Summary for GI Pathology

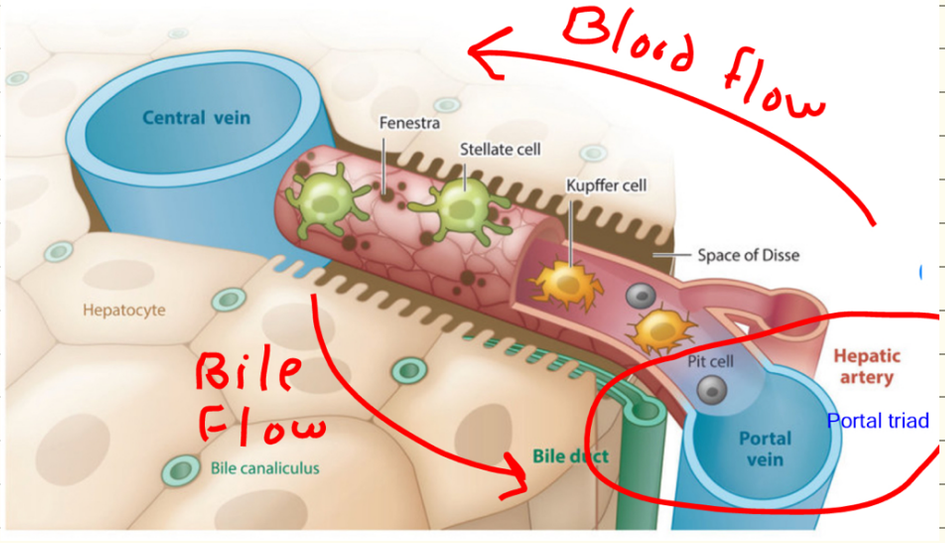
The first 6 Lectures

Lecture 1

The functional unit of the liver is a hexagons structure (The lobule) which is composed of 6 acini that represents the liver parenchyma. Each acinus is composed of plates of hepatocytes radiating to the portal triad (PV: portal vein ,HA: hepatic artery branch (arteriole) ,BD: bile duct) surrounding a CV: central vein. Sinusoids are vascular layers separating cords of hepatocytes .

Each sinus is subdivided into three zones :
Zone 1(periportal) : the usuall entry of inflammations
Zone 2 : (mid zone)
Zone 3 (pericentral) : most liver diseases occur here.

Each zone differs with respect to its metabolic activities, and hepatic injury.



Hepatic injury

1.Inflammation (hepatitis)

2.Ballooning degeneration (accumulation of iron, copper,fat,bile)

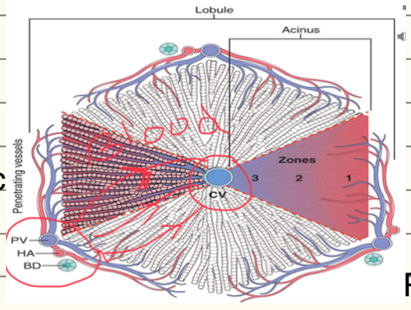
3.steatosis

- Microvesicular : it appears in cases like (Alcoholic liver disease (ALD), Reye syndrome, acute fatty change of pregnancy)
- Macrovesicular : it appears in cases like (obesity, diabetes mellitus(DM))

4. Necrosis: classified depending on the location:

- *centrilobular (zone 3)
- *mid zonal (zone 2)
- *periportal (zone 1)

This picture illustrates the different hepatic zones



Recall that the most commonly affected region From ischemia is zone 3 , From inflammation and viral hepatitis zone 1

Recall that fat accumulation begins at zone 3

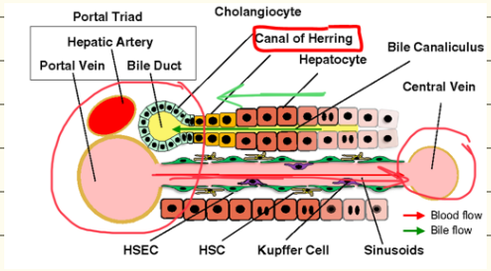
5. Ductular proliferation (the presence of Duct-like structures from stem cell-mediated regeneration

6. Fibrosis (portal ,periportal, pericentral, bridging)

7. Cirrhosis (micronodular (less than 3 mm), macronodular (more than 3 mm)

Regeneration:

