ACUTE INFLAMMATION
Lobular (Zone 2 & 3)

LOBULAR Inflammation/Necrosis
NO Fibrosis, LOBULAR DISARRAY

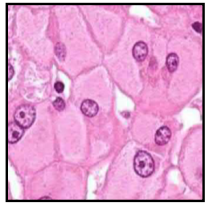
HEPATITIS

Hepatotropic Viruses

Hepatitis A & E

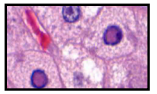
- *RNA viruses (just like C & D); Can't cause chronic infxn*
- *Hepatitis A & E are the only types transmitted via fecal-oral route; All others are spread via percutaneous, mucous, or body fluids*
- *Hep A: Has a vaccine; self limited dz; Supportive tx; diagnose acute infxn +IgM HAV Abs; IgG HAV= lifelong immunity*
- *Hep E: Fulminant hepatitis in 3rd trimester of pregnancy*

Hepatitis B +/- D



Ground glass hepatocytes: Cytoplasmic HepBsAg inclusion from viral proliferation

- *Hep B is the only DNA virus. (partly dsDNA)*
- *Hep D is Defective; needs B for infection*
- *Hep B can cause chronic infection, cirrhosis & HCC, (moreso in infants), but much less commonly than hep C*
- *GROUND GLASS INCLUSIONS = cytoplasmic inclusion pushes nucleus to side due to proliferating endoplasmic reticulum responding to HbsAg PAS-D+, HepB surface Ag+ (stains cytoplasm)*
- *SANDED NUCLEI = HepB core Ag -->*
  - *Stains nucleus in CHRONIC infxn*



Hepatitis C

- *More likely to progress to chronic hepatitis (PORTAL inflammation + interface activity) --> cirrhosis --> HCC*
- *Usually some degree of steatosis in bckgd*

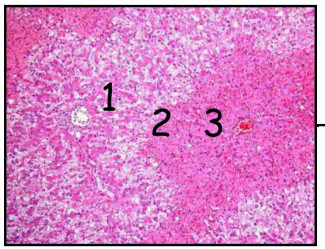
Non-Hepatotropic Viruses

- *SINUSOIDAL LYMPHOCYTOSIS* — EBV
- *"OWL'S EYE"= NUC + CYT INCLUSIONS; likes to infect endothelial cells/ vessels* — CMV
- *Multinucleated, Margination, Molding; Causes geographic liver necrosis & hemorrhage* — HSV
- *"Smudged" nuclei* — Adenovirus

Other Infections

- Cryptococcus
- Granulomatous
- Echinococcus

Acetaminophen toxicity (zone 3)



- ***Most common cause of acute fulminant liver failure***
- *Acellular **zone 3** necrosis; **NO inflammation***
- *It is the **NAPQI metabolite** that is toxic*
- *Tx= NAC (N-acetyl cysteine) to replace the glutathione/NAPQI*

ZONE 1= Potral tracts /Triad = Portal vein + Hepatic artery + Bile duct

ZONE 2 = Intermediate area

ZONE 3= Central vein (Hepatic vein)

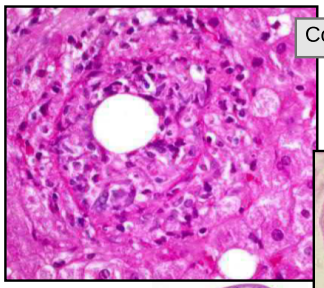
Alcoholic Hepatitis

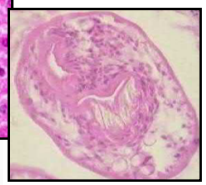
PBC or PSC

(see CHOLESTASIS section)

GRANULOMATOUS

- *AFB+* — TB/MAI
- Fungal- Histo, Blasto, Crypto — *GMS+*
- *Caseating*
- Coxiella burnetii (Q fever) — *Fibrin Ring Granulomas*
- Infections
- Sarcoidosis — *NON-Caseating, Asteroid bodies*





- Echinococcus granulosus
  - *Most frequent species of Echinococcus tapeworm.*
  - *Hydatid cysts release can cause **anaphylaxis***
  - ***Laminated membrane**: Zebra-like pattern; GMS+*
  - ***Scolex** – Hooklets GMS+, birefringent*
  - ***HYDATID SAND**: contains capsules, free scolices and loose hooklets*

- Medication
  - Allopurinol
- PBC — *(see CHOLESTASIS section)*
- Foreign Body
  - Talc (IVDU)

