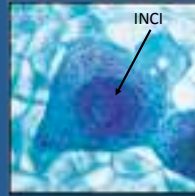


## Mallory Bodies



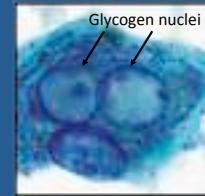
- Cytoplasmic inclusions  
Elongated, ropey to hyaline  
Tend to surround nucleus
- Alcoholic liver disease
  - Other, including HCC

## Nuclear Inclusions



### Intranuclear cytoplasmic invaginations (INCIs)

- Common:  
Benign & malignant hepatocytes
- Uncommon:  
1°, 2° adenocarcinoma

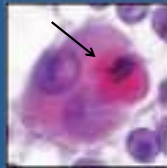


### Nuclear clearing

- Usually due to glycogen
- Diabetes mellitus
  - IV glucose
- Also: hepatitis, cirrhosis, infection, or normal liver

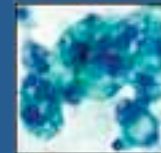
## Councilman Bodies

- Mummified hepatocytes  
Apoptosis, coagulative necrosis  
Nuclei degenerated or lost
- Hepatitis (most common)
  - Cirrhosis
  - Hepatocellular CA



## Steatosis: Fatty Liver

- Liver: primary organ of lipid metabolism
- Steatosis: cytoplasmic lipid accumulation
- Common, nonspecific
- Alcoholism
  - Obesity
- Many others; also, HCC



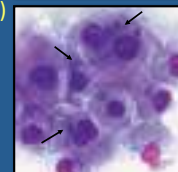
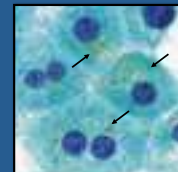
# Pigments

## Lipofuscin

“Wear-&-tear” pigment: ↑ age  
3° lysosomes, residual bodies

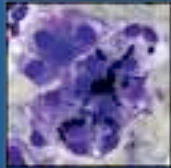
Fine, nonrefractile granules  
Gold-brown (Pap); Dark green (Rom)

Very common, except children  
Decreased/absent in adults =>  
Suspect hepatitis, cirrhosis, HCC



## Bile

Produced by hepatocytes only  
Intracellular or extracellular  
Various shades of green  
Irregular, amorphous, nonrefractile  
Hepatitis, obstructive jaundice,  
primary or metastatic tumors



Malignant cells *making* bile is diagnostic of hepatocellular carcinoma  
Bile in malignant cells or in canaliculi between them => bile production

## Iron (Hemosiderin)

Hepatocytes, Kupffer, or bile duct cells  
Pap: Refractile, coarse, golden brown  
Rom: Nonrefractile, dark blue-green

- Hemosiderosis = simple iron overload
- Hemochromatosis (+ cirrhosis)

Primary (iron overload → cirrhosis)  
Secondary (cirrhosis → iron overload)

HCC rarely has hemosiderin



## Melanin

Not a liver pigment, but included:  
Melanoma often metastasizes to liver  
Melanoma cells resemble hepatocytes  
Melanin can mimic other pigments



Nonrefractile, powdery fine pigment  
Brown-black (Pap)  
Blue-black (Rom)



## Liver Disease

- Diffuse Liver Disease  
Hepatitis, cirrhosis, etc  
FNA Bx *not* commonly used in dx  
May be in DDx nodular liver disease
- Nodular Liver Disease  
Cysts, abscess, granuloma, tumor  
FNA Bx commonly used in dx

## Cirrhosis

Degeneration and regeneration →  
diffuse nodular fibrosis (micro, macro)

Dx: Resists smearing (reticulin)

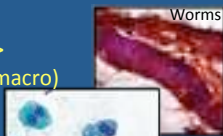
Dual population:

- Reactive hepatocytes +
- Bile duct cells

± Chronic inflam' n, stromal fragments, bile

Mitosis, necrosis also possible

Pearl: Little/no ↑ serum α-fetoprotein



## Liver Cysts

- Congenital

Most common, by far, includes:  
Simple cyst  
Caroli disease (bile ducts)  
Ciliated hepatic foregut cyst  
Polycystic liver disease

