Liver

Pathalogic markers of livers

① Hepatitis (inflammation) → seen in viral infections, drugs, alcohol, and autoimmune

② Ballooning degeneration (irregular clumping of cytoplasm showing accumulation of substances)
↳ seen in chronic liver disease

③ Steatosis: fatty liver → seen in Alcoholic Liver disease, Reye's Sy., DM, obesity, and fatty change of pregnancy
↳ macrovesicular

④ Necrosis: depends on: ① type of necrosis ② location of necrosis ③ Cause of necrosis ④ scatter of inflammation
↳ slide: 15+16
- focal (small group)
- Diffuse (massive + submassive Necrosis) (75% +) (25% – 75%)

⑤ Regeneration: Liver regeneration marks injury
↳ Oval cells (at canal of Hering)

⑥ Fibrosis

⑦ Cirrhosis → prolonged fibrosis

⑧ Ductal proliferation → proliferation of bile ducts in response to liver injury

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⊙ Hepatic failure: a state in which hepatic function is almost totally (80–90%)

Causes: ① Massive Hepatic Necrosis
- fulminant (3 weeks)
- subfulminant (3 months)

& 2 main causes of massive Hepatic Necrosis:
① viral hepatitis
② Drug + chemicals

Drugs: ① Acetominophen
② halothane
③ anti TB drugs, mainly (Isoniazid + pyrazinamide, rifampin)
④ CCl_4
⑤ Mushroom poisining

③ Wilson's disease (improper Cu^{2+} metabolism)
④ heat stroke (dramatic change of body temp.)
⑤ Acute fatty liver of pregnant
⑥ Hepatic vein obstruction
⑦ HDV on HBV (superimposed)
⑧ Autoimmune hepatitis
↳ other causes of Massive hepatic necrosis

② Chronic liver disease: Any disease to liver that causes continuous damage of liver for 6 months.
① HBV, HDV-HBV, HCV
② liver cirrhosis
③ Hepacellular carcinoma

③ Hepatic problem without seen cirrhosis:
① Reye's syndrome (NSAID + varicella zoster in children)
② tetracyclin toxicity
③ Acute fatty liver of pregnancy

Clinical manifestations of Hepatic failure

① Jaundice → No billiruben metabolism
② Hypoalbuminemia → edema
③ Hyperammonemia → Hepatocellular encephalopathy
④ Fetor hepaticus → bad breath due to thiols that pass to lungs
⑤ palmar erytlema → erythema of palms
⑥ Hyperestrogenemia → ↑ estrogen in men
⑦ Spider angiomas → Swollen BV. under skin
⑧ Hypogonadism → ↓ in hormone secretions
⑨ gynecomastia → enlarged breast tissue in men

↳ what clinical features do these produce?

① Multiple organ failure
② coagulopathy → bleeding

③ Hepatic encephalopathy: Disturbance of brain function
↳ due to hepatic impairement: accumulation of NH_3 → toxic to brain

↳ read slides 69-71 for more info

↳ signs: ① Hyper reflexia
② Rigidity
③ ↓ conscienceness
④ Edema in brain
⑤ Seizures
⑥ Asterexis → reflex of hands when wrist is extended
⑦ EEg changes

④ Hepatorenal syndrome → renal defect with no underlying cause

But what is Cirrhosis?

Cirrhosis is the diffused (envolving all liver) of fibrosis, converting all liver in to nodules

↳ characteristics: ① fibrous septae
② encircled Parenchyma by fibrotic bands (forming nodules)
③ Architectural disruption (diffused)

nodules < micro (<3 mm)
macro (>3 mm)

Pathogenisis

① Hepatocellular degeneration → ② Regeneration due to loss of Hepatocytes
→ ③ Progressive fibrosis due to increased death and stimuli
→ ④ finally, vasculature of liver is changed → Cirrhosis

But what is fibrosis?

fibrosis is the process of adding fibrous tissue in parenchyma, due to injury.

