GALLBLADDER

The file isn't reviewed !!

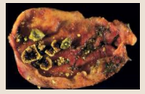
Disorders of the gallbladder

Cholelithiasis

Common disease affecting 10-20% of adults
>80% are asymptomatic

Two main types of gall stones

Cholesterol stones



APPEARANCE

exclusively in GB, single or multiple, multi-faceted, most are radiolucent

- **Pure**: pale yellow
- **Mixed**: gray white to black, containing **calcium carbonate**, phosphates & bilirubin

RISK FACTORS

- **Age**: elderly> young adults
- **Gender**: females (2:1)
- Oral contraceptives (OCPs), pregnancy
- Demography: Western World
- Gallbladder stasis
- Family history.
- Inborn disorders of bile acid metabolism
- Obesity
- Hyperlipidemia
- Rapid weight loss
- Treatment with the **hypo**cholesterolemic

Bilirubin calcium salts (pigment) stones

APPEARANCE

anywhere in biliary tree, contain calcium salts of unconjugated bilirubin (**calcium bilirubinate**), mucin glycoproteins & cholesterol

- **Black**: in sterile GB bile, small, numerous, friable, 50-75% are radiopaque
- **Brown**: in infected bile ducts, single or few, soft & greasy, radiolucent

RISK FACTORS

- Demography: Asians, rural areas
- Chronic hemolytic syndromes
- Biliary infection
- Gastrointestinal disorders:
  . Ileal disease, e.g. Crohn's disease
  . Ileal resection or bypass
- Cystic fibrosis with pancreatic insufficiency

For both types

Pathogenesis

bile **supersaturation** with cholesterol

↓

nucleation: promoted by gallbladder hypomotility (stasis)

↓

Cholesterol crystals remaining long enough to **aggregate**

Clinical presentation

- 70-80% are asymptomatic
- Biliary pain, constant or colicky from an obstructed gallbladder or biliary tree
- Associated with inflammation of gallbladder

Complications

- Empyema; pus in gallbladder
- Perforation; due to obstruction
- Fistulae; induced by the stone
- Inflammation of biliary tree(cholingitis)
- Obstructive cholestasis (jaundice)
- Pancreatitis
- Intestinal obstruction ("gallstone ileus")

Escaping from gallbladder, from cystic to bile duct entering small intestine causing obstruction

Cholecystitis

=> Inflammation of the gallbladder
~ Almost always associated with gallstones
~ One of the most common indications for abdominal surgery
~ Epidemiologic distribution similar to cholelithiasis

CLINICAL FEATURES OF CHOLECYSTITIS
=> Acute & chronic calculous cholecystitis have similar & variable **symptoms**:
minimal nonspecific symptoms to biliary colics to severe RUQ pain
- Fever, nausea, leukocytosis.
=> Acute acalculous cholecystitis: symptoms obscured by general condition
- Dx: **Ultrasonography**
- **Complications**: cholangitis(ascending of infection to bile duct), sepsis, GB perforation, abscess, rupture, cholecyst-enteric fistula, intestinal ileus, ...

ACUTE

Acute calculous cholecystitis

Related to gall stones !!

- Most common reason for emergency cholecystectomy.
- Mostly in absence of bacterial infection; the specimen is sterile
- Symptoms may be mild or sudden & severe

Caused by

- obstruction of GB neck or cystic duct by stones
- Chemical irritation & inflammation of GB wall
- Blood flow compromise due to GB distension & pressure

Acute acalculous cholecystitis: 5-12% of cases

Not Related to gall stones !!

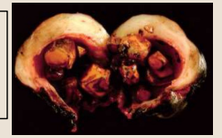
- **Seen** in 1) post-operative states, 2) severe trauma, 3)severe burns, 4) sepsis & 5) postpartum
- **Factors**: 1) dehydration, 2) GB stasis & sludging, 3) vascular compromise, 4) bacterial contamination

Acute on top of chronic

Chronic

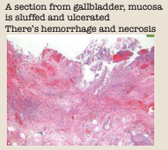
=> +/- history of acute cholecystitis
=> Gallstones almost always present,
=> **Supersaturation** of bile predisposes to chronic inflammation & **stone formation**, **NOT** the obstruction.
=> Variable morphologic appearance: minimal changes, contraction, enlargment, mucosal ulceration or wall thickeninig
=> Histology: Mucosal ulcerations are infrequent; the submucosa and subserosa often are thickened from **fibrosis**, lymphocytes may be only clue of inflammation.

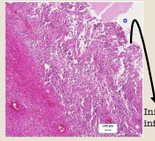
Thickening of the wall of gallbladder
The wall is usually thickened by edema=> in acute cases
And thickened by fibrosis => in chronic cases

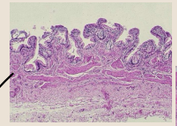


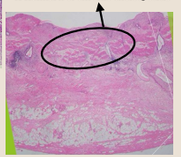
PATHOLOGY OF ACUTE CHOLECYSTITIS

- **Enlarged** (2-3x), tense GB with discolorations due to subserosal/hemorrhages.
- Serosal fibrinous or suppurative exudate
- Stones obstructing GB neck or cystic duct in 90%
- GB lumen filled with turbid bile, +/- fibrin, hemorrhage & pus
- Empyema of gallbladder: full of pus
- Thickened edematous hyperemic wall
- Gangrenous cholecystitis: black necrotic GB
- Histology: edema, **WBC infiltration, congestion, abscess, hemorrhage & necrosis**





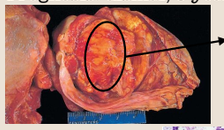


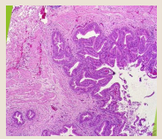


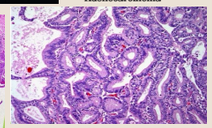
Tumors

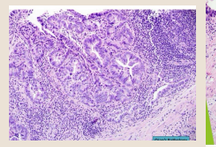
GALLBLADDER CARCINOMA

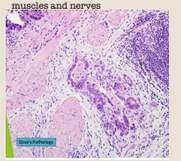
- Commonest extrahepatic biliary tract cancer
- More common in women; peak 7th decade
- Due to recurrent trauma and inflammation: usually associated with stones;
- **Morphology**: Infiltrating or fungating growth pattern, protruding to the lumen of gallbladder
- Most are **adenocarcinoma**.
- Insidious symptoms similar to cholelithiasis
- If obstruction develops early: early diagnosis and treatment.
- Advance stage at diagnosis (late)
- Seeding to peritoneum, GIT, and lungs
- Prognosis: dismal, 5 year survival: 1%











Liver pt.1

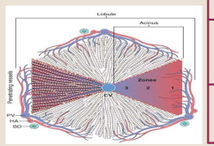
Functions:-

- Metabolic → metabolism of Glucose
- Synthetic → synthesis of proteins as Albumin, clotting factors
- Detoxification of → Drugs, hormones , NH3
- Storage of → Glycogen, TG, Fe, Cu, vit
- Excretory → Bile secretion

