Mechanisms of Human Disease: The Liver
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Objectives
• Overview of basic function and histology of the liver
• Understand the circulation of the liver
• Discuss Vascular Disorders of the Liver
• Discuss Different mechanisms of injury in liver disease and how they present histologically
• Understand the relationship of cirrhosis to portal hypertension and its clinical presentation

Liver Anatomy
• It is helpful to think of liver anatomy in three distinct, but interrelated compartments
Hepatic Circulation

- Lobules are the building blocks of the liver parenchyma
- Shaped like a hexagon with portal tracts at each apex
- Hepatocytes are arranged in linear cords from the periphery to the central vein
Hepatocytes and Vascular Supply

Periportal hepatocytes
- First to receive blood
- Last to undergo necrosis
- First to regenerate

Centrilobular hepatocytes
- Most susceptible to ischemic insults

• Oxygenated blood is supplied to the liver via the:

  1. Portal and Hepatic Vein
  2. Hepatic Vein and Hepatic Artery
  3. Portal Vein and Hepatic Artery
  4. Hepatic artery only

Sinusoids

• Location of mixing nutrient rich portal venous and highly-oxygenated arterial blood as it flows past the hepatocytes
• Cell types and Features of the Sinusoid
  – Kupffer Cells – Macrophage cells
  – Fenestrated Endothelium
    • Large holes in endothelial cells
    • Allow passage of nutrients and lipids from portal blood to the hepatocyte
  – Space of Disse – loosely arranged extracellular matrix
    • Stellate Cells
    • NK cells
    • T and B lymphocytes
  – Microvilli of Hepatocytes
    • Increase surface area available for exchange and absorption
All of the following are true except:

1. The liver has a dual blood supply
2. The hepatic sinusoid is a specialized capillary network
3. Each hepatic lobule has a central vein in the middle and portal triads at the apices
4. Blood leaves the liver via the portal vein
Hepatic Circulatory Disorders

Ischemic Hepatitis

- Ischemic Hepatopathy, Shock Liver
- Acute Liver Injury caused by insufficient oxygen delivery to the liver
- Decreased perfusion usually due to shock or low blood pressure
  - Acute Myocardial Infarction
  - Cardiac Arrhythmia
  - Cardiomyopathy
  - Pericardial Tamponade
  - Shock
  - Dehydration
  - Hemorrhage

Ischemic Hepatitis

Diagnosis
- Marked elevation in transaminases in the setting of shock or circulatory dysfunction

Treatment
- Supportive Care

Prognosis
- Good – usually recover
Budd-Chiari Syndrome

- Hepatic Vein Obstruction / Thrombosis
  - Primary myeloproliferative disorders
  - Inherited disorders of coagulation
  - Antiphospholipid syndrome
  - Paroxysmal nocturnal hemoglobinuria
  - Intra-abdominal cancers
  - Oral Contraceptives
  - Pregnancy

- Presentation
  - Hepatomegaly
  - Ascites
  - Abdominal Pain
  - Hepatic Dysfunction
Budd-Chiari Syndrome

- Centrilobular Congestion

Portal Vein Thrombosis

- Often Asymptomatic
- Diagnosis
  - Ultrasound
  - Abnormal LFT’s
- Can lead to Portal Hypertension
- Caused by hypercoagulable state, trauma, surgery, cirrhosis
- Treatment
  - Anticoagulation, thrombolysis (rare)

Sinusoidal Obstruction Syndrome

- Hepatic venous outflow is due to occlusion of the terminal hepatic venules and hepatic sinusoids
- Bone Marrow Transplant Patients
  - First 3 weeks
  - 25% of recipients of allogeneic BMT
- Chemotherapy patients
- Drugs
  - Azathioprine
Sinusoidal Obstructive Syndrome

• Toxic injury to the sinusoidal endothelium with resulting fibrotic occlusion of small hepatic veins
• Symptoms
  1. Acute RUQ tenderness
  2. Hepatomegaly
  3. Ascites
  4. Weight gain
  5. Jaundice

Patterns of Liver Injury

1. Acute Hepatitis
   - Temporary or new onset inflammation of the liver tissue
   - May or may not be symptomatic
   - Can resolve or become chronic

2. Acute Liver Failure (Fulminant Liver Failure)
   - Sudden loss of hepatic function in the absence of pre-existing liver disease
   - Can lead to multi-organ failure and death or recovery, depending on the cause
   - Results in severe liver dysfunction and may require liver transplantation

2. Chronic Hepatitis → Cirrhosis
   - Inflammation of the liver tissue that lasts at least 6 months
   - Often without symptoms
   - Can progress to cirrhosis
Acute Hepatitis

Pathologic Findings
• Ballooning degeneration
• Apoptosis
• Necrosis
• Inflammation
• Cholestasis

Presentation
• Active hepatocellular damage and necrosis
• Less than 6 months duration
• Significant elevation of ALT or AST in a patient with no previous history of liver disease
• Often asymptomatic
  – Severe cases – jaundice, abdominal pain, nausea, fatigue

