# Pathology

Doctor 2017 | Medicine | JU | GI

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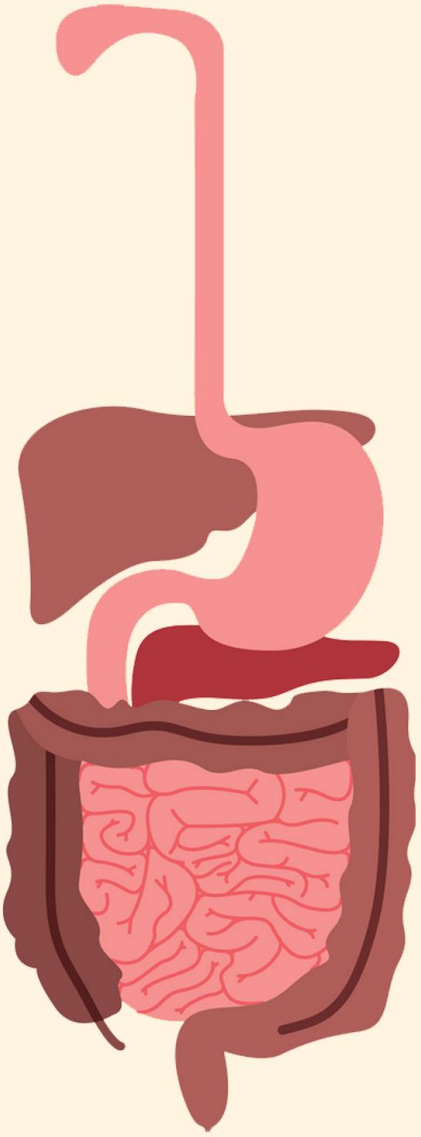


# 2nd system - GI

*I will be providing videos from 'osmosis' as they are very helpful and similar to our course, make sure to watch them after each topic and just skip what's irrelevant.*

## Reye's Syndrome

- Reye's syndrome is a rare form of **progressive encephalopathy** (brain dysfunction) and **fatty infiltration** (microvesicular steatosis) of the liver that tends to occur after 3-5 days of some acute **viral infections** (flu/chickenpox), particularly when **salicylates** (Aspirin) are used.
- The presentation is usually **misleading** where biopsy may show **normal tissue**. Sudden **microvesicular steatosis**; characterized by small intracytoplasmic fat vacuoles (fatty infiltration) accumulating in the cell, is shown on liver biopsy.
- The patient is prone to develop **liver failure**.

### Pathogenesis:

- **Malfunction of mitochondrial** is the main primary cause of disease in Reye's syndrome, in association with salicylate and viral infections.
- It affects the hepatocytes causing **liver damage**, thus it won't function normally in filtering **ammonia** out of the blood. Ammonia will diffuse through the BBB reaching the brain leading to **brain swelling** "edema". There is no inflammation in the liver.
- Due to swelling and **increased** intracranial pressure, the following **stages of encephalopathy** occur:
  1- Quiet, lethargy (fatigue), with vomiting.
  2- Seizure.
  3- May go into coma (25%), which is a serious condition.
  4- Death.
- Fatty change can be in skeletal muscles, heart and kidneys.

https://www.youtube.com/watch?v=Esgq0C2xjdY

## Budd - Chiari Syndrome

- The formation of a **blood clot** (thrombotic occlusion) within the **hepatic vein** leads to Budd–Chiari syndrome. This on the long term may causes **loss of liver function**.
- **It presents with**: abdominal pain, ascites, weight gain, and liver enlargement (Hepatomegaly).

- Suspected in patients having **predisposing factors** to blood clot formation:
  1- **Polycythemia Vera** (PCV): malignancy of the RBCs, is a condition characterized by increased RBC count in the blood which indeed will cause stasis increasing the chance of developing a thrombus.
  2- Exposure to **hormones**; oral contraceptive.
  3- **Pregnancy** and postpartum.
  4- Paroxysmal nocturnal hemoglobinuria; a disease characterized by RBCs destruction.
  5- Mechanical obstruction.
  6- Tumors, e.g. Hepatocellular carcinoma.
  7- Idiopathic in 30% of the cases.
- Mortality rate is **high** if not treated.

