**Introduction to Medical Liver**

### Steatosis/Steatohepatitis

- **Steatosis** = Abnormal accumulation of fat
- **Steatohepatitis** = Fat + inflammation and/or fibrosis

- **Macrovesicular** – Nucleus pushed to the side by large single (large droplet) or multiple small (small droplet) fat vacuoles

- **Microvesicular** – Nucleus remains central with fine fat droplets

### Alcoholic Hepatitis

Hepatocyte injury and inflammation resulting from chronic alcohol consumption

- AST/ALT ratio typically >2

**Micro:** Steatosis, Hepatocyte **ballooning**, Neutrophilic lobular inflammation (black arrow), Mallory-Denk bodies (red arrow), pericellular fibrosis

Histology *can* be identical to NASH!

### Non-Alcoholic Steatohepatitis (NASH)

Associated with **metabolic syndrome**, including obesity, type 2 diabetes, dyslipidemia, hypertension

**Micro:** Steatosis, Ballooning, Lobular lymphs and Neuts, Pericellular fibrosis (exception in pediatric patients, where inflammation is more portal)

**Grade/Stage:** NASH CRN system
Wilson’s Disease

Mutations of copper transport protein (ATP7B gene) results in inability to excrete copper in bile → accumulate copper in liver and other tissues

Variable presentation: Acute or chronic liver disease, neurologic/psychiatric findings, hemolytic anemia, ± Kayser-Fleischer rings

Labs: Low ceruloplasmin, Increased urine copper, AST/ALT ratio >2.2, Alk phos/T. Bili <4

Micro: Variable! Steatohepatitis, possible Malory-Denk bodies and glycogenated nuclei; Later chronic hepatitis

When considering diagnosis → send block for copper quantification

Total Parental Nutrition

Variable steatohepatitis or cholestasis depending on age

Infant

Kids

Adult

Steatosis/Steatohepatitis

Cholestasis

Microvesicular steatosis

Finely divided fat cells accumulate in cytoplasm as a result of Mitochondrial damage, which is often serious

DDX: Reye’s syndrome, inborn errors of metabolism, Drugs, Toxins, Acute fatty liver of pregnancy
Portal Tract Inflammation

**Chronic Hepatitis C**
~90% Develop chronic infection
Antibodies (anti-HCV) indicate exposure
Detection of HCV RNA indicates virus persistence
Newer Meds: Ledipasvir/sofosbuvir (Harvoni) → highly effective
Slow, silent, progressive disease (over decades)
→ cirrhosis (risk of HCC)

**Micro:** Various dense portal lymphocytic infiltrates
   - Periportal interface activity
   - Portal lymphoid aggregates
   - Patchy steatosis
Scattered lobular collections of inflammatory cells ± acidophil bodies

**Chronic Hepatitis B**
~10% Develop chronic disease

**Micro:** Portal chronic inflammatory infiltrates
   - Interface activity, Lobular hepatitis
   - Ground glass inclusions
   - Sanded nuclei

IHC: HBsAg = infected, HBcAg = actively replicating

**Fibrosing Cholestatic Hep B:** Variant with more progressive/worse disease. Usu. Immunosuppressed state (e.g., post-transplant). Extensive cholestasis, bile ductular reaction, hepatocyte swelling, and fibrosis

**Autoimmune Hepatitis**

Strong Female Predominance
Elevated AST/ALT (often marked)
Serology: + anti-Smooth Muscle Antibody, ANA, LKM-1, Elevated IgG

**Micro:** Dense portal infiltrates with marked interface activity → Lymphs & Plasma Cells
   - Lobular injury
   - Regenerative rosette formation
Can have “Overlap” with PBC
Graft-vs-host Disease (GVHD)

Usually post-stem cell transplant (transplanted immunocompetent T-cells attack new host)

Involves skin, liver, GI tract → rash, ↑LFTs, diarrhea, and vomiting

**Micro:** Bile duct epithelial injury (lymphocytic inflammation, withering, drop out)
Mild portal inflammation; Possible endothelitis

**Rejection**

Immune-mediated inflammation/damage in transplanted liver.
Classified as: Acute Cellular, Chronic, and Antibody-mediated

**Acute Cellular Rejection**

**Micro:** 1) Mixed portal tract inflammation (lymphs, including activated lymphs, Eos, etc..), 2) Bile duct damage/inflammation, 3) Endothelitis