CHRONIC HEPATIC DZ

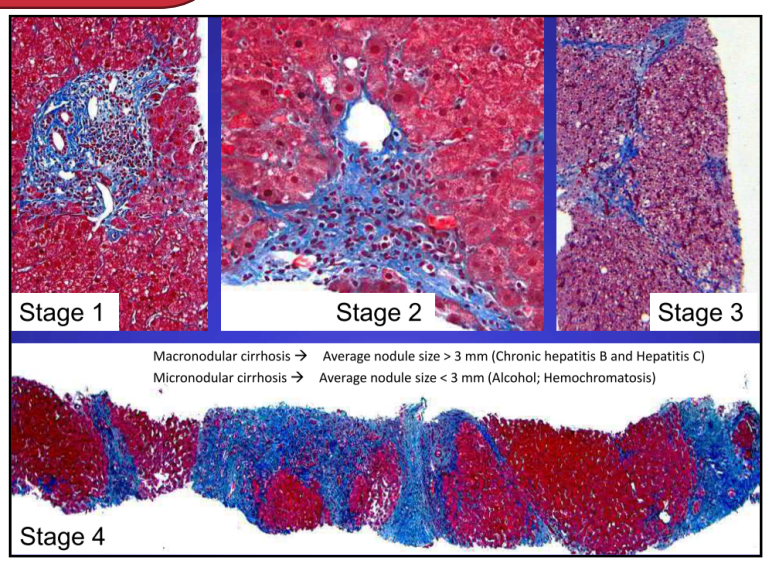
CHRONIC INFLAMMATION
Periportal (Zone 1)

"THE BLUE PORTAL TRACT"

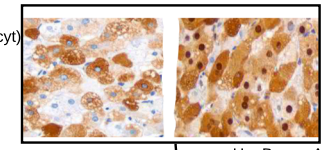
>6 months duration; Necroinflammation: PORTAL/Periportal-based inflammation, Parenchymal injury,Piecemeal necrosis, Variable interface activity/lobular inflammation & hepatocyte injury/necrosis, +/- Scarring or fibrosis

CIRRHOSIS

- STAGE 1= Portal fibrosis
- STAGE 2= Periportal fibrosis
- STAGE 3= Bridging fibrosis
- STAGE 4= Nodular formation
  - MICROnodular = <3 mm (Alcohol; Hemochromatosis)
  - MACROnodular = >3mm (Hep B/C)



Chronic Hepatitis



Require >6 months of symptoms & lab test abnormalities
Biopsy required to grade severity, confirm presence of necroinflammation, stage the scarring, suggest possible etiology & provide diagnosis (if possible)

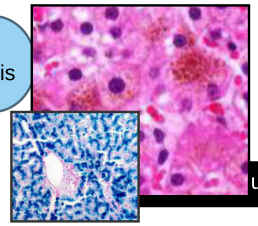
Autoimmune Hepatitis

DONT TREAT WITH STEROIDS PRIOR TO LIVER BIOPSY

- Type 1 — Most common, **ANA+ +/- ASMA**, P-ANCA
- Type 2 — Most common in **Children** **Anti-LKM-1** (more severe disease) & **Anti-LC1**
- Type 3 — Adults 30-50 yo; soluble liver antigen or liver pancreas antigen

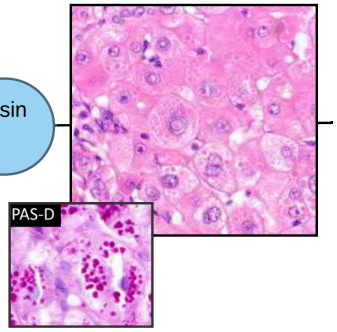
- Autoimmune hepatitis affects predominantly **middle aged women**
- More likely presents as a chronic hepatitis
- Clues to Dx: AST/ALT > 400, Inc IgG
- **H&E: Plasma cell rich portal tract/ interface** & **lobular** activity (**zone 3**) +/- periportal necrosis & **emperipolesis**.
- Responds to corticosteroids

Hereditary Hemochromatosis



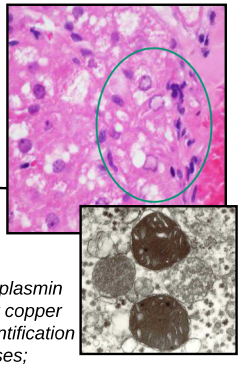
- Most common in middle aged males. Treated with phlebotomy.
- Autosomal recessive mtn in **HFE gene** (**C282Y** - causes highest Fe levels- most common) & **H63D**
- Defect causes increased **IRON** absorption from the gut. Excess iron deposits first in **periportal hepatocytes (zone 1)** then moves to zone 3.
- Inc **Transferrin levels, Inc Fe levels**
- Clinical triad= **Cirrhosis** + **Diabetes** + **Skin hyperpigmentation** --> "Bronze diabetes"
- Also causes **hypogonadism** (due to dec gonadotropins 2/2 pituitary deposits) & **cardiac** arrhythmias, restrictive cardiomyopathy/ heart failure
- **Prussian blue**= inc iron in **zone 1** (periportal) (if mostly in kupffer cells, think iron overload)

Alpha 1 Anti-Trypsin Deficiency



- SERPINA1 gene (chr 14); Autosomal codominant.
  - PiM= normal; PiS & PiZ= most common deficiencies; PiZZ= most severe
- Defective folding of A1AT --> cant transfer from ER to golgi apparatus --> A1At gets stuck in liver (chronic inflammation) so it can't protect against inflammation in lung (PANacinar emphysema)
- PERIPORTAL PAS/D + PINK GLOBULES (look in ZONE1); A1AT IHC avail too.