- Acquired

- Nonneoplastic cysts  
Abscess, hydatid, hematoma
- Neoplastic cysts  
Primary cystic neoplasms  
(similar to pancreatic counterparts)  
Cystic metastases, necrotic tumors



Congenital Hepatic Cyst



Ciliated Foregut Cyst

## Liver Abscess

Serious disease, can be fatal

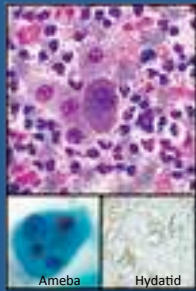
Bacteria: Most common (80%)  
Usually polymicrobial

Fungi: Candida most common

Parasites: Entamoeba histolytica;  
Echinococcus (hydatid)

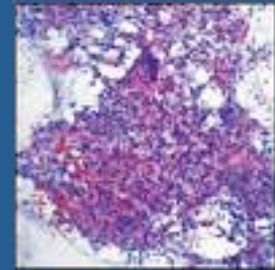
FNA → Abscess (WBCs, histiocytes, etc)

DDx: Tumor cells vs reactive hepatocytes



## Granuloma

Causes are legion



Infections, sarcoid, neoplasms

Dx: Epithelioid histiocytes

± Multinucleated giant cells

Can be minute and focal

=> sampling error!

## Benign Tumors

Focal nodular hyperplasia

Liver cell adenoma

Bile duct hamartoma



## Focal Nodular Hyperplasia

Benign, polyclonal, nonneoplastic  
reactive to vascular abnormality?

F>>M, 30s to 40s, asymptomatic

Solitary (75%); central stellate scar

Dx: "Focal cirrhosis"

Hepatocytes + Bile duct cells

± Reactive changes in either

± Stromal fragments

DDx: Hepatocellular carcinoma

No ↑ α FP, cirrhosis, or mitosis



## Liver Cell Adenoma

Rare benign neoplasm of hepatocytes  
(4 molecular subtypes)

Women (9:1) of reproductive age

Associated w/ steroids, esp OCPs

Often symptomatic (pain, bleeding)

Usually solitary, no central scar

Hemorrhage, necrosis: common

Dx: Hepatocytes only (no bile duct cells)

Larger than normal; ± glycogen, lipid

DDx: WD Hepatocellular CA

No: ↑ α FP, cirrhosis, atypia, mitosis



## Bile Duct Tumors

Adenomas

≤ 1cm, solitary, under capsule

Hamartomas

(Von Meyenburg complexes)

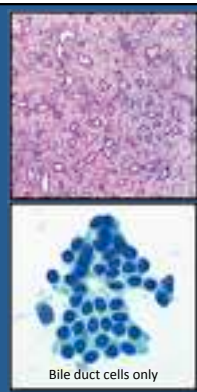
Multiple, anywhere in liver,  
often cystic, associated with  
polycystic liver disease

Both: Bile ducts in fibrous stroma

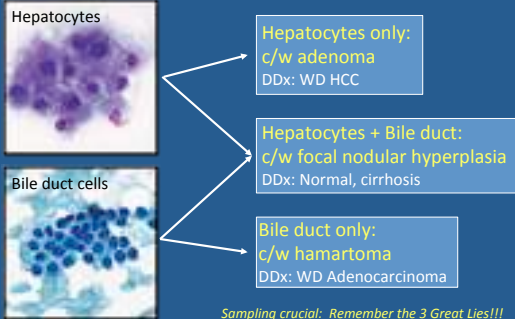
No hepatocytes

(R/O contaminants)

DDx: WD Adenocarcinoma (1°, 2°)



## Summary Benign Liver Tumors



## Hepatocellular Carcinoma

Far most common primary liver cancer

Males >3:1, >60 yrs (wide range)