- Normally: • Collagen IV is present in space of Disse (sinusoids)
  • Collagen I, III, V, and XI are present around central vein, in portal tracts, and in liver capsule

- During fibrosis (active liver injury):

Collagen type I and III are deposited, in Space of Disse (sinusoids)
↳ fibrosis

- who deposits this collagen?
  cells called stellate cells, which lie in spaces of Disse

- what allows activity of of stallate cells and production of collagen?
  ① reactive oxygen species → excessive alcohol + drugs (by CYP450 pathway)
  ② Growth factors → TGF-β
  ③ cytokines → TNF, IL1, lymphotoxins (Active hepatitis)

↳ Stallete cells transform to myofibroblast to produce collagen

• But what happens after we deposite Collagen in sinusoids?

Basic histology: Sinusoids are made of endothelial cells that are FENESTRATED
this means that they contain spaces in order to mix oxygenrich (Hepatic A.) blood with nutrient rich (portal v.) blood

↳ collagen deposition will causes → ① loss of fenestration (no spaces for blood exchange)
② due to loss of spaces, vascular shunts will form
↳ shunts are pathological connections between hepatic A. and portal v.

this will lead to loss of microvilli in hepatocytes → leading to ↓ in transport and function of liver (detoxification of liver)

• what happens when all this occurs?
① Progressive hepatic failure → fibrosis and cell death (no absorptive capacity for O2 for hepatocytes)
② portal vein hypertension → loss of sinusoids
③ Hepatocellular carcinoma

• what causes Cirrhosis?
① Chronic alcoholism (10-15 years)
② viral hepatitis
③ Billiary disease
④ Hemochromatosis → too much iron accumulates in body
⑤ wilson disease → problem in cupper metabolism
⑥ α_1-antitrypsin deficiency

Clinical features of cirrhosis
① Silent
② Anorexia, weight loss, weakness

portal vein Hypertension?

- ↑ resistance of blood in Liver, at the level of sinusoids and central veins
  - ↳ why? fibrosis of sinusoids + Arterial-portal Anastamosis (shunt formation)
  - ↑ BP in portal venous system

- what causes portal vein hypertension?

3 clinical locations

① Prehepatic: blood didn't reach liver yet: ① Portal vein thrombosis
↳ clott formation in portal vein
② Spleenomegally
↳ according to internet, this is a consequence of PV. hypertension

② Post hepatic: after reaching and leaving Livers ① Sever right sided heart failure
② constrictive pericarditis
③ Hepatic vein out flow obstruction

③ Hepatic: at the level of Livers ① cirrhosis (discussed earlier)
② schistosomiasis (reaches PV, obstructing it)
③ Massive fatty change (Pregnant + veyes + alcohol)
④ diffuse granulamatous (sarcidosis and TB)
⑤ nodular regenerative hyperplasia
↳ non cirrhosis reaction (could be familial)

- what happens if portal hypertension occurs?

① Ascitis: collection of fluids in peritoneal cavity (atleast 500mL could be clinically detected)

features of Ascitis:
① Serous fluid
② contains albumin
③ contains same blood conc. of Na^+, k^+, and glucose
④ contain neutrophils } inflammation
⑤ contains lymphocytes + mesotleilium
⑥ If RBC is available → cancer malignant

- what causes Ascitis? leakage of lymph fluid to peritoneum

renal failure due to secondary hyperaldosteranism | hypoalbuminemia | ↑ sinosoidal BP | (20L of lymph instead of 800-1000mL)

② Portosystemic shunts: ↑ Portal pressure → bypasses to wherever systemic portal circulation shares capillaries in body

- ① Hemorrhoids
- ② esophageal varicies
- ③ Retroperitoneal
- ④ falciform ligament (periumbilical + abdominal wall)
  - ↳ called caput medusa

③ Splenomegally: causes hypersplenism (rapid destruction of RBC)

④ Hepatic encephalopathy: discussed earlier

- Diseases:

① Drug induced reactions:
- predictable reaction (dose dependent)
- Unpredictable reactions
  - immune mediated
  - rate of metabolism of patient
    - ↳ they have no specific clinical or histological features. they could present like any viral or autoimmune hepatitis.

- predictables: ① Acetominophen ② tetracyclin ③ antineoplastic ④ CCl_4 ⑤ Alcohol
- unpredictables: ① Chlorpromazin ② halothane ③ Sulfonamides ④ Methyldopa ⑤ Allopurinol

- mechanisms of toxicity:

① direct toxic damage → acetominophen / CCl_4 / mushroom toxins

② immune mediated → Haptens → drugs know to change surface proteins on hepatocytes → making them antigenic → leads to recognition by immune system → Hepatocyte's death.