- By mitosis from the remaining hepatocytes
- By differentiation from stem cells called (cells of canal of herring (which are lined partly by hepatocytes and partly by cholangiocytes, and they are progenitor for hepatocytes and cholangiocytes



Hepatic Failure (When 80-90 % functional capacity is lost)

Causes :

- Massive hepatic necrosis ; that results from :
  *Fulminant viral hepatitis (B,B-D,A,C)
  *Drugs and chemicals (acetaminophen, halothane , anti TB drugs , CCL4, mushrooms poisoning , antidepressants like monoamine oxidase inhibitors)
- Chronic liver disease
- Hepatic dysfunction without overt (apparent) Cirrhosis ; it appears in conditions like (Reye's syndrome, tetracycline toxicity, acute fatty liver of pregnancy

Optional

Massive hepatic necrosis

-Fulminant hepatic failure from the onset of symptoms to hepatic encephalopathy (within 2 -3 wks).
-Subfulminant (within 3 months).

Causes:

1-Viral hepatitis 50 – 65% (B, B-D, A,C hepatitis)
2-Drugs & chemicals 20 – 30%
3-Heat stroke
4-Hepatic vein obstruction
5-Wilson disease
6-Acute fatty liver of pregnancy
7-Massive malignant infiltration
8-Reactivation of chronic HBV hepatitis on HDV superimposed infection
9-Autoimmune hepatitis

Remember : morphologically, there is massive hepatic necrosis .The liver is small , shrunken due to loss of parenchyma.
Scar is mostly absent given the acute nature of the process

SUMMARY

LIVER FAILURE

- Liver failure may follow acute injury or chronic injury, or it may occur as an acute insult superimposed on otherwise well-compensated chronic liver disease.
- The mnemonic for causes of acute liver failure are as follows:
  - A: acetaminophen, hepatitis A, autoimmune hepatitis
  - B: hepatitis B
  - C: cryptogenic, hepatitis C
  - D: drugs/toxins, hepatitis D
  - E: hepatitis E, esoteric causes (Wilson disease, Budd-Chiari syndrome)
  - F: fatty change of the microvesicular type (fatty liver of pregnancy, valproate, tetracycline, Reye syndrome)
- Potentially fatal sequelae of liver failure include coagulopathy, encephalopathy, portal hypertension and ascites, hepatorenal syndrome, and portopulmonary hypertension.

Lecture 2

Alcoholic liver disease

* 80 to 100 mg/dl is the legal definition for driving under the influence of alcohol

*Habitual drinkers can tolerate up to 700 mg/dl without clinical effects .This is due to metabolic tolerance explained by 5-10X induction of cytochrome P450 system

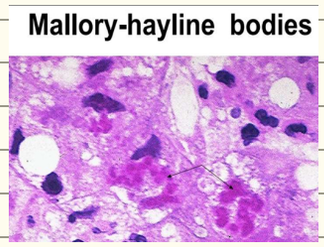
Forms of alcoholic liver disease:

1. Hepatic steatosis (which is seen in almost all drinker drinkers)
2. Alcoholic hepatitis (1-35% of drinkers)
3. Cirrhosis (14% of drinkers).

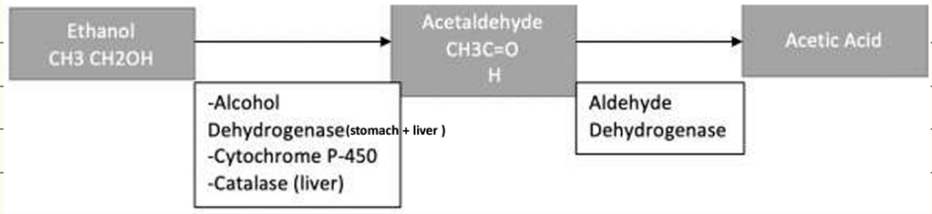
Hepatic steatosis	Alcoholic hepatitis	Alcoholic cirrhosis
*Liver is large (hepatomegaly, 4 -6 kg) soft yellow and greasy ,and upon Continuation of the intake, this can progress to fibrosis, which is irreversible *Recall that fatty change (steatosis) is reversible with complete abstention	Characteristic findings: 1-Hepatocyte swelling (hepatomegaly) & necrosis 2-Mallory-hyaline bodies : (collapsed cytokeratin intermediate filaments) 3- Neutrophilic reaction 4- Fibrosis 5- Cholestasis 6- Deposition of hemosiderin in hepatocytes & Kupffer cells	*Initially years the liver is enlarged yellow then it becomes brown shrunken non- fatty organ, might be less than 1 kg weight *Mallory bodies are only rarely evident at this stage *Irreversible *It can develop rapidly in the presence of alcoholic hepatitis (within 12 yrs).