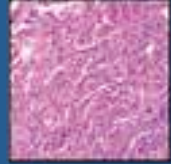
Cirrhosis, hepatitis (B,C), or both

Only ~10% have normal liver

Serum  $\alpha$ -fetoprotein usually elevated  
>500 ng/mL: 50% sensitive; 90% specific

Gross: Single, multiple, diffuse

Can mimic other tumors, notably mets



## Causes of Hepatocellular CA

Diabetes mellitus\* (33%)

Alcohol-related disorders (25%)

Hepatitis B or C virus infection\*\* (25%)

Rare metabolic disorders (<5%)

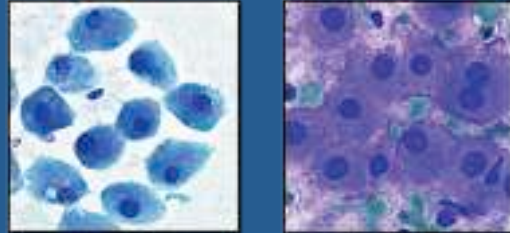
Obesity/metabolic syndrome\* (<5%)

\*Related to hyperinsulinemia?

\*\*HCC is increasing in "baby boomers"  
Decreasing in next generation  
Due to less exposure to HCV?

Altekruse SF, et al: *Am J Gastroenterol* [online]11 February 2014; doi:10.1038/ajg.2014.11

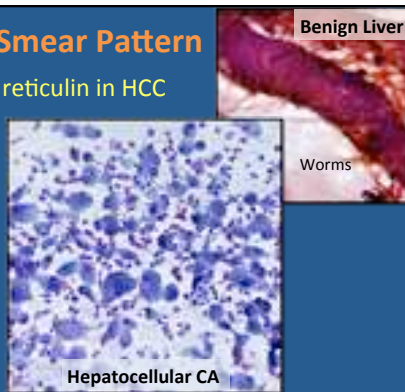
## Hepatocellular Carcinoma



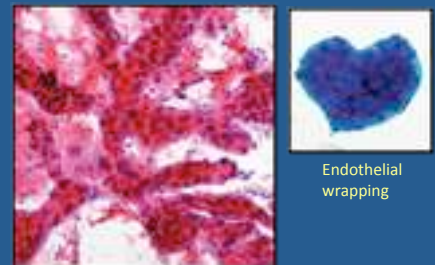
Dx: Liver cells only, no bile duct cells  
Malignant cells look like hepatocytes  
DDx: Metastasis  $\rightarrow$  foreign cells

## 1<sup>st</sup> Clue: Smear Pattern

Decreased reticulin in HCC

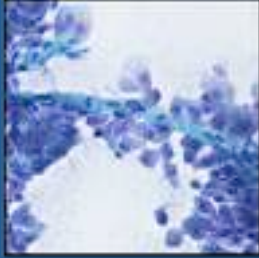


## Trabecular Growth Cell groups wrapped in endothelium



Characteristic of HCC; rare in metastatic tumors  
Thick (>3 cells) in HCC; thin in benign (1-2 cells)

### Capillarization: traversing capillaries



Diagnostically important, but not pathognomonic  
(DDx: Cirrhosis, FNH, adenoma; also metastasis)

### Acinar or pseudoglandular pattern



Mimics AdCA

Clue: Bile

Clue: Hyaline Globules

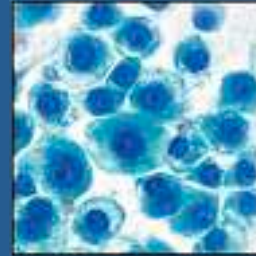
“Glands” may suggest adenocarcinoma

### Cell size



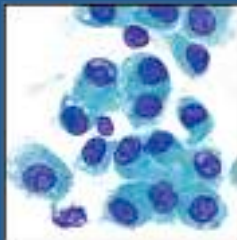
Broad range: microcytes to giant cells

### Nuclei



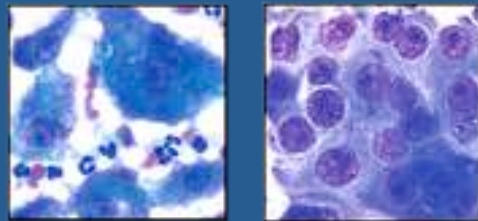
Nuclei: usually central, round, uniformly enlarged  
Anisonucleosis in high grade HCC *and* benign!  
Note that some tumor cells have high N/C ratios

