Fundamental Liver Pathology

Part 2

APPROVED

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I've also included some notes from First Aid 2010 on the slides. They'll be in these red boxes :)
Vascular Injury

- Hepatic Venous Outflow Compromise
  - Budd-Chiari
  - Veno-Occlusive Disease

- Impaired Blood Flow Through the Liver
  - Passive Congestion
  - Cirrhosis

- Impaired Blood Flow Into the Liver
  - Hepatic Artery or Portal Vein compromise
  - Thrombosis
Budd-Chiari

• Hepatic vein thrombosis syndrome
  • Associated with conditions of increased thrombotic tendency (pregnancy, intra-abdominal cancer)
  • 30% of cases are idiopathic
  • High mortality rate
• Morphology:
  – Centrilobular congestion and sinusoidal dilatation
  – Centrilobular necrosis

From First Aid 2010: Budd-Chiari: Occlusion of IVC or hepatic veins --> congestive liver disease (hepatomegaly, ascites, abdominal pain, and eventual liver failure). May develop varices and have visible abdominal and back veins. Absence of JVD.
Veno-Occlusive Disease

• AKA- Sinusoidal Obstruction Syndrome
  • Originally associated with Jamaican bush-tea
  • Now associated with BM transplant and chemo/radiation
  • Mortality rate is up to 30%
• Morphology:
  – Central venous areas have swollen endothelium and collagen deposition
  – Eventual venous obliteration and associated hepatocellular ischemia
Passive Congestion

• Chronic right sided heart failure leads to chronic passive congestion
  • Morphology:
    • Centrilobular sinusoidal congestion
    • Liver plate atrophy

• If left sided heart failure also occurs:
  • Gross:
    • “Nutmeg liver”
  • Morphology:
    • Centrilobular hemorrhagic necrosis

From First Aid: Nutmeg Liver: Due to backup of blood into liver. Commonly caused by right sided heart failure and Budd-Chiari syndrome. Can lead to centrilobular congestion and necrosis can result in cardiac cirrhosis.
Impaired Inflow of Blood

- Hepatic artery obstruction
  - Infarcts to liver are rare because of dual blood supply
    - i.e. following liver transplant; hepatic artery thrombosis may cause infarction and loss of organ
      - can result in fulminant hepatic necrosis and failure and require another transplant
- Portal vein obstruction
  - Manifests as symptoms of portal hypertension: esophageal varices, splenomegaly
    - i.e. metastatic tumor causing hilar lymph node enlargement and compression of the portal vein
Regeneration and Fibrosis

- Following injury, the liver has the ability to regenerate back to its normal state.
- However, with repeated injury, inflammation and/or toxic insult fibrous tissue is formed.
  - Initially, fibrosis may form in the portal tracts, central veins, and/or within the sinusoids.
  - With time, fibrous strands can link regions of the liver (portal-portal, portal-central), this is called **bridging fibrosis**.
  - With continued liver injury, the liver becomes subdivided into nodules of regenerative hepatocytes surrounded by the fibrous tissue—**cirrhosis**.
- Grossly, cirrhosis can be described as micronodular (nodules <3 mm in size) or macronodular.

micronodular is more common

which can become nodules of fibrosis
Clinical Consequences

• Portal HTN
• Shunts
• Coagulopathy
• Hepatorenal syndrome
• Hepatopulmonary syndrome
• Marked risk of hepatocellular carcinoma

With cirrhosis, blood flow can’t go into liver normally because everything is fibrotic --> backup into portal vein --> backup into splenic vein --> backup into spleen --> backup into GI tract --> backup into esophagus (can develop esophageal varices and hemorrhoids in an attempt to get blood back to heart.)

