# Primary Mesenchymal Tumors of the Liver in Children

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## Primary Hepatic Tumors in Children

- **Rare**
- **1%-4%** of all solid pediatric tumors
- In USA there is a frequency of **1.9** malignant hepatic tumors per million per year
- Benign tumors are less frequent

## Primary Hepatic Tumors in Children (Total: 309)

Children's Hospital Boston
1918-2015

| | |
|---|---|
| • **Epithelial** | 70% |
| • **Mesenchymal** | 30% |
| – Hemangioma | 13% |
| – Mesenchymal Hamartoma | 6% |
| – Embryonal Sarcoma | 3% |
| – Other | 8% |

## Mesenchymal Tumors

- Most Hemangiomas, and Mesenchymal Hamartomas **under 2 years**
- 95% of Hemangioma **under 1 year**
- Embryonal Sarcoma in **older children**

## Mesenchymal Tumors

- Mesenchymal Hamartoma
- Angiomyolipoma
- Smooth muscle tumors
- Inflammatory myofibroblstic tumor
- Rhabdomyosarcoma
- Rhabdoid tumor
- Nested stromal-epithelial tumor
- Embryonal sarcoma
- Vascular
  - Hemangioma
  - EHE
  - Angiosarcoma
  - AVM
  - VM
- Other

## Mesenchymal Hamartoma

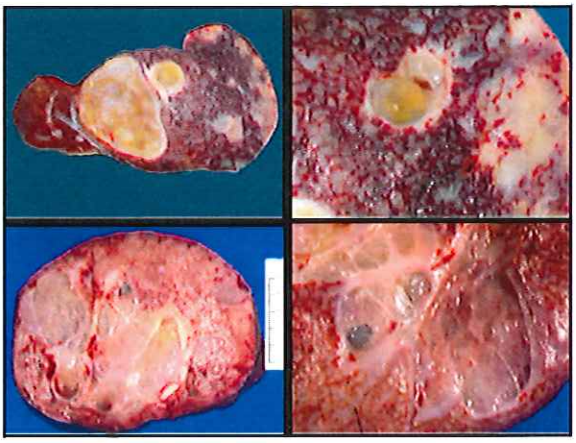
- Benign tumor that develops before birth and presents in young children (**average 15 mo**)
- M:F - **2:1**
- Rarely adolescents or young adults, less than 5% after the age of 5 years

## Mesenchymal Hamartoma

- Present as **abdominal mass**, respiratory distress, anorexia, vomiting, FTT
- Arteriovenous shunts may lead to heart failure
- It may be associated with **placental mesenchymal dysplasia**
- Prenatal detection by ultrasound is not uncommon
- Alpha fetoprotein might be elevated

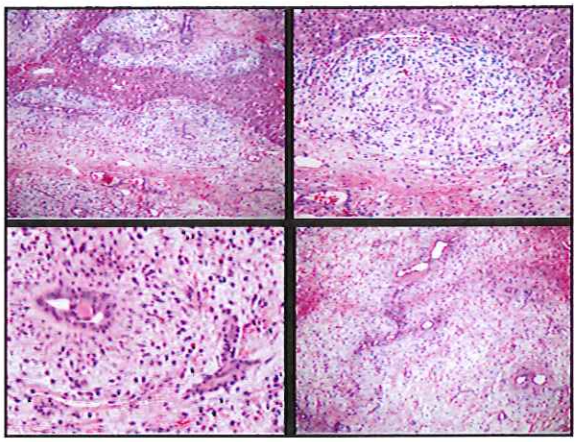
## Mesenchymal Hamartoma

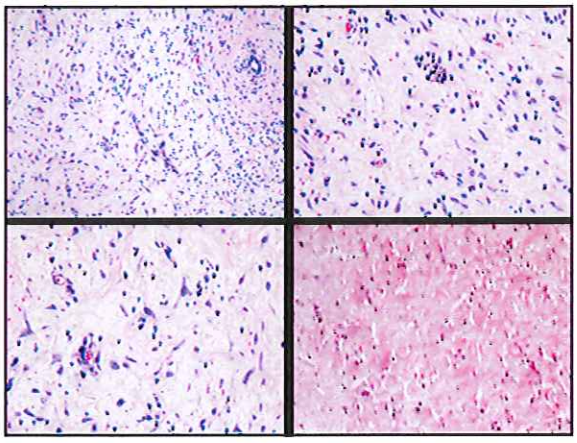
- Large **solid & cytic** mass, more often in the right lobe
- Large tumors may involve nearly the entire liver making excision challenging
- Solid areas are **soft**, **myxoid**, **white-yellow-tan**, **fibrous**
- Cysts contain **fluid** or **mucoid** gelatinous material