Wilson Disease



- ATP7B gene mutation
- Diagnosis:
  - LOW serum ceruloplasmin
  - HIGH 24 hr urinary copper
  - Tissue copper quantification definite in most cases;
  - Targeted next-gen seq avail

- Due to defective COPPER transport in golgi causing accumulation in several organs
  - LIVER= Chronic inflammation, Cirrhosis
  - CNS= Psychiatric manifestations, Dementia
  - EYE = Kayser Flescher rings (deposited in Becemet's membrane)
- H&E: Steatosis, hepatitis, GLYCOGENATED NUCLEI, MALLORY HYALINE, Copper stain by Rhodanine (unreliable method)
- EM: Increased density in the matrix between the inner and outer membranes is characteristic

Mimickers of Chronic Hepatitis

- PSC or PBC

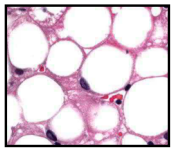
Hepatic involvement by lymphoma

B9 LIVER

Steatosis

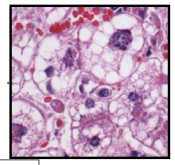
MACROvesicular

Obesity, Diabetes, Metabolic syndrome, Malnutrition, Total parenteral nutrition, Drugs/toxin (alcohol), Wilson's disease, Infection (Heptatits C)



MICROvesicular

Pregnancy (AFLD), Reye's syndrome (kid took ASA), Drugs/Toxins, Valproic acid, Mushrooms, Tetracycline



Central nucleus indented by fat at periphery

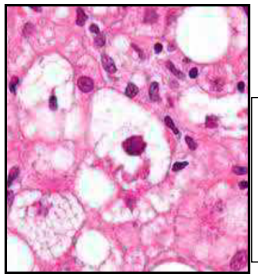
Steatosis/"Chicken wire fibrosis" starts: ZONE 3 in adults; in ZONE1 in kids

FATTY LIVER
Central (Zone 3)

Fat, Mallory bodies
Pericellular fibrosis

STEATOHEPATITIS HISTOLOGY
- *Steatosis*
- *Ballooned hepatocytes*
- *Mallory-Denk bodies*
- *Fibrosis (perivenular/pericentral)*
- *Inflamed lobules (neutrophils)*
- *Megamitochondria*

RISK FACTORS
- *Alcohol*
- *Diabetes*
- *Hypercholesterolemia*
- *Obesity*
- *Drugs (Amiodarone*, MTX, Tamoxifen)*



**Amiodarone causes foamy granular hepatocytes from phospholipids; EM shows lysosome inclusions*

***Mallory-Denk bodies**: Intermediate filaments metabolized by cytokeratin from liver cell injury. Look like "ropey" pink material. Can stain +p62 & Ubiquitin. Mallory Hyaline can be seen in steatohepatitis (esp alcoholic), Amiodarone toxicity, Wilson disease, FNH, HCC.*

Steatohepatitis

Alcoholic Steatohepatitis

Alcoholic= More fibrosis (pericellular), Mallory bodies, PMNs, and some obliteration of central vein.

Non-Alcoholic Steatohepatitis

NASH+ mostly lymphocytes, less PMNs and less Mallory bodies

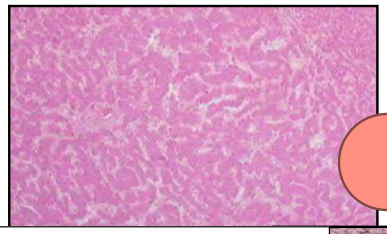
Ischemia

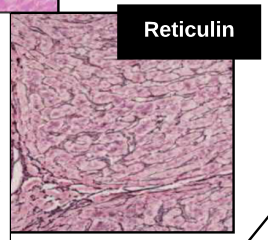
Cardiac failure

- *Zone 3 (central vein) is the most prone to ischemic injury --> causes coagulative necrosis (Z3) without inflammation.*
- *Gross examination= "Nutmeg liver" from areas of hemorrhage & necrosis*