Mallory-hyaline bodies are NOT pathognomonic inclusion of alcoholic liver disease. are also seen in :

1- Primary biliary cirrhosis
2- Wilson disease
3- Chronic cholestatic syndromes
4- Hepatocellular carcinoma



Ethanol metabolism



Mechanism of ethanol toxicity

1- Fatty change

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

decrease in lipoprotein transport from liver due to formation of acetaldehyde adducts with tubulin

decrease in Beta-oxidation of FFA

2- Induction of cytochrome P-450

enhances the metabolism of drugs to toxic metabolites like (acetaminophen)

3. Generation of free radicals (from cytochrome P-450)

4- Acetaldehyde causes hepatocytes lipid peroxidation & antigenic alteration of which can initiate an immune attack

5- Superimposed infections

causes acceleration of liver injury (HCV hepatitis occurs in 30% of alcoholics)

6- Alcohol causes release of bacterial endotoxins and alteration of cytokine regulation

(TNF is a major effector of injury IL6 IL8 IL18)

7- Alcohol causes regional hypoxia

Due to release of endothelins which are potent vasoconstrictors

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Causes of Death in Alcoholic Liver Disease

1-Hepatic failure
2-Massive GI bleeding
3-Infections
4-Hepatorenal syndrome and failure of other organs
5-HCC (hepatocellular carcinoma) which occurs in 3-6% of cases

Optional

Clinical features

- Hepatic steatosis (reversible)
  liver enlargement
  Increase of liver enzyme
  Severe hepatic dysfunction is unusual
- -Alcoholic hepatitis
  . 15-20 yr. of excessive drinking
  . Non-specific symptoms, malaise, anorexia, weight loss
  enlarge liver & spleen
  LFT (liver function test) is abnormal with increasing of liver enzymes
  Each bout of hepatitis →10-20% risk of death→ cirrhosis in 1/3 in few yrs.
- Cirrhosis
- Portal hypertension

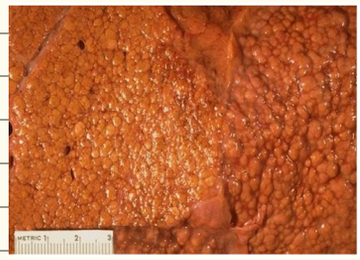
Lecture 3

Cirrhosis :It is a diffuse process characterized by fibrosis & and conversion of the liver parenchyma into nodules.

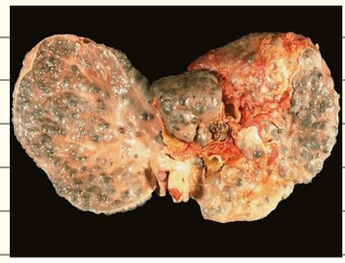
Types :

Micronodular : < 3mm in diameter

Macronodular : > 3mm in diameter



Micronodular



Macronodular

Main characteristics :

*Bridging fibrous

*Parenchymal septae nodules encircled by fibrotic bands

*Diffuse architecture encircled disruption

Causes of cirrhosis

1. Chronic alcoholism
2. Chronic viral infection
3. Biliary disease
4. Autoimmune hepatitis
5. Wilson disease
6. Hemochromatosis
7. a1 -antitrypsin deficiency

Rare causes of cirrhosis

Galactosemia

Tyrosinosis

Glycogen storage disease III &IV storage disease

Hereditary fructose intolerance

Drug induced : methyldopa

Cryptogenic cirrhosis (10%)

Pathogenesis of cirrhosis

1-Hepatocellulardeath

2-Regeneration

3-Progressive fibrosis

4-Vascular changes

1-Loss of sinusoidal endothelial cell fenestration

2-developmentof vascularshunts as (Portal V-hepaticV) (Hepatic A–portal V) >> defect in liver function

3– loss of microvilli from hepatocytes→↓transport capacity of the cells

Around the sinusoids there is a space called space of Disse , where delicate framework of collagen type 4 is present, but in the case of cirrhosis it is replaced by types 1,3.