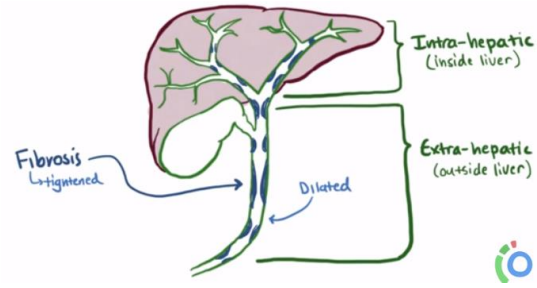
**Morphology:**

- The syndrome can be:
  1- **Acute**: development usually surrounds the parenchyma **around the central vein**, which initiate fibrosis around it.
  2- **Chronic**: associated with fibrosis.
- Swollen, red liver with a tense capsule; because it is engorged with blood.
- Centrilobular congestion and necrosis.
- Thrombi and fibrosis.

## Pathology of the Biliary System: Autoimmune Cholangiopathies

### A- Primary sclerosing cholangitis (PSC):

- Classified as an **autoimmune disease**. It is **Asymptomatic**.
- Characterized by **inflammation**, **obliterative fibrosis** (hardening), and **segmental** dilation of both **intra** and **extra** hepatic bile ducts. Segmental means that not all bile ducts are affected. The dilated areas are ones that aren't affected by fibrosis.

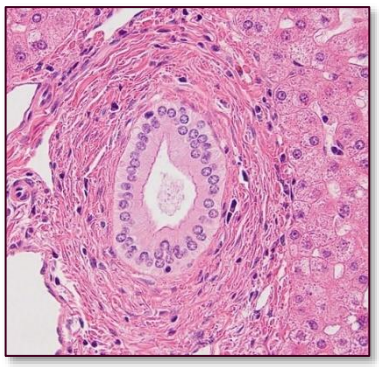



- Associated with **UC**; it coexists with PSC in 70% of patients. In patients with UC, 4% develop PSC.
- Most often occurs in the 3-5 decades, showing more in **men** 2:1.

## Characteristics:

- Since it is an autoimmune disease, elevated antibodies levels in the serum are found. Specific to PSC, an **anti-neutrophil (anti-nuclear) cytoplasmic antibody** is found in **80**% of the cases. This differentiates it other autoimmune disease where its **antimitochondrial** antibodies are prominent (in PSC, only in <10% of the cases).
- **Biliary diseases often show**: fatigue, pruritis (itchy skin) due to bile salt deposition in the skin, jaundice, weight loss, ascites, bleeding and encephalopathy.
- Increased levels of serum **alkaline phosphatase** point a biliary disease too; because the lining hepatocytes of the ducts are major site for the secretion of alkaline phosphatase, damaging will cause a noticeable increment in the enzyme concentration in the blood as it leaves the hepatocytes.

## Morphology:



- Concentric, periductal, **onion-skin fibrosis** around the bile duct and lymphocytic infiltrate.
- Atrophy and obliteration of bile ducts.
- Dilation of bile ducts in **between areas of stricture** *(beaded appearance).*
- **Cholestasis** and **fibrosis**; generally found in all biliary diseases.

## Pathogenesis:

- Gut-derived toxic bacterial products may be implicated in the biliary damage.
- Autoimmune attacks.
- Ischemia of biliary tree.
- It can cause:
  1- **Cirrhosis** due to fibrosis.
  2- **Cholangiocarcinoma** (10 – 15%), which is an adenocarcinoma of the biliary system.
  3- **Portal hypertension** leading to hepatosplenomegaly.

https://www.youtube.com/watch?v=ycDfF0EJssY

### B- Primary biliary Cirrhosis (PBC)

- Chronic, progressive and often a fatal cholestatic liver **autoimmune disease**.
- Non-suppurative, **granulomatous destruction** of medium-sized **intrahepatic bile ducts**, portal inflammation and scarring. The granulomas here are not caused by any infectious process.
- Characterized by **cholestasis**, due to the presence of granulomas surrounding the inflamed bile ducts. It causes the destruction of bile duct with no obvious underlying cause except that it's an autoimmune disease.
- Most often occurs in the age group 20-80 years (peak 40-50yrs), showing more in **females**.