VASCULAR ABNORMALITES

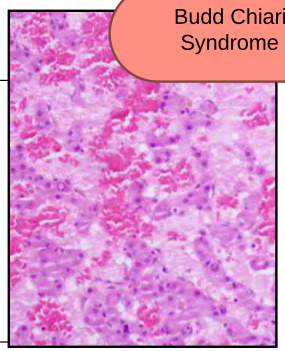
Nodular Regenerative Hyperplasia





- *Nodular Regenerative Hyperplasia is thought to be due to **ischemic atrophy** in areas of liver with less/inconsistent blood flow.*
- *Is a cause of **NON-CIRRHOTIC PORTAL HTN***
- *Pattern of injury from **ischemic atrophy** and **secondary nodular hyperplasia in areas of good blood flow.***
- *A/w rheumatologic disorders, PV, lymphoma, azathioprine*
- ***Diffuse small regenerative nodules (1-3 mm)** throughout liver, but little to **NO FIBROSIS** (trichrome helps confirm)*
- ***Reticulin stain:** Reticulin network compressed between **nodules with variation in size** of hepatocytes.*

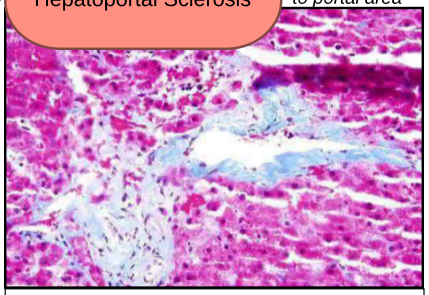
Budd Chiari Syndrome



- *Budd Chiari Syndrome is due to **obstruction of hepatic venous outflow,** usually from thrombosis of 1+ hepatic veins at their openings into the IVC*
- *RF: Hypercoagulable states, infection, malignancies*
- *H&E: Sinusoidal dilation, congestion, hemorrhage & hepatocyte atrophy*
- *DDx: R sided heart failure & sinusoidal obstruction syndrome (hx SCT + chemo a few weeks prior)*

Hepatoportal Sclerosis

Central vein close to portal area



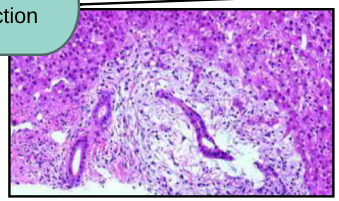
- *Noncirrhotic portal HTN 2/2 portal fibrosis & portal vein obliteration*
- ***Central veins abnormally close to portal areas***
- ***Portal fibrosis** with **portal vein narrowing** or obliteration*
- *DDx: Portal vein thrombosis (May have same morphology; thrombus seen on imaging studies)*

CHOLESTASIS

Cholestasis= presence of bile pigment within bile canaliculi & hepatocytes

Bland (Intrahepatic); No other Changes
- Estrogen/Steroids — *Especially in younger patients taking these hormones & Body builders*
- Bile salt transporter mutations (Byler disease)

Cholestasis with other changes
- Large Bile Duct Obstruction



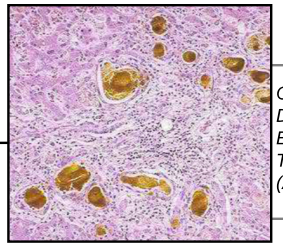
- ***Hepatocyte changes*** *= FEATHERY DEGENERATION, xanthomatous changes, bile infarct*
- ***Portal tract****= Edema & bile ductular reaction/ proliferation;*
- ***Bile ducts****= normal or have reactive changes +/- PMNs*
- ***Signs of chronicity*** *= "Cholate stasis", Copper, Loss of bile ducts, portal fibrosis*

CAUSES OF HYPERBILIRUBINEMIA

- Increased Hemolysis (Production)
- Decreased Conjugation or Excretion
  - Gilbert Syndrome — *Jaundice during times of stress/illness*
  - Rotor Syndrome
  - Dubin Johnson Syndrome — ***cMOAT/MRP2*** *gene mutation causes impaired biliary transport of conj. bili.*; ***BLACK liver*** *grossly*; *PASD & Fontana Masson stain +*
  - Crigler Najar Syndrome

BILIARY INJURY CHOLESTATIC

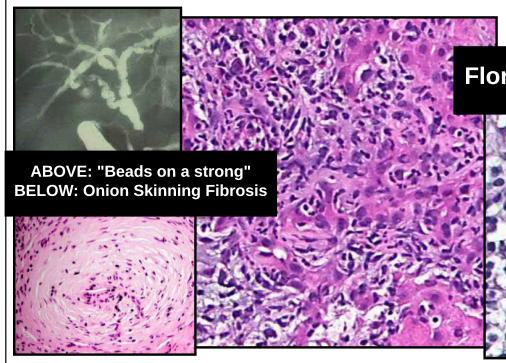
- Acute or Chronic Hepatitis (See Above)
- Ischemic Cholangitis
- Drug Hepatotoxicity
- Sepsis



Cholestasis around DUCTS is a big clue
Ductules with cholestasis around portal tract= EMERGENCY!! CALL CLINICIAN TO NOTIFY THEM OF SEPSIS!
(Although they likely see this clinically already)

