GI PATHOLOGY

Final | Lecture 4-5

LIVER DISEASES

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Color code: **Black** = slides, **Gold** = from doctor or book, Silver = additional from us.

Liver Diseases 2

1. Autoimmune Hepatitis

- Chronic hepatitis with immunologic abnormalities.
- Histologic features are similar to chronic viral hepatitis, even to drug-induced chronic hepatitis.
- Indolent or severe course
- Dramatic response to immunosuppressive therapy
    - A **dramatic response to immunosuppressive therapy in autoimmune hepatitis (AIH)** means the patient's symptoms, liver enzyme levels, and inflammation improve rapidly and significantly after starting treatment—usually corticosteroids

❖ Features:

1. Female predominance (70%)
2. Negative serology for viral Antigens
3. ↑ Serum Ig (>2.5 g/dl)
4. High titers of autoantibodies (80% of cases)
5. The presence of other autoimmune diseases such as RA, thyroiditis, Sjögren's syndrome, and UC in 60% of the cases

❖ The type of autoantibodies:

1. Anti-smooth muscle Abs:
    a. Anti-actin
    b. Anti-troponin
    c. Anti-tropomyosin
2. Liver/kidney microsomal Abs:
    a. Anti-cytochrome P-450 components
    b. Anti-UDP-glucuronosyl transferases
3. 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. Non-alcoholic Fatty Liver Disease

❖ Types:

1. Steatosis (Fatty liver)
2. Steatohepatitis:
    a. Hepatocyte destruction
    b. Parenchymal inflammation

c. Progressive pericellular fibrosis

❖ Predisposing factors:

1. Type 2 DM
2. Obesity:
   a. Body mass index > 30 kg/m² in **Caucasians**
   b. Body mass index > 25 kg/m² in **Asians**
3. Dyslipidemia (↑ TG, ↑ LDL, ↓ HDL)
   - Dyslipidemia is a metabolic disorder characterized by abnormally high or low amounts of any or all lipids or lipoproteins in the blood.

❖ Pathogenesis:

- Associated with a **Metabolic syndrome**, which includes:
  - Insulin resistance
  - Obesity
  - Dyslipidemia

❖ Mechanism of fatty accumulation:

1. Impaired oxidation of fatty acids
2. Increased synthesis & uptake of FFA
3. Decreased hepatic secretion of VLDL

➢ **↑ TNF, IL-6, chemokines → liver inflammation & damage.**

❖ Clinically:

- **NAFLD** is the **most common cause** of **incidental elevation in transaminases**
- Most patients are **asymptomatic**

✓ If symptomatic:

- Non-specific symptoms: fatigue, malaise, RUQ (right upper quadrant) discomfort.
- Severe symptoms.
- Liver biopsy is required for diagnosis
- NAFLD may be a significant contributor to cryptogenic cirrhosis

3. Hemochromatosis

- Excessive accumulation of body iron (liver & pancreas)
- Primary or secondary (genetic or acquired)

❖ Causes of acquired hemosiderosis: (4 causes mentioned)

1. **Multiple transfusions.**
   - Repeated blood transfusions can lead to the accumulation of red blood cells, which contain iron. Over time, this results in iron overload as excess iron deposits in various organs and tissues, a condition known as hemosiderosis.
2. **Ineffective erythropoiesis (thalassemia).**
   - Patients with thalassemia often require chronic blood transfusions.

- Characterized by the destruction of immature red blood cells within the bone marrow.
- leads to increased iron absorption and retention. The shortened lifespan and rapid breakdown of red blood cells further contribute to systemic iron overload.

3. Increased iron intake (Bantu siderosis).
    - Bantu siderosis is observed among certain African populations, particularly the Bantu tribes, who traditionally prepare food and beverages in iron containers. This practice leads to excessive dietary iron intake and subsequent iron accumulation in the body.
4. Chronic liver disease
    - Chronic liver conditions can impair the regulation and excretion of iron, contributing to secondary iron overload.

❖ Features:

1. Micronodular cirrhosis (all patients)
2. Diabetes mellitus (75–80%)
3. Skin pigmentation (75–80%)
4. Cardiomegaly, joint disease, testicular atrophy

✓ **Symptoms appear in the 5th–6th decades, not before age 40**

✓ **Male to female ratio: 5–7:1**

❖ Genetic hemochromatosis

- **Four** variants exist.
- The most common form is an **autosomal recessive disease** of adult onset caused by a mutation in the **HFE gene** on chromosome **6**.