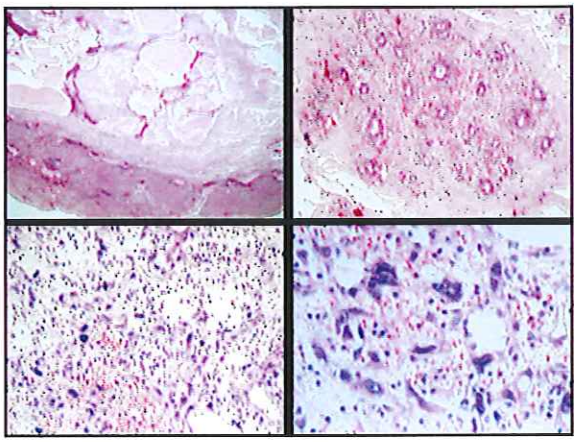


## Mesenchymal Hamartoma

- Primitive loose and myxoid **connective tissue**
- Malformed **portal tract-like structures** with primitive myxoid stroma
- Tortuous **bile ducts** and nests of **liver cells**
- **Cysts** lined by bile duct epithelium do not communicate with the biliary tree
- Dilated **vessels** and **fluid filled spaces**
- **EMH** is common







## Mesenchymal Hamartoma

- **19q13.4** rearrangement (MHLB1, mesenchymal hamartoma of the liver breakpoint 1)) usually with a balanced translocation **t(11;19)(q13;q13.4)**
- **Undifferentiated (embryonal) sarcoma** arising in mesenchymal hamartoma has been reported
- Surgical **excision** of MH is curative

## Angiomyolipoma

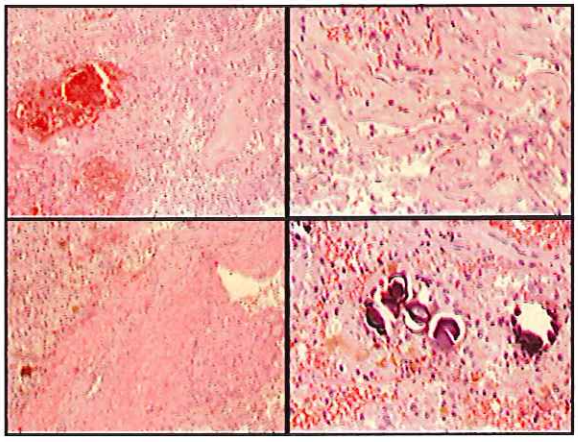
- **Rare** in children – over 10 years of age, female predominance
- 5-10% are associated with **tuberous sclerosis** multiple, coexistent with renal tumors
- Most are **asymptomatic** and found incidentally. Large ones may cause **epigastric pain** or may rupture leading to **hemoperitoneum**

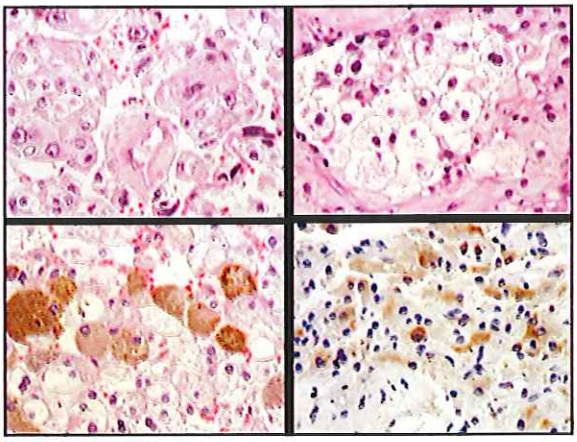
## Angiomyolipoma

- **Benign** tumor (malignant forms are extremely rare)
- Usually **single** and **variable in size** from less the 1 cm to 40 cm
- Well-circumscribed but not encapsulated
- Firm and fleshy with areas of hemorrhage or necrosis

## Angiomyolipoma

- Mixture in variable proportions of
  - only diagnostic component **smooth muscle cells** are usually sheets of **epithelioid cells**, occasionally bundles of **spindled cells**
  - **thick-walled blood vessels** sometimes hyalinized
  - **adipose tissue**
- Melanogenesis
- Foci of **hematopoiesis** may be present



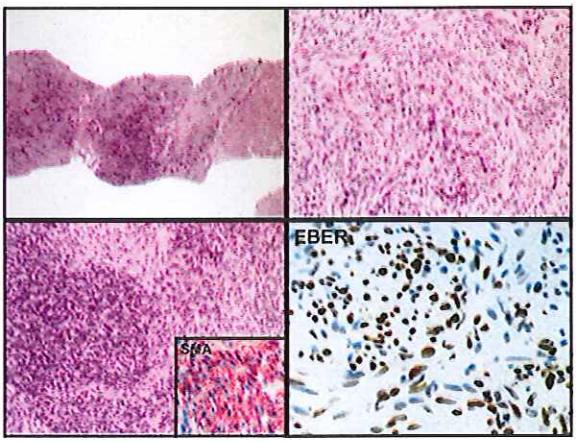


## Angiomyolipoma

- The vascular component may mimic a **vacular malformation**
- Nuclear enlargement, pleomorphism and hyperchromatism **may mimic HCC or sarcoma**
- Myoid cells are **HMB45+**, **Melan A+**, CD117+, SMA+
- Regarded as a tumor of perivascular epithelioid cells (**PECOMA**)