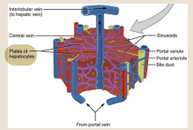
The liver :-

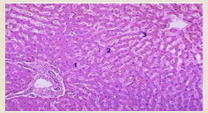
- Net weight:- 1400 – 1600gm (2.5% of body wt)
- Blood supply: Portal vein : 60 – 70% // Hepatic artery : 30-40%
- Microstructure

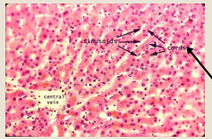
- Hexagonal lobules → 6 acini each →Acinus is divided into 3 zones:



- **Zone 1** Peri**portal** areas – closet to the vascular supply
- **Zone 2** Inrermediate bet. Zone 1&3
- **Zone 3** Peri**central** area







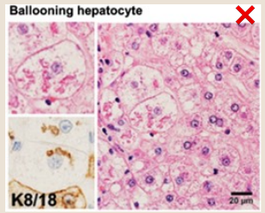
The parenbchyma is organized into **plates of hepatocytes**
Hepatocytes are radially oriented around terminal hepatic vein (central v.)
-Hepatocytes show only minimal variation in the overall size but nuclei may vary in size , number & ploidy esp. with advancing age
-Vascular sinusoids present between cords of hepatocytes

Hepatic Injury Patterns

Inflammation (Hepatitis)

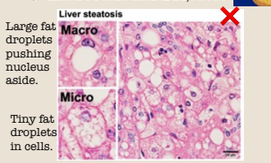
Ballooning degeneration

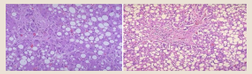
-irregularly clumped cytoplasm showing large, clear spaces.
-Substances may accumulate in viable hepatocytes, including fat, iron, copper and retained biliary material



Steatosis (fatty change)

- **microvesicular**: alcoholic liver disease (ALD), Reye syndrome,acute fatty change of pregnancy
- **macrovesicular**:DM,obese



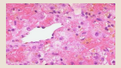


macrovesicular steatosis

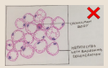
Necrosis

Depending on the type:

Coagulative necrosis :- around central v.



Councilman bodies



Lytic necrosis

Depending on the cause

Ischemic necrosis

Toxic necrosis

Depending on the location

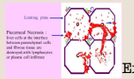
Centrilobular necrosis

Mid zonal

Periportal : interface hepatitis

Focal

Piece meal necrosis & bridging necrosis



Diffuse

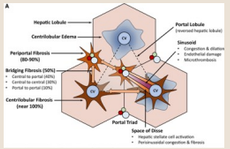
massive & submassive necrosis

Regeneration

-evidenced by increased mitosis or cell cycle markers.
-the cells of the canal of Hering are the progenitor for hepatocytes & bile duct cells (oval cells).

Fibrosis

- portal or periportal fibrosis
- pericentral- around the CV
- **pericellular fibrosis or fibrous tissue may be deposited directly within the sinusoids around single or multiple hepatocytes**
- **Bridging fibrosis**



Cirrhosis

- micronodular
- Macronodular

Micronodular cirrhosis

Macronodular cirrhosis

Ductular proliferation

Hepatic Failure

results when the hepatic functional capacity is almost totally lost (80 – 90%)

Causes

Massive hepatic necrosis

Types
- 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

Chronic liver disease

Hepatic dysfunction without overt cirrhosis

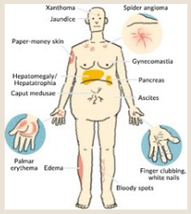
Causes
- **Reye's syndrome**
- **Tetracyline toxicity**
- **Acute fatty liver of pregnancy**

Cirrhosis

Extra..

Clinical features of hepatic failure

1-Jaundice. 2-Hypoalbuminemia →edema
3-Hyperammonemia. 4-Fetor hepaticus (musty or sweet & sour)
5-Palmar erythema hyperestrogenemia. 6-Spider angiomas
7-Hypogonadism & gynecomastia



Consequences of hepatic failure

- **Multiple organ failure** Kidneys and lungs
- **Coagulopathy** → bleeding because of def. factors II, VII, IX, X
- **Hepatic encephalopathy**
  ↓level of consciousness
  Rigidity
  Hyperreflexia
  EEG changes
  Seizures
  Asterixis رجفة مفاجئة عند مد اليد

Hepatorenal syndrome

Hepatorenal syndrome is a type of functional renal failure that occurs in patients with advanced liver disease (especially cirrhosis or acute liver failure), in the absence of any intrinsic kidney pathology (i.e., kidneys look structurally normal).

- وين يبدأ ischemic necrosis أولاً؟
  → Zone 3 ✅ (لأنها الأبعد عن التروية).
- وين يبصير congestive hepatopathy في مرضى فشل القلب الأيمن؟
  → Zone 3 ✅ وتسبب numeg liver.
- التسمم بـ acetaminophen (بنادول) يأثر على أي منطقة؟
  → Zone 3 ✅ لأنها غنية بإنزيمات CYP450 اللي تحول الباراسيتامول إلى مشتقات سامة.
- فين تكون fatty liver / steatosis؟
  → تبدأ غالبًا في Zone 3.

- فين يبدأ Viral hepatitis؟
  → Zone 1 ✅ لأنها الأقرب للدم الوريدي القادم من الأمعاء.
- فين تحصل Toxic injury من المواد القابلة للأكسدة المباشرة؟
  → Zone 1 ✅ (بعض السموم تعمل مباشرة على الخلايا الغنية بالأوكسجين).
- لو المريض عنده hemochromatosis، وين تبدأ ترسبات الحديد؟
  → غالبًا Zone 1 أولًا.

Alcoholic liver disease

Some facts about alcohol

-Alcohol is most widely abused agent
-It is the 5th leading cause of death in USA لأنها ممكن تؤدي إلى :
1.accidents
2.Cirrhosis
-80 – 100 mg/dl is the legal definition for driving under
the influence of alcohol
عشان توصل هاي الكمية بجسم الإنسان لازم
-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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الأشخاص اللي نادرًا ما يشربوا (Occasional drinkers):
200 mg/dL → ممكن يدخل في غيبوبة (coma)
300 – 400 mg/dL → ممكن يصير (respiratory failure) ويموت الشخص

الناس المدمنين أو معتادي الشرب (Habitual drinkers):
ممكن يتحمّلوا تركيز كحول بالدم يوصل حتى 700 mg/dL بدون أعراض واضحة!
السبب: Metabolic Tolerance
جسمهم "تعود" يتعامل مع الكحول لأنه فعل نظام معين في الكبد اسمه:
Cytochrome P-450 System
هذا النظام عبارة عن مجموعة من الإنزيمات بتحلل السموم (والمخدرات) في الكبد
أهم إنزيم هنا: CYP2E1
هذا الإنزيم:
بزيد تحليل الكحول
وبحلل أدوية تانية كمان مثل:
Cocaine
Acetaminophen