There is a high mortality and morbidity with cirrhosis. Die of cirrhosis due to complications with 1) coagulopathy 2) portal hypertension that lead to esophageal varices that result in bleeding out, and 3) renal failure

because cannot metabolize ammonia and have high levels of ammonia in system

can result in ascites

because can no longer produce clotting factors

#1 risk of hepatocellular carcinoma is cirrhosis

With cirrhosis, you also reduce albumin production
the liver is lumpy bumpy
Macronodular cirrhosis usually has nodules >3mm, varied size. Usually due to significant liver injury leading to hepatic necrosis (i.e., postinfectious or drug-induced hepatitis). Carries increased risk of hepatocellular carcinoma.
finely nodular throughout the capsule, looks irregular
Micronodular cirrhosis has nodules <3mm, uniform size. Often due to metabolic insult (ie alcohol, hemochromatosis, Wilson's disease).
Cirrhosis

regenerative hepatocytes with bands of fibrosis surrounding it

blue is fibrosis
Liver Tumors

Benign
- Bile Duct Hamartoma
- Bile Duct Adenoma
- Cysts
- Focal Nodular Hyperplasia
- Hepatic Adenoma
- Regenerative Nodules
- Angiomyolipoma
- Vascular Tumors
- Psuedotumors

Malignant
- Hepatocellular carcinoma
- Cholangiocarcinoma
- Hepatoblastoma
- Metastatic cancer
- Mucinous Cyst
- Mesenchymal tumors
- Lymphoma
- Sarcoma

See page at the end for a chart comparing the major ddx for some of these tumors
Bile Duct Hamartoma

- Due to a malformation of the ductal plate
  - AKA- von Meyenburg complex
  - Spectrum of polycystic disease versus sporadic
  - Usually incidental lesions that are small (< 0.5 cm) and commonly multifocal

- Consist of small-medium sized bile ductules, variably dilated with inspisated bile and dense collagen
Biliary Cysts

• Cystic dilatation of the biliary system
  – Usually an incidental finding found in adults (>40 y/o)
  – When multiple, likely a component of polycystic disease
  – Typically subcapsular

• Cysts are lined by cuboidal epithelium and have a fibrous wall
  – Contain clear, light yellow fluid
  – No ovarian stroma is present

hamartoma can be so dilated that they become biliary cysts

serous type fluid in the cyst

lined by benign, flat cuboidal epithelium (consistent with biliary epithelium)

major ddx for biliary cyst is mucinous cystadenoma. Biliary cyst will not have ovarian stroma
Polycystic Liver Disease

exaggerated form of biliary cyst
Bile Duct Adenoma

• Benign proliferation of bile ductules
  – Typically an incidental finding
  – Less common than BDH
  – Commonly subcapsular, < 2.0 cm and well circumscribed

• Ductules are **uniform in size** and appearance with less dense stroma and bland cytology
  – Main differential is metastatic adenocarcinoma

**Main ddx is bile duct hemartoma**

**Bile Duct Adenoma:**
- Neoplastic process
- Small, uniformly arranged ducts
- Well circumscribed with dense collagen surrounding the ducts
- Will not see atypia or mitotic activity

**Bile Duct Hematoma:**
- More of a malformation, not neoplastic
- Larger ducts arranged haphazardly
Focal Nodular Hyperplasia

• Considered non-neoplastic
  – Occurs in both men and women of all ages.
  – Usually asymptomatic.

• Potential causes:
  – Reactive/reparative process likely due to localized vascular abnormalities
  – Malformation
  – P450 1A1 polymorphism may lead to abnormal steroid metabolism increasing risk of FNH

Focal Nodular Hyperplasia

Gross:

- Ill-defined area with a cirrhosis–like appearance and typically has a characteristic central stellate scar.

Microscopic:

- **Proliferation of all 3 elements** - Cords of benign hepatocytes (<3 cells thick plates), fibrous septa containing inflammatory cells, bile ductules, and prominent (thick walled) arteries.
Focal Nodular Hyperplasia

- stellate scar in center of well circumscribed mass
- normal parenchyma
Focal Nodular Hyperplasia

very cirrhotic looking liver
will see evidence of fibrosis, hepatocytes look bland (not atypical)

will see large blood vessels
cell plates are supposed to be 1-2 cells thick (if goes beyond this - should be concerned for hepatocellular carcinoma). In this, cell plates are still 1-2 cells thick

proliferation of bile ductules
Hepatic Adenoma

- Benign neoplasm of hepatocytes
- Most commonly occurs in young women
- Risk factors:
  - Oral contraceptives/anabolic steroids
  - Homozygous HNF1 mutations (TCF1 gene; 12q).
    - Sporadic or associated with MODY3
  - Glycogen storage diseases
    - i.e. Von Gierke's disease, type Ia.
  - Mutation of the Wnt/β-catenin pathway
    - Increased risk of malignant transformation