❖ Pathogenesis:

1. Primary defect in intestinal absorption of dietary iron
2. Total body iron: 2–6 g in adults, ~ 0.5 g in the liver (mostly in hepatocytes)
3. In disease: > 50 g of iron accumulates → one-third in the liver.
4. In hereditary hemochromatosis, there is a defect in the regulation of intestinal absorption of dietary iron, leading to a net iron accumulation of 0.5–1 g/year.

◊ Iron has no natural pathway for excretion in the body, which is why iron balance is tightly regulated at the level of intestinal absorption. The body only absorbs as much iron as it needs, and this regulation primarily occurs in the duodenum.

◊ In patients with hereditary hemochromatosis, mutations disrupt this regulatory mechanism, leading to uncontrolled and excessive iron absorption. Over time—often years—this leads to progressive iron overload in the body.

◊ The **normal** total body iron content in adults ranges from **2 to 6 grams**, with about **0.5 grams** stored in the **liver**, mainly within hepatocytes.

◊ In contrast, **individuals with hemochromatosis** may accumulate **over 50 grams of iron**, with about one-third of this iron stored in the liver and the rest deposited in various organs such as the heart, pancreas, and joints.

◊ The underlying defect in hereditary hemochromatosis is a mutation in the HFE gene, this mutation leads to a net accumulation of 0.5–1 gram of iron per year due to unregulated absorption.

◊ Clinical symptoms and liver-related complications typically emerge once iron stores **exceed 20 grams,** marking the **threshold** for organ damage to begin manifesting.

- The gene responsible is the **HFE gene**, located on chromosome 6, close to the **HLA gene complex**.
- The HFE gene regulates the level of **hepcidin**, a hormone synthesized in the liver.
- Hepcidin **inhibits** iron absorption from the intestine.
- HFE gene deletion causes iron overload.

❖ Two mutations can occur in the HFE gene:

1. Mutation at nucleotide 845 → tyrosine substitution for cysteine at amino acid 282 (**C282Y**)
2. Aspartate substitution for histidine at amino acid 63 (**H63D**)

✓ 10% of patients have other gene mutations.
✓ Carrier rate for **C282Y** is 1/70.
✓ Homozygosity is 1/200.
✓ 80% of patients are homozygous for the **C282Y** mutation and have the highest incidence of iron accumulation.
✓ 10% of patients are either homozygous for the **H63D** mutation or compound heterozygous for **C282Y/H63D** mutation.

❖ Excessive iron deposition leads to tissue toxicity through:

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

❖ Morphological changes:

1. **Deposition of hemosiderin in different organs:**
    a. Liver
    b. Pancreas
    c. Myocardium
    d. Pituitary
    e. Adrenal
    f. Thyroid & parathyroid
    g. Joints
    h. Skin
2. **Cirrhosis**
3. **Pancreatic fibrosis**
4. **Also there's:**
    ✓ **No inflammation**
    ✓ Fibrosis
    ✓ Cirrhosis

- ✓ Synovitis
- ✓ Polyarthritis (pseudogout) Remember Dr. Mousa 😨 😨
- ✓ Pigmentation of liver
- ✓ Fibrosis of pancreas & myocardium
- ✓ Atrophy of testes

❖ Clinical presentation

- **Male to female ratio: 5–7:1**
- **Appears in the 5th–6th decades**

❖ Symptoms:

− Hepatomegaly.	- Abdominal pain.	- Skin pigmentation
− Diabetes mellitus	- Cardiac dysfunction.	- Atypical arthritis
− Hypogonadism	- ↑ Serum iron and ferritin.	- HCC: 200× increased risk.