**Chronic Rejection**

**Micro:** Bile duct injury → eventual loss/paucity
Chronic vascular damage with foam cell arteriopathy and luminal narrowing

**Antibody-mediated Rejection**

**Micro:** Portal vascular dilation, endothelial hypertrophy, and arteritis, C4d IHC showing >50% staining of vein and capillaries; Often edematous portal tract and cholestasis

Positive Serum Donor-specific Antibody (DSA)
## Cholestasis/Biliary

### Large Duct Obstruction

Mechanical blockage of bile ducts (by gallstones, stricture, or tumor) → usually diagnosed clinically

**Micro:** Portal tract edema, mixed inflammation with prominent neutrophils, and bile ductular reaction

Canalicular cholestasis

With chronic cholestasis → “feathery” degeneration at periportal interface (swollen, vacuolated hepatocytes) → Biliary cirrhosis with “Jig saw” or geographic pattern

**PMNs in duct epithelium or lumen → consider acute cholangitis**

### Primary Biliary Cholangitis

Autoimmune disease with destruction of intrahepatic bile ducts

Usu. Older women with +AMA

**Micro:** “Florid duct lesion” → lymphocytic cholangitis with bile duct injury

+/− Granulomas

Often causes bile ductular reaction and bile duct paucity

### Primary Sclerosing Cholangitis

Progressive fibrosis and stricturing of bile ducts—predominantly seen extrahepatic, but also intrahepatic

Often diagnosed by cholangiography (multiple strictures) → Increased risk of cholangiocarcinoma

Frequently young to middle-age men; associated with UC

**Micro:** Concentric fibrosis of ducts—“Onion Skin”

(not often seen on bx)

Eventual bile duct obliteration
**Biliary Atresia**

Idiopathic prenatal destruction/fibrosis of extrahepatic bile ducts—Most common cause of pathologic infant jaundice
Hepatobiliary scan demonstrates failure of excretion of radiotracer into duodenum. Surgical intervention with Kasai procedure and/or liver transplantation required

**Micro:** Large bile duct obstruction findings—(non-specific, requires clinical/radiographic correlation)

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**Neonatal Paucity of Intrahepatic Bile Ducts**

Can by Non-syndromic or Syndromic (Alagille syndrome—JAG1 mutations; associated with other abnormalities such as cardiac and skeletal)

**Micro:** Interlobular bile ducts absent in > 50% of portal tracts
Ductular reaction may be present

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**Sepsis**

Patients systemically ill with sepsis and/or bacteremia
Often jaundiced

**Micro:** Ductular cholestasis (“cholangitis lenta”)
Ductular reaction with inspissated bile and flattened, atrophic epithelium.
Variable acute inflammation

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**Drug Reaction**

Most common histologic pattern of drug-induced liver injury is cholestasis
Can have several patterns:
Pure cholestasis: Cholestasis with minimal inflammation
Cholestatic hepatitis: Cholestasis with inflammation and hepatocellular damage
Prolonged cholestasis/ductopenia: > 3 months,
Sclerosing duct injury: Fibrosis affecting large bile ducts (similar to PSC)

[https://livertox.nih.gov/](https://livertox.nih.gov/)
Lobular Injury

- Non-specific pattern, can see in many processes
- **Lobular disarray** (normal plate structure disrupted)
- **Lobulitis** (lymphs attacking hepatocytes in lobule)
- **Acidophil bodies** (apoptotic hepatocytes)

Acute Viral Hepatitis

Usu. due to Hep. A or B
Symptoms generally mild

**Micro:** Lobular damage and disarray
Diffuse lobular inflammation
Hepatocyte ballooning/swelling
Hepatocyte necrosis and regeneration
May see mild portal and periportal inflammation

Drug reaction

2 chief mechanisms: **Intrinsic** (predictable, dose-dependent, less inflammation, more necrosis) vs. **Idiosyncratic** (majority of cases, not dose-dependent, more inflammation)

Herbal and botanical drugs are important but often overlooked cause of hepatotoxicity

**Very Diverse findings.** Can mimic many other disorders (e.g., Autoimmune hepatitis)

https://livertox.nih.gov/

Idiopathic Neonatal Hepatitis

**aka Neonatal giant cell hepatitis**

Neonatal jaundice with hepatomegaly, elevated T. Bili and Conj. Bili, variable AST/ALT

Diagnosis of exclusion (must exclude biliary atresia)
Loose association with hypopituitarism

