Unusual Liver tumors including pediatric liver tumors  
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The more usual of the unusual liver tumors include pediatric liver tumors (hepatoblastoma, mesenchymal hamartoma, infantile hemangioendothelioma, embryonal sarcoma and rhabdomyosarcoma), angiomyolipoma, inflammatory myofibroblastic pseudotumor, epithelioid hemangioendothelioma and angiosarcoma: these are the subjects of this brief summary. Other tumors that occur commonly in other body systems may occur rarely in the liver, and are easily diagnosed by knowledge of their pathology in other sites.

**Pediatric liver tumors**

Tumors and pseudotumors of the liver comprise < 2% of tumors in children; approximately a third of these are benign and vascular in nature. Malignant liver tumors make up 1% of pediatric malignancies; the majority of these are hepatoblastomas and hepatocellular carcinomas. Most liver tumors in children under 5 years of age are comprised of hepatoblastoma, infantile hemangioendothelioma and mesenchymal hamartoma, while hepatocellular carcinoma, focal nodular hyperplasia and embryonal sarcoma occur in older children.

**Hepatoblastoma**

Hepatoblastoma is the third most common intra-abdominal malignancy in children following neuroblastoma and Wilm’s tumor. The rarity of this tumor has led to the formation of multi-institutional study groups in an effort to obtain meaningful data regarding biology and prognosis, and pursue advances in its treatment. Such co-operative groups include the Children’s Cancer Group (CCG), Pediatric Oncology Group (POG) and Children’s Oncology Group (COG) in the US, SIOPEL (Société Internationale D’Oncologie Pediatrique) in France and the German Pediatric Liver Tumor Study group.

**Incidence and presentation**

The incidence of hepatoblastoma has increased over the past two to three decades, paralleling the increased survival of low birth weight infants. In an analysis of the SEER (Surveillance, Epidemiology and End Results) database, the incidence of hepatoblastoma in 1993-1997 doubled over that in 1973-1977 from 0.6 to 1.2 per 1,000,000. The strong association of hepatoblastoma with prematurity and birth weight was first reported in a study from Japan, which found that hepatoblastoma accounted for 58% of all malignancies in children with birth weights < 1000g. The relative risk of hepatoblastoma in children with birth weights <1000g is 15.64 vs 2.53 for infants with birth weights of 1000 -1500g and 1.21 for those with birth weights of 2000 -2499 g. The underlying etiopathogenesis is not clear; therapeutic agents used to maintain low birth weight infants possibly play a role. Two-thirds of tumors occur before 2 years of age, and 90% before age 5. A significant number of tumors are congenital. There is a strong association with Beckwith-Wiedemann syndrome (BWS), hemihypertrophy and familial adenomatous polyposis.
Patients present with abdominal distension, abdominal pain, gastrointestinal symptoms, and failure to thrive. Paraneoplastic syndromes like virilization are not uncommon.

**Pathology and prognostic subtypes**
Macroscopically, hepatoblastoma consists of a large mass with a variegated cut surface that may show extensive areas of necrosis and hemorrhage. Tumors that are resected following chemotherapy are usually firm to hard depending due to presence of fibrosis and osteoid.

Microscopically, the tumor may be composed entirely of epithelial elements or an admixture of epithelial and mesenchymal elements. Epithelial hepatoblastoma is composed of varying proportion of cells that resemble early embryonal hepatocytes, fetal hepatocytes or small undifferentiated cells. Some tumors show macrotrabecular areas where the cells are arranged as 5-20 cells thick trabecula. These observations form the basis of the current classification of hepatoblastoma:

**Epithelial:**
Fetal (pure fetal)
  - Well-differentiated (<2 mitoses per 10 HPF)
  - Mitotically active (>2 mitoses per 10 HPF)
Embryonal, or mixed embryonal and fetal
Small cell undifferentiaiated (SCUD, formerly anaplastic)
Macrotrabecular

**Mixed epithelial and mesenchymal type:**
Without teratoid features
With teratoid features

The presence of the small undifferentiated phenotype (SCUD) (previously called “anaplastic” type), even in small amounts, confers a bad prognosis in the form of increased risk of recurrence, which may be resistant to chemotherapy and decrease in disease-free survival. The small undifferentiated cell hepatoblastoma is a “small blue cell tumor” consisting of a monomorphous population of small round to ovoid cells with a high nucleo-cytoplasmic ratio and scant cytoplasm. Thus, all tumors should be thoroughly evaluated for the presence of small cells and a minimum of 1 section per cm of largest tumor dimension should be examined.