4. Wilson Disease

- Autosomal recessive disorder of copper metabolism
- Caused by a mutation in the **ATP7B gene** on chromosome **13**, which encodes an **ATPase** metal ion transporter in the Golgi region
- More than 80 mutations identified
- Gene frequency: 1 in 200
- Incidence: 1 in 30,000

❖ Pathogenesis:

Normally:

1) The main source of copper is dietary intake
2) Copper is absorbed in the intestine (2–5 mg/day)
3) It then forms a complex with albumin in the bloodstream
4) This complex is taken up by hepatocytes
5) Within hepatocytes, copper is incorporated with α-2-globulin to form **ceruloplasmin**
6) Ceruloplasmin is secreted into the plasma, accounting for 90–95% of circulating copper
7) The liver then reabsorbs ceruloplasmin
8) Ceruloplasmin undergoes lysosomal degradation
9) Free copper is subsequently secreted into bile

In Wilson disease:

- Absorbed copper fails to enter the circulation in the form of ceruloplasmin
- Biliary excretion of copper is reduced

- A defective **ATP7B** gene results in failure of copper excretion into bile and inhibits ceruloplasmin secretion into plasma
- This leads to **copper accumulation in the liver**

❖ Copper Accumulation in the Liver Results In:

1. Production of free radicals
2. Binding to sulfhydryl groups of cellular proteins
3. Displacement of other metals in hepatic metalloenzymes

✓ **By the age of 5 years**, copper spills over into the circulation, causing hemolysis and involvement of other organs such as the brain and cornea, as well as the kidneys, bones, joints, and parathyroid glands.

✓ Urinary excretion of copper **increases**.

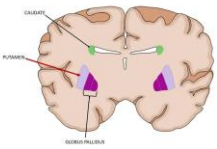
❖ Morphology:

Liver:

1. Fatty change
2. Acute hepatitis
3. Chronic hepatitis
4. Cirrhosis
5. Massive hepatic necrosis

✓ Detected by **rhodanine stain** or **orcein stain** (special stains).

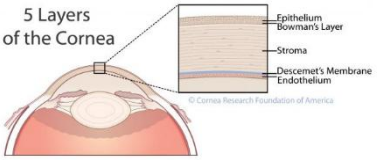
Brain:



- Toxic injury to the basal ganglia, especially the **putamen**, causing **atrophy and cavitation**
  - Putamen is a round structure situated at the base of the forebrain and is the most lateral of the basal ganglia nuclei on axial section.

Eye:

- **Kayser-Fleischer rings**
  - Green-brown deposits of copper in **Descemet's membrane** at the **limbus of the cornea**
  - Known as **hepatolenticular degeneration**



❖ Clinical Presentation

- Onset typically after age 6
- Most common presentation: **acute-on-chronic hepatitis**
- Neuropsychiatric manifestations may occur:
  - Behavioral changes
  - Frank psychosis.

- Parkinson-like syndrome.

❖ Diagnosis:

1. Decreased serum ceruloplasmin level
2. Increased urinary excretion of copper
3. Increased hepatic copper content (>250 mg/g dry weight).

Quiz on this lecture.

5. α-1-Antitrypsin Deficiency

- Autosomal recessive disorder
- Frequency: 1 in 7,000 in the North American white population
- α-1-Antitrypsin is a protease inhibitor, which inhibits elastase, cathepsin G, and proteinase 3. These enzymes are released from neutrophils at the site of inflammation.
- The **pi** gene is located on chromosome 14.
- At least 75 forms of gene mutations are present.
- The most common genotype is pi.MM, which is present in 90% of individuals.
- **PiZZ genotype** results in a decreased level of α-1-antitrypsin in the blood (only 10% of normal), and individuals with this genotype are at high risk of developing clinical disease.

❖ Pathogenesis

- The mutant polypeptide (**PiZ**) is abnormally folded and polymerizes, causing its retention in the ER of hepatocytes.
- Although all individuals with the PiZZ genotype accumulate α-1-AT-Z protein, only 10% of them develop clinical liver disease. This is due to lags in the ER protein degradation pathway.
- The accumulated **α-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

- Intracytoplasmic globular inclusions in hepatocytes, which are acidophilic in H&E sections.
- The inclusions are PAS-positive and diastase resistant.
- Neonatal hepatitis, cholestasis, and fibrosis.
- Chronic hepatitis.
- Cirrhosis.

- Fatty change.
- Mallory bodies.

❖ Clinical Features

- Neonatal **hepatitis** with **cholestatic jaundice** appears in 10–20% of newborns with the disease.
- **Attacks of hepatitis** in adolescence.
- **Chronic hepatitis and cirrhosis.**
- **HCC** in 2–3% of PiZZ adults with or without cirrhosis.