Within the space of Disse , there are Vitamin A and Fat storing cells called Stellate (Ito) cells , upon stimulation they secrete TGF-Beta which is responsible for collagen deposition

The stimuli for activation for stellate :

Reactive oxygen species # Growth factors # Cytokines TNF, ILI, lymphotoxins

Clinical features of cirrhosis

Complications

Silent

Anorexia,weight loss, weakness

1- Progressive hepatic failure
2- Portal hypertension
3- Hepatocellular carcinoma

Definition → ↑ resistance to blood flow at the level of sinusoids and compression of central veins by perivenular fibrosis & parenchymal nodules

Causes

#Prehepatic due to :
1-Portal vein thrombosis
2-Massive splenomegaly

#Hepatic due to :
1- Cirrhosis
2- Schistosomiasis
3-Massive fatty change
4-Diffuse granulomatosis,as sarcoidosis,TB
5-Disease of portal micro circulation as nodular-regenerative hyperplasia

#Posthepatic due to :
1-Severe Right- sided heart failure
2-Constrictive pericarditis
3-Hepatic vein outflow obstruction

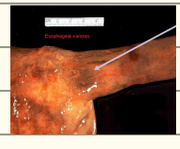
Clinical consequence of portal hypertension

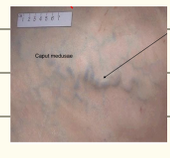
Ascitis: Collection of excess fluid in peritoneal cavity

Features
1- Serous fluid
2-Contains as much as 3g/ml protein(mainly albumin)
3- It has the same concentration as blood of glucose, Na+, & K+
4- Mesothelial cells & lymphocytes
5- Neutrophils= infection 6- RBCs = Dissemnated CANCER

Pathogenesis
1-Sinusoidal ↑ Bp
2- Hypoalbuminemia
3-Leakage of hepatic lymph into the peritoneal cavity
4-Renal retention of Na + & water is due to secondary hyperaldosteronism

Portosystemic shunt : Becauseof ↑ portal venous pressure bypasses develop wherever the systemic&portal circulation share capillary beds





-Sites: 1-Around & within the rectum (Hemorrhoids)
2-Gastroesophagealjunction(varicies)
3- Retroperitoneum
4- Falciform ligament of the liver (periumbilical & abdominal wall collaterals)→caput medusae
5- Gastroesophageal varicies (cause death in 50% of them due to upper GIbleeding)

Splenomegaly :Not necessarily correlated with other features of portal increase in BP

May result in hypersplenism(which associated with excessive restriction of RBCs in the spleen is normally filled with blood, which this leads to peripheral pancytopenia and other complications)

Hepatic encephalopthy

It is a complication of of acute and chronic hepatic failure

it leads to disturbances in brain function behavioural changes to ranging from behavioral changes to marked confusion and stupor (coma) to deep coma and death

Neurological signs:

Rigidity

Hyperreflexia

Asterixis (nonrhythmic rapid extension flexision movements of head and extremities)

Non specific EEG

Brain shows edema and astrocytic reaction.

Pathogenesis

Severe loss of hepatocellular function >>Shunting of blood around damaged liver >>Exposure of brain to toxic metabolic products

↑ NH3 level in blood → generalized brain edema impaired neuronal function

alterations in central nervous system Amino Acids metabolism

Optional

Cell death should occur over a long period of time & accompanied by fibrosis

-In normal liver the ECM collagen (types I, III,V& XI) is present only in :

