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
1912-2015

- Epithelial 70%
- Mesenchymal 30%
  - Hemangioma 13%
  - Mesenchymal Hemangioma 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 nodule/hibridic tumor
- Rhabdomyosarcoma
- Rhabdoid tumor
- Nested stromal-epithelial tumor
- Embryonal sarcoma
- Vascular
  - Hemangioma
  - ENLE
  - Angiosarcoma
  - AVM
  - VST
- 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 & cystic 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 fleshly 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 vascular 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 recplasm
- 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 – octopine 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 globules
- Frequent mitoses some atypical
- Entrapped normal appearing or reactive hepatocytes and bile ducts at the periphery
- Hematopoiesis
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 1916-2003

- 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 Hemangiendothelioma

- 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 Hemangiendothelioma

- 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+
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
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 iodothyronine deiodinase - converts thyroid hormone to inactive 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 inactive form - leading to hypothyroidism