A second unfavorable variant of hepatoblastoma is the macrotrabecular variant, although this has not been borne out in all studies. “Macrotrabecular” describes a growth pattern of cells in trabecula that are 5 to 20 cells thick. The nature of the cells making up this trabecula however is a source of confusion: some authors refer to this subtype when fetal or embryonal cells are arranged in macrotrabecula, whereas others refer to this pattern only when the macrotrabecula are comprised of adult hepatocytes with an appearance not dissimilar to hepatocellular carcinoma. The original reports ascribing bad prognosis to the macrotrabecular pattern referred to the second situation. However, in view of the confusion and the rarity of this phenotype, there is an attempt to further study this group.
from the SIOPEL-3 database by breaking it down into MT-1 composed of adult hepatocyte/ HCC like cells and MT-2 composed of embryonal and/or fetal cells. When made up of adult-type hepatocytes, this pattern may be indistinguishable from hepatocellular carcinoma, and is recognized as a macrotrabecular subtype of hepatoblastoma due to the presence of more recognizable elements of this tumor.

Favorable prognosis is conferred by the well-differentiated pure fetal hepatoblastoma, which is strictly defined as a completely resectable tumor of pure fetal phenotype with < 2 mitoses per 10 high power fields. The favorable prognosis of this subtype is restricted to stage I tumors.

A host of unusual histological patterns are encountered by pathologists at reference centers for the study groups, and are the basis of a recently proposed classification (Zimmermann 2005). These tumors are too rare for the scope of this summary. For practical purposes, when encountered, all morphologically rare subtypes are best forwarded to a reference center.

It has been postulated that the various morphological subtypes of hepatoblastoma reflect various stages of hepatic development. Thus epithelial-mesenchymal hepatoblastoma may reflect the stage of epithelial-mesenchymal transition during hepatic development. The various epithelial components may represent various stages of hepatocyte development. The small cell component has been postulated to represent a tumor of hepatic stem cells but stem cell markers are not consistently demonstrable.

**Genetic and molecular findings**

The most frequently encountered chromosomal abnormalities are triploidy of chromosomes 2 and 20; chromosomal gains of 20 and 8q have been reported to adversely affect prognosis.

The most frequent findings in about 90% of hepatoblastomas are alterations in the β-catenin signaling pathway. β-catenin has two roles: in the nucleus, it acts as a transcription co-factor, which along with TCF/LEF (T cell factor/ lymphoid enhancer factor) leads to transcription of genes like c-myc and cyclin D1. This function is positively regulated through the Wnt signaling pathway, which is activated by numerous growth factors and inhibited by other proteins, an example of the latter is Dickkopf-1. Normally, signaling or cytoplasmic β-catenin is kept in check by cytoplasmic sequestration in the APC-Axin- GSK3β complex where it is targeted for proteosomal degradation. Wnt signaling inhibits degradation of β-catenin, stabilizing it and allowing it to exert its nuclear effects. Stabilized β-catenin also inhibits TNF-α induced apoptosis. The second role of β-catenin is at the cell membrane where it is involved in intercellular adhesion by acting as an adaptor protein linking β-cadherin to the actin cytoskeleton of the cell. Thus the protein is normally expressed on cell membranes. Since β-catenin is central to both the Wnt and cadherin pathways, it is affected by changes in either of these pathways, or by changes in the various proteins involved in its sequestration and degradation. Any mutation or molecular change that leads to increased Wnt signaling, decreased degradation, increased stabilization or decrease in membrane function of β-
catenin leads to increased availability of the protein for nuclear signaling. Mutations of β-catenin are associated with the SCUD phenotype, which imparts a negative prognosis even when present focally in a tumor. It has been observed that foci of SCUD express β-catenin in a nuclear pattern, whereas surrounding more differentiated cells do not show this nuclear localization. Nuclear localization of β-catenin is also found in the invasive front of tumors as opposed to more central portions. These findings suggest that presence of nuclear β-catenin is an indicator of an aggressive clone of cells.

**Imprinting errors** in the 11p15 gene cluster are linked to the Beckwith-Wiedemann Syndrome (BWS). This gene cluster has two domains: Domain 1 has a telomeric location and contains genes for IGF2 (insulin growth factor 2) and H19 (a putative tumor suppressor). Domain 2 has a centromeric location and contains three genes that have been implicated in BWS: KCNQ1, KCNQ1OT1 and CDKN1C, the latter encodes for p57/KIP2 (negative regulator of cell proliferation). The reported abnormalities include uniparental disomy (UPD) with two paternal copies of 11p15, translocations, inversions and loss or gain of methylation.

Analysis of gene expression in hepatoblastoma showed differential expression of genes that were distinct from those seen in hepatocellular carcinoma. These genes included IGF2 (insulin growth factor 2), fibronectin, DLK1 (delta-like 1 homolog: inactivates a gene associated with growth arrest), TGFβ1 (a growth factor associated with many human tumors), MALAT1 (metastasis associated lung adenocarcinoma transcript 1) and MIG6 (mitogen inducible gene 6: unexpected finding as it seems to inhibit the effects of both EGF and HGF). A separate study showed higher expression of PLK1 oncogene in hepatoblastoma and correlated its higher expression with poor outcome: 5-year survival rate of 55.9% for high expression vs 87.0% for low expression (p=0.042). PLK1 is involved in various stages of mitotic progression including centrosome maturation, spindle function, activation of cyclin B/Cdc2 and regulation of anaphase-promoting complex.

