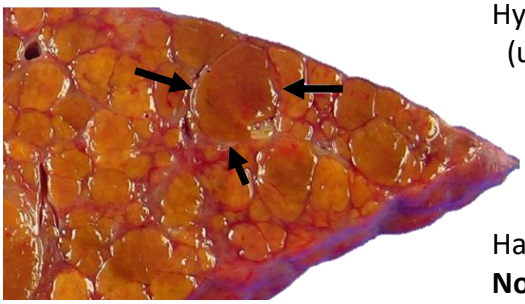
Prepared by Dr. Kurt Schaberg

Hepatocellular Lesions

Note: <u>All</u> of these lesions (usually) stain with Hepatocellular stains (Hepar-1 and Arginase)
Also, canalicular staining with CD10 and pCEA. Positive albumin in situ hybridization.
Cytoplasmic TTF-1. Negative MOC-31. May make Bile.

*Macro*regenerative Nodule

An unusually large regenerative nodule (often >1 cm) that develops in the setting of **<u>cirrhosis</u>**.



Hyperplastic liver parenchyma. Plates may be slightly thickened (usu. 1-2 cells thick, maybe focally 3).

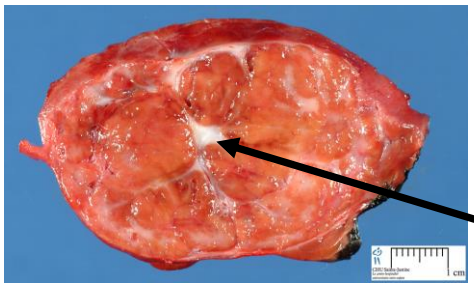
In general, every hepatocyte should touch reticulin, with the exception of rapidly regenerating livers, where things may be focally thicker (up to 4 cells), and fatty liver, where there is less reticulin physiologically.

Have **<u>normal constituents</u>** (bile ducts, arteries, veins, etc…).
No atypia (if there is atypia → dysplastic nodule).

Focal Fatty Nodule

Rare. Benign. Reactive.
Focal, well-circumscribed are of macrovesicular steatosis.
May resemble a mass on imaging.
No architectural changes (only difference from normal liver is fat)

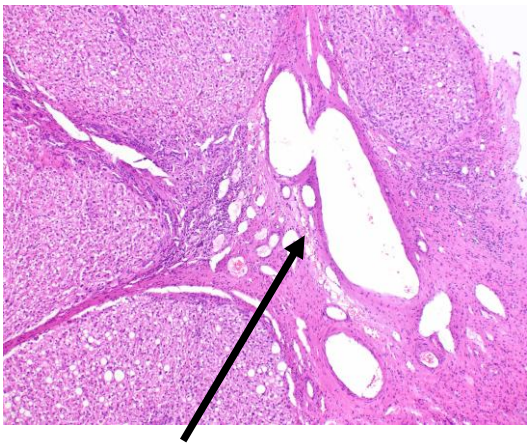
Focal Nodular Hyperplasia (FNH)



<u>Not a true neoplasm</u>; *Think:* **"Focal Cirrhosis"**

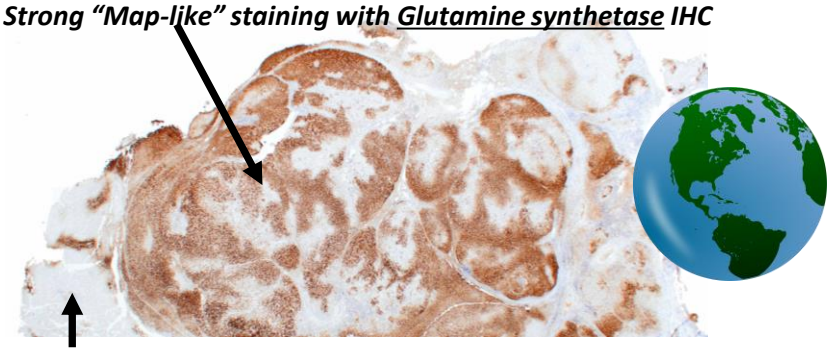
Regenerative hyperplastic response of hepatocytes <u>secondary to vascular abnormalities</u>. Usually younger women. Non-cirrhotic. Very common. Often incidental. Can often Dx on imaging.

Well-circumscribed with **<u>central stellate scar</u>** with fibrous septae with entrapped vessels, bile ducts, and inflammatory cells
Normal plate thickness. No true portal tracts. No capsule.



Central dystrophic vessels.
Often bile ductular proliferation.

Strong "Map-like" staining with <u>Glutamine synthetase</u> IHC



Normal, pericentral staining
Note: In cirrhosis it shows weak, patchy periseptal staining.

On small biopsy, these can resemble an inflammatory adenoma. So consider doing SAA and CRP (strong positive would favor an inflammatory adenoma). Also, don't mistake the "map-like" GS staining in FNH for the diffuse GS staining seen in β-mutated adenomas. Lots of potential pitfalls!

Hepatocellular Adenoma

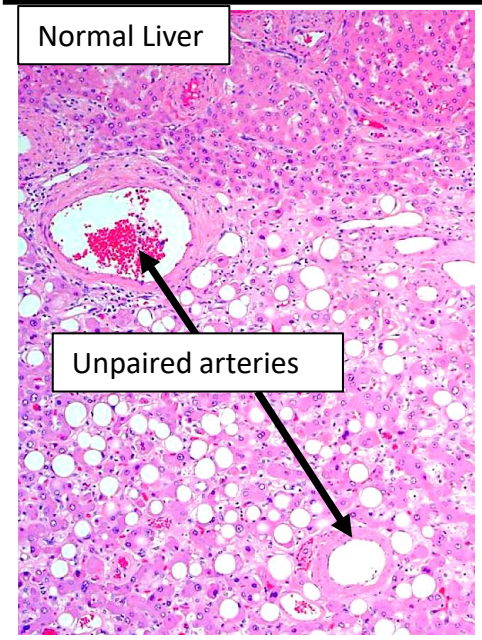
Benign liver neoplasm. *aka Hepatic adenoma*

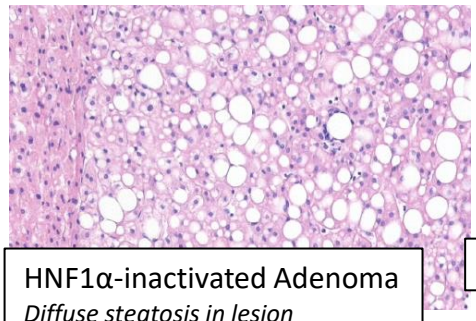
Usually in **women** of childbearing age.
Assoc. with oral **contraceptives**/steroids and fatty liver disease.
Usually incidental finding, but can present with bleeding/rupture.
Usually low of transformation to HCC.

Clinically, in contrast to HCC, AFP *NOT* elevated. *Non*-cirrhotic.