Liver capsule

Portal tracts

Around central vein

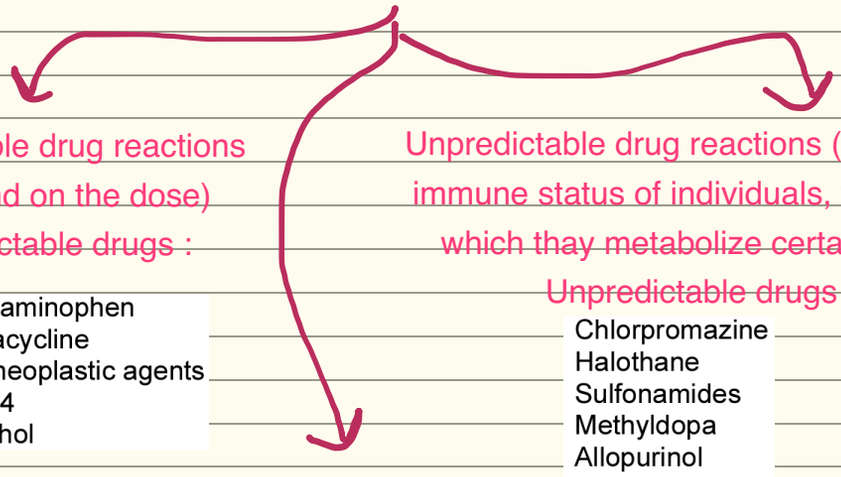
Collagen deposition converts sinusoids with fenestrated endothelial channels that allow free exchange of solutes between plasma and hepatocytes to higher pressure, fast-flowing vascular channels without such solute exchange.

The movement of proteins (e.g., albumin, clotting factors, lipoproteins) (which are synthesized by hepatocytes) between hepatocytes and the plasma is markedly impaired.

- These functional changes are aggravated by the loss of microvilli from the hepatocyte surface, which diminishes the transport capacity of the cell (and the deterioration of liver function gets of cirrhosis).

Lecture 4

Drug induced liver disease



Predictable drug reactions (depend on the dose)

Predictable drugs :

- Acetaminophen
- Tetracycline
- Antineoplastic agents
- CCL4
- Alcohol

Unpredictable drug reactions (depend on immune status of individuals, the rate at which thay metabolize certain drugs

Unpredictable drugs :

- Chlorpromazine
- Halothane
- Sulfonamides
- Methyldopa
- Allopurinol

-Patterns of injury

1-Hepatocellular necrosis
2-Cholestasis
3-Steatosis
4-Steatohepatitis
5-Fibrosis
6-Vascular lesions
7-Granuloma
8-Neoplasms benign & malignant

Autoimmune hepatitis

Chronic hepatitis with immunologic abnormalities, this is why it is responsive to immunosuppressive therapy

Features :

*female predominance

*often associated with other autoimmune diseases like RA,thyroiditis, sjogerrn syndrome, ulcerative colitis

*presence of autoantibodies (very important):

1-Antismooth myuscle abs
- **anti actin**
- **anti troponin**
- **anti tropomyosin**

2-liver/kidney microsomal Abs
- **anti cytochrome P-450 components**
- **anti UDP-glucuronosyl transferases**

(anti-SLA/LP) antibodies.

3-Anti – soluble liver / pancreas antigen

Anti-nuclear antibody : sensitive for AH

Outcome

Chronic hepatitis with increased risk for cirrhosis (5%) which is the main cause of death

Non-alcoholic liver disease

A Liver disease that is characterized by steatosis, Non-alcoholic steatohepatitis, and cirrhosis, although those changes are less prominent than those of alcohol related injury.

Predisposing factors

1- Type 2 diabetes
2- Obesity
3- Dyslipidemia

Pathogenesis

Usually patients with metabolic syndrome (insulin resistance, obesity, dylipidemia) have Non-alcoholic liver disease

Fat accumulates due to impaired oxidation, increased synthesis and uptake of FFA, and decreased hepatic secretion of VLDL

Most patients don't show symptoms, but few develop fatigue ,RUQ discomfort, malaise.

