GIS 10

PATHOLOGY

Done by: Lana Mango

Scientific Correction: Nour Awamleh

Gramatical Correction: Lana Mango

Doctor: Maha Shomaf

Anything written in the slides that wasn't mentioned by the professor will be underlined and between square brackets [like this]

Alcoholic Cirrhosis

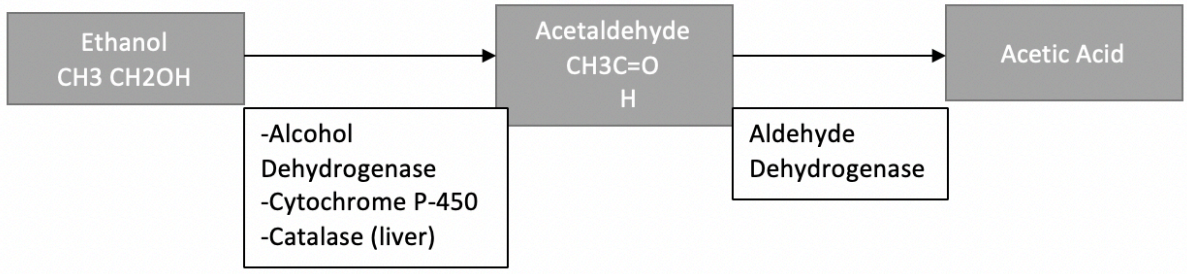
- Develops after **chronic ingestion of alcohol** → Liver toxicity
- Usually develops *slowly*
- It can develop *rapidly* in the presence of ***alcoholic hepatitis*** (within 1-2 yrs).

- Image: Macroscopic appearance of a liver with **Alcoholic Cirrhosis**

Ethanol Metabolism

- **Ethanol** is primarily metabolized in the liver, through the action of enzymes
  1. **Ethanol is Absorbed**
  2. **Absorbed ethanol** is metabolized → **Acetaldehyde**
  3. **Acetaldehyde** is metabolized → **Acetic Acid** is distributed in all tissues and fluid (In direct proportion to blood level)

- Enzymes needed for the metabolism of ethanol:
  1. **Alcohol Dehydrogenase** (stomach +liver)
  2. Cytochrome P-450
  3. Catalase (liver)
- Enzyme needed for the metabolism of Acetaldehyde: **Aldehyde dehydrogenase**



- **Women** have *lower* levels of gastric alcohol dehydrogenase enzyme activity than men → Women **have higher blood alcohol levels** than men after consuming/drinking the same amount of Ethanol. (Due to decreased metabolism of alcohol).
- **Less than 10% of absorbed Ethanol** is excreted unchanged in urine, sweat and breath.
- There is **genetic polymorphism** in aldehyde dehydrogenase that affects ethanol metabolism.
    - **e.g** 50% of Asians [Chinese , Vietnamase & Japanese] have lowered enzyme activity due **to point mutation of the enzyme** Aldehyde Dehydrogenase → Leads to accumulation of acetaldehyde → **Leads to**:
        1. Facial flushing
        2. Tachycardia
        3. Hyperventilation.

Clinical Features of:

➢ Hepatic Steatosis (reversible)

1. **Gross appearance:** Enlargement of the liver
2. **LFT (Liver Function Test):** Increase in liver enzymes

- In this reversible stage, severe hepatic dysfunction is unusual

➢ Alcoholic Hepatitis

- Bouts of Hepatitis developed due to [15-20 years] of excessive drinking
- Indicates the presence of injury

- **Associated with non-specific symptoms, such as:**
    1. Malaise
    2. Anorexia
    3. Weight loss
    4. Enlargement of the liver & spleen
    5. Abnormal liver function test (LFT) enzymes

- Each bout of hepatitis:
    - Increases the risk of death by 10-20%
    - Leads to the development of cirrhosis in 1/3 of the cases in a few years

➢ Cirrhosis

- Presents with complication: **Portal Hypertension**

➢ ***Causes of death in Alcoholic Liver Disease:***

1. Hepatic Failure
2. Hepatorenal Failure
3. Massive upper GI bleeding
4. Infections
5. Hepatocellular carcinoma (HCC)
    - Occurs in **3-6%** of the cases