- patterns of injury:

① necrosis
② cholestasis
③ steatosis
④ steohepatitis
⑤ Fibrosis
⑥ vascular lesions
⑦ granuloma
⑧ Neoplasm formation

① Acetominophen
② halothane
③ anti TB drugs, mainly < Isoniazid, rifampin
④ CCl_4
⑤ Mushroom poisoning
⑥ antidepressant monoamine oxidase inhibitors

Alcoholic liver disease

- 80g/day is associated with liver fatty change
- 200-400mg/dL → produces death, coma, and resp. failure (in occasional drinkers)
- in habitual drinkers, 700mg/dL could be tolerated → metabolic tolerance which could reach up to 5-10 fold in induction of CYP450 (enzyme Cyp 2E1 → metabolizes alcohol, cocaine, acetomenophen)

- But what happens to alcohol (ethanol)

- alcoholic drinks contain ethanol
- ethanol must be converted to a more meable form.
- ethanol —Alcohol dehydrogenase→ acetaldehyde
- Alcohol dehydrogenase (Alcohol DH) is available in stomach and liver
- in women, Alcohol DH's activity is less than that of men's, so women develop higher blood levels of ethanol than men.

acetaldehyde —acetaldehyde dehydrogenase→ Acetic acid → distributed in all tissues

Where is the problem?

- problem is that Ethanol in liver could also be metabolized by CYP450 → CYP450 produces ROS
- excessive ethanol will lead to more ROS formation
- Recall that ROS are among the inducers of Stellate cells to induce FIBROSIS
- Thus excessive alcohol → fibrosis → Cirrhosis eventually

- from where does fatty change come from?

- ethanol —Alcohol dehydrogenase→ acetaldehyde
- acetaldehyde —acetaldehyde dehydrogenase→ Acetic acid

} those 2 reactions produce NADH

- NADH stimulates F.A. synthesis + inhibits B oxydation of F.A

thus fat accumulates in liver cells ←

↳ all this is extra information not mentioned in slides

- 3 forms of alcoholic liver disease:

① Hepatic steatosis: occurs following moderate intake of alcohol
↳ microvesicular steatosis

- liver becomes large, yellow, and greesy (4-6 kilos)
- progresses to diffuse steatosis → fibrosis

- fatty change could regress and is reversible in case of complete stoping of alcohol

Clinical features: - ↑ liver size
- ↑ liver enzyme in blood
- dysfunction of liver isn't usual

② Alcoholic hepatitis: inflammation, associated with those features:

① Hepatocyte swelling and necrosis → due to accumulation of fat, water and proteins

② Mallory hyaline bodies: Cytoplasmic eosinophilic inclusion bodies in degenerating Hepatocytes. They are made of cytokeratin filaments + proteins
↳ these show past of alcohol, but not pathognamonic to Alcohol liver disease
↳ occur in: ① Biliary Cirrhosis
② Wilson disease
③ Chronic cholestatic syndromes
④ Hepatocellular carcinoma

③ neutrophilic infiltration (alcohol allows GI bacterial antigens to reach liver) → neutrophils and kupffer cells react
↳ induce fibrosis due to cytokines production

④ Fibrosis → due to ROS + cytokines

⑤ cholestasis
⑥ hemodesrin → in Kupffer + hepatocytes

Clinical features: - ↑ size of liver and spleen
- ↑ liver function test (hepatocellular death)
- Nonspecific symptoms (weight loss, Anorexia, malaise)
- ↑ risk of cirrhosis + death

③ Alcoholic cirrhosis: - develops slowely (usually)
- develops faster in case of alcoholic hepatitis

Clinical features: - portal hypertension (discussed)

- the 3 forms of Alcoholic liver disease could occur independently of one another, or could occur in consequence.

Causes of death in alcoholic liver disease:

1. hepatic failure
2. Massive G-I bleeding
3. Infections
4. Hepatorenal syndrome
5. Hepatocellular carcinoma.