## EBV-Associated Smooth Muscle Tumors

- **Rare**, typically in **children** in the setting of **immunodeficiency**
- No consistent staining for EBV receptor (**CD21**) in tumor cells
- **All tumor cells** are infected, adjacent normal smooth muscle

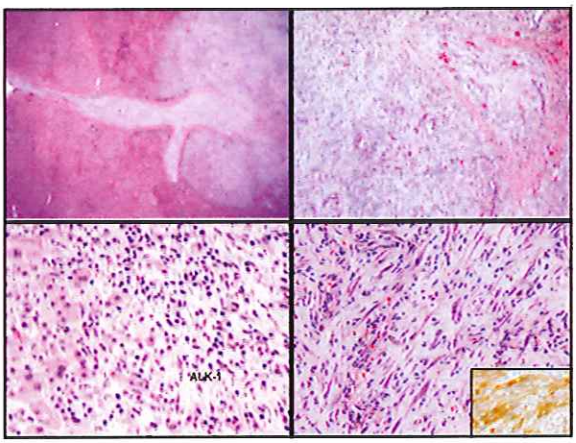



## Immunodeficiency-Related Smooth Muscle Tumors

- **Multifocal** (meta- or synchronous) not uncommon
- Multiple **independent clones** (no mets)
- **Donor** (lung) and **recipient** (liver) origin shown in a heart & lung tx patient
- EBV latent gene expression similar to PTLD – **Growth Program** (EBNA-1, EBNA-2, LMP-1, LMP-2A)

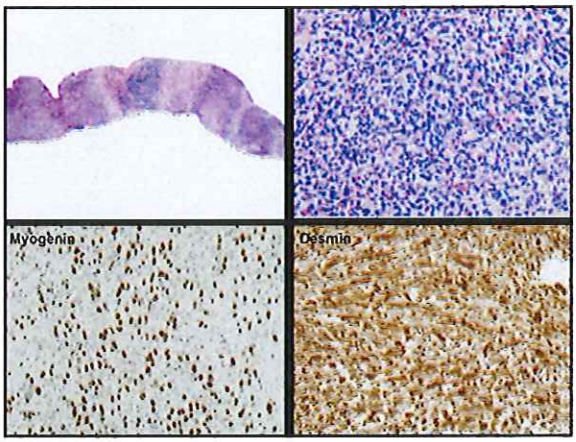
## Inflammatory Pseudotumor

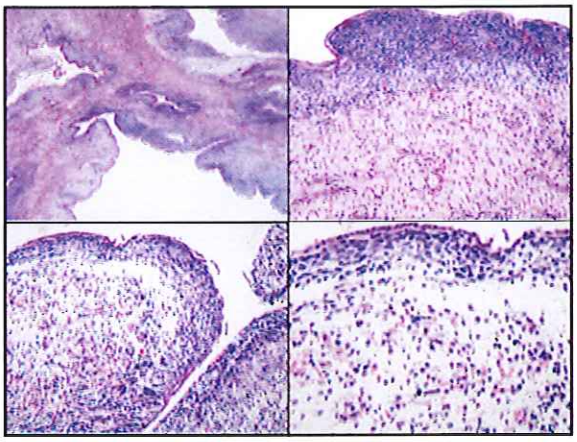
- Plasma cell granuloma, fibroxanthoma, pseudolymphoma
- Benign, non-neoplastic lesion composed of **myofibroblasts** and **inflammatory cells**
- Recurrent fevers, weight loss, abdominal pain




## Rhabdomyosarcoma

- Usually arises along the biliary tract
- Embryonal type rhabdomyosarcoma (Botryoid)
- Most common tumor of the biliary tract in children (1% of rhabdomyosarcomas)
- They may secundarily involve the liver



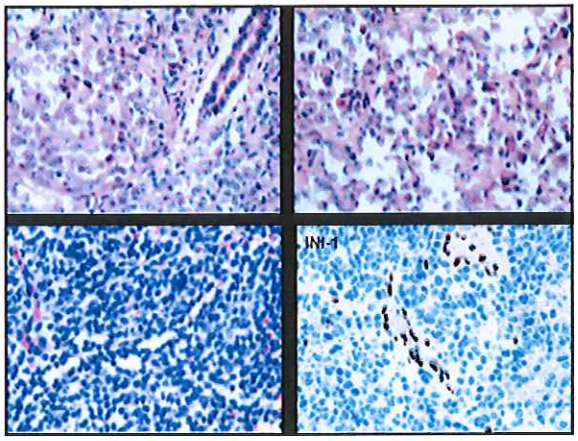


## Embryonal Rhabdomyosarcoma of the Biliary Tract

- 9 Children (1.5 – 5.5 years old)
- Obstructive jaundice
- Fever and hepatomegaly
- 3 extended into the liver parenchyma
- All had botryoid architecture

## Rhabdoid Tumor

- All cases occur **under 1 year** of age.
- Similar to the **renal** or soft tissue rhabdoid tumor of infancy or the ATRT of the CNS
- Highly aggressive neoplasm
- Mutations of the Chromatin Remodelling Complex **SWI/SNF**
- **SMARCB1** mutations



