Updates in Pediatric and Adolescent Liver Tumor Pathology for Pediatricians, Pathologists, and Surgeons

Anita Gupta, MD

Cincinnati Children’s Hospital, Department of Pathology

Abstract:

Liver tumors are rare in children. In the last several years there have been essential updates in the classification of hepatic hemangiomas, hepatoblastoma, and hepatic adenomas. Several symposium’s including Society of Pediatric Pathology, Children’s Oncology Group, and American Society of Pediatric Hematology Oncology have discussed the subtype classification and the development of a clinical practical algorithm. The goal of my talk today is to update pathologists, pediatricians, and surgeons in our audience today with the most recent histopathology classification of pediatric liver tumor pathology.

Key Words: hepatic hemangiomas, hepatic adenomas, hepatoblastoma, pediatric liver tumors

Hepatic Hemangioma can be divided into infantile and congenital hemangiomas. The term “Infantile hemangioendothelioma “ is no longer a term used within the International Society of Vascular Anomalies Classification. Hepatic hemangioma accounts for up to 12% of all liver tumors of which 80% present in the first 6 months of life with a female to male ratio: 2:1. Hepatic hemangiomas are mostly silent lesions maybe discovered on prenatal imaging.

Hepatic infantile hemangioma are much more common than congenital Hemangioma (CH) and usually a clinical diagnosis. The majority are single lesions, however, multifocal and diffuse lesions do occur. Multiple cutaneous lesion → suspect visceral involvement. Imaging may be needed to assess extension and depth of the lesion or to evaluate for visceral organ involvement (US and/or MRI preferred). With time, these lesions typically involute.

A small subset of infantile hemangiomas are symptomatic and may have
cardiac failure secondary to high volume shunting, abdominal compartment syndrome, or even fulminant hepatic failure. On histology, they lesions are composed of capillaries lined by plump endothelial cells with variable intervening stroma. These capillaries may be arranged in lobules more so at the periphery of the lesion. The central portion may have involutional changes and in addition anastomosing vascular channels with papillary fronds lined by plump endothelial cells may be present. Solid endothelial areas, spindling, and cytological atypia are worrisome for conversion into an angiosarcoma. Infantile hemangioma despite the degree of involution have endothelial cell immunoreactive to GLUT-1 (Glucose transporter 1 protein).

Multifocal Lesion Management is dependent from case and includes observation, pharmacotherapy, and embolization (shunts only). Diffuse Lesion Management in aggressive pharmacotherapy, aggressive treatment for hypothyroidism, and lastly even transplantation.

**Congenital Hemangioma** are single, solitary lesion, up to 15 cm in max. diameter. These lesions are fully developed at birth; post-gestation begins to involute. The are more common in girls and clinically they are typically silent found incidentally. These lesions are not associated with hypothyroidism; however they may be associated with mild anemia/thrombocytopenia. On imaging CAT scan shows multilobulated low attenuated mass with central hypodense areas and peripheral enhancement with calcification in 15% of the cases. Magnetic resonance imaging (MRI) is the best imaging study with specificity and sensitivity approximately 85% and 95%, respectively.

Congenital hemangiomas are divided in rapidly involuting, partially involuting, and non involuting subtypes. Most often in the liver we see rapidly or partially involuting. On histology, these lesions are single with central areas of fibrosis, calcification and necrosis. The periphery of the lesion is composed of varying sized lobules of capillaries lined by hobnailed endothelial cells. The center of the lobules have larger vascular channels. The center of the lesion has hemorrhage, necrosis, extramedullary hematopoiesis, fibrosis, and large arteries and veins which may even mimic a vascular malformation however the later does not demonstrate involutional histological changes, and intrinsically grows within the liver within the child/adult.

Treatment options for the majority is to observation alone. Approx. 25% symptomatic. Symptomatic individuals may have arterio-venous or porto-venous shunts resulting in congestive heart failure. Jaundice, tumor rupture with hemoperitoneum, and consumption thrombocytopenia (Kasabach – Merritt syndrome) and fetal hydrops. Indications for intervention include
symptoms, complications, and inability to exclude malignancy; pharmacotherapy or embolization

***Adult Hepatic “Hemangioma” do not exist, these are venous malformations***.

**KEY POINTS/UPDATES HEPATIC HEMANGIOMAS**
- Diffuse hepatic infantile hemangioma may be associated with hypothyroidism: treat hypothyroidism symptoms improve
- Hepatic infantile hemangioma mostly involute with time, close radiology follow up, and on histology GLUT-1 positive
- Not all hepatic hemangiomas are the same
- Not all hepatic “hemangiomas” are hemangiomas
- There is *no such thing* as a hemangioendothelioma in the liver of an infant
- There is *no such thing* as a liver hemangioma in an adult
- Predictable patterns may guide effective therapy