- simple notes about hepatitis (not everything) (read slides)

HAV :
- feco oral (virus shed in bile + feces) • incubation period (IP) = 15-50 days
- Benign and self limited
- virus shed 2-3 weeks before and 1 week after jaundice
- rarely causes fulminant hepatitis

Serology: Anti HAV IgM (→ best marker of disease) appears at onset of symptoms (IgM), then ↓ in few months
IgG persist for life after

- vaccine is available

HBV
- Shed in all body fluid (not feces) + vertical transmission and sexually
- could induce chronic state
- IP (4-26 weeks)
- could cause fulminant hepatitis

Serology:
- HBcAg (core protein forming capsid)
  - ↳ Anti HBc IgM: Appears before symptoms and replaced by IgG
- HBeAg (high transmissability and infectivity) (Acute phase)
  - ↳ anti HBeAb: indicates end of infection
- HBsAg (surface antigen)
  - ↳ Anti HBs IgG: rise after acute phase is over and remains for months after HBsAg disappearance.
- If HBsAg remain elevated for 6 months, chronic infection.

DNA polymerase, HBx protein → appear after HBsAg, signifying active disease + persistant infection

- post infection:
  1. Hepatitis with recovery
  2. Nonprogressive chronic hepatitis
  3. progressive chronic ending in cirrhosis
  4. fulminant hepatitis with massive necrosis
  5. Acute carrier.

HCV

- Blood borne + sexual + vertical transmission
- could cause fulminant Hepatitis
- causes Hepatocellular carcinoma
- HCV infection doesn't confer immunity, due to genetic instability.
  ↳ IgG + genomic instability of the virus → useless when re infection (if it occurs) due to
- cause chronic disease
- IPC 2-26 weeks)

Serology: RNA is detectable in blood for 1-3 weeks with ↑ in serum transaminases

we could either find
- HCV Abs detectable during acute infection (50-70% of patients)
- HCV Abs detectable after acute infections (30-50% of patients)

- in chronic state, HCV RNA is always present, despite Abs
- ↑ in aminotransferases in normal periods is quite usual.

HDV

- transmitted Parenteral (Close personal contact)
- always associated with HBV (defective virus)
  ↳ encapsulated with HBsAg
- IPC 4-7 weeks)

Serology: detectable in blood + liver in early days of acute symptomatic disease

you could have
- IgM against HBV + HDV (coinfection)
- IgM against HBsAg and IgM against HDV → ? Superinfection (HBV infected individual acquires HDV alone)
  ↳ more severe.

IgM is short lived + shows recent infection.

HEV

- water borne
- no vaccine
- self limited, except in pregnancy
- no chronic disease/carrier state
- IPC 6 weeks)

Serology: RNA is detected in stool before + liver before clinical symptoms

IgM appears during infection
IgG appears when symptoms resolve

- viruses that cause asymp. disease + recovery: All
- " " " symp disease with or without Jaundice: All

pre jaundice: uncommon in HCV; malaise, fatigue, fever, muscle pain, Nausea, loss of appetite + serum like sickness (Fever, rash, athralgia)

Post jaundice: conjugated hyperbilirubinemia, dark urine, pruritis (itch), Prolonged prothrombone time (clotting time is long), ↑ serum alk. phosph. + hyperglobureneamia

- " " " chronic/chronic carriers: B+C
- " " " fulminant necrosis: B, B+D, C, A (Rarely)

- For blood transfusion, we test for HBC + HCV
- Fulminant liver disease is same as massive hepatic necrosis
- chronic hepatitis

- **Morphology of chronic hepatitis**

-Mild to severe

1.Protal inflammation

2.Lymphoid aggregate

3.Necrosis of hepatocytes-councilman bodies → acidophilic globule of cells surrounded by normal cells of liver → cells undergo necrosis

4.Bile duct damage

5.Steatosis

6.Interface hepatitis → dying of hepatocytes surrounding the portal triad

7.Bridging necrosis & fibrosis (necrosis of terminal venules of portal tract)

8.Fibrosis

9.Ground-glass appearance → dull, hazy and flat appearance of pink (caused by HBsAg)

10.Sanded nuclei → eosinophilic inclusions in hepatocytes nucleus due to chronic HBV

11.Lobular disarray → mentioned in first slides

↳ includes multiple features (Ballooning degeneration, spotty necrosis, mononuclear cells infiltrate)