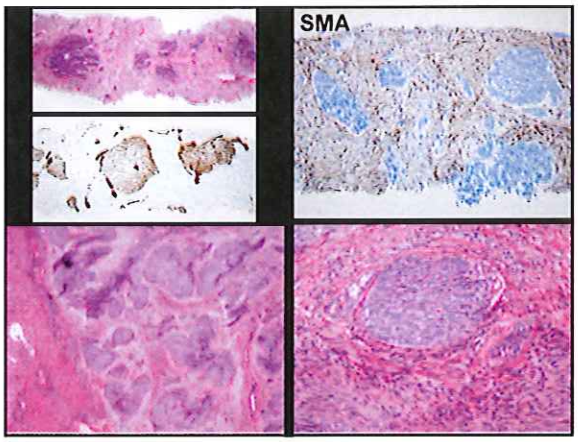


## Nested Stromal-Epithelial Tumor

- 1st-2nd decade of life
- Presentation
  - Incidental calcified mass
  - abdominal mass
  - Cushing syndrome – ectopic ACTH production
- Low malignant potential with local recurrence but no metastasis

## Nested Epithelial-Stromal Tumor

- **Nests** of spindle & epithelioid cells with extensive **desmoplasia**
- Low mitotic count
- Calcification and Ossification
- **Bile ducts** around or within the nests
- Vim, CK, CD57, WT1 (nuclear), ACTH



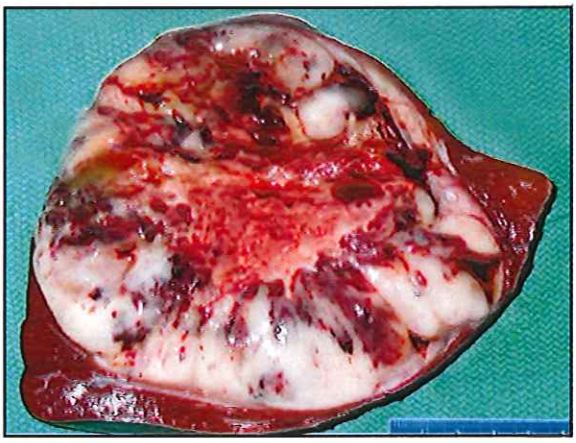

## Embryonal Sarcoma

### Clinical Presentation

- Primarily Children **6-10 years** (>50%)
- Abdominal **pain or mass**. Anorexia, vomiting, lethargy, and malaise.
- Rupture may occur
- Cardiac murmur (Extension into inferior vena cava and heart)
- **Li-Fraumeni** Syndrome
- Usually **normal AFP**

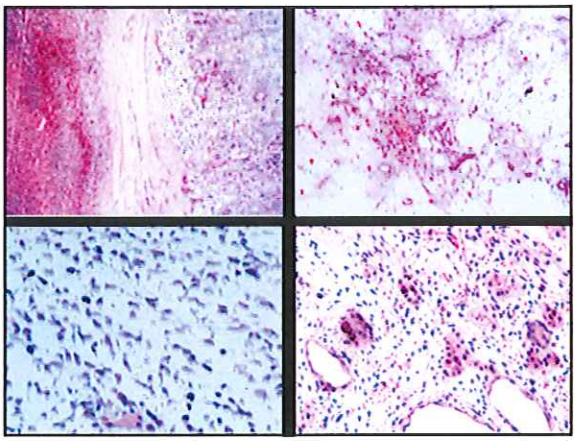
## Embryonal Sarcoma
### Gross

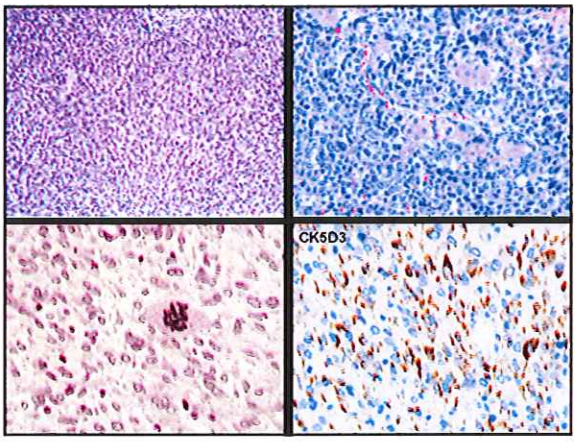
- Usually **right** lobe
- Usually **large** & single
- **Well-demarcated**
- Cut section soft, gelatinous areas, **solid & cystic**
- Areas of **necrosis** & **hemorrhage**