Liver biopsy is required for diagnosis
NAFLD is the most common cause of incidental increase is liver transaminases (ALT,AST)
NAFLD may contribute significantly to cryptogenic cirrhosis

Hemochromatosis : Excessive accumulation of iron in the body especially in the liver and pancreas

Genetic Hemochromatosis (primary)

Causes:

Mutations in HFE gene (most common) on chr.6

- Tyrosine substitution for cystine (C282Y) (most common)
- Aspartate substitution for histidine (H63D)

Acquired hemochromatosis (secondary)

:Causes of acquired hemosidrosis

multiple transfusions-1 — exposed to overdose of iron
ineffective erythropoiesis (thalassemia)-2
increased iron intake (Bantu sidrosis)-3 — there diet contains increased amount of iron
chronic liver disease-4 — chronic= ↑ deposition

premature rupture&death of RBCs before they are released in circulation due to hematological problem (i.e.thalassemia patients >>there RBCs are

Pathogenesis

HFE gene regulates the levels of hepcidin hormone synthesized in the liver and Negatively regulates the iron absorption from the intestine

So once there is mutation in this gene, the only regulatory mechanism for iron in the body is lost

Clinical presentation (very important)

M:F 5 – 7 :1 — 5 – 6 the decades
Hepatomegaly *
Abdominal pain
Skin pigmentation
D.M — Due to destruction of pancreatic islets *
Cardiac dysfunction — congestive heart failure, edema,…)
Atypical arthritis — (it predisposes also for Pseudo-gout)
Hypogonadism — (e.g. amenorrhea in the female, impotence and loss of libido in the male).
↑serum Fe ferritin
HCC 200x ↑in the risk

Death from cirrhosis or cardiac disease

Lecture 5

Wilson disease

Autosomal recessive

Accumulation of copper in the body

Mutations in ATP7B gene on chr.13

Pathogenesis

Due to the mutation mentioned above, there will be decrease in the ability to incorporate Copper with Alpha-2-globulin (Apoceruloplasmin) to form Ceruloplasmin which is the Copper-transporting protein within the plasma, so the levels of Copper would increase in contrast to Ceruloplasmin,which would decrease, ***moreover*** there will be decrease in the liver's ability to excrete the Copper in bile, so it will damage hepatocytes, then will be released to plasma, depositing in different organs and causing the following manifestation :

6-40 years-old patient

#Kayser-fleischer rings (in the limbus of the cornea)

Behavioral changes and Parkinson like disease

#acute on chronic hepatitis

- **DX**

1- ↓ in serum ceruloplasmin level
2- ↑ in urinary exc. Of Cu. The most specific
3- ↑ hepatic content of copper The most sensitive
> 250 mg/gm dry wt.

Alpha-1-antitrypsin Defeciency

Autosomal recessive

Alpha-1-anti trypsin is a protease inhibitor, so at the end of inflammation, it dampens down the inflammatory process, in order not to harm our tissues and organs

This gene for this protein is located on chr.14, and there are.different genotypes of it (piMM) is the most common,which is the normal one, but in the case of (piZZ) genotype, there will be high risk for developing clinical disease, especially in smokers.

Pathogenesis

In the case of (piZZ) genotype , it is abnormally folded, in the ER of hepatocytes, this accumulation will stimulate auto phagocytosis of the mitochondria,leading to liver damage, moreover, in the case of lung damage (due to smoking for example) there will be an inflammatory process , but that mediator which was responsible for dampening inflammation is lost , so it will be progressive enough to cause emphysema

Morphology

-Intracytoplasmic globular inclusions in hepatocytes which are acidophilic in H&E. sections
-The inclusions are PAS-+ve & diastase resistant
-Neonatal hepatitis cholestasis & fibrosis
Chronic hepatitis
Cirrhosis
Fatty change
Mallory bodies

Clinical picture

-neonatal hepatitis with cholestatic jaundice appears in 10 – 20% of newborns with the disease
-Attacks of hepatitis in adolescance
-chronic hepatitis & cirrhosis
-HCC in 2- 3 % of Pizz adults + cirrhosis

Reye's syndrome

Medical condition that results from giving salicylate (aspirin for example) for children after viral illness.
It is characterized by fatty change in the liver and encephalopathy
There will abnormal liver function tests, vomiting lethargy, and 25% may go into coma

Pathogenesis

-Derangement of mitochondrial function along or in combination with viral infection & salicylate
-Microvesicular steatosis
-Brain edema
-Absent inflammation
-Sk. Muscles, heart, kidneys – fatty change

Budd-Chiari Syndrome

It occurs due the thrombotic occlusion of more than one hepatic vein, this will lead to blood congestion and necrosis around the central vein.
Clinical picture : hepatomegaly, weight gain, ascitis, abdominal pain