### Nuclear membrane



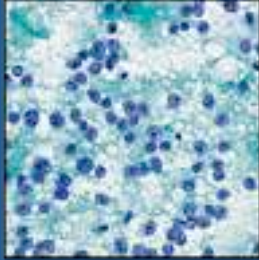
Irregular nuclear membranes common  
INCIs favor HCC over adenocarcinoma

### Chromatin, Nucleoli



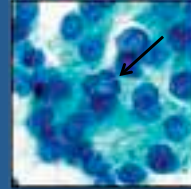
Chromatin usually coarse in HCC  
*and* benign hepatocytes  
*Fine* chromatin abnormal => HCC  
Note macronucleoli ( $\geq$  RBC)

### Naked atypical nuclei



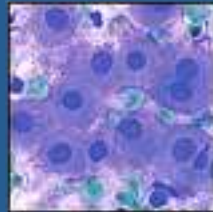
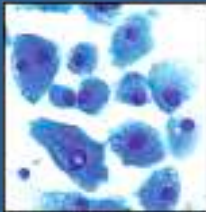
“Showers” of naked atypical nuclei common  
DDx: Benign liver; lymphoma, anaplastic carcinoma

### Mitosis, N/C ratios



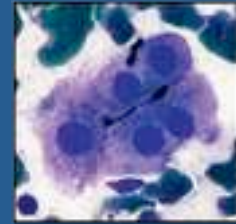
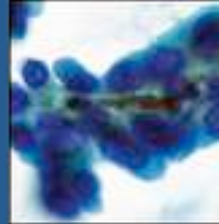
Mitotic figures, esp atypical => malignancy,  
but are unusual in low-grade HCC

### Cytoplasm



Distinct cytoplasmic granularity a key  
feature of hepatocytic differentiation  
Note: *Absence* of cytoplasmic pigments,  
eg, lipofuscin or hemosiderin in HCC

### Bile Production



Bile production by malignant cells  
pathognomonic of HCC  
Look for bile in cytoplasm, canaliculi  
Mere presence of bile is nonspecific!

### Hyaline Material



Hyaline globules in HCC



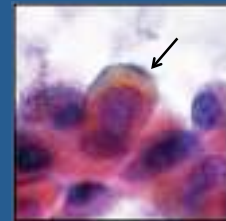
Mallory Body in HCC

Hyaline globules are common in HCC,  
favor HCC over 1° or 2° AdCA  
Note: HGs also in benign liver diseases

### Steatosis, Glycogen




Steatosis: ~20% of HCCs,  
can be extensive  
Can mimic liposarcoma  
or signet ring cell CA




Glycogen: ~80% of HCCs,  
can also be extensive  
Mimics clear cell CA

### Special Studies



**Reticulin Stain**  
(CD34: capillaries)


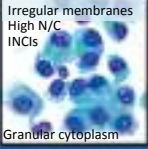




Shows abnormal architecture, loss of reticulin, and widening of the liver cell plates characteristic of HCC



**HepPar-1**

HepPar-1, glypican-3\*, TTF-1 (cyto), CAM5.2 + AE1/AE3, MOC-31-  
\*Negative in benign liver

### Review

**Note absence of lipofuscin, iron pigment**  
...the dog that didn't bark in the night

### Fibrolamellar HCC



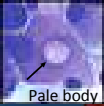
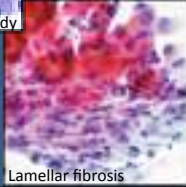
Rare, young pts (10-35)\*; F ≈ M  
Central scar, but not specific  
No: cirrhosis, steroids, ↑α-FP