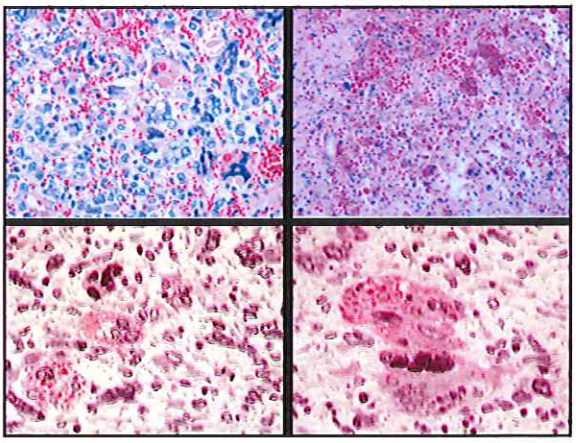


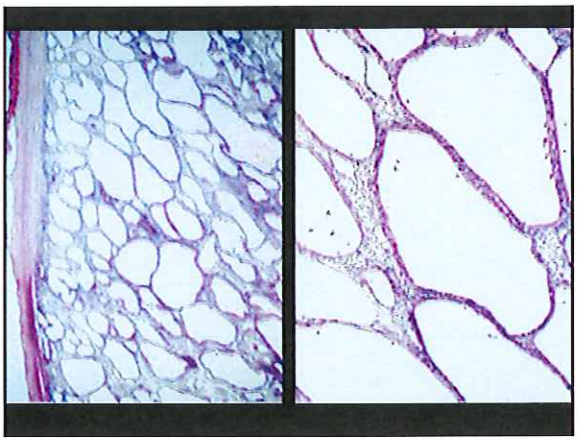
## Embryonal Sarcoma
### Light Microscopy

- **Pseudocapsule**
- Loose to dense whorls or sheets of **stellate** or **spindle-shaped** cells with ill-defined outlines in a **myxoid** stroma
- Bizarre **anaplastic multinucleated cells** often containing PAS+ diastase resistant **glubules**
- Frequent **mitoses some atypical**
- Entrapped normal appearing or reactive **hepatocytes** and **bile ducts** at the periphery
- **Hematopoiesis**




CK5D3





## Embryonal Sarcoma
### Cytogenetics

- Complex karyotypes
- Cases arising in Mesenchymal Hamartoma harbor **19q13.4** including t(11;19)
  - **MALAT-1** gene (11q13)
  - MHLB1 ? gene (19q13.4)
- Mutations of TP53

## Hepatic Vascular Lesions
### Children's Hospital Boston 1918-2003

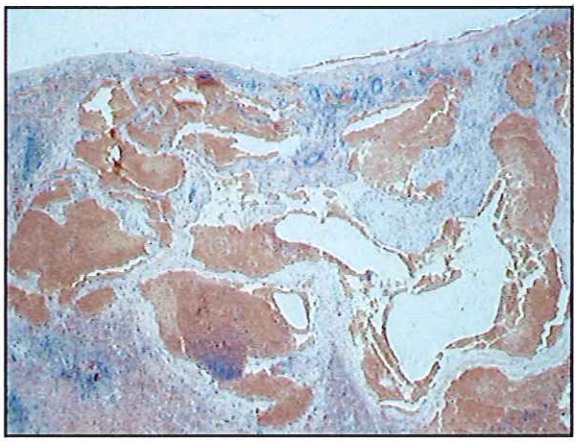
| | |
|---|---|
| • Hemangioma | 33 |
| • Arteriovenous Malformation | 3 |
| • Venous Malformation | 1 |
| • Vascular Lesion, *NOS* | 3 |

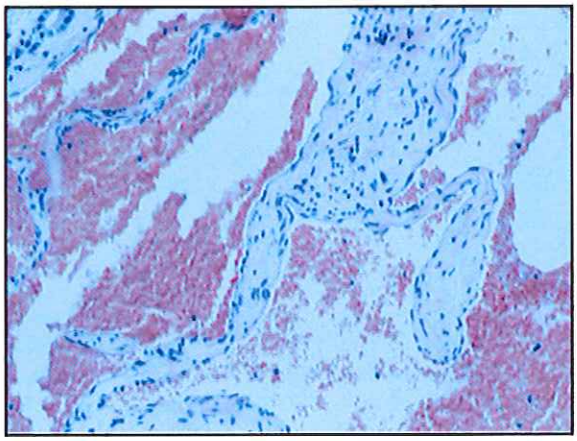
## Hemangioma

- **Uncommon**
- Vast **majority** hepatic vascular lesions
- Controversy exists over **nature** and **nomenclature**
- Major clinical and pathologic differences exist between **solitary** and **multiple** hepatic hemangioma

## Hepatic "Cavernous Hemangioma"

- Lesions typically in **adults**, especially women
- Most often **single** lesion 3-30cm
- Three small **incidental lesions** in our experience (12,16,22 years)
- Most have **thin-walled large channels** with flat (or modestly plump) endothelium
- Nature and nosology **controversial**