**Registry : www.liverhemangioma.org BOSTON CHILDREN’S HOSPITAL**
- Collection of real-time clinical information, imaging, (histology)
- Centralized expert review, categorization and recommendations
- Local control and decision-making for each patient
- Prospective longitudinal clinical and imaging follow-up
- **No charge**

**Hepatoblastoma** is the most common primary malignant hepatic tumor in infancy and childhood comprises upto 55% of all pediatric liver tumors. The vast majority (80% to 90%) of patients present before 5 years of age. Some of the risk factors include prematurity and low birth weight, Beckwith-Wiedemann Syndrome and Familial Adenomatosis Polyposis (later multifocal lesions). Clinically, enlarging abdominal mass, 90% have marked elevation of serum alpha fetoprotein, 20% have extrahepatic disease, and some cases have association with paraneoplastic syndromes, including thrombocytosis and gonadotropin-induced precocious puberty. A subgroup of hepatoblastoma (small cell and rhabdoid) show low or normal levels of serum AFP; this group is associated with an aggressive clinical course.
Hepatoblastoma have heterogeneity with multiple histological subtypes in one tumor. Clinical significance of the histological subtypes unknown at this time except for pure fetal type (good prognosis by surgery). Some histological types are chemotherapy-resistant. Post-chemotherapy changes include tumor differentiation vs. HCC-like changes.

**Methods in Pathology**

**Towards an international pediatric liver tumor consensus classification: proceedings of the Los Angeles COG liver tumors symposium**

Dolores López-Terrada¹, Rita Alaggio², Maria T de Dávila³, Piotr Czauderna⁴, Eiso Hiyama⁵, Howard Katzenstein⁶, Ivo Leuschner⁷, Marcio Malogolowkin⁸, Rebecka Meyers⁹, Sarangarajan Ranganathan¹⁰, Yukichi Tanaka¹¹, Gail Tomlinson¹², Monique Fabré¹³, Arthur Zimmermann¹⁴ and Milton J Finegold¹⁵

¹Department of Pathology, Texas Children’s Hospital, Baylor College of Medicine, Houston, TX, USA; ²Division of Pathology, Department of Medicine-DIMED, Pathology Unit, Padova, Italy; ³Departamento de Patología, Hospital de Pediatría Prof. Dr. J.P. Garrahan, Buenos Aires, Argentina; ⁴Department of Surgery and Urology for Children and Adolescents, Medical University of Gdańsk, Gdańsk, Poland; ⁵Department of Surgery, Natural Science Center for Basic Research and Development, Hiroshima University Hospital, Hiroshima, Japan; ⁶Aflac Cancer Center, Children’s Healthcare of Atlanta, Emory University School of Medicine, Atlanta, GA, USA; ⁷Institut für Pathologie, UNI-Klinikum Campus, Kiel, Germany; ⁸Department of Pediatric Oncology, Medical College of Wisconsin, Milwaukee, WI, USA; ⁹Department of Pediatric Surgery, Primary Children’s Medical Center, University of Utah, Salt Lake City, UT, USA; ¹⁰Department of Pathology, Children’s Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA; ¹¹Division of Pathology, Kanagawa Children’s Medical Center, Yokohama, Japan; ¹²Division of Pediatric Hematology-Oncology, University of Texas Health Science Center, San Antonio, TX, USA; ¹³Department of Pathology, Institut de Cancerologie Gustave Roussy, Villejuif, France and ¹⁴Institute of Pathology, University of Bern, Bern, Switzerland

***** UPDATED CLASSIFICATION*****

- **Epithelial type**
  - Fetal subtype
    - Clear cell type, less than 2 mitosis in 10/hpf; entire lesion, not biopsy – “PURE FETAL”
    - Crowded/ mitotically active type, 2 or more mitosis in 10/hpf
      - Embryonal, small cells with increased N:C ratio and angulated nuclei
      - Small cell type – low AFP
- Rhabdoid type – low AFP
- Mixed Epithelial
- Cholangioblastic
- Macrotrabecular or mitotically active type (resembles HCC).

**Mixed epithelial and mesenchymal type**
- Without teratoid features (squamous, osteoid, cartilage not teratoid)
- With teratoid features

**Transitional Liver Tumors** are liver tumors found within young and adolescent children with morphology of both hepatocellular carcinoma and hepatoblastoma.

**Familial Adenomatous Polyposis** has a risk of developing HB is 750 – 7500x higher in individuals with FAP than the general population. Mutations in the APC gene located on chromosome 5q21, and 10% of all individuals with HB have an APC germline mutation. In addition, individuals with FAP can develop hepatic adenomas, hepatocellular carcinoma, and bile duct adenomas.