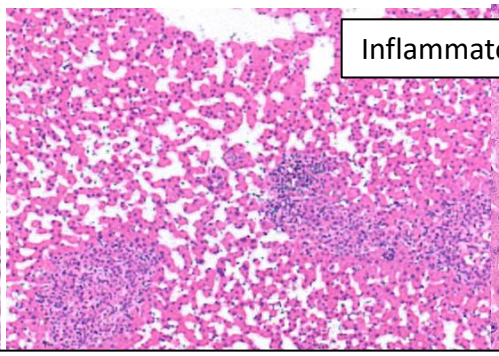
Benign-appearing hepatocytes.
Normal plate thickness (1-2 cells thick) (can highlight with reticulin)
Unpaired arteries, absent bile ducts. Minimal atypia. No/rare mitoses.
IHC: Ki67 2-3% (matches background liver); Variable CD34.
Negative Glypican-3. Stains below are helpful only for subtyping.

Management: usually resect or ablate tumors >5cm or if higher risk of transformation (male, β-catenin activation)

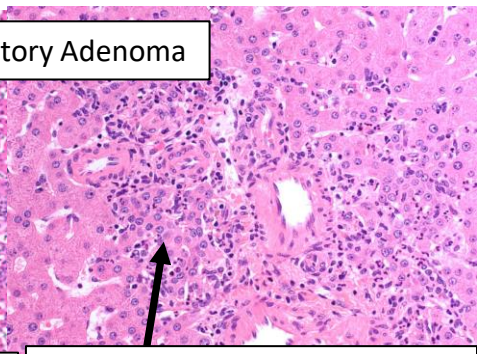




HNF1α-inactivated Adenoma
Diffuse steatosis in lesion



Sinusoidal dilation and foci of inflammation

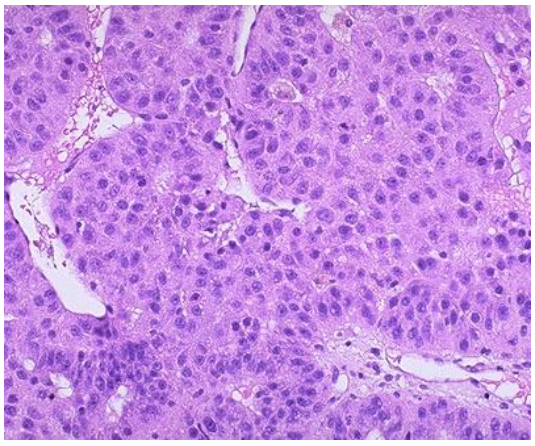


Bile ductular proliferation in fibrous septae with unpaired arteries, forming "pseudo portal tracts"

	Inflammatory *(Telangiectatic)*	***HNF1α-inactivated***	***β-catenin mutant*** *(activated or inactivated)*
Frequency	*~40%*	*~30%*	*~20%*
Molecular	IL-6/JAK/STAT activation	Biallelic inactivation of HNF1A	CTNNB1 activating mutations/deletions leading to different levels of WNT pathway activation
Unique histology	Inflammatory infiltrate, peliosis, and bile ductular reaction in fibrous septae.	Diffuse steatosis (macro or micro). Ballooned clear cells. Often microadenomas in background.	Can see pigment (lipofuscin, bile)
Unique IHC	Stain with serum amyloid A and CRP (usually diffuse). *Warning: Stain can be dirty!*	Loss of LFABP staining	Diffuse, strong glutamine synthetase. Nuclear B-catenin (often focal)
Unique clinical		Associated with adenomatosis (>10 adenomas).	
HCC Risk	Low risk	Low risk	Depends on specific mutation. Highest risk

Unclassified (~10%) → None of the above.

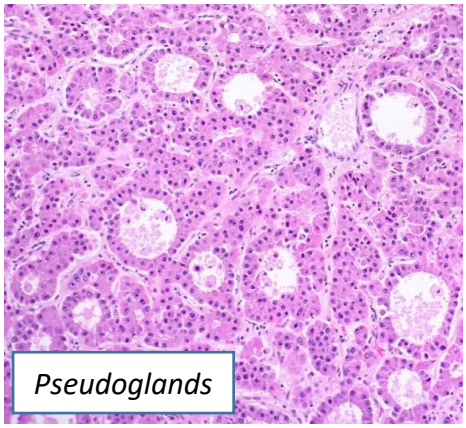
Hepatocellular Carcinoma



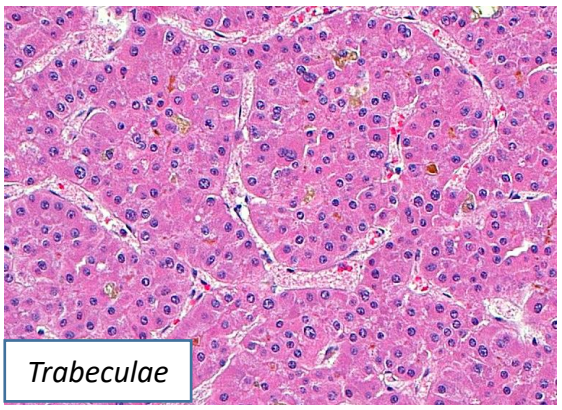
Malignant tumor with hepatocellular differentiation.
Often occurs in setting of **cirrhosis** (associated with chronic liver damage such as viral hepatitis, EtOH, and NASH)
Male predominance. Average age ~65yrs.

Dx often made *clinically* (Radiology + ↑ **AFP** = HCC)
Treat often with embolization, resection, or transplant

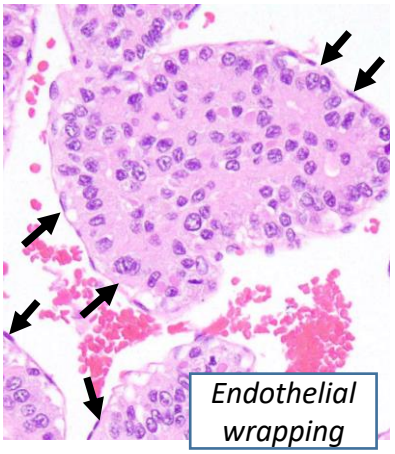
Loss of normal architecture: Widening of plates (>2 cells thick)
Absent portal tracts, often unpaired arteries.
Architecture and cytologic atypia varies and includes pseudoacini/pseudogland formation and wide trabeculae.
Often bile production by tumor cells.
Endothelial wrapping around tumor cell clusters.



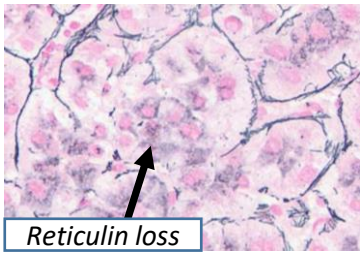
Pseudoglands



Trabeculae



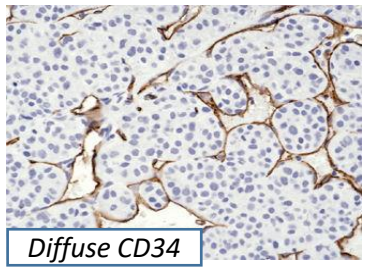
Endothelial wrapping



Reticulin loss

Stains: *(these stains are mostly helpful for supporting malignant vs benign liver lesions)*

Reticulin→ Widening of hepatic plates *(most important stain).*
Not every cell touches reticulin anymore→ > 2 cells thick.
Warning: fatty areas have physiologically decreased reticulin.



