MASTER STUDY SHEET - LIVER PATHOLOGY & METABOLIC LIVER DISEASES

Organized exactly from the uploaded lecture content, with the same medical terms preserved and arranged for memorization.

1. Drug-Induced Liver Disease (DILD)

Drug Reactions

1) Predictable (Intrinsic)

- Dose-dependent reactions.

2) Unpredictable (Idiosyncratic)

Depends on:

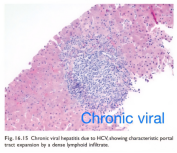
1. The immune response of the host to the antigenic stimulus.
2. The rate at which the host metabolizes the agent.

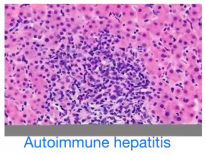
Important Notes

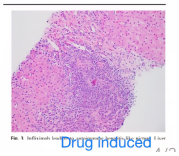
- Injury may be immediate or may take weeks to months.
- Drug-induced chronic hepatitis is clinically and histologically indistinguishable from chronic viral or autoimmune hepatitis.

Histologic Pattern

- Necrosis and inflammation.







Drugs Causing Liver Injury

Predictable Drugs	Unpredictable Drugs
Acetaminophen Tetracycline Antineoplastic agents CCl4 Alcohol	Chlorpromazine Halothane Sulfonamides Methyldopa Allopurinol

Special Notes (Extra)

Chlorpromazine

- An agent that causes cholestasis in patients who are slow to metabolize it.

Halothane

- Halothane and its derivatives can cause a fatal immune-mediated hepatitis after repeated exposure.
- The damage begins in centrilobular hepatocytes but extends to encompass entire lobules in most severe cases.

Mechanism of Drug Injury

Mechanism	Examples
Direct toxic damage	Acetaminophen CCl4 Mushroom toxins
Immune-mediated damage	-

Patterns of Injury

1. Hepatocellular necrosis.
2. Cholestasis.
3. Steatosis.

4. Steatohepatitis.
5. Fibrosis.
6. Vascular lesions.
7. Granuloma.
8. Neoplasms benign & malignant.

Table: Patterns of Injury in Drug- and Toxin-Induced Hepatic Injury (Extra)

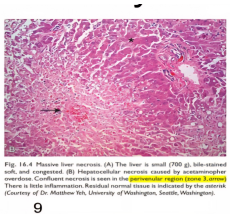
Pattern of Injury	Morphologic Findings	Examples of Associated Agents
Cholestatic	Bland hepatocellular cholestasis, without inflammation	Contraceptive and anabolic steroids, antibiotics, HAART
Cholestatic hepatitis	Cholestasis with lobular necrosis and inflammation; may show bile duct destruction	Antibiotics, phenothiazines, statins
Hepatocellular necrosis	Spotty hepatocyte necrosis	Methyldopa, phenytoin
Hepatocellular necrosis	Massive necrosis	Acetaminophen, halothane
Hepatocellular necrosis	Chronic hepatitis	Isoniazid
Fatty liver disease	Large and small droplet fat	Ethanol, corticosteroids, methotrexate, total parenteral nutrition
Fatty liver disease	"Microvesicular steatosis" (diffuse small droplet fat)	Valproate, tetracycline, aspirin (Reye syndrome), HAART
Fatty liver disease	Steatohepatitis with Mallory-Denk bodies	Ethanol, amiodarone
Fibrosis and cirrhosis	Periportal and pericellular fibrosis	Alcohol, methotrexate, enalapril, vitamin A and other retinoids
Granulomas	Noncaseating epithelioid granulomas	Sulfonamides, amiodarone, isoniazid
Granulomas	Fibrin ring granulomas	Allopurinol
Vascular lesions	Sinusoidal obstruction syndrome (veno-occlusive disease): obliteration of central veins	High-dose chemotherapy, bush teas
Vascular lesions	Budd-Chiari syndrome	Oral contraceptives
Vascular lesions	Peliosis hepatis: blood-filled cavities, not lined by endothelial cells	Anabolic steroids, tamoxifen

Drugs That May Cause Acute Liver Failure

1. Acetaminophen - most common.
2. Halothane.
3. Anti-tuberculosis drugs (rifampin, isoniazid).
4. Antidepressant monoamine oxidase inhibitors.
5. Toxins as CCl4 & mushroom poisoning.

