GI
PATHOLOGY

#6

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SECONDARY BILIARY CIRRHOSIS:

• caused by: **prolonged obstruction to extra hepatic biliary tree.**

• Any condition which is responsible for obstruction of the biliary tree end up with developing of cirrhosis as:

• **Causes:**

1) Cholelithiasis (The formation of gallstones).

2) Biliary atresia (One or more bile ducts are congenitally narrow, blocked, or absent).

3) Malignancies.

4) Strictures (The common bile duct is abnormally narrow).

PRIMARY BILIARY CIRRHOSIS:

• **A chronic, progressive and often fatal cholestatic liver disease.**

↓

*which is characterized by the accumulation of bile material in biliary system.

• Characterized by the formation of: **Non-suppurative granulomatous destruction of medium-sized intra-hepatic bile ducts with Portal inflammation and scarring.**

• This condition affects the: **aga 20-80yrs (peak 40-50yrs).**

• **F>M**, much more common in females.

• **Insidious onset,** because it's prolonged process that develops over years and it can present with **Pruritis, jaundice**.

• It may cause **cirrhosis over 2 or more decades** after initial presentation.

- Also it's characterized by:

• **Increase alkaline phosphatase and cholesterol.**

• **Hyperbilirubinemia indicates hepatic decompensation** and initiation of hepatic failure 'cause of the execrative pathway of bile is obstructed.

-failure of the liver to compensate for the functional overload resulting from the disease.

• Presence of auto-antibody **anti-mitochondrial antibodies** are present **in more than 90%** of the patients**, particularly, antimitochondrial pyruvate dehydrogenase antibodies.**

• **Associated conditions** & autoimmune diseases: **Sjogren syndrome, Scleroderma thyroiditis, RA (rheumatoid arthritis), Raynaud's phenomenon, MGN (membranous glomerulonephritis), and celiac disease.**

Morphology

• **Interlobular bile ducts are absent or severely destructed (florid duct lesion).**

• **Intra-epithelial inflammation.**

• **Granulomatous inflammation** that usually centered around destructed bile duct → this is **hallmark** of primary biliary cirrhosis.

• **Bile ductular proliferation.**

• **Cholestasis** (blockage of bile flow).

• **Necrosis of parenchyma**

• In long term, the whole process of destruction and inflammation can result in development of **cirrhosis.**

****Extra info**: the florid duct lesion, defined as a granulomatous destruction of the bile ducts, is the histological hallmark of PBC.

SINUSOIDAL OBSTRUCTION SYNDROME (VENO-OCCLUSIVE DISEASE)

• A condition in which some of the small veins in the liver are obstructed.

• **Originally described in Jamaican drinkers of bush-tea containing** a chemical called **pyrrolizidine alkaloids** which associated with the infection of the liver.

• **This occurs in the first 20-30 days after bone marrow transplantation**

• due to **(causes)**:

1) **Drugs as cyclophosphamide.**
2) **Total body radiation** → which is a pre-transplantation step in patients receiving bone marrow transplantation.

- These 2 agents (chemotherapeutic agent & radiation) are given to a patient with malignancy in order to cause death of malignant cells. However, they also affect liver sinusoid causing this disease. In other

words, it is a complication of radiation to the whole body or high-dose chemotherapy given before a bone marrow transplant.

• **Incidence:**

- 20% in recepients of allogeneic marrow transplant.

• **Clinical presentation:**

- Can vary **from mild——to——severe.**

- In sever forms it can cause **death if does not resolve in 3 months.**

- Also, it can be resolved within 3 months after transplantation, regeneration takes place and complete resolution can occur.

• **Mechanism:**

- Exposure to **toxic** agents (e.g., cyclophosphamide) causes **injury to** the hepatic venous endothelium.

sinusoidal endothelium → emboli formation **→ blockage of blood flow → passage of blood into space of Disse →** stimulation of **stellate cells activation → fibrosis.**

****Some Recommended videos, they WILL HELP!**

• (1512) Primary sclerosing cholangitis causes, symptoms, diagnosis, treatment & pathology – YouTube

• (1512) Primary biliary cholangitis causes, symptoms, diagnosis, treatment & pathology – YouTube

PELIOSIS HEPATIS

- It's an another form of vascular diseases:

• Characterised by **sinusoidal dilatation.**

• **Causes:**

1-anabolic steroids usage.

2-oral contraceptive.

3-danazol drug.

• **Pathogenesis:** the underlying mechanism is **unknown** and not fully understood.