Diffuse CD34

CD34→ Diffuse sinusoidal ("capillarization") (normally just gets pericentral area)
Glypican-3→ +/- (Positive staining supports malignancy. Negative in benign)
Ki67→ significantly higher level than background liver supports HCC
AFP→ staining supports malignancy

Often negative stains:
MOC31 and CK7 → Strong/diffuse staining favors cholangiocarcinoma

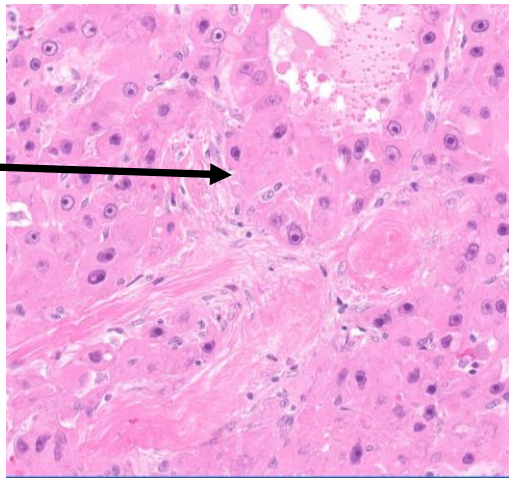
Metastatic <u>Mimickers</u> of HCC to consider:
Neuroendocrine tumor
RCC variants
Paraganglioma
Adrenal cortical carcinoma
(and Cholangiocarcinoma)

If in doubt, do Arginase, Hepar1, etc… to support hepatocellular differentiation

Grade	Findings
1 Well-differentiated	Closely resembles normal liver (mild atypia). Often requires stains to separate from adenoma/nodule.
2 Moderately-differentiated	Moderate atypia (malignant), but findings still suggestive of hepatocellular differentiation
3 Poorly-differentiated	Overt/marked atypia. Often requires studies to support hepatocellular differentiation

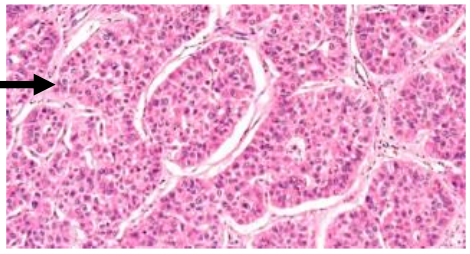
Subtypes:

Fibrolamellar HCC → Often young, non-cirrhotic patients. Normal AFP. Often large, solitary. Large oncocytic tumor cells with bands of lamellar fibrosis. Cytoplasmic pale bodies. Recurrent DNAJB1-PRKACA translocation. Stain with CD68 and CK7.
Classically thought to be better prognosis, but this is likely mostly due to demographics (younger, non-cirrhotic patients).



Steatohepatitic HCC → Assoc with Hep C with NASH.
Macrovesicular steatosis, ballooning degeneration, M-D bodies.
Can be hard to recognize on biopsy (esp. if background NASH)!

Macrotrabecular-Massive HCC → Thick trabeculae (usu. >10 cells) of poorly-differentiated cells coated by endothelial cells and surrounded by vascular space. Aggressive subtype with high AFP and TP53 mutations or FGF19 amplification.



Other subtypes: Clear cell→ >80% clear (glycogen-rich) cells
Scirrhous→>50% tumor has dense intratumoral fibrosis
Chromophobe→ Light, almost clear cytoplasm
Neutrophil-rich→ Numerous/diffuse neutrophils. Produce GCSF. Worse prognosis
Lymphocyte-rich→ more lymphocytes than tumor cells. Better prognosis.

What if you're having a hard time distinguishing between HCC and Adenoma on a biopsy?

Sometimes, on a small biopsy, there can be equivocal findings, such as equivocal reticulin loss, mildly increased Ki67 (above background), or some cytologic or architectural atypia (like focal pseudoglands).

Consider saying, "*Well-differentiated Hepatocellular neoplasm*" and explain what is limiting your Dx (e.g., fragmentation, small size, equivocal architectural changes). Also consider sending in consultation.

Dysplastic Nodule

Premalignant precursor lesions for HCC.
Found (almost) exclusively in **cirrhotic livers**.

More atypia than background liver, but not enough for Dx of HCC.
Stains: No reticulin loss (otherwise→ HCC)
May have focal Glypican 3

If microscopic (<1mm): Dysplastic foci

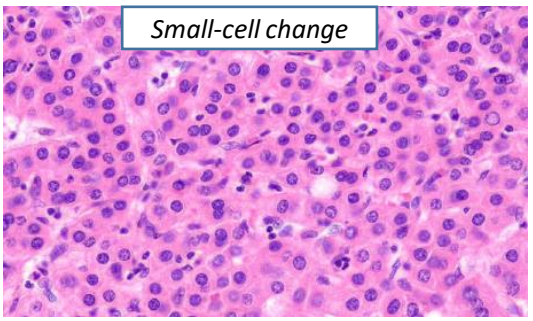
Small-cell change: Higher N:C ratio, decreased cell volume, cytoplasmic basophilia. Mild atypia.

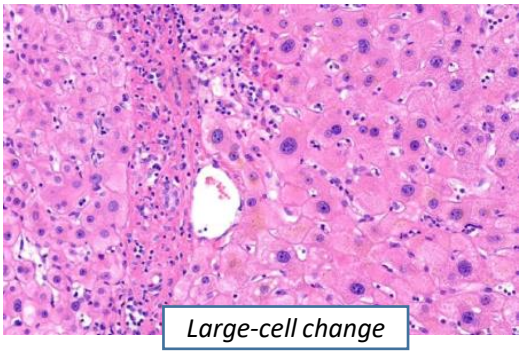
Large-cell change: Nuclear and cellular enlargement. Pleomorphism & hyperchromasia.

Can classify as Low or High-grade depending on level of atypia.

Only diagnose on resections as could be under sampled HCC!

Exist on a spectrum with macroregenerative nodule and HCC, so knowing when to "draw the line" can be challenging!





Hepatoblastoma

Most common malignant liver tumor in Children.
Usually single mass in kid ~2 years old.
Elevated serum AFP. Assoc. w/ Beckwith-Wiedmann.

Shows a variety of epithelial and mesenchymal cell types recapitulating hepatic ontogenesis.

Epithelial patterns:
Fetal→ thin trabeculae or nests of cells resembling hepatocytes with clear to eosinophilic cytoplasm.

Embryonal→ Solid nests or glandular/acinar structures with pseudorosettes and papillae. Scant basophilic cytoplasm. Big, coarse nuclei. More mitoses.