Forms of alcoholic liver disease

Hepatic steatosis
(90-100% of drinkers)
-Can occur following even moderate intake of alcohol in form of → microvesicular steatosis
-Chronic intake → diffuse steatosis
-Liver is large (4 – 6 kg) soft yellow & greasy
-Continued intake →fibrosis
-Fatty change is **reversible** with complete absention from further intake of alcohol

Could develop into →

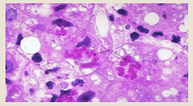
Alcoholic hepatitis
(1- 35% of drinkers)

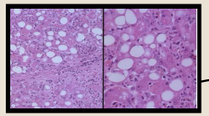
Could develop into →

Characteristic findings

- **Hepatocyte swelling & necrosis**
  -Accumulation of fat & water & proteins
  -Cholestasis
  -Hemosidrein deposition in hepatocytocytes & kupffer cells
- **Mallory-hayline bodies**
  -easinoplilic cytoplasmic inclusions in degenerating hepatocytes formed of **cytokeratin intermediate filaments & other proteins**

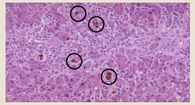
Mallory-hayline inclusions are characteristic but **not pathognomonic** of alcoholic liver disease.
- they are also seen in :
1-Primary biliary cirrhosis
2-Wilson disease
3-Chronic cholestatic syndromes
4-Hepatocellular carcinoma





Mallory's hyaline is seen here, but there are also neutrophils, necrosis of hepatocytes, collagen deposition, and fatty change. These findings are typical for acute alcoholic hepatitis.

- **Neutrophilic reaction**
- **Fibrosis**
  -Sinusoidal & perivenular fibrosis
  -Periportal fibrosis
- **Cholestasis**



bile plugs

- **Mild deposition of hemosiderin in hepatocytes & kupffer cells**

Cirrhosis
(14% of drinkers)
-Usually it develops slowly
-Initially the liver is enlarged yellow but over years it becomes brown shrunken non-fatty organ s.t < 1 kg in wt.
→ mixed micro & macronodular
-Laennec cirrhosis = scar tissue
-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).

Pathogenesis of alcoholic liver disease

=> Short term ingestion of 80gm of ethanol/ day (8bears) → mild reversible hepatic changes (fatty liver)
=> 50 – 60gm/day → borderline effect
=> Long term ingestion (10-20yrs) of 160gm of ethanol per day → severe hepatic injury
-Women are more susceptible to hepatic injury due to ↓gastric metabolism of ethanol .
-Only 8 – 20% of alcoholics develop cirrhosis

Causes of death in alcoholic liver disease

- hepatic failure
- Massive GI bleeding
- Infections
- Hepatorenal syndrome
- Hepatocellular carcinoma (HCC) in 3-6% of cases

Ethanol metabolism

- 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.

ETHANOL CH_3CH_2OH —(Alcohol dehydrogenase)—> ACETALDEHYDE $CH_3CH{=}O$ —(aldehyde dehydrogenase)—> ACETIC ACID
(stomach + liver)
Cytochrome P-450
Catalase (liver)

Scenario	Dominant Enzyme
Occasional/social drinking	Alcohol Dehydrogenase
Chronic/heavy alcohol use	CYP2E1

Mechanism of ethanol toxicity

Fatty change

Pathogenic Chain: Alcohol-Induced Fatty Liver (Steatosis)

1 Alcohol metabolism increases NADH ➡ Ethanol is metabolized to acetaldehyde and then to acetate, generating excess NADH in cytosol and mitochondria.

2 High NADH disrupts fat metabolism ➡ Inhibits β-oxidation of fatty acids (requires NAD^+).

➡ Stimulates lipid synthesis → triglyceride accumulation in hepatocytes.

3 Acetaldehyde damages microtubules ➡ Forms adducts with tubulin and impairs microtubule function. ➡ This hinders lipoprotein transport → ↓ export of triglycerides → fat retention in liver.

4 Increased peripheral lipolysis ➡ Alcohol enhances fat breakdown in adipose tissue → ↑ free fatty acids (FFA) enter the liver → more fat buildup.

5 Impaired secretion of lipoproteins ➡ Hepatocytes fail to assemble/secrete VLDL particles, which normally carry fats out → more fat stays in the liver.

6 Decreased mitochondrial fatty acid oxidation. ➡ Mitochondria overwhelmed or damaged → ↓ β-oxidation → further fat accumulation.

Cytochrome P-450 induction ➡ **Alcohol induces CYP2E1 → increases toxic metabolite production (e.g., from acetaminophen) → adds oxidative stress on liver cells.**

Increased free radical production

Alcohol induces Cytochrome P-450 (CYP2E1) ➡ Leads to generation of reactive oxygen species (ROS) ➡ Oxidative stress damages cellular membranes, proteins, and DNA.

Alcohol directly affect microtubular & mitochondrial function & membrane fluidity

Acetaldehyde causes lipid peroxidation & antigenic alteration of hepatocytes → immune attack

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

Alcohol → release of bacterial endotoxins into portal circulation from the gut → inflammation of the liver

Alcohol → regional hypoxia in the liver due to release of endothelins which are potent vasoconstrictors → ↓ hepatic sinusoidal perfusion

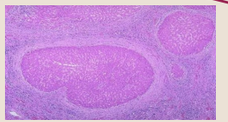
Alteration of cytokine regulation
- TNF is a major effector of injury
- IL6 IL8 IL18

Clinical features of alcoholic liver disease كمان مرة 🥺🥺

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(liver function test)
Each bout of hepatitis →10-20% risk of death
→ cirrhosis in 1/3 in few yrs.

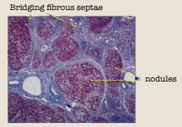
Cirrhosis
Leading to Portal hypertension



Cirrhosis

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

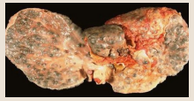
Main characteristics
1.Bridging fibrous septae
2.Parenchymal nodules encircled by fibrotic bands
3.Diffuse architecture disruption



Types

Micronodules
< 3mm in diameter

Macronodules
> 3 mm in diameter



Causes of cirrhosis

- Chronic alcoholism
- Chronic viral infection HBV & HCV
- Biliary disease
- Hemochromatosis
  a genetic or acquired disorder in which iron-binding protein accumulates in various tissues, typically leading to liver damage
- Autoimmune hepatitis
- Wilson disease
- α-1- antitrypsin deficiency
- Galactosemia
- Tyrosinosis
- Glycogen storage disease III &IV
- Lipid storage disease
- Hereditary fructose intolerance
- Drug induced e.g methyldopa

} Rare

- Cryptogenic cirrhosis 10% with no identifiable cause

Pathogenesis of cirrhosis

Hepatocellular death
Cell death should occur over a long period of time
↓
Regeneration
↓
Progressive fibrosis
↓
Vascular changes

1 Loss of sinusoidal endothelial cell fenestration
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) between hepatocytes and the plasma is markedly impaired.
+++++++
2 development of vascular shunts as
Portal v- hepatic v
Hepatic a – portal v
→defect in liver function
+++++++
3 Loss of microvilli from hepatocytes →
↓ transport capacity of the cells