Causes

1-PCV
2-Pregnancy
3-Postpartum
4-Oral contraceptive
5-PNH
7-Mechanical obstruction
8-Tumors as HCC
9-Idiopathic in 30% of the cases

Morphology

-Swollen liver , red with tense capsule
-centrilobular congestion & necrosis
-Fibrosis
-Thrombi

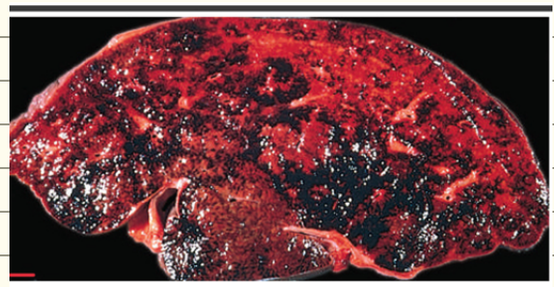


Fig. 16.32 Budd-Chiari syndrome. Thrombosis of the major hepatic veins has caused severe hepatic congestion.

Peliosis Hepatis

It is a sinusoidal dilatation that is caused by :
*anabloic steriods, *oral contraceptives,*danazol
Clinical picture: silent, or it can lead to intra abdominal hemorrhage and possibly liver failure
It is reversible

Lecture 6

Primary sclerosing cholangitis M>F

Inflammation, obliterative fibrosis and segmental dilation of the obstructed intrahepatic and extrahepatic bile ducts

in 70% of patients with Primary seclerosing cholangitis (PSC), they have also ulcerative colitis , but only 4% of ulcerative colitis they have PSC

Morphology

-Concentric periductal onion-skin fibrosis & lymphocytic infiltrate
Atrophy & obliteration of bile ducts-
Dilation of bile ducts inbetween areas of stricture-
Cholestasis & fibrosis-
Cirrhosis-
Cholangiocarcinoma (10–15%)-

Clinical presentation

- asymptomatic
- persistent ↑ serum alkaline phosphatase
- fatigue, pruritis, jaundice, wt loss, ascitis, bleeding, encephalopathy

- antimitochondrial Abs < 10% of cases
- **Antinuclear cytoplasmic Abs** in 80% of cases

Pathogenesis

Several features of PSC suggest immunologically mediated injury to bile ducts

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Primary biliary Cirrhosis F>M

Non- suppurative granulomatous destruction of medium-sized intrahepatic bile ducts, portal inflammation and scarring. It is chronic disease and often fatal

Increase in **Alkaline phosphates**
Antimitochondrial Antibodies are present in more than 90% of the cases
hyperbilirubinemia = hepatic decompensation

often associated with other conditions: sjogern syndrome,thyroiditis, scleroderma, RA, celiac disease,MGN, Ryanauds phenomenon.

Morphology

- **Interlobular bile ducts are absent or severely destructed (florid duct lesion)**
- **Intra epithelial inflammation**
- **Granulomatous inflammation**
- **Bile ductular proliferation**
- **Cholestasis**
- **Necrosis of parenchyma**
- **Cirrhosis**

Secondary biliary cirrhosis

-Prolonged obstruction to extrahepatic biliary tree
-Causes:
1-cholelithiasis
2-biliary atresia
3-malignancies
4-stricutres

Sinusoidal obstruction syndrome (Veno-occlusive disease)

It occurs in the first 20-30 days after bone marrow transplantation (20% of recipients) , which is caused by drugs like cyclophosphamide, and total body radiation

Pathogenesis

Toxic injury to sinusoids leads to emboli formation, which blocks blood flow , and the blood moves out through fenestrations into space of Disse, activating stellate cells, leading to Fibrosis

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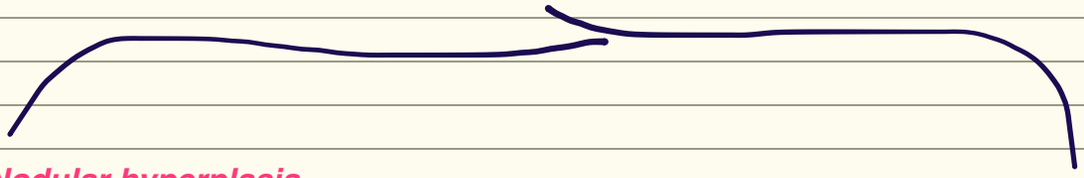
Liver Nodules