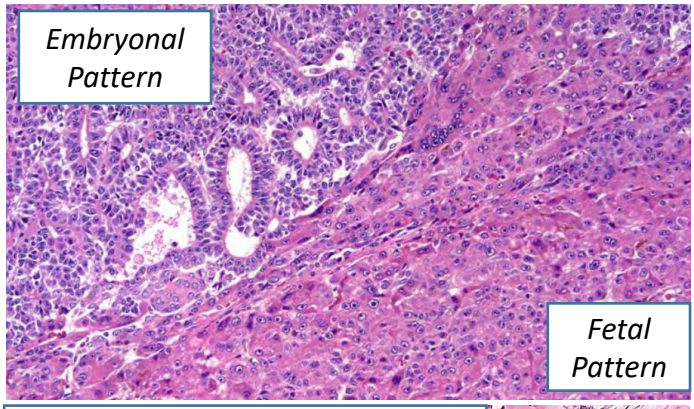
Small cell undifferentiated (SCUD)→ solid sheets of discohesive small cells wit abundant mitoses and necrosis. Can show loss of INI1→ worse prognosis.

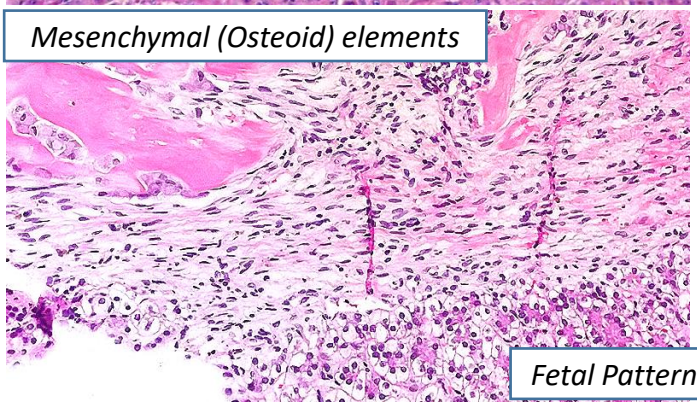
Mesenchymal ("teratoid") component include variably mature fibrous tissue, osteoid, and cartilage

Often associated extramedullary hematopoiesis.

Frequent WNT/ß-Catenin mutations
Nuclear localization by IHC→ worse prognosis

IHC: Glypican-3 often positive in all 3 main epithelial patterns. Hepar1 often negative in SCUD.





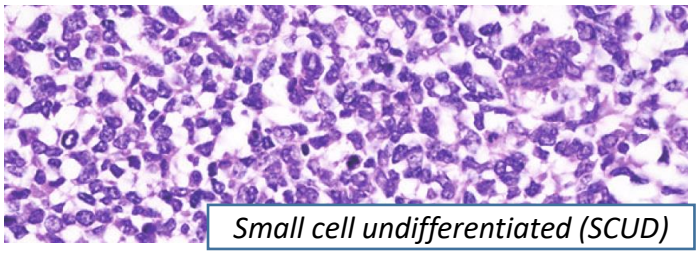


Table 2 Hepatoblastoma classification

Epithelial	
Fetal	'well-differentiated': uniform (10–20 μ in diameter), round nuclei, cords with minimal mitotic activity (<2 per ×10/400 microscopic fields), EMH[a] 'crowded' or mitotically active (>2 per ×10/400 microscopic fields); conspicuous nucleoli, less glycogen 'pleomorphic, or poorly differentiated' moderate anisonucleosis, high N/C, nucleoli 'anaplastic' marked nuclear enlargement and pleomorphism, hyperchromasia, abnormal mitoses
Embryonal	10–15 μ in diameter, high N/C, angulated nuclei, primitive tubules, EMH
Macrotrabecular	epithelial HB (fetal or embryonal) growing in trabeculae of >5 cells thick (between sinusoids)
Small-cell undifferentiated	5–10 μ in diameter, no architectural pattern, minimal pale amphophilic cytoplasm, round to oval nuclei with fine chromatin and inconspicuous nucleoli, +/− mitoses; +/− INI1[b]
Cholangioblastic	bile ducts, usually at periphery of epithelial islands, can predominate
Mixed	
Stromal derivatives	spindle cells ('blastema'), osteoid, skeletal muscle, cartilage
Teratoid	mixed, plus primitive endoderm; neural derivatives, melanin, squamous and glandular elements

[a]EMH, extramedullary hematopoiesis.
[b]Pure small-cell undifferentiated needs to be differentiated from malignant rhabdoid tumors (discohesive, eccentric irregular nuclei, prominent nucleoli, abundant cytoplasmic filaments including cytokeratin and vimentin, negative nuclear INI).

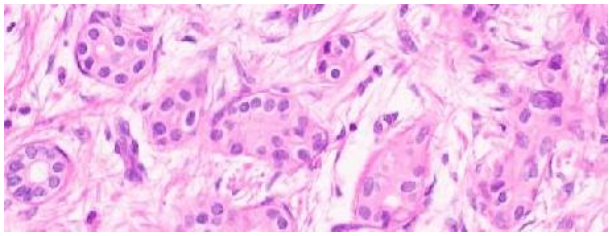
From: López-Terrada et al. Modern Pathology. 2014 PMID: 24008558
Check out the article for more info on classification, including IHC, etc..

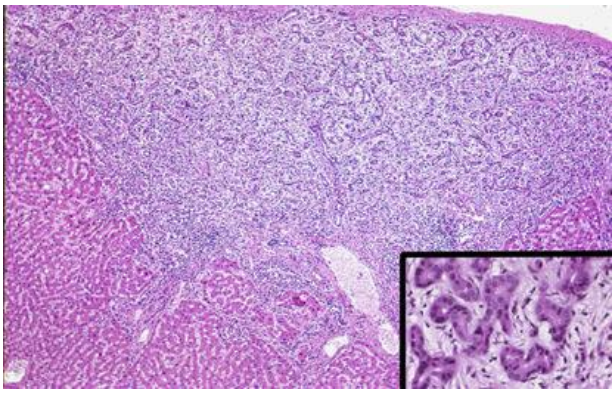
Biliary Lesions

Note: The epithelium in <u>all</u> of these lesions stain with CK7, CK19, and MOC31 (among other stains). These lesions are negative for hepatocellular stains (Hepar-1, Arginase, and Glypican-3).