Clinical features of cirrhosis

- Silent
- Anorexia, wt loss, weakness

Complications

- Progressive hepatic failure
- Portal hypertension
- Hepatocellular carcinoma

Normal liver	Vs.	**Cirrhosis**
the ECM collagen (types I, III,V& XI) is present only in : - Liver capsule - Portal tracts - Around central vein delicate framework of type **IV** collagen & other proteins lies **in space of Disse**		types **I & III** collagen & others are deposited **in the space of Disse** ↓ The major source the **perisinusoidal stellate cells (Ito cells)** which lie in space of Disse Which are acting normally as **storage cells** for vit A & fat ↓ Upon stimulation 1- reactive oxygen species 2-Growth factors 3-cytokines TNF, IL-I, lymphotoxins ↓ Those cells become **myofibroblast- like cells** ↓ producing transforming growth factor β (**TGF-β**)

Portal hypertension

Definition

- ↑ resistance to portal blood flow at the level of sinusoids & compression of central veins by perivenular fibrosis & parenchymal nodules
- Arterial – portal anastomosis develops in the fibrous bands →increase in the blood pressure in portal venous system
=> This contribute to portal hypertension by imposing arterial pressure on the normally low pressure portal venous system.

يعني تو متش ضغوط على كتكوت زغنوط

Causes

- I.Prehepatic
  - Portal vein thrombosis
  - Massive splenomegaly
- II. Post hepatic
  - Severe Rt.- sided heart failure
  - Constrictive pericarditis
  - Hepatic vein out flow obstruction
- III. Hepatic
  - Cirrhosis
  - Schistosomiasis
  - Massive fatty change
  - Diffuse granulomatosis as sarcoidosis, TB
  - Disease of portal microcirculation as nodular regenerative hyperplasia

Clinical consequences

Ascitis

Definition Collection of excess fluid in peritoneal cavity
-It becomes clinically detectable when at least 500 ml have accumulated

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

Pathogenesis 1-Sinusoidal ↑ Bp
↑ مقاومة مرور الدم داخل الكبد،
هذا يبعمل ارتفاع في ضغط الدم داخل (sinusoids)،
↑ الضغط هذا بيؤدي إلى دفع السوائل نحو (peritoneal cavity).
2-Hypoalbuminemia
3-Leakage of hepatic lymph into the peritoneal cavity
Normal thoracic duct lymph flow is 800-1000 ml/day in cirrhosis is 20L /day
4-Renal retention of Na+ & water due to 2ry hyperaldosteronism

Portosystemic shunt

Definition
Because of ↑portal venous pressure bypasses develop wherever the systemic & portal circulation share capillary beds

Sites
- Around & within the rectum (Hemorrhoids)
- Retroperitoneum
- Gastroesophageal junction (varicies)
- Falciform ligament of the liver (periumbilical & abdominal wall collaterals) → caput medusae

Gastroesophageal varicies appear in 65% of pts. with advanced cirrhosis & cause death in 50% of then due to UG1 bleeding

Splenomegaly

-Usu. 500-1000 gms (Normal <300gms)
-Not necessarily correlated with other features of portal ↑Bp
-May result in **hypersplenism**

Hepatic encephalopthy

-It is a **complication** of acute & chronic hepatic failure
-Disturbance in brain function ranging from behavioural changes to marked confusion & sutpor to deep coma & death
-The changes may progress over hrs. or days

Neurological signs:
Rigidity // Hyper-reflexia
Non – specific EEG // Seizures
Asterixis (non-rhythmic rapid extension flexion movements of head & extremities .)
-Brain shows edema & astrocytic reaction

Pathogenesis of hepatic encephalopathy
-Physiologic factors important in development of hepatic encephalopathy :-
1-Severe loss of hepatocellular function
2-Shunting of blood around damaged liver
↓↓
Exposure of Brain to toxic metabolic products
↑ NH3 level in blood → generalized brain edema impaired neuronal function
alteration in central nervous system
AA metabolism

Drug – lnduced liver disease

The injury m.b immediate or takes weeks to months

Drug reactions:-

Predictable (intrinsic)

depends on the dose (dose-dependent)

Predictable drugs:
Acetaminophen
Tetracycline
Antineoplastic agents
CCL4
Alcohol

Mechanism of drug injury :
Direct toxic damage
e.g acetaminophen
CCl4
mushroom toxins

Drug-induced chronic hepatitis is clinically & histologically indistinguishable from chronic **viral or autoimmune** hepatitis

Unpredictable (idiosyncratic) غريب

depend on :
a-The immune response of the host to the antigenic stimulus
b-The rate at which the host metabolizes the agent

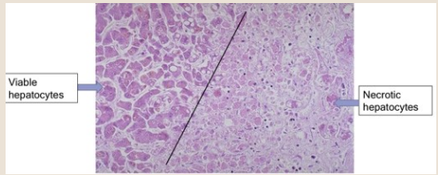
Unpredictable drugs
Chlorpromazine
Halothane
Sulfonamides
Methyldopa
Allopurinol

Mechanism of drug injury :
Immune-mediated damage

Drugs that may cause acute liver failure
1-Acetaminophen "most common"
2-Halothane
3-Antituberculosis drugs (rifampin, isoniazid)
4-Antidepressant monoamine oxidase inhibitors
5-Toxins as CCL4 & mushroom poisoning

Patterns of injury

- Hepatocellular necrosis
  - Massive necrosis → 500 – 700 gm liver
  - Submassive necrosis
  - Patchy necrosis
- Cholestasis
- Steatosis
- Steatohepatitis
- Fibrosis
- Vascular lesions
- Granuloma
- Neoplasms benign & malignant



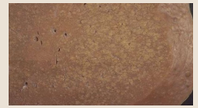
Hepatitis

Fulminant/Subfulminant hepatitis

Hepatic insufficiency that progresses from onset of symptoms to hepatic escephelopathy in 2-3 wks
Subfulminant (up to 3 mon)

Causes :
1-Viral hepatitis 50 – 65%
HBV 2x > HCV
2-Drugs & chemical 25- 50%
e.g Isoniazid , halothane , methyldopa & acetominophen
3-Obstruction of hepatic vein
4-Wilson's disease
5-Acute fatty change of pregnancy.
6-Massive tumor infiltration
7-Reactivation of chronic hepatitis B
8-Acute immune hepatitis

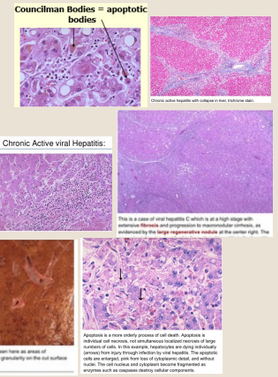
Morphology :
-↓ liver size (500 – 700 gm)
-Necrosis of hepatocytes
-Collapsed reticulin tissue
الشبكة الداعمة (الهيكل الداخلي) للعضو انكمشت أو انهارت
-Inflammatory infiltrate
-Regenerative activity of hepatocytes
-Fibrosis