Cirrhosis

➢ ***What is Cirrhosis?***

Diffuse process characterized by:

1. **Fibrosis**
2. Conversion of **liver parenchyma into new nodules**

➢ ***Characteristics:***

1. Bridging fibrous septa
2. Parenchymal nodules encircled by fibrotic bands
3. Diffuse architectural disruption

➢ ***Types of Cirrhosis:***

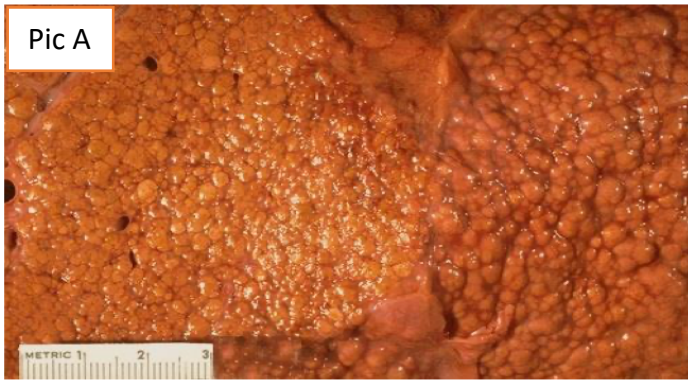
1. **Micronodular**: Nodules that are **< 3 mm** in diameter.

- **Gross appearance (Pic A):**
    - small nodules that are **< 3 mm** in diameter.

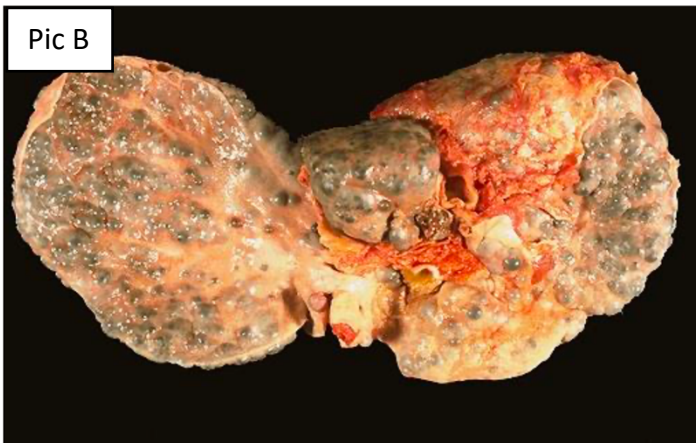
2. **Macronodular**: Nodules that are **> 3 mm** in diameter.

- **Gross appearance (Pic B):**
    - Small nodules which *coalesce* to form large nodules (> 3 mm diameter)
    - Appearance of the liver is **disfigured**.

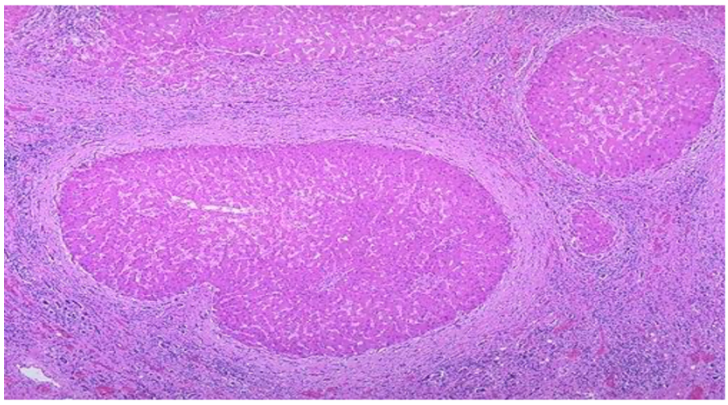
Pic A



Pic B



➢ ***Microscopic Appearance of Cirrhosis:***



- Diffuse: Involves the entire liver
- Island of parenchyma surrounded by a thick fibrous capsule
- Infiltrated by inflammatory cells (**Main finding)**

➢ **Causes of Cirrhosis:**

1. Chronic Alcoholism (most common)
2. Alpha-1 Antitrypsin deficiency
3. Biliary disease
4. Wilson disease
5. Hemochromatosis

> **Extra:** **Hemochromatosis** is a disorder where too much iron builds up in your body (Iron overload)