Morphology

- Massive necrosis -> 500-700 gm liver.
- Submassive necrosis.
- Patchy necrosis.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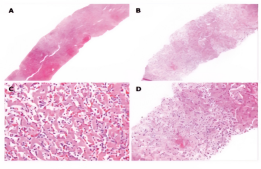
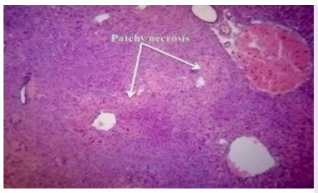

Massive and submissive



Patchy

2. Autoimmune Hepatitis

- Chronic hepatitis with immunologic abnormalities.
- Histologic features are similar to chronic viral hepatitis.
So I look for Negative serology or viral antibody
- Indolent or severe course, slowly progressive Can progress into cirrhosis
- Dramatic response to immunosuppressive therapy.

In viral hepatitis, immunosuppressive therapy is not administered as it worsens their conditions , so it is important to differentiate between them

- Risk for autoimmune hepatitis is associated with certain HLA alleles.
- Triggers for the immune reaction may include viral infections or drug or toxin exposures.

Features

1. Female predominance (70%).
2. Negative serology for viral Ags.
3. Increased serum Ig (>2.5 g/dL).
4. High titers of autoantibodies (80% of cases).
5. The presence of other autoimmune diseases as RA, thyroiditis, Sjogren syndrome, UC in 60% of the cases.

The Type of Autoantibodies

Autoantibody Type	Details
Anti-smooth muscle Abs	Anti-actin Anti-troponin Anti-tropomyosin
Liver/kidney microsomal Abs	Anti-cytochrome P-450 components Anti-UDP-glucuronosyl transferases
Anti-soluble liver / pancreas antigen	(Anti- SLA/LP) antibodies
Anti-nuclear antibody	Sensitive for AH

Outcome Very similar to the viral hepatitis

- Mild to severe chronic hepatitis.
- Full remission is unusual. Usually kept on immunosuppressants for treatment
- Risk of cirrhosis is 5%, which is the main cause of death.

Summary Extra

- There are two primary types of autoimmune hepatitis.
- Type 1 autoimmune hepatitis is most often seen in middle-age women and is characteristically associated with anti-nuclear and anti-smooth muscle antibodies.
- Type 2 autoimmune hepatitis is most often seen in children or teenagers and is associated with anti-liver kidney microsomal autoantibodies.
- Autoimmune hepatitis may either develop with a rapidly progressive acute disease or follow a more indolent path; if untreated, both are likely to lead to liver failure.
- Plasma cells are a prominent and characteristic component of the inflammatory infiltrate in biopsy specimens showing autoimmune hepatitis.

3. Nonalcoholic Fatty Liver Disease

Types

1. Steatosis (Fatty liver).
2. Steatohepatitis: hepatocyte destruction, parenchymal inflammation, progressive pericellular fibrosis.

Predisposing Factors

1. Type 2 DM.
2. Obesity: body mass index >30 kg/m2 in Caucasians, >25 kg/m2 in Asians.
3. Dyslipidemia (increased TG, increased LDL, decreased HDL). These are related to development of atherosclerosis

Pathogenesis

- Metabolic syndrome.
- Insulin resistance. Type 2 DM
- Obesity.
- Dyslipidemia.

In these patients you should consider the presence of steatohepatitis

Mechanism of Fatty Accumulation

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

Any condition associated with inflammation is going to affect hepatocytes >>destruction>>releasing mediators

- Increased TNF, IL-6, chemokines -> liver inflammation & damage.
- They are produced in increased amounts in the setting of metabolic syndrome.

Clinically

- NAFLD is the most common cause of incidental increase in transaminases. (ALT, AST)
- Most patients are asymptomatic. So it's discovered by coincidence if they have liver function test for any reason
- Non-specific symptoms: fatigue, malaise, RUQ discomfort.
- Severe symptoms.
- Liver biopsy is required for diagnosis.
- NAFLD may be a significant contributor to cryptogenic cirrhosis.

1-Non-specific symptoms
2-Fatty infiltration is not so pathognomonic, it just tells us the underlying cause and helps in evaluating the degree of inflammation/fibrosis/damage of hepatocytes/...

Therapy (Extra)

- Current therapy is directed toward obesity reduction and reversal of insulin resistance.
- Lifestyle modifications that lead to weight loss (diet and exercise) appear to be the most effective form of treatment.