Von Gierke's disease: glucose 6-phosphatase deficiency. Would present with severe fasting hypoglycemia, increased glycogen in the liver, increased blood lactate, hepatomegaly
Hepatic Adenoma

Gross:
- Usually solitary and ill-defined \(\text{(no capsule)}\)
  - \(> 10\) lesions = “adenomatosis”

Microscopic:
- Proliferation of bland hepatocytes, plates \(\leq 3\)-cells thick.
  - Steatosis is common
- Isolated („naked“) arteries
  - Leads to a risk of hemorrhage, especially with large size
- No bile duct differentiation

hepatocellular carcinoma would have a capsule

arteries not associated with veins or bile ducts

in FNH, you would see bile duct differentiation
Hepatic Adenoma

they are taken out when >5 cm because high risk of hemorrhaging and rupturing (due to lots of thin walled vessels)

ill defined - hard to say where lesion ends and begins
MALIGNANT TUMORS
Hepatocellular Carcinoma

- **Globally**
  - ~600,000 cases per year
  - Fifth most common cancer and third leading cause of cancer-related death worldwide.
  - M:F is as high as 8:1

- **United States**
  - Liver cancer is one of most rapidly increasing cancers
  - ~24,000 new cases in 2010
  - 80%-90% occurring in cirrhotic livers.

hepatocellular carcinoma and cholangiocarcinoma incidence increased by 3%
Trends in US Cancer Death Rates

Annual Percent Change, 1996-2005

#1 growth of death rate due to 1) incidence increasing 2) treatment has not improved while treatments for other cancers have improved
Risk Factors for hepatocellular carcinoma

- **Cirrhosis** #1 risk factor
  - Viral Hepatitis (HCV, HBV)
  - Alcoholic steatohepatitis
  - Non-alcoholic steatohepatitis
  - Autoimmune hepatitis
  - Hemochromatosis, Alpha-1-Antitrypsin deficiency
  - Thorotrust, aflatoxins and anabolic steroid exposure.

Surveillance should be with ultrasound or CT/MRI at 6 to 12 month intervals (AFP is not adequate).

El-Serag HB. *Gastroenterology* 2004;127:1372-80

- even if you’re not cirrhotic, HBV alone is a risk factor
- increasing with obesity epidemic
- these are hereditary

also increased incidence of HCC with Wilson's disease. Findings of HCC: jaundice, tender hepatomegaly, ascites, polycythemia, hypoglycemia. Commonly spread by hematogenous dissemination. Increase in alpha fetoprotein. HCC may lead to Budd-Chiari syndrome
Hepatocellular Carcinoma

Gross:

– Solitary/ multiple nodules that typically arise in a background of cirrhosis
  • Bile stained or paler than surrounding liver
  • Can have well-circumscribed or irregular borders, but tend to have a capsule

– Satellite nodules and venous invasion is common.
  • Worse prognostic features
Hepatocellular Carcinoma

well circumscribed, with capsule, looks paler than rest
Hepatocellular Carcinoma

this vein is full of tumor
Hepatocellular Carcinoma

Histology:

- Hepatocytes with increased nuclear:cytoplasmic, atypia, and thickened liver cell plates (>3)
  - Reticulin stain maybe helpful
- Variable Patterns/Subtypes:
  - Trabecular
  - Acinar/Pseudoglandular
  - Solid
  - Scirrhous
  - Giant cell
  - Clear cell
  - Fibrolamellar
Trabecular

Pseudoglandular

Solid

Scirrhous

All of these are HCC

cell plate is 6-7 cell plates thick

no longer reticulin framework left, reticulin negative

with this, ddx is cholangiocarcinoma
Clear Cell

Giant Cell

Normal Reticulin

HCC Reticulin

- Highlighting thin cell plates
- See big pleomorphic cells
- 6-7 cells in between
Fibrolamellar Variant