Bile Duct Adenoma

Benign bile duct neoplasm.
Usu. <1 cm, <u>subcapsular</u>, and <u>well-circumscribed</u>.
Small, uniform, normal-looking small ducts with cuboidal cells and regular nuclei. No or modest lumens.
Clinically, may mistake intraoperatively for a metastasis

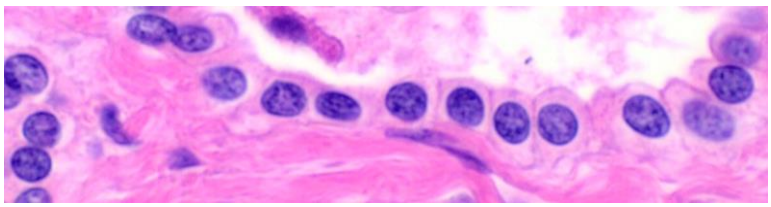


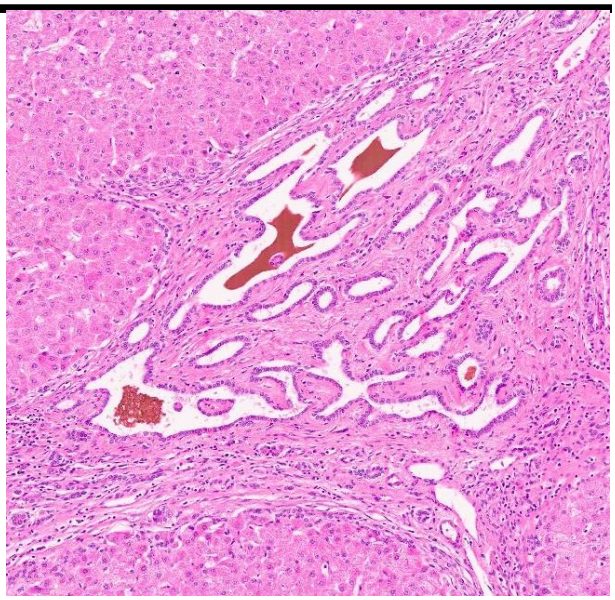


Frequent BRAF V600E mutations.

Bile Duct Hamartoma
aka Von Meyenburg Complex

Benign, may be multiple. Usu. small (several mm)
Irregular to round interanastamosing bile **<u>dilated</u> <u>bile ducts</u>**
Associated with **fibrous/hyalinized stroma**
Lumens **contain bile** and proteinaceous material.
Lined by bland, often attenuated, biliary epithelium.
Increased in Adult Polycystic Kidney Disease.



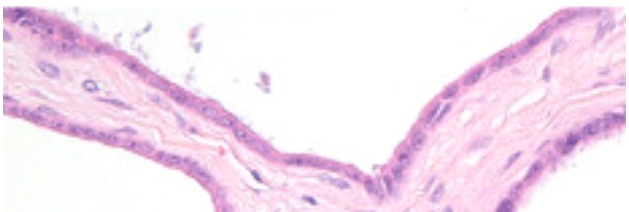


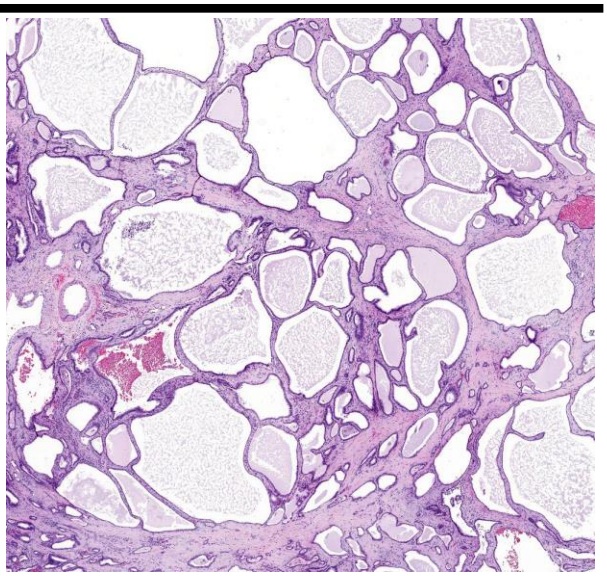
Biliary adenofibroma

Rare! Risk of malignant transformation.
Microcystic and tubuloacinar glandular structures lined by non-mucin-secreting biliary epithelium set within fibroblastic stroma.

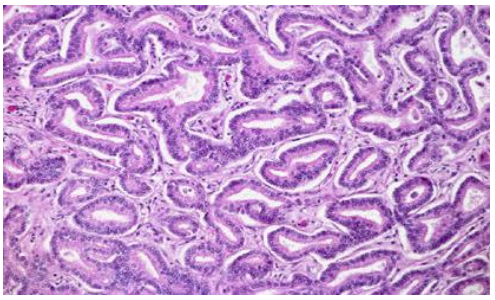
Can see superimposed dysplasia/proliferation.

Think: Looks like a BIG (often >2cm) bile duct hamartoma.



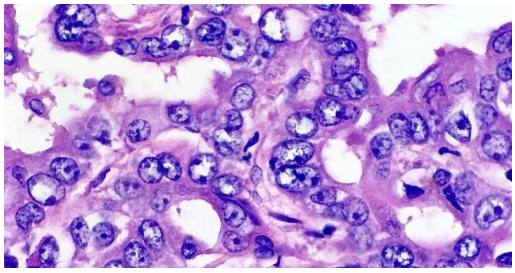


Intrahepatic Cholangiocarcinoma



Adenocarcinoma arising from intrahepatic bile ducts
Must **clinically distinguish from metastasis as considerable morphology and IHC overlap.**

Ductal or tubular pattern of growth of cuboidal to columnar cells set in desmoplastic fibrous stroma with variable lumen formation.



Two main pathways/types:
Large duct type: Arises near hilar region.
Risk factors: PSC & liver flukes *(→ BilIN)*

Small duct type: Arises peripherally.
Risk factors: Cirrhosis, hepatitis.

Non-specific IHC profile, but (+) Albumin ISH supports intrahepatic

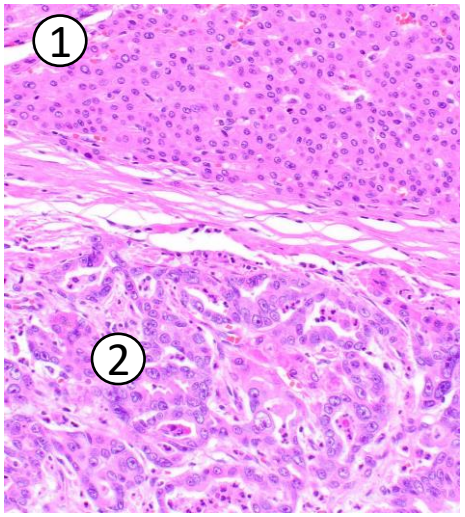
Combined Hepatocellular - Cholangiocarcinoma

A single biphenotypic tumor with *distinct, separate* areas of 1) hepatocytic and 2) cholangiocytic differentiation based on H&E morphology.

Expression of IHC markers alone is *not* sufficient.

Treated and prognosis similar to cholangiocarcinoma (Worse than HCC, No transplantation).

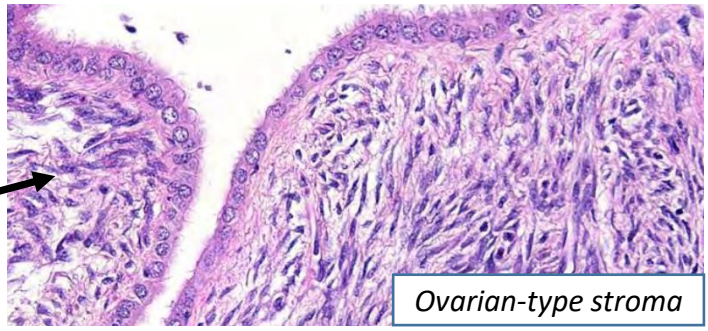
Some tumors are composed of one cell type with intermediate features (IHC and morphology) and are called "intermediate cell carcinoma."