6. Reye Syndrome

- Fatty change in the liver and encephalopathy.
- Occurs in children <4 years old.
- 3–5 days after a viral illness.
- Increased liver enzymes and abnormal liver function tests (LFTs).
- Vomiting and lethargy.
- 25% may progress into a coma.

❖ Pathogenesis

- Derangement of mitochondrial function alone or in combination with viral infection and salicylates.
- Microvesicular steatosis.
- Brain edema.
- Absent inflammation.
- Skeletal muscles, heart, and kidneys show fatty change.

7. Budd–Chiari Syndrome

- Thrombotic occlusion of the hepatic vein
- Hepatomegaly
- Weight gain
- Ascites
- Abdominal pain

❖ Causes:

1. Polycythemia vera (PCV)
2. Pregnancy
3. Postpartum
4. Oral contraceptives

5. Paroxysmal nocturnal hemoglobinuria (PNH)
6. Mechanical obstruction
7. Tumors, such as HCC
8. Idiopathic in 30% of cases

❖ Morphology

- **Swollen** liver, red with a tense capsule.
- **Centrilobular** congestion and **necrosis.**
- Fibrosis.
- Thrombi. (blood clots)

❖ Clinically

- Mortality rate is **high** if not treated

8. Primary Sclerosing Cholangitis

- Inflammation, obliterative fibrosis, and segmental dilation of the obstructed intrahepatic and extrahepatic bile ducts.
- In PSC, ulcerative colitis (UC) coexists in 70% of patients.
- In patients with UC, 4% develop PSC.
- Affects individuals in their 3rd to 5th decades.
- Male to female ratio is 2:1.

❖ Clinical Features:

- Asymptomatic patients.
- Persistent **increase** in serum alkaline phosphatase.
- Fatigue, pruritus, jaundice, weight loss, ascites, bleeding, encephalopathy.
- **Antimitochondrial antibodies** in <10% of cases.
- **Antinuclear cytoplasmic antibodies** in 80% of cases.

❖ Morphology:

- Concentric periductal **onion-skin fibrosis** and lymphocytic infiltrate.
- Atrophy and obliteration of bile ducts.
- Dilation of bile ducts between areas of stricture.
- Cholestasis and fibrosis.
- Cirrhosis, cholangiocarcinoma (10-15%).

❖ Pathogenesis:

- Exposure to gut-derived toxins.
- Immune attack.

- Ischemia of the biliary tree.

9. Primary Biliary Cirrhosis

- Chronic, progressive, and often fatal cholestatic liver disease.
- **Non-suppurative granulomatous destruction** of medium-sized intrahepatic bile ducts, portal inflammation, and scarring.
- Affects individuals aged 20-80 years (peak incidence at 40-50 years).
- Female to male ratio is greater than 1:1.

❖ Clinical features:

- Insidious onset
- Pruritus, jaundice
- Cirrhosis over 2 or more decades
- Increased alkaline phosphatase and cholesterol
- Hyperbilirubinemia, leading to hepatic decompensation
- Antimitochondrial antibodies (>90%) present
- Antimitochondrial pyruvate dehydrogenase

❖ **Associated conditions:** Sjögren's syndrome, scleroderma, thyroiditis, rheumatoid arthritis (RA), Raynaud's phenomenon, membranous glomerulonephropathy (MGN), celiac disease.

❖ Morphology:

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

10. Secondary Biliary Cirrhosis

- Prolonged obstruction of the extrahepatic biliary tree

❖ Causes:

a. Cholelithiasis
b. Biliary atresia
c. Malignancies
d. Strictures

11. Sinusoidal Obstruction Syndrome (Veno-occlusive Disease)

- Originally described in Jamaican drinkers of bush-tea containing **pyrrolizidine alkaloids**
- This occurs in the first 20-30 days after bone marrow transplantation, caused by:
  1. Drugs such as cyclophosphamide
  2. Total body radiation

❖ Incidence:

- 20% in recipients of **allogeneic marrow transplants.**

❖ Clinical Presentation

- Mild to severe.
- Death if not resolved within 3 months.