- Young adults (20 – 40 y/o)
- No association with viral hepatitis or cirrhosis
- Better prognosis than HCC
- Gross:
  - Single firm sclerotic mass
- Microscopic:
  - Well differentiated, eosinophilic cytoplasm, commonly nested or in cords, separated by parallel lamellae of dense collagenous connective tissue; +/- pale bodies
Potential Treatments

CURE

- Resection
- Transplantation

LOCAL CONTROL/BRIDGING

- RFA
- TACE
- Yttrium
- Chemotherapy
- Radiation

PALLIATION

- if small enough. Problem with this is that cirrhotic livers are not able to regenerate itself --> mortality/morbidity

- tumors 2-3 cm in size, not more than 3 tumors - then they are transplant candidate

- radio frequency ablation

- chemo embolization of tumor

- all of the methods included in the overlap of yellow and bluish circles are ways to try to make patient able to undergo resection/transplantation
**Hepatoblastoma**

- **#1 liver tumor in children** (90% <5 y/o and 70% <2 y/o)
  - Patients present with an enlarging abdomen
  - Paraneoplastic syndromes- anemia/thrombocytopenia
  - 90% present with elevated AFP (negative = more aggressive)

**Gross:**

- Single/multiple heterogeneous mass(es) most commonly involving the right or both lobes (75%)

*right lobe is the largest lobe
*can cross into left lobe if tumor is very large
Hepatoblastoma

a lot of central hemorrhage and necrosis
Hepatoblastoma

Microscopic:

- **Epithelial Type**
  - **Fetal**
    - Most reminiscent of mature hepatocytes
    - Good prognosis
  - **Mixed fetal and embryonal**
    - Embryonal - small, hyperchromatic cells with increased N:C
  - **Macrotrabecular**
    - Similar to HCC
  - **Small cell undifferentiated**

- **Mixed Epithelial and Mesenchymal Type**
  - With or without teratoid features

- **Hepatoblastoma, NOS**

-Embryonal is small round blue cell tumor

Fetal type looks pale, and embryonal type looks dark

Can also have malignant osteoid, cartilage, muscle
Hepatoblastoma

darker appearance

trabecular appearance

macrotrabecular type

light areas = fetal
darker areas = embryonal

mesenchymal component
Hepatoblastoma

Treatment:

• Surgical excision with adjuvant chemotherapy is the treatment of choice
  – Neoadjuvant chemo may allow for surgical resection of previously “unresectable” tumor

• Liver transplantation is another option

• Prognosis is mainly dependent on tumor stage

  - look at morphology, size of tumor, metastasis

  - if small enough. good treatment

  - to shrink down tumor
Cholangiocarcinoma

- Intrahepatic malignant proliferation of bile ducts
- Older adults; M=F
- Patients typically have non-cirrhotic livers and present with obstructive symptoms or pain
  
  
  - Caroli’s disease, parasitic infection (clonorchis), Thorotrast, PSC

  if occur more toward hilum, can present with pancreatitis

  spectrum of polycystic disease

  primary sclerosing cholangitis
Cholangiocarcinoma

- **Gross**
  - Firm, sclerotic mass with various growth patterns and +/- pigment
  - Hilum = Klatskin tumor

- **Histology**
  - Proliferation of malignant glands with dense fibrosis

- **Treatment**
  - Surgical excision and/or chemotherapy

- **Prognosis** is mainly dependent on tumor stage
Cholangiocarcinoma

- malignant, atypical morphology
- gland formation

- dense collagen/fibrosis
Metastatic Carcinoma

• The most common malignancy in the liver
  – Occurs in 50% of all metastasizing tumors.
  – Form mass(es) but can also be diffuse (sinusoidal)

• Most common origins:
  – Intra-abdominal malignancy (CRC, pancreas, NET, GIST, etc.), breast, lung, melanoma, lymphoma, leukemia
Gallbladder

- Cystic duct leaves gallbladder and drains into common bile duct.
- Common bile duct meets up with pancreatic duct.
- Ampulla of Vater leads to duodenum.