Primary Sclerosing Cholangitis

- Fibroinflammatory disease affecting ***INTRA****- &* ***EXTRA****-***HEPATIC BILE DUCTS/tree**, leading to **STRICTURES** and biliary **CIRRHOSIS**
- **MALES**, 25 – 60 year old; P-ANCA+
- Assoc with **ULCERATIVE COLITIS** (65% occur in pts w/ UC)
- ERCP or MRCP: **"BEADS ON A STRING"** 2/2 segmental **strictures** and **dilations** of bile ducts (due to fibrous obliteration of bile ducts with periductal fibrosis & ductopenia)
- Inc risk of **cholangiocarcinoma**
- Small duct PSC: variant of PSC involving only
- **ONION SKINNING FIBROSIS** around bile duct affecting larger potral tracts (may not be seen on liver biopsy).
  - Look for bile duct proliferation, bile duct damage

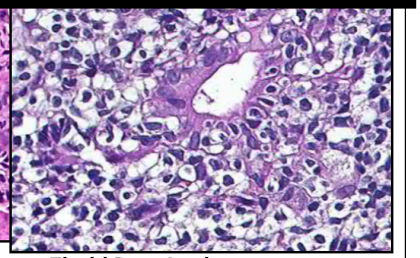


ABOVE: "Beads on a strong"
BELOW: Onion Skinning Fibrosis

Bile ductular reaction. Cholangiocytes proliferating with accompnaying PMNs bordering the portal tract

Primary Biliary Cirrhosis/ Cholangitis

Florid Duct Lesion INTRAhepatic BD

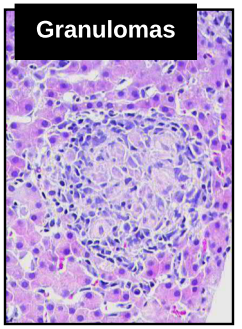


Florid Duct Lesion with destruction of intrahepatic bile ducts in older females

IgM Anti-Mitochondrial Ab+

- *Primary biliary cholangitis (formerly PB cirrhosis) is an autoimmune disease with progressive destruction and* ***loss of INTRAHEPATIC BILE DUCTS***
- ***FEMALES,*** *40 – 60 years old; fatigue, abdominal pain, jaundice, pruritus.*
- *Elevated* ***IgM= AMA (ANTI-MITOCHONDRIAL Ab)***
  - *Autoimmune cholangiopathy = AMA neg PBC*
- *Histology*
  - *Chronic cholestasis*
  - ***FLORID BILE DUCT LESION/ BILE DUCT DESTRUCTION*** *(lymphs, PMNs, histiocytes)*
  - ***Noncaseating granulomas***
  - *Increased* ***copper*** *accumulation*

Granulomas



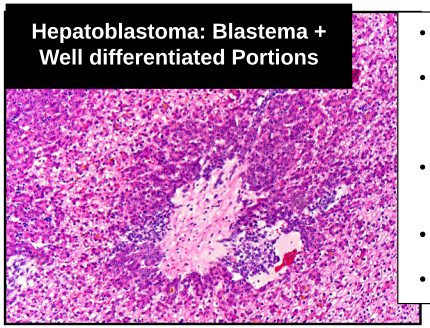
MALIGNANT LIVER TUMORS

Hepatoblastoma

- Fetal
- Embryonal
- Macrotrabecular
- Small cell undifferentiated

Epithelial Type

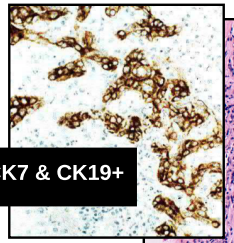
Mixed Epithelial/ Mesenchymal Type

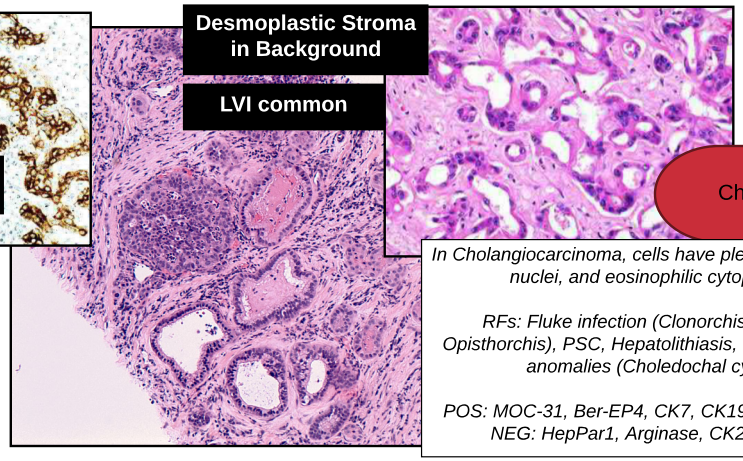


- *Hepatoblastoma is a malignant tumor found in **children***
- *[illegible] **tocytes** and [illegible] cross a spectrum of differentiation, from **blastema** to **well differentiated** cells.*
- *The cells are small and show **alternating light and dark density of the cytoplasm** on low power.*
- ***Pseudorosettes** and **extramedullary hematopoiesis** are frequently found.*
- ***High serum AFP**.*

Pseudorosettes

Cholangiocarcinoma





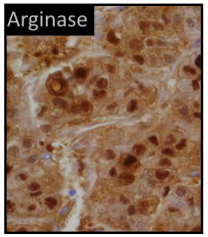
In Cholangiocarcinoma, cells have pleomorphic round nuclei, and eosinophilic cytoplasm.