Summary: Nonalcoholic Fatty Liver Disease

- Nonalcoholic fatty liver disease (NAFLD) is associated with the metabolic syndrome, obesity, type 2 diabetes, and dyslipidemia and/or hypertension.
- NAFLD may show all the changes associated with alcoholic liver disease: steatosis, nonalcoholic steatohepatitis (NASH), and cirrhosis, although the features of steatohepatitis (such as hepatocyte ballooning, Mallory-Denk bodies, and neutrophilic infiltration) often are less prominent than they are in alcohol-related injury.
- Pediatric NAFLD is increasingly being recognized as the obesity epidemic spreads to pediatric age groups, although its histologic pattern differs somewhat from that seen in adults.

4. Hemochromatosis

The most common metabolic disease that primarily affects the liver.

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

*all organs can be affected by deposition of iron.

Hemochromatosis :primary/inherited

Hemosidrosis : secondary/acquired

In the case of hemosidrosis., there will be also accumulation of iron like hemochromatosis but less than it (so the patient's condition is less severe, could be given some drugs)

Causes of Acquired Hemosiderosis

1. Multiple transfusions. exposed to overdose of iron
2. Ineffective erythropoiesis (thalassemia).
3. Increased iron intake (Bantu siderosis).
4. Chronic liver disease.

Chronic = ↑ deposition

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

Features

1. Micronodular cirrhosis (all patients).
2. D.M (75-80%).
3. Skin pigmentation (75-80%).

Involvement of pancreas... Iron deposition occurs in islet cells, causing destruction of beta cells which are the source of insulin

due to iron deposition in subcutaneous tissue

So, when you see a patient with multiple manifestations related to multiple organ involvement (liver,heart,joints,testes,...) mainly cirrhosis with enlargement of liver, diabetes, skin pigmentation, remember hemochromatosis

4. Cardiomegaly, joints disease, testicular atrophy.

Epidemiology and Genetics

- Symptoms appear [5th-6th decades], not before age 40. middle age
- M:F ratio 5-7:1.
- Genetic hemochromatosis (4 variants).
- The most common form is autosomal recessive disease of adult onset caused by mutation in the HFE gene on chromosome 6.

Pathogenesis

- Primary defect in intestinal absorption of dietary iron.
- Total body iron 2-6 gm in adults; 0.5 gm in liver mostly in hepatocytes.
- In disease >50 gm Fe accumulated -> 1/3 in liver.
- In hereditary hemochromatosis there is a defect in regulation of intestinal absorption of dietary iron leading to net iron accumulation of 0.5-1 gm/year.
- The gene responsible is HFE gene located on chromosome 6 close to HLA gene complex.
- HFE gene regulates the level of hepcidin hormone synthesized in liver.
- Hepcidin -> decreases Fe absorption from intestine.
- HFE gene deletion causes iron overload.

Mutation in HFE gene>>↓ Hepcidin>>excessive uncontrolled absorption >>iron overload

HFE Gene Mutations

1. Mutation at 845 nucleotide -> tyrosine substitution for cysteine at amino acid 282 (C282Y). The most common
2. Aspartate substitution for histidine at amino acid 63 (H63D).

- 10% of patients have other gene mutations.
- Transferrin receptor 2.
- Carrier rate for C282Y is 1/70.
- Homozygosity is 1/200.
- 80% of patients are homozygous for C282Y mutation & have the highest incidence of iron accumulation.
- 10% of patients are either homozygous for H63D mutation or compound heterozygous for C282Y/H63D mutation.

Excessive Fe Deposition -> Toxicity of the Tissues

1. Lipid peroxidation.
2. Stimulation of collagen formation.
3. DNA damage. > damage of hepatocytes > releasing toxic chemicals (Normally the hepatocytes are the stores of iron)

Morphological Changes

1) Deposition of hemosiderin in different organs:

- Liver.
- Pancreas.
- Myocardium.
- Pituitary.
- Adrenal.
- Thyroid & parathyroid.
- Joints.
- Skin.

1. Cirrhosis.

2. Pancreatic fibrosis.

- With hemosiderin deposition in the joint synovial linings, an acute synovitis may develop.
- There is also excessive deposition of calcium pyrophosphate, which damages the articular cartilage and sometimes produces disabling polyarthritis, referred to as pseudogout.

Additional Morphologic Features

This process is usually releated to increased deposition rather than inflammation.

*If we suspect an increase in iron deposition, we can use a special stain called Prussian Blue stain (iron particles appear blue)

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

Glands >> Manifestations releated to endocrine insufficiency

Clinical Presentation → Death from cirrhosis or cardiac disease

- M:F 5-7:1, 5th-6th 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, importence and loss of libido in the male)
- Increased serum Fe ferritin.
- HCC 200x increase in the risk.