❖ Mechanism

- Toxic injury to sinusoidal endothelium → emboli → blockage of blood flow
- Passage of blood into the space of Disse → increased stellate cells → fibrosis

12. Peliosis Hepatis

- Sinusoidal dilation

❖ Causes:

a. Anabolic steroids.
b. Oral contraceptives.
c. Danazol.

❖ Pathogenesis:

- Unknown

❖ Clinical Features:

- Asymptomatic
- Intra-abdominal hemorrhage
- Liver failure
- **Reversible**

13. Liver Tumors

- **Benign**
- Most common is **cavernous hemangioma**
- Usually <2 cm

- Subcapsular

A. Liver Cell Adenoma

- Young females
- History of oral contraceptive intake
- May rupture, especially during pregnancy, causing severe intraperitoneal hemorrhage
- Rarely may contain HCC
- Misdiagnosed as HCC

B. Liver Nodules

Focal Nodular Hyperplasia	Macroregenerative Nodules	Dysplastic Nodules
Well-demarcated hyperplastic hepatocytes with a central scar Non-cirrhotic liver Not a neoplasm, but nodular regeneration Caused by local vascular injury Predominantly in females of reproductive age No risk of malignancy 20% of cases have a cavernous hemangioma	Cirrhotic liver Larger than cirrhotic nodules No atypical features Reticulin is intact No malignant potential	Larger than 1 mm Cirrhotic liver Atypical features, pleomorphism, and crowding High proliferative activity High or low dysplasia Precancerous (monoclonal, positive gene mutations) Types: Small-cell dysplastic nodules Large-cell dysplastic nodules

C. Hepatocellular Carcinoma

- 5.4% of all cancers

❖ **Incidence:**

- <5/100,000 population in North and South America, North and Central Europe, and Australia
- 15/100,000 population in the Mediterranean
- 36/100,000 population in Korea, Taiwan, Mozambique, and China

- Blacks > Whites
- **M:F ratio:**
  3:1 in low-incidence areas (typically >60 years)
  8:1 in high-incidence areas (typically 20-40 years)

❖ Predisposing Factors

1. **Hepatitis carrier state**
   - Vertical transmission increases the risk by 200X
   - Cirrhosis may be absent
   - Affects the young age group (20-40 years)
2. **85% of cases of HCC occur in countries with high rates of chronic HBV infection**
3. **Cirrhosis**
   - In Western countries, cirrhosis is present in 85-90% of cases
   - Affects individuals >60 years
   - Associated with HCV and alcoholism
4. **Aflatoxins**
5. **Hereditary tyrosinemia (in 40% of cases)**
6. **Hereditary hemochromatosis**

❖ Pathogenesis

1. **Repeated cycles of cell death and regeneration**
   - HBV, HCV, gene mutations, and genomic instability
2. **Viral integration**
   - HBV DNA integration leads to clonal expansion
3. **HBV DNA integration leads to genomic instability, not limited to the integration site**
4. **HBV X-protein**
   - Leads to transactivation of viral and cellular promoters
   - Activation of oncogenes
   - Inhibition of apoptosis
5. **Aflatoxins** (fungus Aspergillus flavus)
   - Mutation of p53
6. **Cirrhosis**
   a. HCV
   b. Alcohol
   c. Hemochromatosis
   d. Tyrosinemia (40% of patients develop HCC despite adequate dietary control

❖ Morphology

1. **Hepatocellular Carcinoma (HCC)**
2. **Cholangiocarcinoma (CC)**

3. **Mixed**

- Unifocal
- Multifocal
- Diffusely infiltrative
- Vascular invasion is common in all types
- Well-differentiated to anaplastic

D. Fibrolamellar Carcinoma

- Typically affects individuals aged 20-40 years
- Male to female ratio is 1:1
- No relation to HBV or cirrhosis
- Better prognosis
- Single, hard, scirrhous tumor

E. Cholangiocarcinoma

- Desmoplastic metastasis
- Vascular metastasis to lungs, bones, adrenals, and brain in 50% of cases

❖ Clinical Presentation (C/P)

- Abdominal pain, malaise, weight loss
- Increased α-fetoprotein in 60–75% of patients
  - ✓ **α-Fetoprotein 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

❖ Prognosis

- Death within 7–10 months

❖ Causes:

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

Quiz on this lecture.

Overall Quiz.

Feedback Form.

V1	Larger than 1 **c**m → … 1 **m**m