of lipoproteins from hepatocytes

e. ↓ oxidation of FFA by mitochondria

2-Induction of cytochrome P-450 enhances the metabolism of drugs to toxic metabolites (e.g acetominophen) leading to increase the injury of the liver

3. ↑free radicals production due to (+) of cytochrome P-450 leads to membrane & protein damage **within hypatocytes**
4. Alcohol directly affect microtubular & mitochondrial function & membrane fluidity
5. Acetaldehyde causes lipid peroxidation & antigenic alteration of hepatocytes → immune attack
6. Superimposed HCV infection causes acceleration of liver injury (HCV hepatitis occurs in 30% of alcoholics)

7. Alcohol → release of bacterial endotoxins into portal circulation from the gut → inflammation of the liver
8. Alcohol → regional hypoxia in the liver due to release of endothelins which are potent vasoconstrictors → ↓ hepatic sinusoidal perfusion
9. Alteration of cytokine regulation

- TNF is a major effector of injury
- IL6 IL8 IL18

Clinical features

-Hepatic steatosis (reversible)

↑ liver

↑ liver enz.

Severe hepatic dysfunction is unusual

-Alcoholic hepatitis

. 15-20 yr. of excessive drinking

. Non-specific symptoms, malaise, anorexia, wt. loss

↑ liver & spleen

↑ LFT

Each bout of hepatitis →10-20% risk of death

→ cirrhosis in 1/3 in few yrs.

-Cirrhosis

Portal hypertension

- **Causes of death in alcoholic liver disease**

1-Hepatic failure

2-Massive GI bleeding

3-Infections

4-Hepatorenal syndrome (Multiorgan failure)

5-HCC (hypatocellular carcinoma) in 3-6% of cases