Mechanisms of Human Disease: The Liver, Part 3

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Objectives

- Review of Genetic Causes of Liver Disease, including hemochromatosis, Wilson's disease, alpha-1 anti-trypsin deficiency
- Common non-malignant hepatic nodules
- Clinical and pathologic findings for primary malignant tumors of the liver

Hemochromatosis

- Disease of Iron Overload
  - Hereditary Hemochromatosis
  - Secondary Hemochromatosis
    - Excessive Transfusions or hemolysis
    - Sickle Cell Disease, Thalassemia
- Iron deposition in parenchymal tissues, most commonly the liver
- Treatment
  - Phlebotomy
  - Chelation
Hereditary Hemochromatosis

- HFE (hereditary Fe) gene mutation
  - ONE OF THE MOST COMMON GENETIC DISORDERS
  1. C282Y Homozygous
     - 57% of patients
  2. H63D homozygous (1%)
  3. C282Y/H63D compound heterozygous mutation (4-7%)
- Excessive Absorption of dietary iron

Hemochromatosis

- Diagnosis
  - Elevated Serum iron
  - Elevated Ferritin
    - Often >1000
    - Transferrin saturation 95% (>60%)
  - Genetic testing for the HFE gene mutation
    - 30% will have other rare genetic mutations
  - Liver biopsy for quantitative iron studies and histologic examination

Liver biopsy with brown pigmented hepatocytes
Wilson’s Disease

• Copper accumulation
  – Liver and Brain
• Autosomal Recessive Disorder (ATP7B gene)
  – Responsible for linking copper to ceruloplasmin for release into bloodstream
  – Copper is stuck in the liver b/c it can not incorporate into ceruloplasmin
  – Copper starts spilling out of hepatocytes leading to deposition in other tissues
• Impaired copper excretion in Wilson’s disease
• Symptoms
  – Start between ages of 6-20
  – Neuropsychiatric (copper deposition in brain)
  – Psychosis, Parkinson-like tremors, depression
  – Kayser Fleischer rings (copper ring in eye)
  – Liver Failure
• Treatment
  – Copper chelation
  – Liver Transplantation

Wilson’s Disease

• Diagnosis
  – Low Ceruloplasmin
    • Non copper-bound ceruloplasmin is rapidly degraded in blood stream
  – Increased urinary copper
  – Liver biopsy for quantitative copper analysis
  – Kayser-fleischer Rings in Eyes

Kayser-Fleischer Ring
Alpha-1 Antitrypsin Deficiency

- Defective production of A1AT in the liver
- Errors in coding sequence prevent its export from the hepatocyte
  - Abnormal accumulation of the protein results in cell death, inflammation, fibrosis, and cirrhosis
- May also have early-onset COPD
  - Lack of alpha-1 antitrypsin in lung tissue
- Autosomal recessive disorder
- Many allelic variants
  - PiZZ has only 10% of normal circulating levels of A1 protein and is most common allele to cause hepatic disease

Alpha 1 antitrypsin deficiency
PAS STAIN

Acute Fatty Liver of Pregnancy

- Sudden catastrophic illness occurring exclusively in the 3rd trimester
- Microvesicular fatty infiltration
  - Acute Liver Failure and Encephalopathy
- Significant perinatal and maternal mortality
- Requires early diagnosis and intervention
Hepatic Nodules

- Focal Nodular Hyperplasia (FNH)
  - Most common non-malignant tumor
  - Localized overgrowth of hepatocytes
  - Solitary
  - Central Stellate Scar
  - 20-40 year old Adults
  - No Malignant Potential
  - No treatment necessary

Well demarcated nodule, generally lighter than the surrounding parenchyma and usually contains a central stellate scar.

FOCAL NODULAR HYPERPLASIA
Nodular Regenerative Hyperplasia

- Transformation of the hepatic parenchyma into small regenerative nodules in the absence of fibrosis
- Can lead to Non-Cirrhotic Portal Hypertension
- Difficult diagnosis to make on liver biopsy.
- Associated Conditions
  - Solid organ transplantation
  - Bone marrow Transplantation
  - HIV
Hepatic Adenoma

- A benign tumor that forms in the liver
- Common in young women
- Associated with pregnancy and oral contraceptive use
- Usually solitary lesions
- Cords of normal hepatocytes with absent portal tracts
  - Intrahepatic mass which is often difficult to distinguish from cancer
  - Risk of rupture in larger tumors
  - Rare risk of transformation into hepatocellular carcinoma
  - Associated with rare metabolic disorders and glycogen storage diseases
  - Resection indicated in tumors > 5cm as risk of malignant transformation increases

Hepatic Adenoma

- Sheets and cords of normal hepatocytes
- Absent portal tracts
- Prominent solitary arterial vessels
HEMANGIOMA

- Most common benign tumor of the liver
- Microscopically
  - Benign vascular channels and fibrous tissue