**Characteristics:**

- Insidious onset with **slow** progression.
- **Complications**: pruritis, jaundice, increased levels of Alkaline phosphatase and cholesterol in the serum, and hyperbilirubinemia; hepatic decompensation. It can also cause cirrhosis.
- **Antimitochondrial** antibodies in > **90**%, releasing antimitochondrial pyruvate dehydrogenase.
- **Associated conditions**: Sjogren syndrome, Scleroderma thyroiditis, Rheumatoid arthritis, Raynaud's phenomenon, Membranous glomerulonephritis and celiac disease.

**Morphology:**

- **Interlobular** bile ducts are **absent** or **severely destructed** (florid duct lesion).
- Intraepithelial inflammation.
- **Granulomatous inflammation**; which is a characteristic of PBC.
- Bile ductular proliferation.
- Cholestasis, necrosis of parenchyma and cirrhosis.

### C- Secondary biliary cirrhosis

- Much more common than primary and can be very serious.
- It is a form of cirrhosis which develops in the liver secondary to prolonged extrahepatic obstruction and cholestasis. There are no antibodies in the blood as seen in the PBC.
- In most cases, extra-hepatic cholestasis is due to: cholelithiasis, biliary atresia, malignancies or strictures.

https://www.youtube.com/watch?v=CQtHOMzLzwU

*Primary sclerosing cholangitis (PSC) may sound similar to Primary biliary Cirrhosis (PBC). To avoid this confusion, this is an extra table:*

| Barone Rocks | Primary Biliary Cirrhosis PBC | Primary Sclerosing Cholangitis PSC |
|---|---|---|
| **Clinical** | • Females > Males<br>• Middle age<br>• Fatigue & pruritis<br>• Cholestatic Labs | • Males > Females<br>• 20-40's<br>• Progressive obstructive jaundice<br>• Cholestatic Labs |
| **Site of Involvement** | Intrahepatic | Intrahepatic & Extrahepatic |
| **Cause of Obstruction** | Granulomatous inflammation destroying bile ducts | Fibrosis destroying bile ducts |
| **Key Microscopic Feature** | Florid duct lesion (granulomas) | Concentric "onion-skin" fibrosis around bile ducts |
| **Diagnostic clue** | Anti-mitochondrial antibodies (AMA) - Antibodies against the subunit of pyruvate dehydrogenase complex | Beaded appearance of bile ducts on cholangiogram/ERCP/MRCP<br><br>Baronerocks.com |
| **Association** | Other autoimmune disorders Sjögrens, RA, etc. | Ulcerative colitis |
| **Long-term Complication** | Cirrhosis | Cirrhosis<br>Cholangiocarcinoma |

## Sinusoidal Obstruction Syndrome

- Previously known as **Veno-occlusive disease**. It is a complication of **bone-marrow transplant procedures**, incidence is about **20%** in recipients of bone marrow transplant. Usually occurs after 20-30 days after bone marrow transplantation.
- To ensure a successful bone marrow transplantation, the following is done:
  1- Chemotherapy using **cyclophosphamide** is given.
  2- Total body **radiation**; to clear all malignant cells in the blood.
    ⇨ This may lead to the destruction of the **sinusoidal endothelial lining**; which stimulate the **stellate** cells initiating **fibrosis**, and thus causing Veno-Occlusive disease.

> ***Note:*** *Hepatic **stellate cells**, also known as **perisinusoidal** cells, are **profibrogenic** cells found in the **space of Disse** (a small area between the sinusoids and hepatocytes). Upon stimulation they initiate liver **fibrosis**.*

- Originally described in **Jamaican** drinkers of **bush-tea** containing high levels of pyrrolizidine alkaloids; which affects endothelium lining of sinusoids.
- **Clinical presentation:** mild – severe. Death if does not resolve in 3 months.
- **Mechanism**: Toxic injury to sinusoidal endothelium → Emboli (Thrombus) → Blockage of blood flow → Blood goes into the space of Disse → Stimulate stellate cells → Fibrosis.

## Peliosis Hepatis

- It is a vascular condition characterized by **sinusoidal dilatation** throughout the liver.

**Caused by:**

1- **Anabolic steroids:** Peliosis hepatis is caused by certain drugs but most commonly it is caused by steroids (androgen) overdose, particularly in men using hormones for body building.

2- **Oral contraceptives**: in females.

3- **Danazol**; a weak androgen, anabolic steroid and progestogen.