**KEY POINTS/UPDATES HEPATOBLATOMAS**
- Updated Heptablastoma Classification
  - PURE FETAL on resection specimen; no adjuvant chemotherapy
  - Can not make a diagnosis of “Pure Fetal” on biopsy
  - Pure Fetal different from Crowded Fetal
  - Small cell and rhabdoid variants have low AFP; aggressive in nature; INI-1 +/-
  - Macrotrabecular – similar to HCC
- Transitional Liver Cell Tumor: commonly adolescents; poor prognosis
- Children with FAP can have multiple type of liver neoplasms in the same liver
**Hepatic Adenomas** are rare in children and their pathogenesis is poorly understood. These neoplasms are often associated with androgen-anabolic steroids, genetic metabolic diseases including glycogen storage disease, diabetes mellitus, Familial Adenomatous Polyposis, oxcarbazepine therapy (anti-seizure drug), mesocaval shunts, and others.

Subclassification of Hepatic Adenomas in Adults (WHO)

- HNF1α mutation adenomas
- β-catenin mutation adenomas
- Inflammatory adenomas
- Unclassified adenoma

**Hepatocyte Nuclear Factor 1α Mutation (HNF1α)** is found in 30-45% of all adult adenomas. 90% of the cases have biallelic somatic mutations while 10% have germline mutation. The later is associated with Maturity Onset Diabetes (MODY 3) and adenomatosis (10 or more hepatic adenomas). On histology, these lesions have steatosis and bland cytology. Partial (>70%) or complete loss of Fatty Acid Binding Protein indicates inactivation of HNF1α transcription factor. Currently, FABP is thought to be 100% sensitive and specific for the HNF1α mutation.

**β-catenin Mutation** is found in 10-15% of all adult adenomas. These tumors are primarily seen in males. There is an activated WNT/β-catenin pathway. GLUL, target of β-catenin, results in overexpression of glutamine synthetase. Some associations include androgens, Glycogenosis, Familial Adenomatous Polyposis. On histology, these adenomas have pseudoacinar formation and cytological atypia. β-catenin focal nuclear expression and overexpression of glutamine synthetase indicates β-catenin activation/mutation. Immunostains are 85% sensitive and 100% specific for the mutation.

**Inflammatory adenoma** were previously known as ‘Telangiectatic Focal Nodular Hyperplasia’ and comprise of 40% all adult adenomas. There is a female predominance. On histology, these lesions have inflammatory infiltrates, ductular reaction, dystrophic arteries, and sinusoidal dilation (increased GGT). Concomitant β-catenin mutation is seen in 10% of these adenomas. C-Reactive Protein (CRP) is overexpressed in inflammatory adenomas. 60% associated with gp130 mutation resulting in overexpression of IL-6. Immunostains are thought to be 91% sensitive and specific.
Unclassifiable Adenomas comprise of 10% of all adult adenomas, lack distinguishing histology features, and do not have known mutations or inflammation.

Limited data is available in children. At Cincinnati Children’s Hospital we have been using the liver adenoma immunopanel which is composed of Glypican 3, β-catenin, Fatty Acid Binding Protein, Glutamine synthetase, and C-Reactive protein for the last few year. We recently presented data at the Society of Pediatric Pathology meeting in March 2014 in San Diego California in regards to the use of this immunopanel in pediatric liver adenomas in 29 cases and found the following:

- 5 cases of HCC associated with β-catenin activated HA supports aggressive therapy of solitary HA of this subtype.
- The presence of tumors with concomitant HFN1α inactivation and activation of β-catenin pathway (not reported previously) support the multi-step carcinogenesis hypothesis of cancer

References:


4: Bioulac-Sage P, Rebouissou S, Thomas C, Blanc JF, Saric J, Sa Cunha A, Rullier...


Anita Gupta, MD  
Assistant Professor  
Pathology and Lab Medicine  
Cincinnati Children’s Hospital  
MLC 1035, 3333 Burnet Avenue  
Cincinnati, OH 45229-3039  
USA  
Anita.gupta@cchmc.org  
513-636-3924  

Graduated from Mahadevappa Rampure Medical College, Gulbarga, Karnataka. I did my residency in Anatomic and Clinical Pathology at Northwestern Memorial Hospital, Chicago, Illinois followed by a pediatric pathology fellowship at The Children’s Hospital of Denver.

Currently I am Assistant Professor transpiring into an Associate Professor as of July 1, 2014, at Cincinnati Children’s Hospital Medical Center in Cincinnati, Ohio, USA with certification in pediatric and anatomic pathology by the American Board of Pathology.

In addition to general pediatric pathology, specialties include vascular anomalies, pediatric liver tumors, ciliopathies, and cardiac biopsies, I have 23 publications in peer reviewed journals primarily in vascular anomalies and pediatric GI/Liver. In addition over 50 posters/or platform presentations at national and international meetings (United States Canadian Anatomic Pathology Meeting, Society of Pediatric Pathology, and International Society of Vascular Anomalies). Lastly I give several teaching/didactic lectures to medical students, residents, fellows, and multidisciplinary physicians locally and nationally.