Chronic Hepatitis

Symptomatic, biochemical or serelogic evidence of continuing or relapsing hepatic disease for more than 6 months with histologically documented inflammation & necrosis
-Progressive or non progressive
-HBV , HCV, HBV-HDV

Morphology of chronic hepatitis
-Mild to severe
1.Protal inflammation
2.Lymphoid aggregate
3.Necrosis of hepatocytes-councilman bodies
4.Bile duct damage
5.Steatosis
6.Interface hepatitis
7.Bridging necrosis & fibrosis
8.Fibrosis
9.Ground-glass appearance
10.Sanded nuclei
11.Lobular disarray



Liver pt.2

1 Autoimmune Hepatitis

Definition
- Chronic hepatitis with immunologic abnormalities
-Histologic features are similar to chronic viral hepatitis
-Indolent or severe course
-Dramatic response to immunosuppressive therapy
يعني بيستجيبوا لمثبطات المناعة

Features
1-Female predominance (70%)
2-Negative serelogy for viral antigens.
3- ↑ serum IgG (>2.5 g/dl)
4-High titers of autoantibodies (80% of cases)
5-The presence of other autoimmune diseases as RA, thyroiditis, sjogern syndrome, Ulcerative Colitis in 60% of the cases

The types of autoantibodies
- I. **Anti-smooth muscle antibodies Anti-SMA**
  anti actin
  anti troponin
  anti tropomyosin
- II. **liver/kidney microsomal antibodies LKM**
  anti cytochrome P-450 components
  anti UDP-glucuronosyl transferases
  على الهامش
  catalyzes the transfer of glucuronic acid to lipophilic substrates, converting them into hydrophilic compounds that are excreted.
- III. Anti – soluble liver / pancreas antigen

Outcome
- Mild to severe chronic hepatitis
- Full remission is unusual
- Risk of cirrhosis is 5% which is the main cause of death

2 Nonalcoholic Fatty Liver Disease

Types
Steatosis (Simple Fatty Liver): Accumulation of fat (mainly triglycerides) within hepatocytes
No inflammation or cell damage

Steatohepatitis
hepatocyte destruction
parenchymal inflammation
progressive pericellular fibrosis
(Steatohepatitis = fat + inflammation and damage)

Predisposing factors
- Type 2 DM
- Obesity : body mass index
  > 30 kg /m2 in caucasians
  > 25 kg /m2 in Asians
- Dyslipidemia (↑ TG, ↑LDL, ↓HDL)

Pathogenesis
Metabolic syndrome
. Insulin resistance
. Obesity
. Dyslipidemia

Mechanism of fatty accumulation
1.Impaired oxidation of fatty acids
2.Increased synthesis & uptake of FFA (Accumulated in liver)
3.Decreased hepatic secretion of VLDL (VLDL is used by the liver to export fat into the blood.)
. ↑ TNF , IL6 , chemokine
→These are inflammatory signals (cytokines) cause liver inflammation & damage

Clinically
~ Most common cause of accidentally discovered high liver enzymes (↑ ALT, AST).
~ Most patients are asymptomatic → no obvious symptoms.
If present, symptoms are non-specific, such as:
-Fatigue. -General discomfort (malaise). -(RUQ) pain
~ Severe symptoms may appear later if the disease progresses (e.g., in cirrhosis).
~ Liver biopsy is required for diagnosis and to differentiate between:
Simple fatty liver (steatosis) or Inflamed liver (steatohepatitis)
~ NAFLD may contribute significantly to cryptogenic cirrhosis ("Cryptogenic" means cause is unknown, but NAFLD is often the hidden cause).

3 Hemochromatosis

Definition
Excessive accumulation of iron in the body, especially in the liver and pancreas.

Types
Primary (Hereditary)
Genetic disorder (**autosomal recessive**)
Caused by mutations (commonly in the HFE gene).
Leads to increased intestinal iron absorption.
Iron gradually accumulates in organs → damage.

Secondary (Acquired) = Hemosiderosis
Caused by external factors leading to iron overload

Causes of acquired hemosidrosis
- multiple transfusions
- ineffective erythropoiesis (thalassemia) => where bone marrow keeps trying to make RBCs, stimulating iron absorption
- increased iron intake (Bantu sidrosis)
- chronic liver disease

Features
- Micronodular cirrhosis (all patients)
- D.M (75 – 80%)
- skin pigmentation (75-80%)
- cardiomegaly , joints disease, testicular atrophy

Epidemiology
- Symptoms appear 5th – 6th decades not before age 40
- M:F ratio 5 - 7: 1

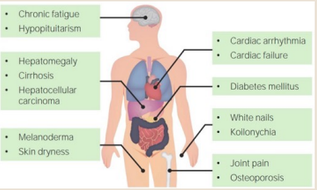
Pathogenesis
-1ry defect in intestinal absorption of dietary iron.
-Total body iron 2-6gm in adults 0.5gm in liver mostly in hepatocytes => In disease >50gm Fe accumulated → 1/3 in liver
In herediatary hemochromatosis there is a defect in regulation of intestinal absorption of dietary iron leading to net iron accumulation of 0.5 – 1 gm/yr
The gene responsible is **HFE gene** located on **chr.6** close to HLA gene complex
-HFE gene regulates the level of **hepcidin** hormone synthesized in liver. {Hepcidin → inhibits (-) Fe. absorption from intestine.}
Extra=> { Ferroportin (basolateral membrane) Transports iron out of the enterocyte into the bloodstream.
Hepcidin (from liver): Binds to ferroportin → Degrades it → ↓ Iron export → So, hepcidin reduces iron absorption into blood.}
-HFE gene deletion causes iron overload

Continued…

Morphological changes
- **Deposition of hemosiderin in different organs**
  Liver,Pancreas,Myocardium, Pituitary, Adrenal ,Thyroid & parathyroid ,Joints ,Skin
- **Cirrhosis**
- **Pancreatic fibrosis**

-No inflammation
-Fibrosis
-Cirrhosis
-Synovitis
-Polyarthritis(pseudogout)
-Pigmentation of liver
-fibrosis of pancreas & myocardium
-Atrophy of testes

Clinically
- Hepatomegaly
- Abdominal pain
- Skin pigmentation
- D.M
- Cardiac dysfunction
-Atypical arthritis
- Hypogonadism
- ↑ serum Fe ferritin
- Hepatocellular carcinoma 200x ↑ in the risk



Types of Mutations in Hereditary Hemochromatosis

C282Y Mutation:

Location: Nucleotide 845

Amino acid change: Cysteine → Tyrosine at position 282. **Most clinically significant mutation.**

Carrier rate: 1 in 70

Homozygosity rate: 1 in 200

C282Y Mutation: 80% of pts. are homozygous for (C282Y) mutation & have the highest incidence of iron accumulation

H63D Mutation:

Amino acid change: Histidine → Aspartate - at position 63

- Less severe than C282Y
- 10% of pts. are homozygous for H63D mutation

Compound Heterozygotes (C282Y/H63D):

About 10% of patients

May develop mild to moderate iron overload

Other mutations:

Found in ~10% of patients

May involve other iron-regulating genes (e.g., TFR2, HAMP, HJV)

Excessive Fe deposition → toxicity of the tissues :

1. Lipid peroxidation
2. Stimulation of collagen formation
3. DNA damage

4 Wilson Disease

Definition

autosomal Recessive disorder of Cu metabolism

-mutation in **ATP7B gene** on **chr. 13** which encodes an ATPase metal ion transporter in Golgi region.