Acute Hepatitis: Etiology

• Viral Hepatitis
  – Hepatitis A, B, C, E
  – CMV, EBV, Adenovirus, HSV
• Excessive Alcohol Intake
• Drug-Induced Liver Injury
• Autoimmune Hepatitis
• Circulatory Dysfunction
  – Ischemia, Budd Chiari, Portal vein thrombosis
**Ballooning Degeneration**

NASH
ETOH
Acute Hepatitis

**Apoptosis**

**Regeneration**

HEPATO CYTES PROLIFERATE IN RESPONSE TO TISSUE RESECTION OR CELL DEATH
Cholestasis

Acute Liver Failure: Definition

• Rare, but serious clinical syndrome
• Sudden loss of hepatic function in a person without evidence of preexisting liver disease

Key Clinical Features
• Coagulopathy (INR > 1.5) AND
• Any degree of Hepatic Encephalopathy
• Both occurring within 24 weeks of the first onset of symptoms in patients without underlying liver disease
  – Exceptions – Can present as ALF but still have had underlying liver disease
    • Wilson’s Disease
    • Vertically-acquired HBV
    • Autoimmune Hepatitis

Acute Liver Failure: Etiologies

• Viral
  – Hepatitis A or B
  – HSV
• Drugs (Acetaminophen, Antibiotics)
• Autoimmune Hepatitis
• Wilson’s Disease
• Vascular Causes
  – Ischemia, SOS, Budd Chiari
• Acute Fatty liver of Pregnancy
• Toxins (amanita phalloides mushroom)
• Rare
  – Reye Syndrome, galactosemia, tyrosinemia
Acute Liver Failure

• Symptoms on Presentation
  – Confusion
  – Fatigue
  – Jaundice
  – Abdominal Pain

• Disease progresses rapidly
  – Develop encephalopathy and coagulopathy within 8 weeks of the acute hepatitis
  – If not transferred to a transplant center, pt can progress to multi-system organ failure and death within days
  – Emergency liver transplantation may be required if patient does not recover

MASSIVE HEPATIC NECROSIS

Chronic Hepatitis

• Inflammation in the liver that lasts at least 6 months
• Often asymptomatic until cirrhosis develops
  – Fatigue, poor appetite
• Degree of liver injury can vary from mild fibrosis to rapid progression to cirrhosis
• Diagnosis is made by laboratory testing
  – Biopsy is often needed to confirm the diagnosis
Chronic Hepatitis: Etiologies

- Hepatitis B, C, or D (Hep E, rarely)
- Autoimmune hepatitis
- Drugs
- Wilson’s Disease
- Alpha-1 Antitrypsin Deficiency
- Hemochromatosis
- NASH
- Alcohol
FIBROSIS

RESPONSE TO INFLAMMATION OR DIRECT TOXIC INSULT

Grade: Degree of Inflammation
Stage: Degree of Fibrosis
Chronic Hepatitis: Classification System

- **Fibrosis**
  - Portal.............STAGE 1
  - Periportal.......STAGE 2
  - Bridging.........STAGE 3
  - Cirrhosis.........STAGE 4

- **Inflammation**
  - Minimal..........GRADE 1
  - Mild...............GRADE 2
  - Moderate.........GRADE 3
  - Severe............GRADE 4

**Example diagnosis**

Chronic hepatitis with mild inflammatory activity, Grade 2 and bridging fibrosis, Stage 3

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**Cirrhosis**

- A **DIFFUSE** process characterized by **FIBROSIS** and a conversion of normal architecture into structurally abnormal **NODULES**.

- 12th most common cause of death in US
CIRRHOTIC LIVER

CIRRHOSIS

CIRRHOTIC NODULES

MOST COMMON ROUTE TO HEPATIC FAILURE

MACRONODULE  MICRONODULE
Cirrhosis: Collagen stain
Blue = fibrosis

Cirrhosis: Etiologies
• Alcoholic Liver disease
• Viral Hepatitis
• Non Alcoholic Liver Disease (NASH)
• Chronic Biliary Obstruction
• Hemochromatosis
• Wilson’s Disease
• Alpha-1 Antitrypsin Deficiency
• Metabolic Disorders
• Drug-Induced Liver Injury
• Autoimmune Liver Disease
• Primary Sclerosing Cholangitis
• Primary Biliary Cholangitis
• Cardiac Cirrhosis (Passive Congestion)
• Budd Chiari

Cirrhosis: Clinical Symptoms
• Asymptomatic
• Non-specific Symptoms
  – Anorexia
  – Loss of Muscle Mass
  – Weakness
  – Fatigue
Cirrhosis: Clinical Symptoms

- Lower Extremity Edema
- Abdominal Distension (Ascites)
- Gastrointestinal Bleeding (esophageal varices)
- Confusion (Hepatic Encephalopathy)
- Muscle Wasting and loss of muscle mass
- Muscle Cramping
- Gynecomastia
- Jaundice / Scleral Icterus