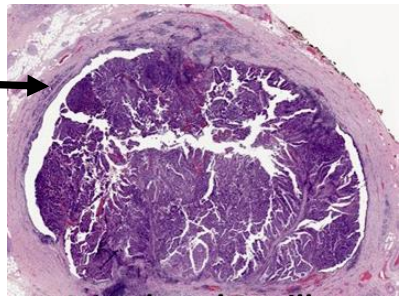
Additional Tumors (that you also see in the pancreas):

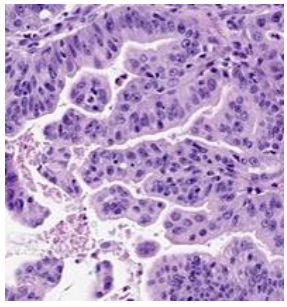
Both of these can have superimposed dysplasia and progress to carcinoma. So, make sure they are sampled well to exclude malignancy.

Mucinous Cystic Neoplasms:
Ovarian-type stroma surrounding mucinous epithelium. Multilocular cystic with no communication to ducts. Lined by cuboidal cells. Almost exclusively in women. Ovarian stroma stains with Inhibin, ER



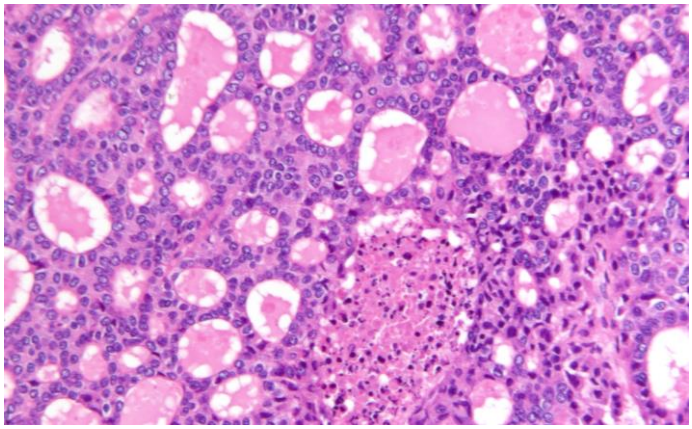
Intraductal Papillary Neoplasms:
Grossly visible, papillary, villous, or polypoid lesions growing in the bile duct lumen.





Biliary intraepithelial Neoplasia (BilIN):
Microscopic, non-invasive lesions with low to high-grade dysplasia.

Cholangioblastic cholangiocarcinoma



(This is a newer entity that isn't in the WHO yet)
Usually **younger women** with large liver mass.
Relatively **indolent**. Normal background liver.

Tubulocystic architecture.
Monotonous, neuroendocrine-like cytology

IHC: (+)CK7, **Inhibin**, Albumin ISH
(±)focal synaptophysin (pitfall!)

Molecular: **NIPBL::NACC1 fusion**

Hepatic Ductular Lesions DDX

Can be a hard DDX, particularly on Frozen!

	Adenocarcinoma *(cholangiocarcinoma or pancreatic)*	Bile Duct Hamartoma	Bile Duct Adenoma	Benign Ductular Proliferation
Gross	Variable. Usually larger (primary cholangiocarcinoma) or multiple (metastasis).	Single or few discrete nodules, related to portal tracts.	Subcapsular. Single. <1cm.	Small, related to portal tract.
Circumscription	Infiltrative: PNI, infiltrates hepatic plates	Circumscribed	Circumscribed (wedge or round)	Ill-defined
Duct distribution	Ductules distributed irregularly	Regular	Regular	Scattered ducts, mostly stroma
Regularity	Variably shaped ductules	Dilated, branched	Mostly uniform	Vaguely lobular or linear
Bile in ducts?	No	Yes	No	Maybe
Atypia	Present (4:1, hopefully!)	Absent	Mild	Mild
Stroma	Fibroinflammatory (desmoplastic)	Dense collagen	Hyalinized or cellular	Inflamed stroma with collagen

Mutant p53 and/or Ki67 >10% favors an adenocarcinoma.
BRAF V600E stain can be positive in many Bile duct adenomas.

Based on a talk by Dr. Rhonda Yantiss, USCAP 2015. Annual meeting
And a Table in the WHO Classification of Digestive System Tumors, 2019.

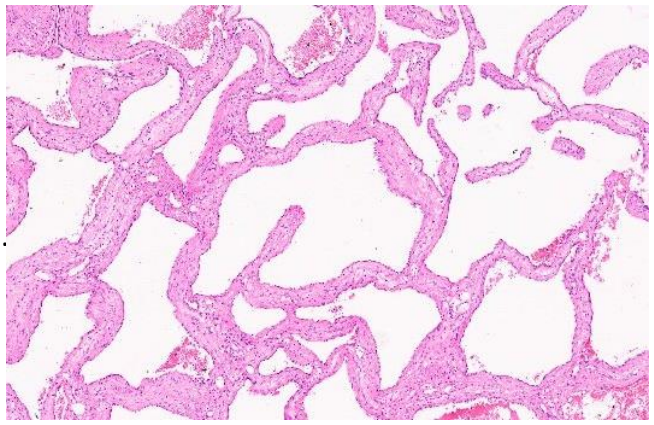
Cholangiocarcinoma IHC:
These tumors have a relatively non-specific IHC profile, so close clinical correlation is necessary.
(+): CK7 (~90%), CK19 (~90%), MOC31, cytoplasmic polyclonal CEA, Albumin ISH (~80%).
(+/-): CK20 (often patchy), CDX2,
(-): Hepar1, Arginase, Glypican-3 *(these being positive strongly favors HCC)*

Some warnings: Rare cholangiocarcinomas can stain with TTF1 and Napsin.
Some Met's can stain with Albumin ish. Nothing is 100%!

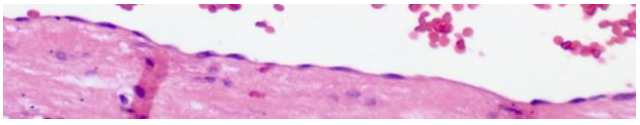
Vascular Lesions

Note: <u>All</u> of these lesions stain with endothelial markers, including CD31, ERG, and FLI-1.

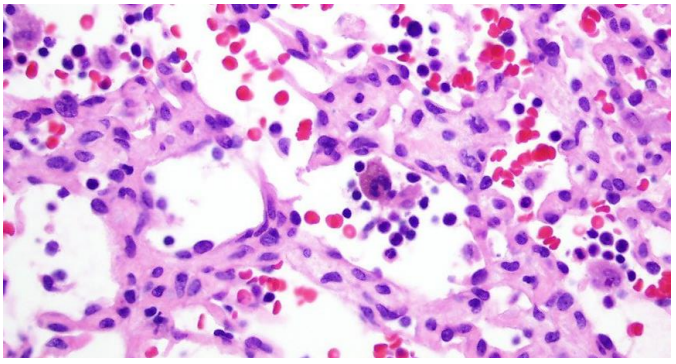
Cavernous Hemangioma



Most common tumor of the liver.
Thought to be malformations and non-neoplastic.
Often asymptomatic and diagnosed radiographically.
More common in females.
Fibrous septae lined by single layer for flat endothelial cells.
Can thrombose, sclerose, and calcify.