**Pathogenesis:**

- Its pathogenesis is unknown.
- **Asymptomatic** disease, however, it can cause complications of **intra-abdominal hemorrhage** and **liver failure**.
- It is a **reversible** process once the underlying cause is treated or stopped.

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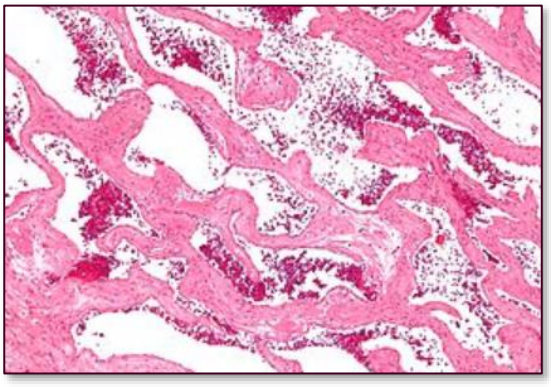
## Liver Tumors and Nodules

- Liver masses are **mostly** due to **secondary malignancies** rather than being primary.
- The liver is one of the **most common** sites to have secondaries; metastasized cancer from the **GIT**, precisely the **colon** *(portal drained organs metastasize to the liver).*

### A- Primary Benign Tumors

1- **Cavernous hemangioma:**

- The **most common** benign tumor of the liver.
- A collection of **dilated** blood vessels forms a lesion.
- **Subcapsular lesions**; present on the surface of the liver. Usually <2cm.
- The blood vessels filled with blood are **swollen** and may rarely **rupture**. This might be spontaneous, or due to biopsy or fine needle aspiration leading to intraperitoneal **hemorrhage**.



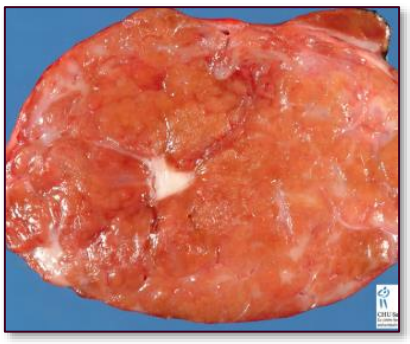
## 2- Hepatocellular adenoma (HA):

- Rare benign tumor associated with the **hepatocytes**.
- Highly associated with **hormonal intake**. Therefore, patients are usually **young females** (using oral contraceptive intake). In men, it is due to **steroid intake**.
- The adenoma may **rupture** especially during **pregnancy** causing severe **intraperitoneal hemorrhage**.
- Hepatocellular **carcinoma** rarely arises from hepatocellular adenoma. HA is often **misdiagnosed** as Hepatocellular carcinoma.

## 3- Liver Nodules

### a- Focal nodular hyperplasia (in non-cirrhotic liver):

- **2nd** most common benign tumor after cavernous hemangioma, it is totally **benign** and **won't** become malignant.
- It appears as a **mass lesion** (nodular aggregation) in an otherwise **normal** liver, most frequently in young-middle aged females (reproductive age) but may happen in all ages.
- **Well-demarcated** hyperplastic hepatocytes with **central scar** in a **non-cirrhotic** liver; nodules are similar to those of cirrhosis, but they are **localized** and not diffused unlike cirrhosis.



- May arise from **local vascular injury** (hepatic ischemia).
- **20%** of cases have **cavernous hemangioma**.

### b- Micro-regenerative Nodules (in cirrhotic liver):

- Usually **part of cirrhotic liver**: the continuous degeneration-regeneration creates nodules that become prominent. They are **larger** than cirrhotic nodules.
- **No atypical features** under the microscope; reticular fibers of the liver are **intact**.
- It has **no** malignant potential.

### c- Dysplastic Nodules (in cirrhotic liver):

- Usually it is difficult to diagnosis; hard to differentiate it from hepatocellular carcinoma.
- Nodules are larger than 1 mm in size in a **cirrhotic liver**.
- **Types**: small cell dysplastic nodules, large cell dysplastic nodules.

- **Atypical features:**
  1- Pleomorphism and crowding.
  2- High proliferative activity.
  3- Can be of high or low dysplasia.
  4- **Precancerous** (monoclonal, gene mutation); there's a potential to become malignant.

https://www.youtube.com/watch?v=4f4H3xBhF9I

## B- Primary Malignant Tumors

1- **Hepatocellular carcinoma (HCC):** arising from the hepatocytes.

