The Normal Liver

- Acinar/lobular architecture
- Portal tracts
- Hepatic plates & sinusoids
- Central veins

Normal liver architecture

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Histologic Types of Liver Injury

- Necrosis
- Hepatocyte degeneration/regeneration
- Hepatitis (acute and chronic)
- Steatosis (fatty change)/steatohepatitis
- Cholestasis (bile accumulation)
- Fibrosis and cirrhosis

Chronic Hepatitis
Key Histologic Features

- Portal tract mononuclear inflammation
- Periportal activity
  - Extension beyond limiting plate (“piecemeal necrosis”)
- Lobular Activity
  - Lobular mononuclear inflammation
  - Lobular hepatocyte necrosis
- Fibrosis, Cirrhosis

Acute vs. Chronic Viral Hepatitis

	Acute	Chronic
Causes	HAV,HBV,HCV	HBV,HCV
Inflamm-distrib	Lobular	Portal±lobular
Inflamm-cells	Lymphocytes Macrophages	Lymphocytes Plasma cells
Necrosis	+ - +++	-/+
Sequelae	Resolution Chronic hepatitis Post-hepatitic scarring	Chronic carrier Cirrhosis

Chronic Hepatitis- Etiologies

- Viral
  - Hepatitis B,C
- Autoimmune
  - Autoimmune hepatitis
  - Primary biliary cirrhosis
- Drug reaction
- Others (Wilson's disease, lymphoma)

Autoimmune hepatitis

- **Clinical:** **F>M, young-midage, abrupt or insidious onset, relapsing course; liver only or a/w systemic auoimmune phenomena**
- **Labs:** **↑transaminases; +ANA (type I), +α–LKM (type II), +α-SLA (type III)**
- **Histology:**
  - **chronic hepatitis with marked piecemeal necrosis, lobular involvement**
  - **numerous plasma cells**

Primary Biliary Cirrhosis

- Clinical: middle age, F>>M; insidious onset
  - a/w other autoimmune syndromes
- Labs: inc. AP, +AMA
- Histologic stages:
  - I. Florid duct lesion: BD damage, granulomas
  - II. Ductular proliferation, periportal hepatitis
  - III. Scarring and fibrosis
  - IV. Cirrhosis

Chronic Hepatitis -Differential Diagnosis

	HCV	AIH	PBC
Portal Inflamm.	++	+	++
Piecemeal Necrosis	++	+++	++
Lobular Inflamm	+	+++	+/-
Plasma Cells	+	++	+/-
BD Damage/Loss	+	-/+	+++
BD Proliferation	+	-	+++
Granulomas	-	-	++

Cholestasis

Definition: Accumulation of bile in hepatic tissue

Etiologies:

- Bile duct obstruction
- Drug reaction
- Sepsis
- Acute viral hepatitis
- Graft-versus-host disease
- Other (cholestatic syndromes):
  - Cholestasis of pregnancy, benign recurrent cholestasis

Cholestasis-pathology

Acute-Subacute

- Bile accumulation
  - canalicular, centrilobular
  - (late) bile lakes
- Hepatocyte "feathery" degeneration
- Portal tract inflammation (PMNs)
- Bile duct proliferation

Chronic

- Fibrosis

Primary Sclerosing Cholangitis

- Clinical: adults, M≈F, a/w ulcerative colitis
  jaundice, pruritus, RUQ pain
- Radiology: Strictures ("beading") of bile ducts
- Histology:
  - Periductular concentric fibrosis
  - Bile duct inflammation, proliferation, and loss
  - Parenchyma: cholestasis
  - Progression: fibrosis, cirrhosis

Drug-induced Liver Disease

Microsteatosis	Tetracycline, salicylates
Macrosteatosis	EtOH, methotrexate
Cholestasis	Cyclosporine, OCS
Necrosis	Acetominophen
Hepatitis	Isoniazid, phenytoin
Granulomas	Allopurinol, sulfonamides
Fibrosis/cirrhosis	EtOH, methotrexate, amiodarone
Venous occlusion	Cytotoxic chemotherapy

Steatosis- Etiologies

- Microvesicular
  - Reyes Syndrome
  - Drug reactions (e.g. tetracycline)
  - Fatty liver of pregnancy
- Macrovesicular
  - Alcohol
  - Drug reaction (e.g. steroids)
  - Others (obesity, diabetes, malnutrition)

Cirrhosis-etiologies

- Alcohol (60-70%)
- Chronic viral hepatitis (10-20%)
- Biliary (5-10%)
  - Primary biliary cirrhosis
  - Secondary (i.e.chronic biliary obstruction)
- Metabolic (5%)
  - Hemochromatosis, Wilson's disease
  - α1-antitrypsin deficiency
- Cryptogenic (10-15%)

Cirrhosis- assessment of cause

- Pattern of nodules and fibrosis
- Bile ducts
- Blood vessels
- Steatohepatitis?
- Pattern of hepatitis
- Abnormal deposits

Wilson's disease

- Autosomal recessive disorder of copper overload
- Incidence 1:30,000
- Age of onset: 3-40 years
- Molecular defect:
  - ATP7B gene, 13q12
  - membrane ATPase with copper-binding domains
  - missense mutations in ATP-binding domain

Wilson's disease- hepatic pathology

- Early (precirrhotic):
  - chronic hepatitis, steatosis
  - balooning, Mallory bodies , apoptotic bodies
  - glycogenated nuclei
  - Cu stain may be negative
- Fulminant hepatic failure
- Late (cirrhotic)

Hepatocellular Neoplasms and Masses

With cirrhosis

- **Macroregenerative Nodule**
- **Borderline (dysplastic) Nodule**
- **Hepatocellular Carcinoma**

Without cirrhosis

- **Hepatic adenoma**
- **Focal nodular hyperplasia**
- **Fibrolamellar HCC**
- **HCC**
- **Nodular regenerative hyperplasia**

Hepatic malignancies

- Overall, metastases most common

Primary Hepatic malignancies

- Hepatocellular CA 65-70%
- Intrahepatic cholangioCA 20%
- HCC-cholangioCA 2%
- Sarcomas, lymphoma, other 2-3%

HCCa vs regenerative nodule

Feature	HCC	Regen nodule
Plates>2 cells thick	++	-
Small cell change	++	-/+
Portal tracts	-	+
Infiltrative edge	+/-	-

Fibrolamellar HCC

- young adults, M=F
- Low **association** with cirrhosis (<10%), HBV, HCV
- Gross: Firm circumscribed mass, central fibrous septa
- Micro: Nests, cords of eosinophilic tumor cells
  Lamellar bands of colagen surrounding tumor cells
- Prognosis: slow growing, resected 5 year suvival 40-50%
- Ddx: FNH, HCC, metastatic CA