Located under the right lobe of the liver (under segments 5, 6).
Disorders of the Gallbladder

• Cholelithiasis (Gallstones)
  – In general afflicts over 10% of adults in northern hemisphere
    • Prevalence rates are higher in Latin American countries (20 – 40%) and lower in Asian countries (3 – 4%)
  – 2 main types
    • Cholesterol stones (80%)
    • Bilirubin calcium salts (pigment stones)
      – i.e. Sickle cell patients

More common in women
• 4+ „F“s (female, fat, forties, fertile, +family (hereditary))

Most common cause of extrahepatic bile duct obstruction

gallstones form when solubilizing bile acids and lecithin are overwhelmed by increased cholesterol and/or bilirubin or gallbaladder stasis

more from First Aid

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Most common cause of extrahepatic bile duct obstruction

gallstones form when solubilizing bile acids and lecithin are overwhelmed by increased cholesterol and/or bilirubin or gallbladder stasis
Gallstones

Cholesterol Stones: yellow, crystalline, hard or friable

Pigment Stones: bilirubin and calcium salts
Cholecystitis

- Inflammation of the gallbladder wall
  - Frequently occurs in association with gallstones
- Acute cholecystitis
  - Sudden onset
  - Inflammation (PMNs), edema, and hemorrhage of the gallbladder wall
- Chronic cholecystitis
  - More common
  - Inflammation, thickening, and fibrosis of the gallbladder wall, and Rokitansky-Aschoff Sinuses

- Inflammation of the gallbladder wall rarely occurs due to ischemia or infectious (CMV).
- Acute cholecystitis not operated on often because risk of rupture is higher --> peritonitis. Usually give some antibiotics/pain meds first until inflammation goes down and then go to surgery.
- There would be an increase in alkaline phosphatase if bile duct becomes involved (ie ascending cholangitis).
Chronic Cholecystitis

- Thickened, inflamed, and fibrotic gallbladder wall
- Rokitansky-Aschoff Sinuses
  - Dilated outpouchings of the mucosal glands into the wall
Gallbladder Tumors

- Most are adenocarcinoma
  - Rarely discovered at a resectable stage
  - Poor prognosis
  - Slightly more common in women
  - Most common in the elderly (60 – 70 years of age)
  - Gallstones are present in 60 – 90% of the cases

- Gross morphology
  - Exophytic mass
  - Diffusely infiltrating mass

- Morphology
  - Malignant infiltrating glands

- Extrahepatic adenocarcinoma (outside liver)
- Gallstones
- Gross morphology
  - Exophytic mass
  - Diffusely infiltrating mass

- Morphology
  - Malignant infiltrating glands

- Most are primary

- Intrahepatic cholangiocarcinoma (within liver)

- Chronic injury, inflammation, fibrosis (fibrosis increases risk of cancer just like in cirrhosis of liver)

- Both adenocarcinoma and cholangiocarcinoma involve malignant gland formation in biliary system

- Invade liver

- Intraluminal

- Through wall of gall bladder into liver
Adenocarcinoma of the Gallbladder

- exophytic

Ugly-looking glands that may have central necrosis, a lot of atypia in epithelium
<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Characteristics</th>
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</table>
| Bile Duct Hamartoma        | *More of a malformation, not neoplastic  
* Larger ducts  
* Variable size  
* Haphazard arrangement of bile ducts |
| Bile Duct Adenoma          | *Neoplastic process  
* Small ducts  
* Uniformly arranged ducts  
* Proliferation of bile ducts |
| Biliary Cyst               | *No ovarian stroma  
* Lined by benign, flat cuboidal epithelium  
* Contain serous type fluid in cyst |
| Mucinous cystadenoma       | *Ovarian stroma                                                   |
| Focal Nodular Hyperplasia  | *Non-neoplastic/reactive process  
* Characteristic central stellate scar  
* Proliferation of all 3 elements (hepatocytes, fibrous stroma with bile ducts, arteries)  
* See bile duct differentiation |
| Hepatic Adenoma            | *Neoplasm  
* Benign  
* Proliferation of hepatocytes  
* No capsule  
* Isolated arteries  
* No bile duct differentiation  
* Cell plates <3 cells thick |
| Hepatocellular Carcinoma   | *Malignant  
* Capsule  
* Cell plates >3 cells thick |