6. Chronic viral infection (HBV & HCV)
7. Autoimmune Hepatitis
8. Rare causes:
   - Galactosemia
   - Tyrosinosis
   - Glycogen storage disease (3 and 4)
   - Hereditary fructose intolerance
   - Lipid storage disease
   - Drug induced: e.g., Methyl dopa
9. Cryptogenic Cirrhosis (10% of cases): The underlying cause is unknown

➢ ***Pathogenesis of Cirrhosis***

The mechanism involves:

1. Hepatocellular **death** (Death of hepatocytes)
   - It is the initial step involved in the mechanism of Cirrhosis development
   - Occurs over a long period of time.
   - Accompanied by **fibrosis** (**Reminder**: Fibrosis is one of the main characteristics of Cirrhosis)
2. **Regeneration** of hepatocytes

3. Progressive **Fibrosis**
4. **Vascular** Changes

CELL DEATH → CELL REGENERATION → FIBROSIS → VASCULAR CHANGES

➢ ***Effect of Cirrhosis on ECM components and stellate cells:***

	Normal	Cirrhosis
ECM **Collagen (types I, III, V& XI)**	Are present **only** in: **1. Liver capsule** **2. Portal tracts** **3. Around the central vein**	Are deposited in the space of Disse → **This interferes with the exchange function of hepatocytes**
Delicate framework **of type IV collagen** & other proteins:	Lie in the **space of Disse.**	
Perisinusoidal stellate cells **(Ito cells)**	They act as storage cells for: 1. **Vitamin A** 2. **Fat**	-They are the main source of collagen **in cirrhosis.** **-They lie in the space of Disse.** How? -When these stellate cells are **stimulated by TGF-Beta** (A common mediator released during the inflammatory process), they start to **produce collagen**

The stimuli for the activation of Stellate cells and production of collagen are:

1. Reactive oxygen species
2. Growth factors
3. Cytokines (TNF, IL-1, Lymphotoxins- commonly secreted at the site of inflammation)

➢ ***Vascular changes*** Include:

1. Loss of **sinusoidal endothelial cell** fenestration **(Normally responsible for the exchange between hepatocytes and the blood)** → Associated with the loss of function of hepatocytes.
2. Development of **vascular shunts**:

a) Portal vein-hepatic vein
b) Hepatic artery-Portal vein

→ The development of shunts produces **defects in liver function**, by the redirection of blood in the abnormal direction.

3. Loss of **microvilli** from hepatocytes → Decrease in transport capacity of the cells → Functional abnormality of hepatocytes

➢ ***Clinical features of Cirrhosis:***

1. **Remains silent for years**, due to the functional capacity of the parenchymal hepatocytes.
2. **Anorexia**, **weight loss**
3. **Weakness**

➢ ***Complications of Cirrhosis:***

1. Progressive hepatic failure
2. **Portal hypertension:**

- Normally: Portal circulation has LOW blood pressure
- In Cirrhosis:
  - **Sinusoidal Fibrosis** → **Increases resistance of blood flow** at the level of sinusoids
  - **Perivenular Fibrosis and parenchymal nodules** → **Compression of the central vein**

  → All of which lead to increase in blood pressure of portal circulation → **PORTAL HYPERTENSION** → Results in Arterial- portal anastomosis in the fibrous bands → which leads to increase in blood pressure of Portal Venous System

3. Hepatocellular Carcinoma (HCC)

Portal Hypertension

➢ *Causes of Hypertension:*

- **Pre-hepatic:**

1. Massive splenomegaly (Enlargement of the spleen)
2. Portal vein thrombosis

- **Hepatic:**

1. **Cirrhosis (main cause of portal hypertension)**
2. Schistosomiasis
3. Massive fatty change
4. Diffuse granulomatosis, as in **Sarcoidosis** and **TB**
5. Disease of portal microcirculation, such as: Nodular **Regenerative Hyperplasia**

- **Post-hepatic:**

1. Hepatic vein outflow obstruction
2. Severe right sided heart failure
3. Constrictive pericarditis

➢ *Manifestations/ Clinical consequences of Portal Hypertension:*

1. **Ascites (will be covered in this lecture)**
2. **Portosystemic Shunts (will be covered in this lecture)**
3. Hepatic Encephalopathy
4. **Splenomegaly (will be covered in this lecture)**

➢ Ascites:

Collection of excess ascitic fluid in the peritoneal cavity

Dx

Detected clinically when at least 500 ml of fluid is collected in the cavity.