الإنزيم هذا يساعد في:

إدخال النحاس في البروتينات.

التخلص من النحاس الزائد عبر ال bile.

> 80 mutations

-Gene freq. 1:200

-Incidence is 1:30000

وجدوا أكثر من 80 نوع من الطفرات الجينية لهذا الإنزيم، وهو شائع جدًا يعني من بين 200 شخص بتلاقي 1 عنده الطفرة، لكن بالعادة ما في أي مرض لأنه نسبة ظهور المرض القفلية 1 شخص من كل 30000 عندهم هاي الطفرة

Pathogenesis

Main source of Cu is from diet →

Absorption of ingested Cu (2-5 mg/d) in intestine →

Complex with **albumin** in bloodstream →

Hepatocellular uptake →

Incorporation with α-2-globulin to form **Ceruloplasmin** →

Sec. into plasma (90 – 95% of plasma Cu) →

Hepatic uptake of ceruloplasmin →

Lysosomal degradation → Secretion of free Cu into bile

In Wilson disease absorbed Cu Fails to enter the circulation in the form of ceruloplamin & the biliary excertion of Cu. is ↓.

فيتراكم النحاس بالكبد، وممكن احيانًا يخرج من الكبد وعن طريق ال blood circulation يوصل لاماكن تانية

Defective function of ATP-7B →

1. failure of Cu. excretion into bile
2. inhibits sec. of ceruloplasmin into the plasma → Cu in liver is high. accumulation in liver

Cu. Accumulation in the liver reults in

- Production of free radicals
- Binding to sulfhydryl groups of cellular proteins
- Displacement of other metals in hepatic metalloenzymes

النحاس الزائد يُنافس مع معادن أخرى (مثل الزنك أو الحديد) المرتبطة بالإنزيمات.

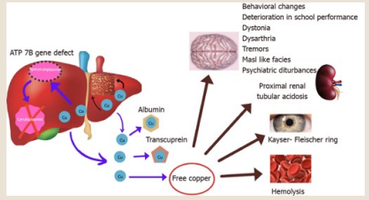
وهاي الإزاحة تؤدي إلى تعطيل الإنزيمات المهمة في عمليات الأيض

-By the age of 5yrs. Cu. Spills over to circulation causing hemolysis & involvement of other organs as brain & cornea also kidneys, bones joints & parathyroid glands

-Urinary exc. Of cu. ↑

الكبد ما بقدر يتخلّص من النحاس.

بيبدا يتراكم ويعمر 5 سنين او اكثر، بيبلّش يفيض ويخرّب اعضاء الجسم.



Morphology

Liver

1-Fatty change

2-Acute hepatitis

3-chronic hepatitis

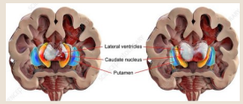
4-cirrhosis

5-massive hepatic necrosis

rhodanine stain or orcein stain

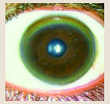
Brain

Toxic injury to basal ganglia esp. the putamen causing atrophy & cavitation



Eye

kayser- fleischer rings green – brown depositis of Cu. in descemet membrane in the limbus of the cornea (hepatolenticular degeneration)



Clinically

-Presentation > 6 yrs of age

-Most common presentation is acute on chronic hepatitis

-Neuropsychiatric presentation can occur

~ behavioral changes

~ Frank psychosis

~ Parkinson disease- like syndrome

Diagnosis

- ↓ in serum ceruloplasmin level
- ↑ in urinary exc. Of Cu.
- ↑ hepatic content of copper > 250 mg/gm dry wt.

5

α-1-Antitrypsin Deficiency

Definition

شو هو الـ α-1-antitrypsin؟

هو بروتين واقي (protective protein) بيتصنع بالكبد، وبيدور في الدم.

وظيفته الأساسية هي:

يمنع إنزيمات معينة (بنسميها proteases) من إنها تكسّر الأنسجة.

* ليش مهم؟

لما يصير التهاب (مثلاً التهابات الرئة أو أي عدوى)، الخلايا المناعية – خصوصًا (neutrophils) – بتفرز إنزيمات قوية جدًا لتدمير البكتيريا، منها:

Elastase

Cathepsin G

Proteinase 3

هاي الإنزيمات تشبه "مقصات" أو "مناشير" بتقص البروتينات، بس الخطر إنها ممكن تضر الأنسجة الطبيعية كمان.

وهنا بيجي دور α-1-antitrypsin:

✅ هو مثل "درع واقي" يمنع هاي الإنزيمات من إنها تخرب نسيج الجسم، خصوصًا الرئة.

الجين المسؤول عن إنتاج α-1-antitrypsin:

اسمه: **Pi gene** أو **SERPINA1**

موقعه: (Chromosome 14)

لو صار (mutation) في هذا الجين Aut. Recessive:

❌ الجسم ما بيصنع كمية كافية من α-1-antitrypsin أو

❌ البروتين نفسه بيكون مش شغال

At least 75 forms of gene mutation are present

-The most common genotype is **pi.MM** present in 90% of individuals

-PiZZ genotype → ↓ level of α-1- antitrypsin in blood (only 10% of normal) are at high risk of developing clinical disease.

Genotype	مستوى α-1-antitrypsin
PiMM	طبيعي
PiMZ	↓ قليل
PiZZ	منخفض جدًا (10%)

Pathogenesis

أولًا: شو بصير بالجسم لما يكون الشخص PiZZ؟

الشخص عنده طفرات في الجين Pi (هذا الجين بيعطي شفرة لبروتين α-1-antitrypsin)

في حالة PiZ، البروتين اللي بينتج:

❌ بيكون مطوي بشكل خاطئ (misfolded protein)

** وين بصير التخريب؟

البروتين بيتصنع في خلايا الكبد (hepatocytes) داخل:

المصنع الداخلي للخلية = Endoplasmic Reticulum (ER)

لكن لأنه البروتين مطوي غلط (mutant PiZ):

❌ ما بيقدر يطلع من الـ ER => بيضل جواته وبيبدأ يتجمع (polymerize) على شكل كتل

** طيب شو النتيجة؟

الكبد بيحاول يتخلص من هاي الكتل باستخدام نظام التنظيف الذاتي

اسمه: Autophagy

لكن هاي العملية:

مش فعّالة دائمًا , ولما تشتد، الخلية بتبدأ تأكل حالها بنفسها (خاصة الميتوكوندريا) autophagocytosis of the mitochondria

وهذا اللي يؤدي إلى (cirrhosis)

** كل الأشخاص PiZZ عندهم تجمّع البروتين بالكبد

❗ لكن فقط 8–10% منهم develop clinical liver disease

السبب؟ ← اختلاف قدرة خلايا الكبد على التخلّص من البروتين الغلط (ER degradation system varies)

• So ,The accumulated a-1-AT-Z is not toxic, but the autophagocytic response stimulated within the hepatocytes appears to be the cause of liver injury through the **autophagocytosis of mitochondria.**

• 8-10% of patients develop significant liver damage.