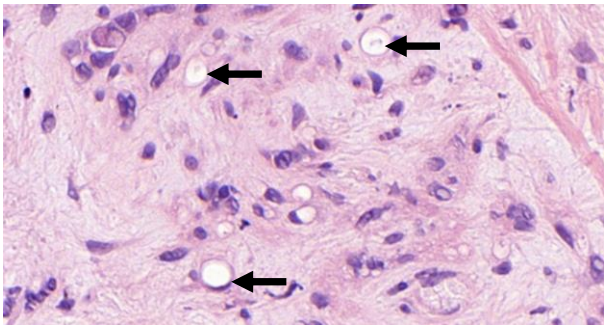


Anastomosing Hemangioma



Rare. Benign. *(warning: angiosarcoma mimic!)*
Tightly-packed capillary-sized, anastomosing vessels.
Hobnail endothelial cells.
Frequent thrombi, hyaline globules, and extramedullary hematopoiesis.
<u>Not</u> allowed (otherwise consider angiosarcoma):
Significant atypia, multilayer, mitoses, necrosis.

Epithelioid Hemangioendothelioma

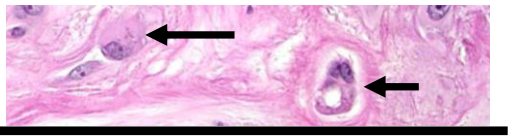


Low-grade malignancy. Usually middle aged.

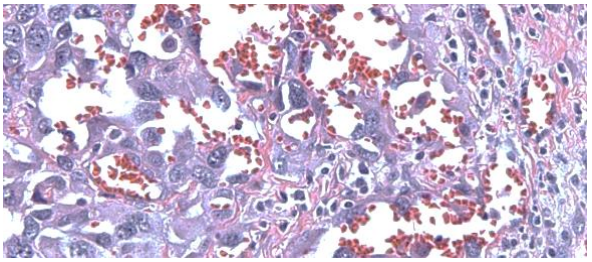
Eosinophilic, slightly epithelioid, **signet ring-like** "blister" cells → represent intracytoplasmic lumina (often contain RBCs). **Associated myxoid to fibrous stroma.**

Often multifocal & infiltrative. Non-cirrhotic.

Molecular: **WWTR1-CAMTA1 fusion.** Less often YAP1-TFE3.
Sometimes focally positive for cytokeratins by IHC

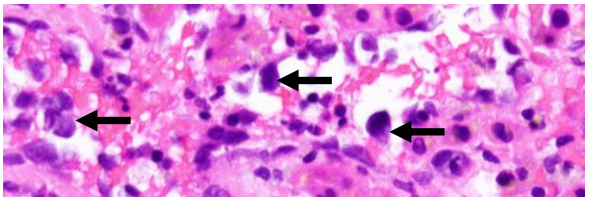


Angiosarcoma



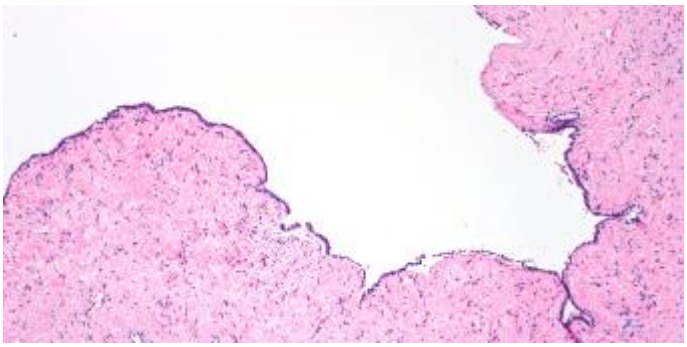
<u>Malignant</u> endothelial tumor. Most common liver sarcoma.
Usually **large and/or multifocal**. Very bad/aggressive.
Can be mass-forming or non-mass forming.

Spindled to epithelioid cells. Variably **atypical** endothelial cells with **multilayering and mitoses**.
Variable vasoformation (can be solid, form anastomosing spaces, or grow subtly through sinusoids →).
Like to grow along pre-existing vascular spaces.
Assoc. with exposure to Vinyl Chloride or Thorotrast.



Other Lesions

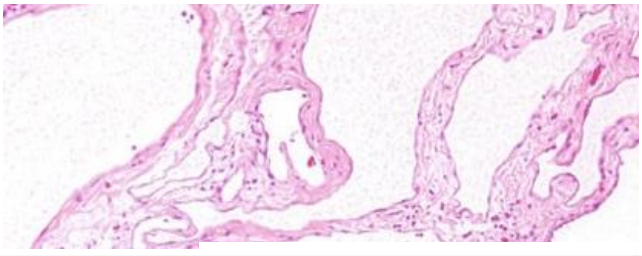
Simple (Solitary) Biliary Cyst



Most common hepatic cyst. Female predominance.
Lined by a single layer of cuboidal to columnar biliary epithelium overlying fibrous tissue.
No ovarian-type stroma (unlike MCN)

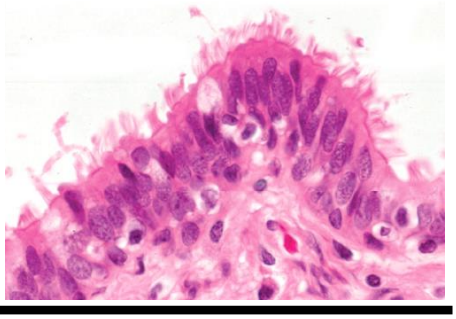
Usually small, unilocular, subcapsular, and asymptomatic. Do not communicate with ducts.
Multiple associated with polycystic kidney disease.

Mesothelial Cyst



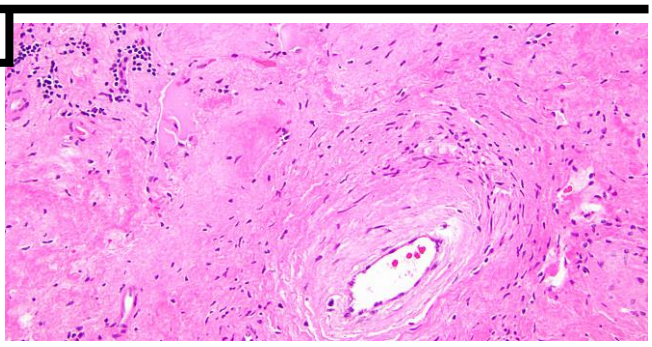
Lined by mesothelial cells.
Highlight with IHC: D2-40, WT-1, Calretinin
Always subcapsular.
Usually hilar location.