Focal Nodular hyperplasia

Well demarcated hyperplastic hepatocytes with central scarring due to local vascular injury

Non-cirrhotic liver

Not neoplasm , commonly seen in females of reproductive age

20% of cases have cavernous hemangioma (to be discussed in the next page)

Macroregenerative Nodules

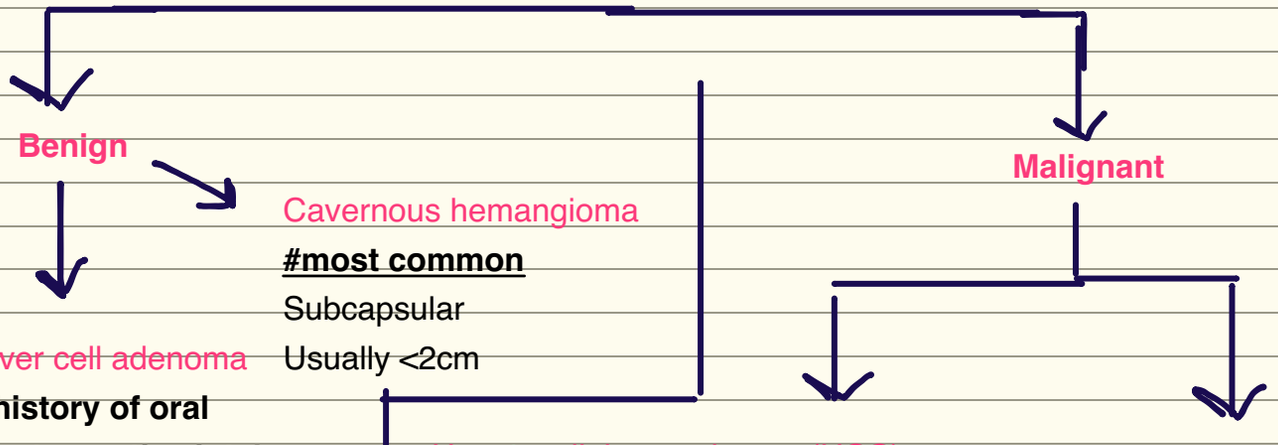
No risk for malignancy

Cirrhotic liver

Larger than cirrhotic nodules

Reticulin is intact

Liver tumors



Benign

Cavernous hemangioma

#most common

Subcapsular

Usually <2cm

Liver cell adenoma

#history of oral contraceptive intake

may rupture especially during pregnancy causing severe intraperitoneal hemorrhage

Misdiagnosis of HCC

Malignant

Hepatocellular carcinoma (HCC)

Males more common than females

Predisposing Factors :

1. Chronic HBV infection (very common)
2. Cirrhosis
3. Alcoholism
4. Chronic HBV infection
5. Aflatoxins
6. Hereditary hemochromatosis

Fibrolamellar Carcinoma

M=F

Metastasis: vascular- lungs , bones, adrenals , brain

Pathogenesis

*Due to repeated regenerations that is associated with **HBV,HCV,** leading to genomic instability

* **HBV** integration of genetic material leading to clonal expansion and genomic instability and ~~**X-protein** which leads to trans activation~~ of cellular promoters

*Aflatoxins lead to mutation of p53

***Cirrhosis**

Clinical picture: Abdominal pain, malaise , weight loss , *increase in alpha-feto protein in 60-75% of cases*

The Increase in alpha-feto protein is als seen in other conditions :

1-yolk sac tumor
2-cirrhosis
3-massive liver necrosis
4-chronic hepatitis
5-normal pregnancy
6-fetal distress or death
7- fetal neural tube defect

Morphology

1. Hepatocellular carcinoma
2. Cholangiocarcinoma
3. Mixed

- Unifocal
- Multfiocal
- Diffusely infiltrative

Prognosis

- Death within 7 -10 months
- **Causes:**

1-Cachexia
2-GI bleeding
3-Liver failure
4-Tumor rupture and hemorrhage

Vascular invasion is common in all types
well differentiated —-anaplastic cells

تم بفضل الله وتوفيقه
صلوا على رسول الله

Done by : Abdalrhman Froukh