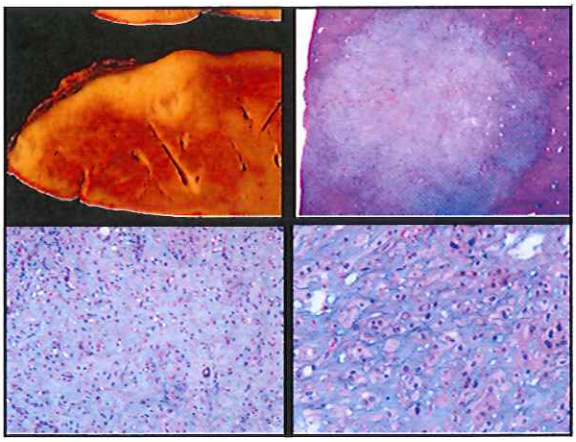


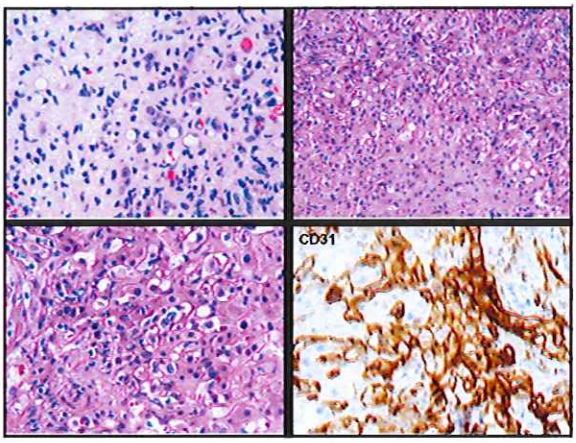
## Epithelioid Hemangioendothelioma

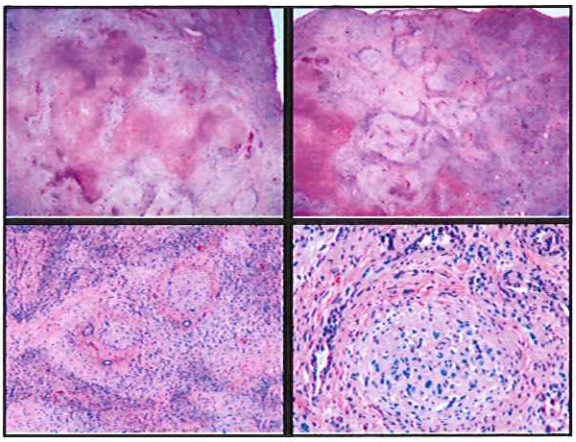
- **Distinctive** vascular tumor
- Association with **oral contraceptives**
- No gender predilection or more common in **females**
- 50% present with upper abdominal **pain** or **discomfort**, rarely with **jaundice**, **Budd-Chiari syndrome** or **liver failure**

## Epithelioid Hemangioendothelioma

- **Multiple**, often involving both lobes
- **Targetoid** appearance
- Infiltrate **sinusoids** and **veins**
- Cords or strands in **myxoid** or sclerotic stroma
- Plump cells with **acidophilic cytoplasm** often **vacuolated**
- **CD31+, CD34+**