HEMANGIOMAS

HEMANGIOMA

VASCULAR ENDOTHELIAL LINED SPACES
• A 40 yo woman undergoes a CT Scan because of a kidney stone. CT demonstrates a liver mass and she is sent for evaluation. She has no abdominal pain, fever, weight loss, or history of liver disease. Only medication is OCP, which she has been on for 17 years. Exam and labs are completely normal. CT scan is shown below:

• Which of the following would you recommend next?
  1. MRI liver
  2. Surgical consultation
  3. Biopsy of the liver lesion
  4. Stop oral contraception
  5. No further tests

**Hepatoblastoma**

• Most common primary malignant liver tumor of childhood
• M>F
• RUQ mass found on physical exam
• Elevated alpha fetoprotein
• Primary hepatocellular malignancy
Risk factors for hepatocellular carcinoma includes all EXCEPT:

- Hepatitis C
- Alcoholic liver disease
- Hemochromatosis
- Aflatoxin
- Herpes virus
**Hepatocellular Carcinoma**

- 5th Most common malignancy worldwide
- Incidence is rising in US due to rising cases of HCV
- Symptoms are usually vague, if present at all
- Usually detected on imaging unless advanced
  - Weight loss, worsening liver function
- Can be seen as a variety of pathological features
- 95% of HCC cases occur in patients with cirrhosis
- Exception to this rule
  - HCC can occur independent of cirrhosis in Hepatitis B

**Hepatocellular Carcinoma: Causes**

- Cirrhosis (of any cause)
  - NASH
  - Alcohol
  - Hepatitis C
  - Hemochromatosis
- Chronic Hepatitis B
- NASH – cases reported in advanced fibrosis
- Food contaminants: Aflatoxin (Africa)
- Hereditary Tyrosinemia (Highest risk – 40%)

**Hepatocellular carcinoma**

- Pathogenesis
  - Accumulation of mutations because of repeated cycles on cell death and regeneration (chronic hepatitis)
  - Integration of viral DNA (HBV)
- Clinically
  - Vague symptoms
  - 50% elevated alpha fetoprotein (AFP)
  - Detected on imaging studies
- Treatment
  - Surgery
  - Radiofrequency ablation
  - Transarterial Chemoembolization (TACE)
  - Radioembolization (Y-90)
  - Liver Transplantation
FIBROLAMELLAR VARIANT OF HCC

- Rare variant of HCC
- Occurs in younger women
- Not usually associated with cirrhosis or HBV
- Characterized by areas of dense collagenous fibrosis and large polygonal tumor cells
- Better Prognosis
Which of the following statement about hepatic adenoma is CORRECT?

1. More common in males
2. Contains a central stellate scar
3. Associated with cirrhotic liver
4. Growth is estrogen sensitive
5. High rate of malignant transformation

CHOLANGIOCARCINOMA

- Malignancy of the bile ducts (within or outside the liver)
- 10% Intrahepatic
  - Arising from bile ducts within the liver
- Extrahepatic
  - Arising from bile ducts outside the liver
    - Perihilar (hilar) 50-60%
    - Distal bile duct 20-30%
    - Periampullary

Cholangiocarcinoma Risk Factors

- Primary sclerosing cholangitis
- Congenital fibropolyycystic disease of the biliary system
  - Caroli’s Disease
- Cirrhosis
- Exposure to Thorotrast
- Liver fluke; *Opisthochis sinensis*
Cholangiocarcinoma
Gross and clinical findings

• Intrahepatic
  – Not detected until late; massive lesion or treelike tumor tracking along the portal system
  – Often presents as biliary obstruction or a symptomatic mass.
• Extrahepatic
  – Small lesions at the time of diagnosis
  – Biliary obstruction, cholangitis, RUQ pain

Intrahepatic Cholangiocarcinoma

• Adenocarcinoma
• Dense fibrous stroma
• Sometimes combined with an HCC

Extrahepatic Cholangiocarcinoma

• Often a very small tumor
• Can present as obstructive jaundice
  – LFT’s often elevated due to biliary obstruction
• Almost all are adenocarcinomas
• Special Variant:
  – Klatskin Tumor (Hilar / Perihilar)
• Diagnosis: ERCP
- Perihilar (hilar) 50-60%
- Distal bile duct 20-30%
- Peri-ampullary

ERCP with contrast in the biliary tree
METASTATIC COLON CANCER

Metastasis to the liver

- ADULTS
  - Breast, lung, colon and pancreas
- Children
  - Neuroblastoma, Wilms tumor and rhabdomyosarcoma

Match the Following

- Alcoholic Hepatitis
- Wilson’s Disease
- Alpha-1 Anti-trypsin Deficiency
- Hepatitis B
- Hemochromatosis
- Ground Glass Inclusion
- Diabetes, cirrhosis, Cardiac failure
- Mallory’s Hyaline
- Low Serum Ceruloplasmin
- Repeated Infections, Emphysema