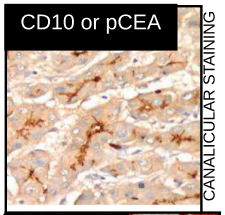
RFs: Fluke infection (Clonorchis sinensis, Opisthorchis), PSC, Hepatolithiasis, Thorotrast, BD anomalies (Choledochal cysts)

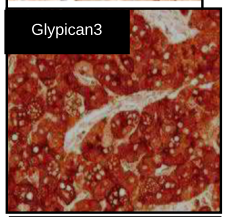
POS: MOC-31, Ber-EP4, CK7, CK19, Mucicarmine
NEG: HepPar1, Arginase, CK20, CDX2

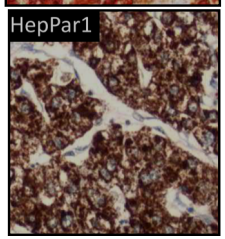
Metastatic Disease

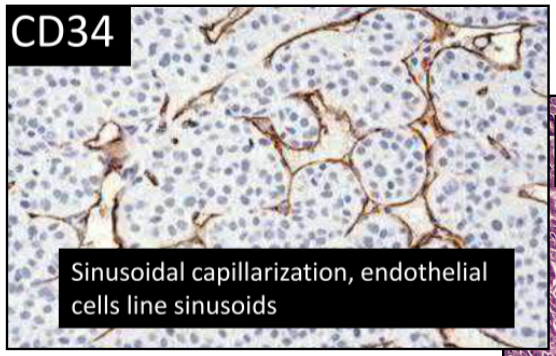
Hepatocellular Carcinoma

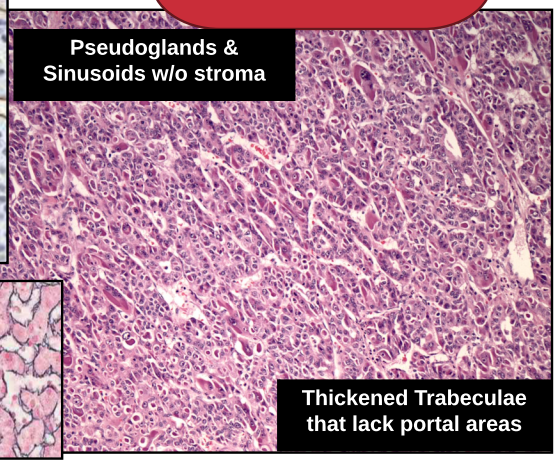


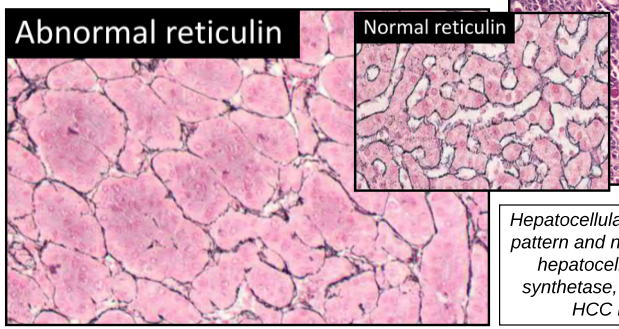








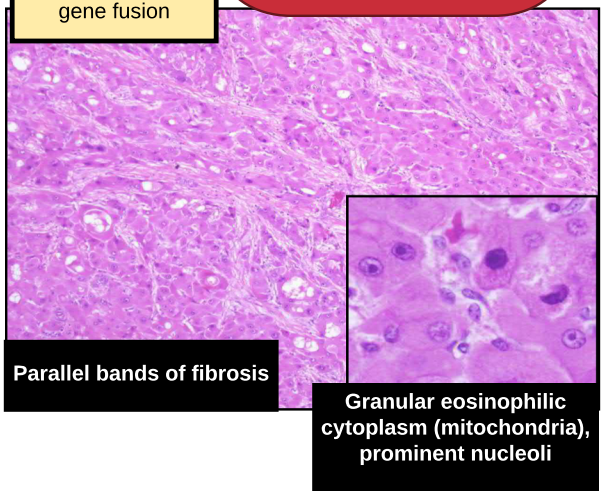




Hepatocellular carcinoma is positive for polyclonal CEA in a canalicular pattern and negative for monoclonal CEA. Compared to non-malignant hepatocellular lesions, HCC is positive for Glypican-3, glutamine synthetase, CD34 and HSP-70. Compared to metastatic carcinoma, HCC is positive for HepPar1, arginase1, and Glypican3.