CD31

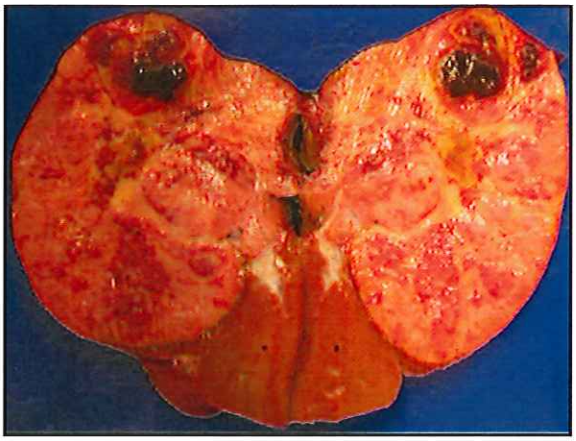


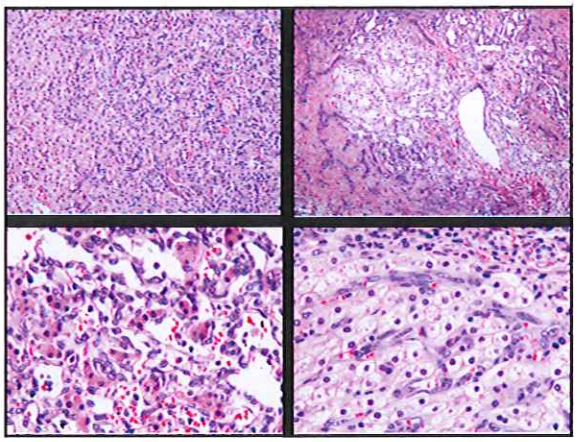
## Epithelioid Hemangioendothelioma

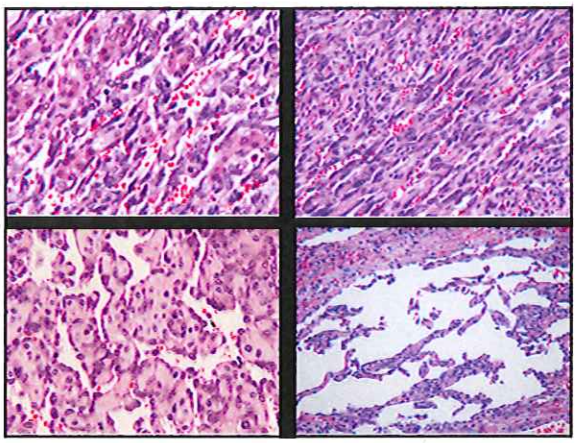
- **WWTR1-CAMTA1** fusion gene t(1;3)
- **Monoclonal** WWTR1-CAMTA1 from **different nodules** = metastatic spread, not multifocallity
- **YAPI-TFE3** in a subset of EHE with
  - voluminous cytoplasm
  - mild to moderate cytologic atypia
  - Vasoformative
  - Not yet described in EHE primary of the liver

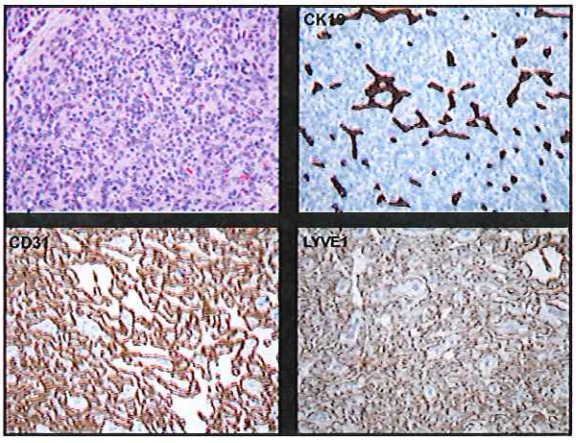
## Hepatic Angiosarcoma

- **Uncommon** lesion in childhood
- Literature difficult to assess
- Most lesions occur in the first few years of life **beyond infancy**
- In some cases, **hemangioma** seems to have been a **precursor lesion**
- Vascular tumors beyond infancy should be carefully assessed for the possibility of malignancy
- Usually **fatal** course



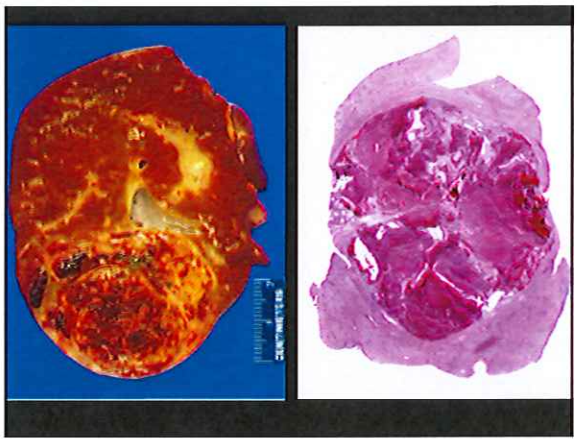


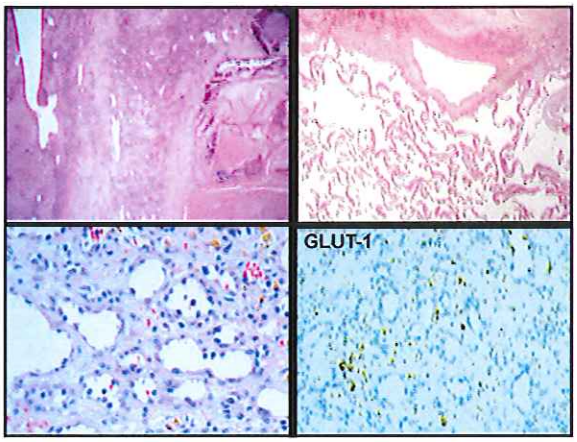



CK19
CD31
LYVE1

## Solitary Hepatic Hemangioma

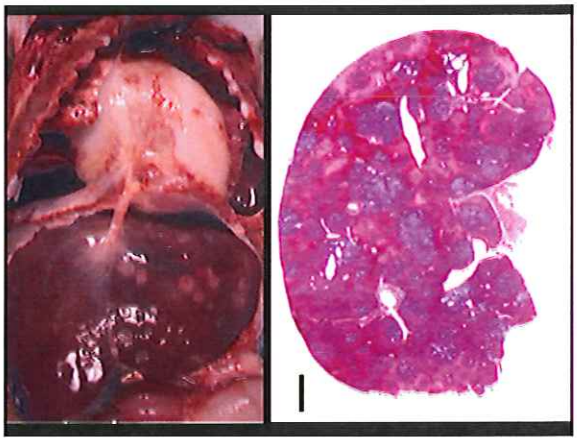
- Most detected at or shortly after **birth**
- Most have an early **intrauterine onset**
- Rarely **skin** hemangiomas
- Imaging usually diagnostic; **biopsy not required**
- Most are similar pathologically to **RICH**
- Lesions will **involute**
- Large shunts may require **embolization**
- ?Role for **anti-angiogenic** therapy in some