Clinical Question

- A 26 yo female presents with abdominal pain over the last 3 days. Physical exam shows hepatomegaly and shifting dullness. She reports no prior PMH. She has been OCP’s for the past 5 years. A liver biopsy shows centrilobular congestion and necrosis.
- Which of the following best describes the patient’s condition?
  - Ischemic Hepatitis
  - Autoimmune Hepatitis
  - Budd Chiari Syndrome
  - Sinusoidal Obstruction Syndrome
  - Cirrhosis

Portal Hypertension

- Increase in the blood pressure within a system of veins called the portal venous system
- If vessels in the liver are blocked due to liver damage, blood cannot flow properly through the liver.
  - High pressure in the portal system develops
How Cirrhosis Leads to Portal Hypertension

- Increased vascular resistance
  - Distortion of vascular architecture
  - Increase in vascular tone
  - Contraction of myofibroblasts around hepatic sinusoids
  - Increased production of vasoconstrictors (endothelin-1)
  - Reduced release of vasodilators (NO)

**How to Cirrhosis Leads to Portal Hypertension**

- Increased Portal inflow
  - Splanchnic Vasodilation
    - Increased Nitric Oxide production
  - Angiogenesis
    - New vessel formation

\[ \Delta \text{Pressure} = \text{Resistance} \times \text{Flow} \]

Portal Hypertension

- Increase in the porto-systemic pressure gradient
- Pre-hepatic
  - Portal / Splenic Vein thrombosis
- Post-hepatic
  - Budd-Chiari Syndrome
  - Right-Side Heart Failure
- Intra-hepatic non-cirrhotic
  - Schistosomiasis
  - Sinusoidal Obstruction Syndrome
- Cirrhosis
Portal Hypertension

- Portal hypertension leads to the development of intra- and extrahepatic venous collaterals
  - Esophageal Varices
- Shunts are created to allow blood to by-pass the intrahepatic resistance to blood flow
  - They serve to lower portal pressure

Complications of Cirrhosis

- Related to portal hypertension and hepatic dysfunction:
  - Ascites
  - Variceal bleeding
  - Hepatic encephalopathy
  - Hepatorenal syndrome
- Unrelated to portal HTN:
  - Hepatocellular carcinoma
The histological changes are associated with which of the following diseases:

A. Esophageal varices  
B. Alcoholism  
C. Chronic Hepatitis B infection  
D. All of the above  
E. None of the above

Clinical Vignette

• A 46 yo female with chronic hepatitis C infection, long-term alcohol use, and cirrhosis presents to the ER with confusion, disorientation, and somnolence. She responds to verbal stimuli and makes attempts at answering questions. She is drowsy, but arousable. She has asterixis on physical exam. Which of the following is the most likely diagnosis?
  
  – Hepatic Encephalopathy  
  – Delirium  
  – Alcohol Withdrawl  
  – Cerebrovascular Accident

Clinical Correlate: Hepatic Encephalopathy

• Reversible neuropsychiatric abnormalities seen in patients with liver failure  
• Requires presence of portal hypertension (diversion of portal blood into the systemic circulation)  
• Ammonia – Neurotoxic at elevated concentrations  
  – Liver clears portal vein ammonia, converting it to glutamine and urea preventing entry into systemic circulation  
  – Advanced liver disease – unable to clear blood ammonia, which is then shunted to systemic circulation
Clinical Correlate

- A 58 yo man with a history of chronic alcohol use and chronic Hepatitis C infection that has not been treated is admitted to the hospital with increasing abdominal girth, right upper quadrant tenderness, and a 15 lb weight gain over the past 3 months. The patient had a liver biopsy 5 years ago showing grade 3, stage 4 chronic hepatitis. He has no prior history of jaundice, ascites, gastrointestinal bleeding, or confusion. He has never had an endoscopy. He continues to drink alcohol.

- Physical exam reveals shifting dullness in the abdomen with a palpable spleen tip, but no apparent hepatomegaly. There is no jaundice. There are multiple spider nevi and palmar erythema. There is no leg edema. The neurological exam is non-focal with no asterixis.

Laboratory Values

- Albumin = 3.1 g/dL (3.5-5)
- ALT = 46 U/L (5-40)
- AST = 54 U/L (5-40)
- Alk Phos = 130 U/L (30-130)
- T.Bilirubin = 3.8 mg/dL (0.2-1.2)
- Direct bilirubin = 0.5 mg/dL (0-0.2)
- INR = 1.8
- Platelet Count = 112,000/L (150-450)
- AFP = 4 ng/mL (<20)
- Creatinine = 1.5

All of the following should statements about the laboratory findings are correct EXCEPT?

A. Low platelet count is suggestive of portal hypertension
B. The INR would likely not correct with PO vitamin K administration
C. The INR would likely not correct with IM vitamin K administration
D. Low alpha fetoprotein level makes hepatocellular carcinoma very unlikely
E. AST>ALT is not unusual for chronic hepatitis C in the cirrhosis stage
All of the following should be considered next in his management EXCEPT:

• A. Diagnostic paracentesis to exclude spontaneous bacterial peritonitis
• B. Treatment of hepatitis C with an anti-viral agent
• C. Upper endoscopy to assess for the presence of gastroesophageal varices
• D. Referral to a liver transplant center for evaluation
• E. Start lactulose for hepatic encephalopathy