Features

1. Serous fluid
2. Has the same concentration of **K+, Na+ and glucose** as the blood.
3. Contains **3g/ml of protein** (mainly **albumin**).
4. Small number of **mesothelial** cells and **lymphocytes**.
5. **Neutrophils** → An indication of infection.
6. **RBCs** → An indication of disseminated cancer

Results from

1. **Sinusoidal increase of blood pressure**
2. **Leakage of hepatic lymph** into the peritoneal cavity

Normally: Normal thoracic duct lymph flow of 800-1000 ml/day
Cirrhosis: 20L/day

3. **Hypo-albuminemia**: Decrease in synthesis of albumin in the liver
4. **Secondary Hyperaldosteronism** leads to: Renal retention of Na+ and water

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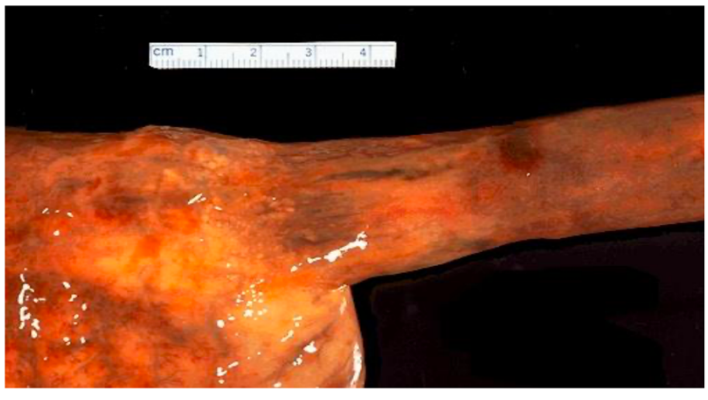
➢ Portosystemic Shunts

Portal Hypertension leads to formation of bypasses in areas where systemic and portal circulation share capillary beds.

Sites of formation of bypasses

1. **Gastroesophageal Junction**:
   Gastroesophageal Varices

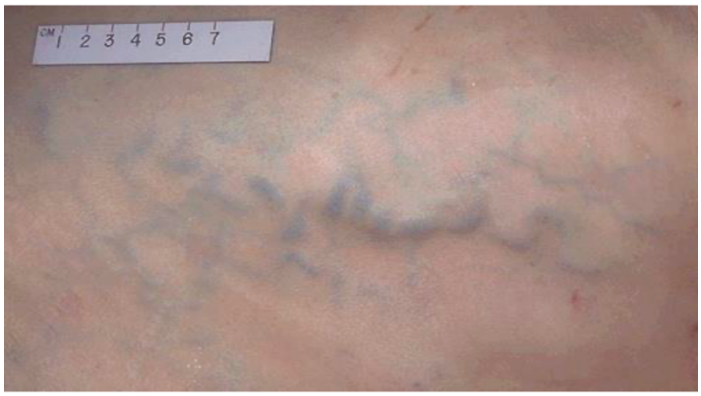


- **Gastroesophageal varices** appears in 65% of patients with advanced cirrhosis.
- **It causes death** in 50% of these patients due to upper GI bleeding.
- **Image**: esophageal varices with elongated dark areas representing the dilated varicose veins.

2. **Falciform ligament of the Liver (**Between the paraumbilical and abdominal wall collaterals) → Forms **caput medusae**

Caput Medusa

- **Image: Varicose dilated veins** in the **anterior abdominal wall** of a cirrhosis patient.
- Radiates from the umbilicus towards the periphery.



3. **Retroperitoneum**
4. **Around and within the rectum → Hemorrhoids**

➢ Splenomegaly

- Weight of the spleen:
  - **Normal:** <300 grams
  - **Cirrhosis:** 500-1000 grams
- Enlargement isn't always associated to other features of portal hypertension
- Results in **Hypersplenism** → Destruction of blood elements → Increase the risk or possibility of bleeding

- **Image:** Splenomegaly, with enlarged congested spleen in a cirrhosis patient.