**Micro:** Lobular disarray with prominent giant cell transformation
Absent to mild lobular inflammation (despite name)
Canalicular and hepatocellular cholestasis
Minimal portal tract changes and preserved bile ducts
**Altered Blood Flow**

**“Shock Liver”**
Liver hypoperfusion of any cause
Massive elevation in AST & ALT (thousands)

**Micro:** Central coagulative necrosis (zone 3)
Collapse of reticulin plates

Other causes of Central Necrosis:
Acetaminophen toxicity (indistinguishable histologically)

**Congestive Hepatopathy**
Caused by hepatic venous outflow obstruction
Can be due to RHF, Budd-Chiari, etc...
Grossly: Nutmeg liver

**Micro:** Central zone sinusoidal dilatation, congestion, hepatic plate atrophy, and necrosis
Chronic cases can lead to central vein and sinusoidal fibrosis → Cirrhosis

**Sinusoidal Obstruction Syndrome**
**aka Veno-Occlusive Disease**
Sinusoidal endothelial injury; Often due to chemotherapy or Stem Cell Transplantation

**Micro:** Central vein obliteration (best seen on trichrome) →
Sinusoidal dilation/congestion; Sinusoidal endothelial edema

**Cirrhosis**
Common End-Stage for many liver disorders

Regenerative nodules surrounded by fibrosis (want to see both for Dx)

Cirrhotic tissue can fragment with small biopsies
**Miscellaneous**

**Iron Overload** *aka Hemosiderosis*

With excessive transfusions or iron supplementation

Iron accumulates in Kupffer cells (sinusoidal macrophages) first. When those are saturated, then it is deposited in hepatocytes

**Hereditary Hemochromatosis**

Inherited disorder of iron metabolism

HFE gene mutations cause increased iron absorption & storage

Iron accumulates first in periportal hepatocytes

→ progressively involves all zones & bile duct epithelium

Less Kupffer cell involvement (relatively)

**Glycogenic Hepatopathy**

Poorly-controlled diabetes → abundant glycogen stores → Hepatomegaly and elevated LFTs

A component of Mauriac Syndrome (with delayed puberty and Cushingoid features)

**Micro:** Diffuse glycogenation of hepatocytes

Demonstrated by PAS stain (Diastase sensitive)

Absence of inflammation

**α1-Antitrypsin Deficiency**

Genetic disorder characterized by abnormal α-1-antitrypsin protein synthesis

PiZZ phenotype accounts for most cases

→ Chronic liver disease and emphysema

**Micro:** Eosinophilic, PAS-D (+) globules within periportal hepatocytes are characteristic

Neonatal hepatitis features cholestasis and hepatocyte injury (too early for globule formation)
### Acute Hepatitis
*Marked Transaminitis (AST & ALT >5x normal)*

- Non-Hepatotropic Virus (CMV, EBV, Adeno)
- HAV & HEV: Fecal oral transmission; only acute
- HBV: Ground Glass inclusions
- AIH: Plasma cells
- Adverse drug reaction
- Massive altered hepatic blood flow (e.g., Shock)

### Chronic Hepatitis
*Mild Transaminitis (AST & ALT <5x normal)*

- HBV: 5% develop chronic hepatitis
- AIH: + ANA, ASMA, Elevated IgG; Interface necroinflammatory lymphoplasmacytic infiltrate
- HCV: 80% develop chronic hepatitis; nodular aggregates of lymphocytes
- Hereditary Hemochromatosis: + HFE genetic mutation
  Elevated Transferrin saturation and serum ferritin
- Wilson’s: Increased liver copper quantification; + ATP7B gene; AST/ALT ratio >2.2, Alk. Phos./T. Bili <4
- A1AT Deficiency: PiZZ phenotype, Hyaline globules in hepatocytes stain with PAS with diastase stain
- Alcoholic: Clinical history of alcohol, AST:ALT > 2, more likely to show neutrophils and Mallory’s hyaline
- NASH: Diabetes or metabolic syndrome, Obesity
- Drug reaction

### Cholestatic Hepatitis
*Elevated Alk Phos. & GGT; +/- Bili Jaundice*

- Large duct obstruction
- PBC: Female, + AMA, IgM, lymphocytic cholangitis and florid duct lesion
- PSC: Male, IBD, diagnosed with cholangiography, concentric fibrosis around bile ducts, risk of cholangiocarcinoma
- Drug reaction

### Cirrhosis/Liver Failure
*Synthetic Dysfunction (Elevated INR, Low Albumin, Low platelets)*