**Dx: Dyshesive cells**


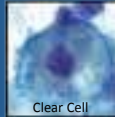


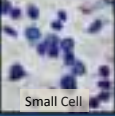
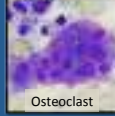
- Large nuclei + nucleoli
- Oncocytic cytoplasm (key\*)
- Pale bodies (fibrinogen)
- Lamellar fibrosis

**Good prognosis only if resectable**  
Trilineage: Hepatic, Biliary, NE?

\*Ordinary HCC more common  
\*\*Oncocytes can occur in ordinary HCC

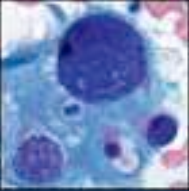





### Other HCC Variants

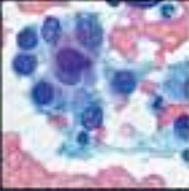
<b>Acinar or Adenoid HCC</b> DDx: Adenocarcinoma		
<b>Clear Cell HCC</b> DDx: Metastatic renal cell CA		
<b>Giant or Spindle Cell HCC</b> DDx: Sarcoma, Melanoma		

**Small cell HCC**  
DDx: Metastatic lung cancer

### Liver Cell Dysplasia



**Large cell dysplasia**  
Nucleus & cytoplasm enlarge  
N/C ratio maintained  
Nuclei are abnormal  
Low grade lesion




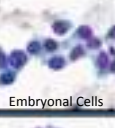

**Small cell dysplasia**  
Cells small, high N/C ratios  
Nuclei lack significant atypia  
Basophilic cytoplasm  
Histo: "too many cells"  
High grade lesion

### Hepatoblastoma

Most common pediatric liver cancer  
Boys > girls; ↑↑α-FP; ± β-catenin mutations  
No cirrhosis; ± congenital defects, Beckwith-Wiedemann, FAP

- Epithelial Cells**  
Anaplastic, Embryonal, Fetal (± EMH [clue])
- Mesenchymal Component**  
Primitive, osteoid, or cartilage  
± Teratoid elements,

**DDx: Hepatocellular CA (> pleomorphism)**  
Metastatic pediatric malignancies

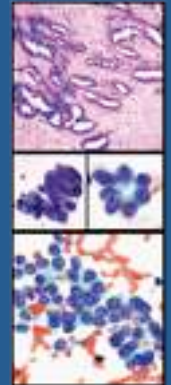


## Hepatoblastoma vs Hepatocellular CA

Favors Hepatoblastoma	Favors Hepatocellular CA
Infant < 5 yrs	Older, >10 yrs
Congenital anomalies	Storage disease
Extreme ↑ serum αFP	↑ serum αFP
Otherwise normal liver	Cirrhosis, hepatitis
Primitive cells	More hepatocytic differentiation
Mesenchymal component	Marked pleomorphism
Extramedullary hematopoiesis	Tumor giant cells

## Cholangiocarcinoma

Distant 2<sup>nd</sup> to hepatocellular CA  
 Clin/radiol similar to HCC  
 Except M = F, no cirrhosis, no ↑ αFP  
 Risk: Conditions → biliary stasis & inflam'n (cholangitis, stones, etc) liver flukes, cysts, HBV/HCV?  
 Dx: ~Pancreatic Adenocarcinoma  
 DDx: HCC, Metastatic AdCA  
 Pearl: Clinical Hx, Immuno



## DDx Cholangiocarcinoma

- **HCC:** Usually straightforward  
 Immunochemistry (HepPar1, Glypican3)
- **Metastatic AdCA:** Can be difficult  
 Metastatic pancreas or biliary cancer!  
 Clinical history/immuno can be helpful
- **Reactive atypia of biliary cells:**  
 Orderly, cohesive sheets uniform cells;  
 regular ranks, files; little/no crowding;  
 smooth membranes; fine chromatin