Regular phlebotomy results in steady removal of excess tissue iron, and with this simple treatment life expectancy is normal

Summary: Inherited Metabolic Liver Disease

- Hemochromatosis is most commonly caused by mutations in the HFE gene and less commonly by mutations in other genes, all of which result in decreased hepcidin levels or function and increased intestinal iron uptake.
- It is characterized by accumulation of iron in the liver, pancreas, and other tissues.

5. Final Integrated Summary Table

Disease	Key Points
Alcoholic liver disease - Hepatic steatosis	Macrovesicular fatty change that may be reversible with alcohol cessation.
Alcoholic hepatitis	Requires sustained, long-term consumption. Swollen and necrotic hepatocytes with neutrophilic infiltration. Mallory bodies: intracytoplasmic eosinophilic inclusions of damaged keratin filaments.

Disease	Key Points
Alcoholic cirrhosis	Final and usually irreversible form. Sclerosis around central vein may be seen in early disease. Regenerative nodules surrounded by fibrous bands in response to chronic liver injury -> portal hypertension and end-stage liver disease.
Nonalcoholic fatty liver disease	Metabolic syndrome (insulin resistance); obesity -> fatty infiltration of hepatocytes -> cellular ballooning and eventual necrosis. May cause cirrhosis and HCC. Independent of alcohol use.
Autoimmune hepatitis	Chronic inflammatory liver disease. More common in females. May be asymptomatic or present with fatigue, nausea, pruritus. Often positive for anti-smooth muscle or anti-liver/kidney microsomal-1 antibodies. Labs: increased ALT and AST. Histology: portal and periportal lymphoplasmacytic infiltrate.

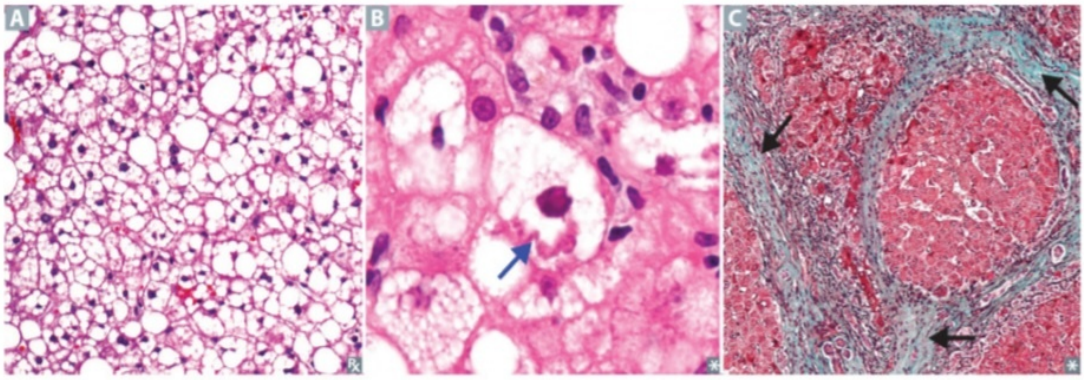
Extra

Alcoholic liver disease

Hepatic steatosis — Macrovesicular fatty change A that may be reversible with alcohol cessation.

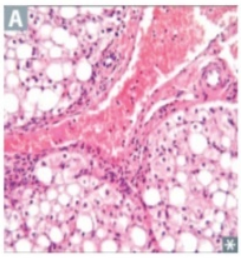
Alcoholic hepatitis — Requires sustained, long-term consumption. Swollen and necrotic hepatocytes with neutrophilic infiltration. Mallory bodies B (intracytoplasmic eosinophilic inclusions of damaged keratin filaments).

Alcoholic cirrhosis — Final and usually irreversible form. Sclerosis around central vein (arrows in C) may be seen in early disease. Regenerative nodules surrounded by fibrous bands in response to chronic liver injury → portal hypertension and end-stage liver disease.



Nonalcoholic fatty liver disease

Metabolic syndrome (insulin resistance); obesity → fatty infiltration of hepatocytes A → cellular "ballooning" and eventual necrosis. May cause cirrhosis and HCC. Independent of alcohol use.



Autoimmune hepatitis

Chronic inflammatory liver disease. More common in females. May be asymptomatic or present with fatigue, nausea, pruritus. Often ⊕ for anti-smooth muscle or anti-liver/kidney microsomal-1 antibodies. Labs: ↑ ALT and AST. Histology: portal and periportal lymphoplasmacytic infiltrate.