- These patients can be **asymptomatic.**
- **Intra-abdominal hemorrhage.**
- **Liver failure** in severe cases**.**
- If the underlying cause is removed, the process can be **reversible** and hepatocytes can be preserved.

LIVER TUMORS

- Liver tumors can be primary or secondary (metastasis which is more common).

- **Benign tumors:**

1- Cavernous hemagioma → they cause haemorrhage.

- The **most common** benign liver tumor.
- Small in size, **usually less than 2 cm** in diameter.
- **Subcapsular** in location.

2- Liver cell adenoma

- Usually occurs in **young females** usually with **history of oral contraceptive intake.**
- **It may rupture especially during pregnancy** when it can enlarge rapidly, **causing severe intraperitoneal hemorrhage.**
- Males on steroids for muscle building also can present with liver adenoma
- Usually, they are benign **rarely may contain (HCC)** hepatocellular carcinoma.
- **May be misdiagnosed as HCC.**

****Extra info**: Estrogen stimulates the development of hepatocellular adenoma, thus Liver cell adenoma is associated with oral contraceptive intake and pregnancy.

****Recommended video:**

- **(1513) Benign liver tumors causes, symptoms, diagnosis, treatment & pathology – YouTube**

❖ LIVER NODULES

- they can mimic hepatic masses.

1- Focal Nodular Hyperplasia.

- **Well demarcated hyperplastic hepatocytes with a central scar**, forming localized non-diffused nodules.
- **Present in non-cirrhotic liver**
- **Not a neoplasm but shows nodular regeneration.**
- Occurs due to **local vascular injury.**
- Most common in **females of reproductive age.**
- **No risk of malignancy.**
- **20% of cases have cavernous hemangioma.**

****Extra info:** Diagnosis of liver nodules is very important because these can be misdiagnosed with malignant one!

2- Macroregenerative Nodules.

- Present in **cirrhotic liver**, BUT more prominent and **larger than cirrhotic nodules**.
- **No atypical features.**
- **Reticulin** (which's a special stain) background of the parenchyma **is intact.**
- **No malignant potential.**

3- Dysplastic nodules.

- **Larger than 1 mm.**
- Present within **cirrhotic liver** → some cirrhotic nodules develop dysplastic changes so it's called dysplastic nodules.
- **Atypical** nuclear and cellular **features,** the cells are **pleomorphic and** there's **crowding** → They show dysplastic features in form of nuclear hyperplasia and pleomorphism.
- **High proliferative activity.**
- The degree of dysplasia can be variable, it can be **high or low dysplasia.**
- **Precancerous (monoclonal, they have gene mutations).**

- **Types:**

1. Small – cell dysplastic nodules

2. Large – cell dysplastic nodules

MALIGNANT LIVER TUMORS

1- Hepatocellular carcinoma (HCC) → a primary cancer.

- Represents **5.4% of all cancers,** so it's not common.
- **Incidence** can vary:

*** <5/100,000 population in North and South America, north and central Europe, and Australia. (Low in developed countries)**

***15/100,000 population in the Mediterranean. (Intermediate)**

***36/100,000 population in Korea, Taiwan, Mozambique, and China. (High)**

- **Blacks > white** → it affects the black more than white.
- **M:F ratio** is variable:

3:1 in low incidence areas, with the age of incidence **>60 years.**

8:1 in high incidence areas, with the age of incidence between **20-40 years.**

• Predisposing Factors:

1-Hepatitis carrier state.

- **Vertical transmission** (from mother to child) **increases the risk of malignancy 200 times.**
- In this case **cirrhosis may be absent.**
- **young age group (20-40 yrs).**

2-Chronic hepatitis B infection.

- **> 80% of cases of HCC occur in countries with high rates of chronic HBV infections** (countries where HBV is endemic).

3-Cirrhosis.

- **In western countries cirrhosis is present in 85-90% of cases** of HCC.
- These cases are usually associated with individuals of old age **(>60 years).**

• **HCV** (hepatitis C virus) **and alcoholism** are common predisposing factors for development of cirrhosis.

4-Aflatoxins.

- One of the most important predisposing factors in African countries.

- They are poisonous carcinogens and mutagens that are produced by Aspergillus flavus.

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

- An amino acid metabolic disorder that involves impaired break down of the amino acid tyrosine. It affects the liver and kidneys.

6-Hereditary hemochromatosis.