Fibrolamellar carcinoma

DNAJB1-PRKACA gene fusion



*Fibrolamellar carcinoma contains nests of **ONCOCYTIC** cells surrounded by collagen bundles (lamellar fibrosis). The collagen bundles can form a **CENTRAL SCAR** appearance grossly. There is NO underlying liver disease. AFP Neg. It is more common in the **YOUNG**, and has a **GOOD PROGNOSIS** with treatment. CK7 & CD68 stain lysosomes*

BENIGN LIVER TUMORS

Hemangioma

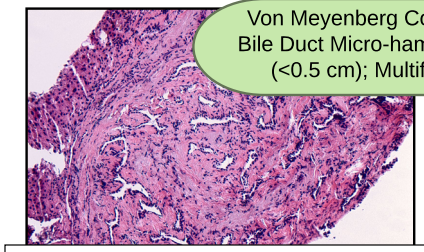
Most common benign tumor of liver *(usually solitary). Bland, blood-filled spaces. Diagnosed on imaging. Not usually biopsied due to risk of bleeding!*

Epithelioid Hemangioendothelioma

- *Low grade malignant vascular neoplasm;* ***Mets*** *to abdominal LN, lung, omentum or peritoneum poss.*
- ***t(1;3)*** ***WWTR1-CAMTA1 fusion***
- *Multinodular; Ill-defined border*
- *Abundant stroma with* ***myxoid*** *appearance*
- *Dendritic or epithelioid tumor cells with* ***cytoplasmic vacuoles containing RBCs***
- *POS: CD34, ERG, CD31, Fli1, Factor VIII, D2-4*

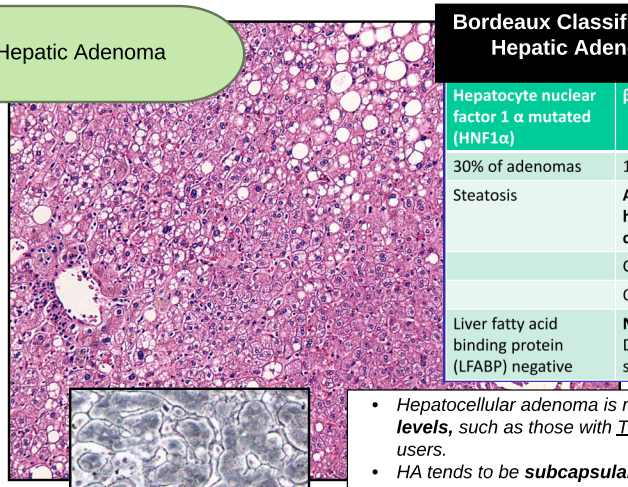
t(1;3) *WWTR1-CAMTA1* fusion

Von Meyenberg Complex Bile Duct Micro-hamartoma (<0.5 cm); Multifocal



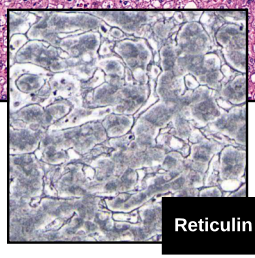
Von Meyenburg complexes (bile duct microhamartomas) *can be found* ***subcapsular*** *or* ***deep*** *within the liver. At* ***0.5 cm or less****, they are smaller than bile duct adenomas, and frequently* ***multifocal****. They are composed of* ***branched irregularly shaped and curved ductules with dilatation.*** *They are* ***less cellular*** *than bile duct adenoma, & have* ***more dense, fibrotic stroma****.*

Hepatic Adenoma



Bordeaux Classification of Hepatic Adenomas

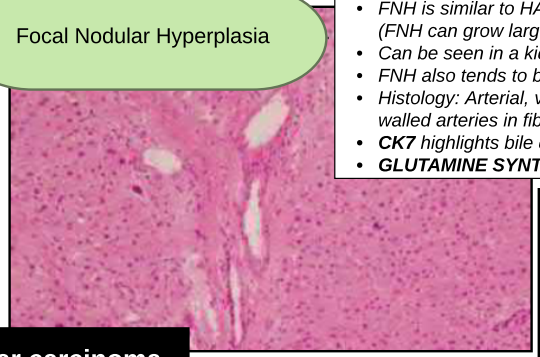
Hepatocyte nuclear factor 1 α mutated (HNF1α)	β catenin	Inflammation	Not otherwise specified
30% of adenomas	10%	50%	10%
Steatosis	**Associated with hepatocellular carcinoma**	No mutations for HNF1α or β catenin	No mutations for HNF1α or β catenin
	Cytologic atypia		
	Obesity	Obesity	
Liver fatty acid binding protein (LFABP) negative	**Nuclear beta-catenin** Diffuse glutamine-synthetase	C-reactive protein + Serum amyloid A +	