- Hepatocellular carcinoma accounts for **5.4% of all cancers**.

### Incidence:

- **High rates in Asia** (Korea, Taiwan, Mozambique, china) and Africa → 36/100000.
- In Mediterranean → 15/100000.
- **Low rates** in America, central Europe and Australia → <5/100000.
- **M:F ratio:** (3:1) in low incidence areas in **>60 years**, and (8:1) in high incidence areas between the ages of **20-40 years.**
- Blacks > white.
- It is more frequent among men due to having **more predisposing factors**.

### Predisposing Factors:

1- >85% of cases of Hepatocellular carcinoma occur in countries with high rates of chronic **HBV** infection, in which it is transmitted vertically, the carrier state starts from infancy. Along with being exposed to **Aflatoxins**, this increases the risk for HCC dramatically.

➔ The peak age of incidence here is among the ages of **20-40 years**, and **cirrhosis** is mainly **absent**.

2- In western countries, cirrhosis is present in 90% of Hepatocellular carcinoma, largely owing it to **HCV** and **alcoholism**.

➔ The peak age of incidence here is **>60 years**, with **cirrhosis** being **present**.

3- Hereditary tyrosinemia (in 40% of cases).

4- Hereditary hemochromatosis.

## Pathogenesis:

1- The most underlying factor to Hepatocellular carcinogenesis are **viral infections** (HBV, HCV) and **toxic injuries** (Aflatoxins, alcohol).
   - **Aflatoxin** (found in decaying food) synergizes with **HCV/HBV** to increase the risk further.

2- Chronic liver diseases cause the emergence of HCC; background of **cirrhosis**.
   - Cirrhosis can occur: due to **HCV**, **Alcohol**, **Hemochromatosis**, and **Tyrosinemia**.

3- HCC can be induced by **acquired mutations** in oncogenes and tumor suppressor genes.
   - Aflatoxins cause **TP53 mutation** inducing carcinogenesis.
   - In HBV and HCV, repeated cycles of cell death and regeneration increases the risk of gene mutations and **instability**.
   - HBV integration in the DNA leads to clonal expansion and **genomic instability**. Also, it's **X-protein**, leads to activation of oncogenes and inhibition of apoptosis inducing tumor formation.

## Morphology:

- Primary malignant liver tumors can be: HCC, Cholangiocarcinoma "discussed below" or both (mixed).
- **HCC may appear grossly as:**
  1- Unifocal: single tumor
  2- Multifocal: multiple tumor, common in secondary malignancies.
  3- Spread Diffusely

  ⇨ **Vascular invasion** is common in all types

- HCC ranges from **well-differentiated** (looks like normal hepatocytes) to **highly anaplastic** lesions.

## Clinical presentation:

- Manifestations are often **masked** by **cirrhosis** or **chronic hepatitis** symptoms.
- Mainly upper **abdominal pain, malaise and weight loss**.
- Increased serum levels of **α-fetoprotein in 60-75%** of patients, but it is neither specific nor sensitive to HCC.

- **α-fetoprotein increases with:**

**1-** Yolk sac tumor
**2-** Massive liver necrosis
**3-** Fetal distress or death
**4-** Cirrhosis
**5-** Normal pregnancy
**6-** Fetal neural tube defect

**Prognosis**:

- It is **poor**, death occurs within 7 -10 months.
- **Death usually occurs due to**: Cachexia, GI bleeding, liver failure, tumor rupture and hemorrhage.

### 2- Cholangiocarcinoma "adenocarcinoma":

- It is the **second most common** primary **malignant** liver tumor after **HCC**, arising from the epithelium of the biliary system; **extra** and **intra** hepatic ducts.
- Cholangiocarcinoma are **desmoplastic**, they are very hard due to large amount of fibrous tissue.
- **Metastasis** is hematogenous to the lungs, bones, adrenals, and brain, in **50%** of patients with cholangiocarcinoma.

### 3- Fibrolamellar hepatocellular carcinoma:

- Typically affects young adults of 20-40 years.
- Frequency among males is the **same** for females.
- It has **no** relation to **HBV or cirrhosis** with **better** prognosis than single hard scirrhous (fibrous) tumors.

https://www.youtube.com/watch?v=zv04qtEM8qw

**Good Luck**

*Contact me without hesitation if you need anything.*