## Mesenchymal Tumors

- Benign**
- Mesenchymal hamartoma
  - Hemangioma
  - Angiomyolipoma
  - Inflammatory pseudotumor
- Malignant**
- Undifferentiated (embryonal) sarcoma
  - Epithelioid hemangioendothelioma
  - Angiosarcoma

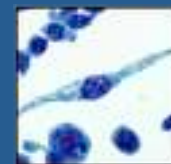
## Hemangioma

Most common benign liver tumor  
 Multiparous women, hormonal?  
 Usually asymptomatic, incidental  
 Angiography may be diagnostic  
 Biopsy risks hemorrhage  
 Only done to exclude cancer  
 FNA: Many cases only blood  
 Stromal fragments with spindle cells  
 Capillaries (diagnostic): cell blocks  
 (Absence of malignant cells)  
 Vascular markers (CD34, CD31, FacVIII)  
 DDx: Vascular or spindle cell tumors



## Sarcoma

Primary sarcomas rare  
 Mets more common  
 DDx: Spindle cell CA



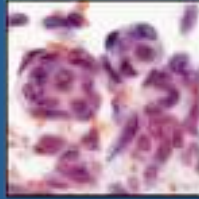
Sarcomatoid HCC

## Angiosarcoma

Most common 1° liver sarcoma  
 Idiopathic vs PVC, arsenic, steroids,  
 Thorotrast, etc  
 ±Cirrhosis, no ↑α-FP

Angiography for dx: Bx risky

Dx: Often very bloody, necrotic  
 Spindle, epithelioid, bizarre cells  
 Tubules, whorls: recap vessels  
 Neolumens: ICLs with RBCs  
 Extramedullary hematopoiesis  
 CD31, CD34, Factor VIII; ±CK, EMA



Neolumens

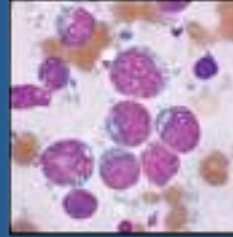
## Malignant Lymphoma

1° rare; 2° more common  
 Most = Large B-cell NHL

Also: Hepatosplenic T cell  
 Hepatitis C: risk factor

Cytology:

- Dispersed cell pattern
- Lymphoid morphology (DQ)
- Lymphoglandular bodies



Primary Hepatic Lymphoma

## Metastases

Far more common than primary cancer  
 GI tract, lung, breast, kidney, others

Most = adenocarcinoma

Also: small cell, squamous, melanoma

DDx: HCC: Glypican-3+, HepPar-1+

Metastatic AdCA: MOC-31+, CK7+

CDX2, TTF-1, ER/PR, Melan A, etc

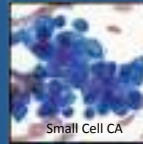
## Metastatic Carcinomas



Colorectal CA



Signet Ring CA



Small Cell CA



Hepatocytoid CA

## Typical Immunoreactions for HCC, CholangioCA, Met AdCA

	AE1/3	CK 7	CK 19	CK 20	HepPar1 Glypican3	MOC-31	TTF-1
Hepato-cellular CA	-	-	-	-	+	-	+
Cholangio-carcinoma	+	+	+	-	-	+	-
Metastatic AdenoCA	+	-	-	+	-	+	...

\*Cytoplasmic, not nuclear, staining  
 \*\*Colorectal, GI primaries; others (-)  
 \*\*\*Nuclear staining Thyroid, Lung CAs  
 Note: CholangioCA negative for markers  
 such as HepPar1, TTF-1, CDX2, ER/PR

## Summary

- Benign/Reactive: Hepatocytes + Ductal cells
- FNH: Hepatocytes + Ductal cells + Mass
- Adenoma: (Benign) Hepatocytes only + Mass
- HCC: (Malign) Hepatocytes only
- BD Hamartoma: (Benign) Ductal cells only
- CholangioCA: (Malign) Ductal cells only
- Metastasis: (Malign) Foreign cells

## Hepatoscopy



*Thank you*



## Classic Medical Student Question



A guy with a glass eye gets a liver biopsy.

What's the diagnosis?