Reticulin

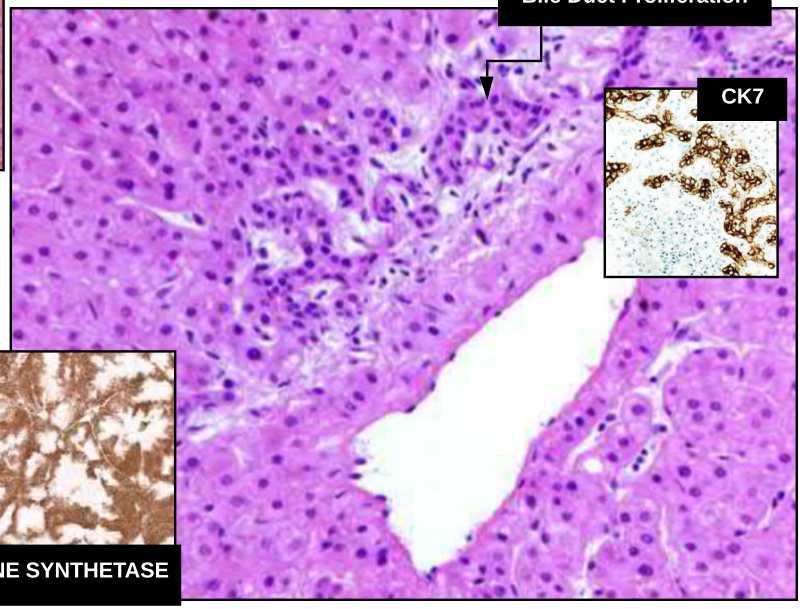
- *Hepatocellular adenoma is more common in people with* ***abnormal sex hormone levels,*** *such as those with* ***Turner's syndrome (45 XO), anabolic steroid*** *or OCP users.*
- *HA tends to be* ***subcapsular****, is* ***soft, tan-yellow, lacks a central scar.***
- *Microscopically, it has* ***benign hepatocytes*** *with a* ***variable amount of glycogen,*** *variable* ***steatosis****, and* ***frequent vascularization*** *by* ***unpaired arteries and veins****.*
- *HA= Only arterial + venous prolif (****NOT bile ducts!)****.*
- *There should NOT be cirrhosis in the background!!*
- *Reticulin stain: 1 - 3 cell thick hepatocyte trabeculae with prominent blood vessels.*
- *Tx requires surgery to prevent rupture/malignant transformation*

Focal Nodular Hyperplasia



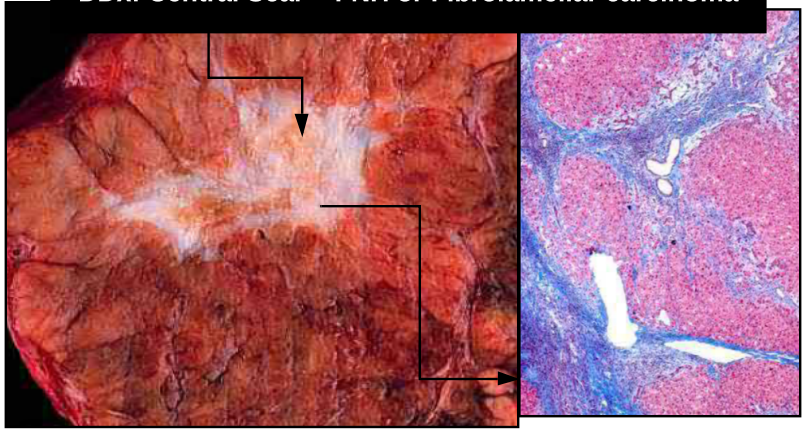
- *FNH is similar to HA; is also a/w abnormal sex hormone levels, FNH is more strongly a/w* ***oral contraceptives****, (FNH can grow larger or smaller with OCP use/cessation).*
- *Can be seen in a kid after chemo.*
- *FNH also tends to be* ***subcapsular****, but it has a* ***CENTRAL SCAR*** *grossly*
- *Histology: Arterial, venous AND* ***BILE DUCT PROLIFERATION.*** *Hepatocytes are divided into nodules by thick walled arteries in fibrous septae with a* ***ductular reaction*** *at the junction btw septae & parenchyma.*
- ***CK7*** *highlights bile duct proliferation*
- ***GLUTAMINE SYNTHETASE = MAP-LIKE STAINING PATTERN***

Bile Duct Proliferation



CK7

DDx: Central Scar = FNH or Fibrolamellar carcinoma



Central radial scar with weird vessels, proliferating ductules, Map-like staining with Glutamine Synthetase

GLUTAMINE SYNTHETASE