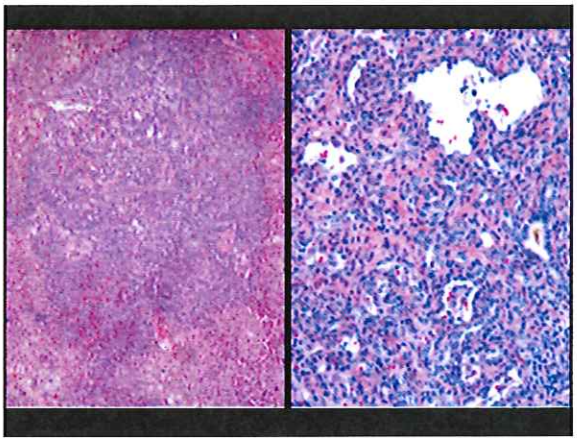


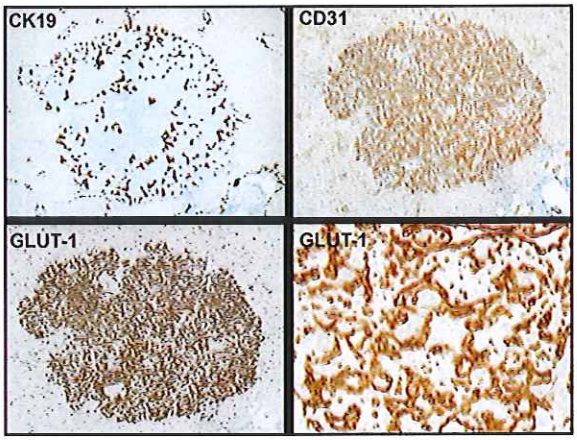


## Multiple Hepatic Hemangiomas

- Symptomatic infants usually present **beyond neonatal** period
- Most have hemangiomas in **skin** (or elsewhere)
- **Postnatal** onset
- Pathology shows **proliferative phase** hemangioma
- Eventual **involution** expected
- **Anti-angiogenic** agents often necessary
- Some tumors **refractory** to therapy
- Some express **type 3 iodothyronin deiodinase** - converts thyroid hormone to innative form - leading to **hypothyroidism**

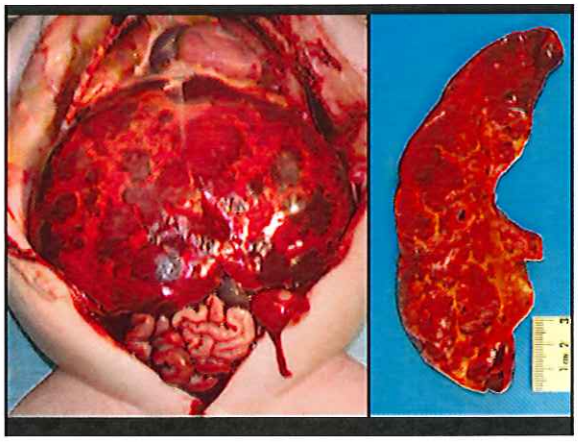


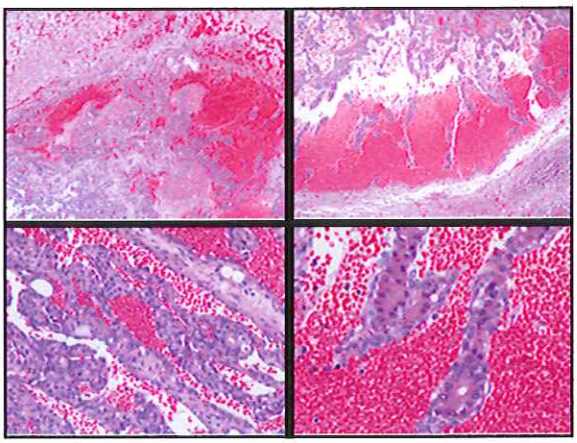


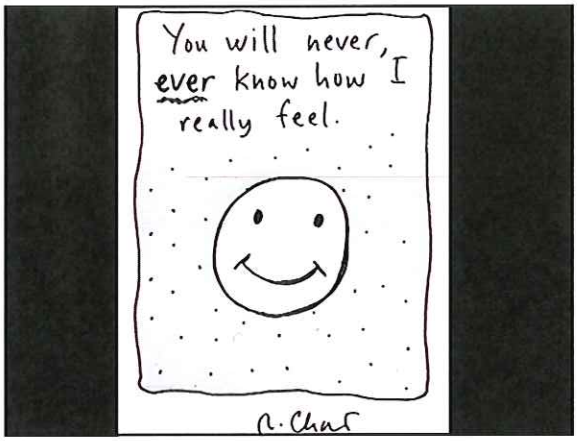



## Diffuse Hepatic Hemangiomas

- The liver is nearly totally replaced by larger nodules
- Abdominal **compartment syndrome**
- May arise from undetected multifocal
- Corticosteroids, hormone replacement, embolization
- All express **type 3 iodothyronin deiodinase** -converts thyroid hormone to innative form - leading to **hypothyroidism**






You will never, ever know how I really feel.