• **Pathogenesis:**

1-Repeated cycles of cell death (degeneration) **and regeneration** due to **HBV** and **HCV** infections. They are associated with increased risk for the development of **gene mutations** and **genomic instability** that is required for cancer development.

2-Viral integration HBV DNA integration in the host DNA**, which leads to clonal expansion** of viral DNA in hepatocytes.

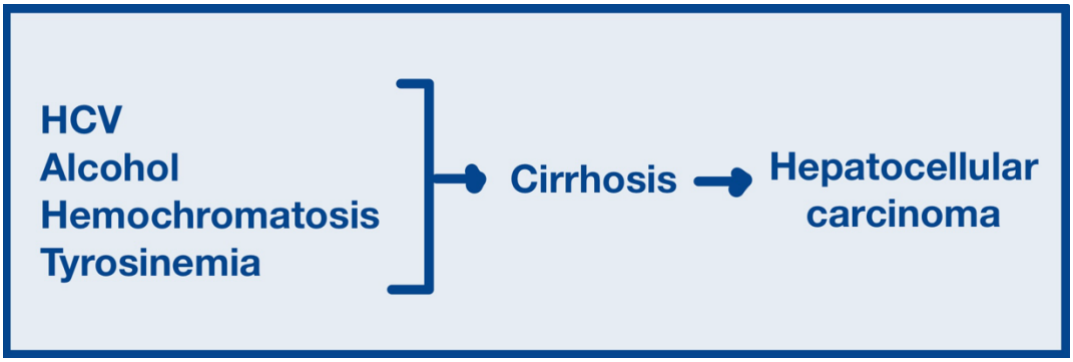
3- HBV DNA integration leads to genomic instability that is not limited to the integration site.

4- The viral protein of **HBV**, called **X-protein**, **leads to transactivation of viral and cellular promoters, activation of oncogenes, and inhibition of apoptosis**, all of which are early steps in carcinogenesis.

5- Aflatoxins (fungus Aspirgillus flavus). Can cause **mutation of p53**.

6- Cirrhosis.

- HCV, Alcohol, Hemochromatosis, Tyrosinemia (40% of patients develop HCC despite adequate dietary control).



Morphology:

- There're 3 types of primary liver malignancy:

1-HCC (Hepatocellular carcinoma) → (Hepatocyte origin).

2-CC (Cholangiocarcinoma) → (Epithelium of biliary duct origin).

3-Mixed of both types.

- Liver tumor can be:

- **Unifocal** → primary > secondary tumor.
- **Multifocal** → secondary (metastatic) > primary tumor.
- **Diffusely infiltrative** (involving the whole liver).
- **Vascular invasion is common** mode of metastasis **in all types.**
- Regard grading, liver tumor can vary

from Well differentiated **—to— Anaplastic** differentiation (poorly differentiated).

Continuation of **Malignant** Liver Tumors:

2- Fibrolamellar Carcinoma specific form of hepatocellular carcinoma.

- Affects individuals at young age group: **20-40 years.**
- **M=F**
- **Has no relation to HBV or cirrhosis.**
- **Has better prognosis** than the conventional type of HCC.
- Presents as **single hard scirrhous tumor.**
- tumor cells have eosinophilic cytoplasm.

3- Cholangiocarcinoma (CC).

- Cancer in the epithelial cells of hepatic bile ducts.

- They **are desmoplastic**. That's why we should think of any metastatic tumor with high desmoplastic reaction to be of biliary system.

Metastasis:

➢**vascular** metastasis to the **lungs, bones, adrenals, and brain** occurs, **in 50% of cholagiocarcinoma.**

Clinical picture of liver tumors:

- **Abdominal pain, malaise, and weight loss** (non-specific symptoms).
- **Increase in α-fetoprotein levels in 60-75% of patients.**

α-fetoprotein also increases with:

1- Yolk sac tumor

2-cirrhosis

3- massive liver necrosis

4-chronic hepatitis

5-normal pregnancy

6- fetal distress or death

7-and fetal neural tube defect

****Extra info**: It's not specific to HCC, but the age and presentation of HCC are totally specific. Thus, the increase in α-fetoprotein (in patients with the specific age and presentation of HCC) **MUST** indicate the presence of a liver tumor.

Prognosis of liver cancer:

- **Death within 7-10 months.** after diagnosis.
- **Causes:**

1)Cachexia (severe weight loss).

2) GI bleeding.

3) Liver failure.

4) tumor rupture and hemorrhage.

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