Ciliated Hepatic Foregut Cyst



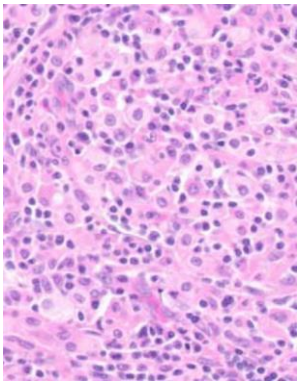
Lined by ciliated columnar epithelium.
Cyst wall contains smooth muscle.
Presumed embryonic foregut remnant (like bronchogenic cyst).
Usually subcapsular and relatively small.

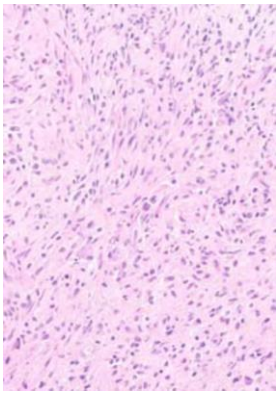
Segmental Atrophy and Nodular Elastosis



Benign pseudotumor resulting from vascular injury impacting a segment or subsegment.
Usually subcapsular.
Morphology varies over time:
Parenchymal collapse→ Elastosis → fibrosis.
During collapse phase, may see residual liver tissue.

Inflammatory Pseudotumor





Benign. Can be single or multiple.
Male predominance.

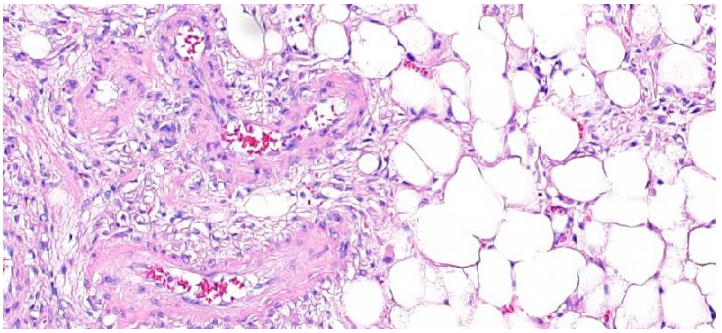
Fibrotic mass-forming inflammatory lesions.
Often thought to be infection related, with most representing healing abscesses.
Lymphocytes, plasma cells, fibroblasts, histiocytes.

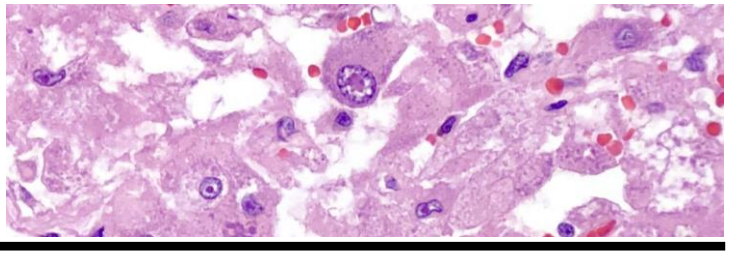
Other clinical associations: Biliary tract obstruction, Syphilis, IgG4 disease.

Angiomyolipoma

PEComa subtype.

Nearly always benign in the liver.
Think of this if you see **fat**.
Variable admixture of fat, smooth muscle, and thick-walled blood vessels.
Epithelioid and/or spindled cells with granular eosinophilic to clear cytoplasm, nested to trabecular growth.
Associated with tuberous sclerosus.
Variable expression of smooth muscle and melanocytic markers
IHC: (+)CathepsinK, HMB45,
(+/-) SMA, MelanA, CD68, S100, CD117
Warning: Epithelioid ones can mimic HCC! →





Embryonal Sarcoma of the Liver

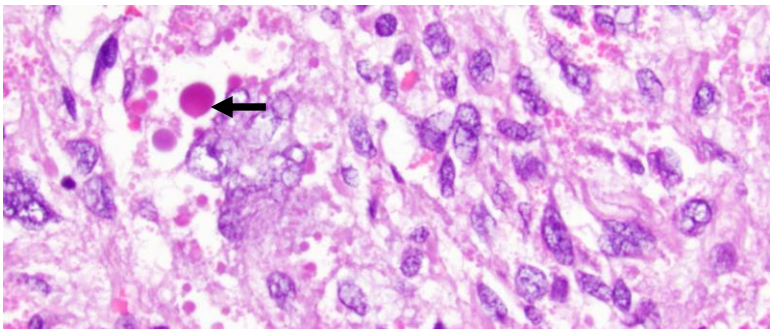
Malignant. Rare. Usu. older <u>children</u>.

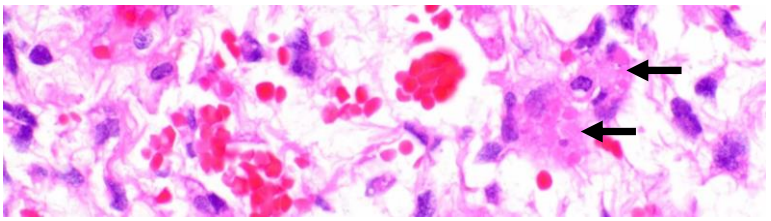
Undifferentiated mesenchymal cells: spindled, stellate, and pleomorphic giant cells loosely arranged in myxoid stroma. Lots of mitoses.

Characteristic <u>eosinophilic intracellular hyaline globules</u> (PAS+ →).

IHC: Non-specific. Limited CK, Desmin, etc.

Previously bad prognosis, but improving.



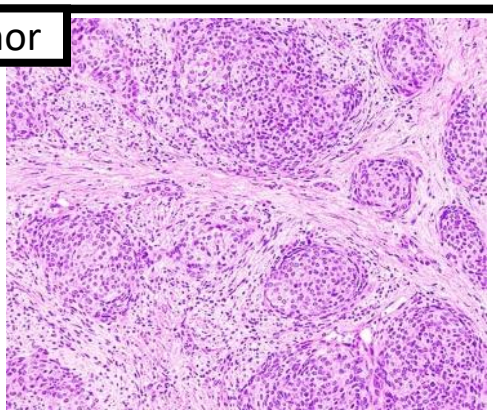


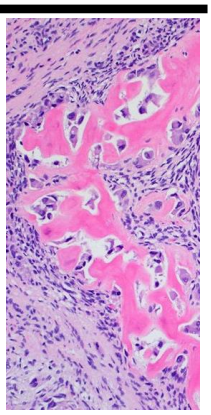
Calcifying nested stromal-epithelial tumor

Rare. Benign/Low-grade.

Bland and uniform epithelioid and spindled cells. Nested architecture surrounded by cellular myofibroblastic stroma and psammomatous calcifications and ossification.

IHC: CK, WT-1, CD56, nuclear β-catenin.





Mesenchymal hamartoma of the liver

Rare. Benign developmental abnormality.
Kids, usually presenting before 3 yrs.
Multicystic loose connective tissue mass accompanied by a ductular component in lobulated islands.
Ductal plate malformation-pattern.