Morphology

شو رح يلاحظ الـ pathologist لما يفحص كبد المريض under microscope ؟

1. Inclusions in hepatocytes: ←

فيه كتل كروية (globular inclusions) داخل السيتوبلازم هاي الكتل:

لونها زهري أو أحمر (acidophilic) على صبغة H&E

لأنها بروتينات متجمعة ومطوية بشكل خاطئ

2. اختبار خاص: PAS stain ←

لما يستخدموا صبغة PAS (Periodic Acid-Schiff):

تطلع الكتل إيجابية (PAS +ve) لأنها فيها سكريات مرتبطة بالبروتينات (glycoproteins)

ولما يضيفوا Diastase enzyme (اللي يهضم السكريات العادية):

الكتل بتضل موجودة ! → يعني Diastase-resistant

3. في الأطفال (حديثي الولادة): ←

ممكن يظهر مرض اسمه:

Neonatal hepatitis

فيه (Jaundice)،(Cholestasis)، (Fibrosis)

4. في مراحل لاحقة: ←

Chronic hepatitis

Cirrhosis

Fatty change

5. Mallory bodies ←

أحيانًا بنشوف Mallory-Denk bodies:

بنشوفها غالبًا in alcoholic hepatitis ، بس ممكن كمان تظهر بهالحالة

Clinical features

In Newborns

Neonatal hepatitis with cholestatic jaundice appears in 10–20% of newborns with the disease.

In adolescance

Attacks of hepatitis

In adults

Chronic hepatitis & cirrhosis

Hepatocellular carcinoma (HCC)

2–3% من البالغين المصابين بـ PiZZ ± cirrhosis ممكن يتطوّر عندهم سرطان

6

Reye Syndrome

Definition

✓ Fatty change in liver & encephalopathy
< 4 yr.
3 – 5 d after viral illness
.....
✓ ↑ liver (Hepatomegaly)
✓ Abnormal Liver Function Tests (LFT)
✓ Vomiting
✓ lethargy
الطفل بيصير نايم طول الوقت، ما برد، شكله تعبان جدًا
وهذا بسبب تأثير الأمونيا والسموم على الدماغ (Encephalopathy)
✓ 25% may go into coma

Pathogenesis

~ Derangement of mitochondrial function along or in combination with viral infection & salicylate

النتيجة: الكبد والأنسجة ما بتقدر تنتج طاقة كفاية، فبتتراكم الدهون داخل الخلايا.

~ Microvesicular steatosis

~ Brain edema

~ Absent inflammation

المميز في Reye syndrome إنه ما في التهاب حقيقي داخل الكبد
يعني لا كريات دم بيضاء، ولا علامات التهاب ← بس فيه تراكم دهون
~ مش بس الكبد بيتأثر! كمان بيصير Fatty change في:
Sk. Muscles, heart, kidneys

Vascular Liver Diseases

Budd – Chiari Syndrome

=> Thrombotic occlusion of the hepatic vein

Clinical Features

-Hepatomegaly. -Wt.gain

-Ascitis. -Abd. Pain

Causes

PCV (Polycythemia Vera)

مرض دموي يزيد فيه عدد خلايا الدم ← الدم يصير أكثر لزوجة ↑ خطر التجلط.

Pregnancy

(hypercoagulable state) خلال الحمل الجسم طبيعيًا بيكون في حالة ميل للتخثر

لحماية الأم من النزيف.

Postpartum

نفس فكرة الحمل، الجسم بيبقى في حالة ↑ تخثُّر

Oral contraceptive pills (OCPs)

PNH (Paroxysmal Nocturnal Hemoglobinuria)

مرض دم نادر يؤدي إلى تكسر خلايا الدم، ويزيد فرصة حدوث جلطات وريدية غير طبيعية

Mechanical obstruction

Tumors as HCC

Idiopathic in 30% of the cases

Morphology

-Swollen liver , red with tense capsule

-centrilobular congestion & necrosis

-Fibrosis

-Thrombi

Clinically

Mortality rate is high if not treated

Sinusoidal Obstruction Syndrome (Veno-occlusive disease)

=> Thrombotic occlusion of sinusoids in Jamaican

ناس شربوا شاي أعشاب (bush tea) يحتوي على alkaloids سامة اسمها pyrrolizidine alkaloids ← سببت تلف في أوعية الكبد.

~ occurs in the first 20-30 days after bone marrow transplantation

Causes

1-Drugs as cyclophosphamide

2-Total body radiation

Incidence

20% in recepients of allogeneic marrow transplant

Allogenic يعني من متبرع آخر ، مش من نفس الشخص

Mechanism(Pathogenesis):

Toxic injury ←

مثل: Cyclophosphamide &&& Total body radiation

بتأثر على الطبقة المبطنة لل sinusoids ←

(sinusoidal endothelium)

بصير فيها: Necrosis + swelling ← بتطلع الخلايا الميتة وتعمل emboli ←

انسداد مرور الدم في ال sinusoids ←

الدم بيروح لـ space of Disse ← بيفعّل stellate cells ←

stellate cells ←

← بتنتج كولاجين ← يؤدي إلى fibrosis

Clinical presentation

Mild – severe

Death if does not resolve in 3 months

Peliosis Hepatis

كلمة "Peliosis" معناها:

وجود فراغات مليئة بالدم داخل نسيج الكبد، بدون Vascular endothelium واضح.

(sinusoidal dilatation)

(blood-filled spaces) تكوّن فراغات مليئة بالدم

أحيانًا تتكسر جدران sinusoids ← ينزف الدم بحرية داخل نسيج الكبد

Causes:

1-anabolic steroids منشطات عضلية

2-oral contraceptive

3-danazol دواء هرموني

Pathogenesis

Unknown

Clinical presentation

-Asymptomatic

-Intra abdominal hemorrhage

-Liver failure

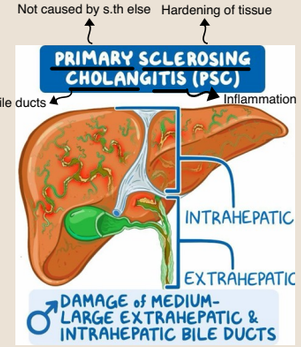
It’s reversible!!

8

Biliary Liver Diseases

Primary sclerosing cholangitis

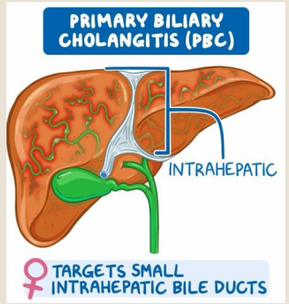
- -Inflammation , obliterative firosis, & segmental dilation of the obstructed intra hepatic & extra hepatic bile ducts
- -Ulcerative colitis coexists in 70% of PSC patients
  - patients of ulcerative colitis , 4% develop primary sclerosing cholangitis
- - more in 3rd-5th decades (30-50yrs)
  Male: Female => 2:1
- - asymptomatic pts.
  Later, they could develop fatigue, pruritis, jaundice, wt loss, ascitis, bleeding, encephalopathy
- **(Lab findings):**
  1. ↑ alkaline phosphatase بشكل مستمر
  2. Antimitochondrial Ab (AMA):
     فقط أقل من 10% يظهر عندهم
  3. Antinuclear cytoplasmic Ab (p-ANCA): موجود في 80% من الحالات
- **Morphology**
  - -Concentric periductal onion-skin fibrosis & lymphocytic infilrate
  - -Atrophy & obliteration of bile ducts
  - -Dilation of bile ducts inbetween areas of stricture
  - -Cholestasis & fibrosis leading to
  - -Cirrhosis, cholangiocarcinoma (10 – 15%)
- **Pathogenesis**
  -Exposure to gut derived toxins -Immune attack
  -Ischemia of biliary tree



Autoimmune disease

Primary biliary cholangitis (Primary biliary Cirrhosis)

- - chronic, progressive & often fatal cholestatic liver disease
  -Non-suppurative **granulomatous destruction** of medium-sized intrahepatic bile ducts, portal inflammation & scarring
- Associated conditions: sjogern syndrome , Scleroderma thyroiditis, RA, Raynaud's phenomenon تغير لون الأصابع.
  Membranous Glomerulonephritis (MGN), celiac disease.
- -Age 20-80yrs (peak 40-50yrs)
  -F>M
- -Insidious onset
  -Pruritis, jaundice
  -Cirrhosis over 2 or more decades
- **(Lab findings):**
  - ↑ Alkaline phosphatase & cholesterol
  -Hyperbilirubinemia = hepatic decompansation
  -Antimitochondrial Abs > 90%
  -Antimitochondrial pyruvate dehydrogenase
- **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

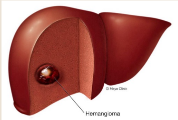
Mechanical obstruction

- Prolonged obstruction of extrahepatic biliary tree
- -Causes:
  1-cholelithiasis
  2-biliary atresia
  3-malignancies
  4-strictures

9 Benign Liver tumors

Cavernous Hemangioma

- Usually <2cm
- Subcapsular



لا يتحول إلى سرطان

هي كتلة غير سرطانية (حميدة) داخل الكبد، مكوّنة من:

- 🔶 شعيرات دموية صغيرة وكبيرة
- 🔶 شكلها مثل الكهف أو المغارة مليانة دم

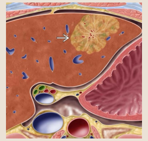
Liver cell adenoma

- Young female
- History of oral contraceptive intake
- May rupture esp. during pregnancy <u>causing severe intraperitoneal hemorrhage</u>
- Rarely <u>may contain HCC</u>
- misdiagnosis of HCC

10 Liver Nodules

Focal noudular hyperplasia

- Well demarcated hyperplastic hepatocytes with central scar.
- <u>Non-cirrhotic liver</u>
- Not neoplasm but nodular regeneration
- Local vascular injury
- Females of reproductive age
- No risk of malignancy
- 20% of cases have cavernous hemagnioma



Macroregenerative Nodules

- <u>Cirrhotic liver</u>
- Larger than cirrhotic nodules
- <u>No atypical features</u>
- Reticulin is intact
- No malignant potential

Dysplastic nodules

- Larger than 1 mm
- <u>Cirrhotic liver</u>
- <u>Atypical features</u>, pleomorphism and crowding
- High proliferative activity
- High or low dysplasia
- Precancerous (monoclonal, + gene mutations)

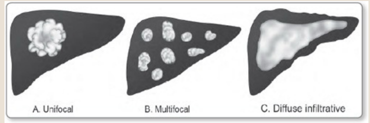
Types

- Small – cell dysplastic nodules
  Risk of developing HCC ⬆️⬆️
- Large – cell dysplastic nodules
  Risk of developing HCC ⬆️

11 Malignant Liver tumors

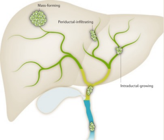
Hepatocellular carcinoma(HCC)

- Unifocal
- Multifocal
- Diffusely infiltrative



Mixed

Cholangiocarcinoma



- mass-forming lesion
- Periductal infiltrating
- Intraductal

α-feto protein increases also with:

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.

metastasis

- Desmoplastic Mets
- Vascular –> to lungs, bones, adrenals, brain

Clinical presentation

abd. Pain, malaise, wt. loss

increase **<u>α-feto protein</u>** in 60 – 75% of pts.

Prognosis

- Death within 7 -10 months
- Causes:

1-Cachexia 2-GI bleeding

3-Liver failure 4-Tumor rupture and hemorrhage

Incidence

< 5/100000 population in N&S America & central Europe , Australia

5/100000 population in Mediterranean

6/100000 population in Korea, Taiwan

ozambique, china

Blacks > white

M:F ratio

1 in low incidence areas. >60yr

1 in high incidence areas. 20-40yr

5.4% of all cancers

Predisposing Factors

1. Hepatitis carrier state
   - the vertical transmission increases the risk 200X
   - cirrhosis may be absent !!!
   - young age group (20-40yr)
2. > 85% of cases of HCC occur in countries with high rates of chronic **HBV inf**

3-**Cirrhosis** :- In western countries cirrhosis is present in 85-90% of cases > 60yr

HCV & **alcoholism** cause cirrhosis => leading to HCC

4. **Aflatoxins**
5. Hereditary **tyrosinemia** (in 40% of cases)
6. Hereditary **hemochromatosis**

Pathogenesis

1️⃣ Repeated cycles of cell death & regeneration

HBC, HCV => lead to gene mutations && Genomic instability

2️⃣ Viral integration, HBV DNA intergration which leads to clonal expansion نسخ كثيرة من خلية واحدة بها طفرة

=> this leads to Genomic instability حتى خارج موقع الدمج

3️⃣ HBx Protein – من HBV

HBx اسمه HBV بروتين خاص بفيروس

لعدة transactivation يعمل & apoptosis يثبّط & Oncogenes يفعّل

.فيروسية وخلوية promoters

4️⃣ Aflatoxins (fungus Aspirgillus flavus)

mutation of p53

5️⃣ Cirrhosis , that's caused by:-

- HCV
- Alcohol
- Hemochromatosis
- Tyrosinemia (40% of pts. Develop HCC despite adequate dietary control)

Special type of HCC

Fibrolamellar carcinoma

20-40 yr. M=F

No relation to HBV or cirrhosis

better prognosis

single hard scirrhous tumor