**Prognosis and treatment**
The prognosis of hepatoblastoma has improved dramatically over the last three decades since the advent of cisplatin-based chemotherapy. The single most important prognostic determinant of hepatoblastoma is complete resectability. However, most children present with large or multifocal tumors that cannot be safely resected either due to their size or proximity to and/or involvement of major vascular structures. Preoperative chemotherapy causes the tumor to shrink, allowing successful and complete resection. The success of chemotherapy is complemented by progress in knowledge and techniques of imaging, anesthesia and surgery.

Clinical stage obviously imparts prognostic significance. Various staging systems have been employed by various study groups. To facilitate comparison, all groups employ the **PRETEXT (pretreatment extent of disease)** system formulated by SIOPEL, which has been shown to have high correlation with overall survival and event-free survival. The PRETEXT system is also useful in assessing the efficacy of neoadjuvant chemotherapy and predicting surgical resectability. The system defines four stages depending upon the
number of sectors involved by the tumor. Extrahepatic growth is indicated by alphabetical modifiers, the VPEM system: V for involvement of hepatic or caval veins, P for involvement of portal vein, E for presence of extra-hepatic tumor and M for distant metastases.

Post-operative staging systems include the TNM staging system of the International Union against Cancer, or a simplified staging system adopted by COG:

Stage 1: complete resection of tumor
Stage 2: microscopic residual tumor
Stage 3: unresectable tumor (or macroscopic residual tumor); lymph node metastases
Stage 4: metastatic disease

As mentioned above, histological patterns with distinct prognostic implications are SCUD, macrotrabecular and well-differentiated pure fetal hepatoblastoma. The emergence of these histological prognostic patterns has led to some controversy on the role of presurgical chemotherapy for every hepatoblastoma, even when it is completely resectable. The argument against chemotherapy in completely resectable tumors is dictated by two situations: first, surgical resection is curative in the well-differentiated pure fetal phenotype when the defining criteria are strictly adhered to; harmful adjuvant therapy is therefore unnecessary in these patients. Secondly, foci of small cell undifferentiated hepatoblastoma may be ablated and their prognostic implication missed by presurgical chemotherapy.

With the ongoing revolution in molecular and genetic research, we can look forward to further definition of prognostic subtypes based on the presence or absence of genetic and molecular markers. Nuclear localization of $\beta$-catenin and presence of PLK1 have already been shown to have negative prognostic impact. In fact, the emphasis of current is to define histological, molecular and genetic factors that will allow precise tailoring of therapy to individual cases.

**Role of transplantation**

Liver transplantation offers a viable therapeutic option for patients with unresectable disease limited to the liver after chemotherapy; this includes tumors invading all four sectors or tumors in close proximity to major vascular structures. In such cases, liver transplantation offers 80% long-term disease-free survival compared to 30% long-term survival following rescue transplantation for incomplete resection. The persistence of viable extrahepatic deposits after chemotherapy, not amenable to surgical resection, is considered to be the only absolute contraindication to liver transplantation. The 1-, 5- and 10-year patient survival of 135 pediatric patients with hepatoblastoma in the UNOS database from 1987-2004 was 79%, 69% and 66% respectively. The primary cause of death was metastatic or recurrent disease, accounting for 54% of deaths. The main parameters that correlated with graft and patient survival on univariate and multivariate analysis were pretransplant medical condition and transplant era.

**Mesenchymal hamartoma**

Mesenchymal hamartoma is a tumor of infancy, the average patient being 15 months of age. The tumor may not uncommonly be present prenatally and is more common in male
children. Patients present with an enlarging abdomen. Imaging studies show a well-delineated heterogeneous cystic mass in the liver. Macroscopically, the tumor is well-circumscribed, large, smooth and fluctuant. Sectioning reveals a soft myxoid, cystic surface that exudes thin fluid or soft gelatinous material. Microscopically, the main component is loose, edematous connective tissue containing acid mucopolysaccharides and bile ducts, vessels and liver cell nodules. Microscopically, the lesion extends out into the surrounding liver belying the macroscopic demarcation. Surgical resection is curative. Rare instances of malignant transformation are present in literature. Controversy exists over whether this lesion represents a developmental anomaly or a true neoplastic process. Proponents of the former idea believe the lesion arises as a result of ductal plate malformation. However, the demonstration of a translocation consistently involving 19 q 13.4 in a handful of cases seems to argue to the contrary.

Infantile hemangioendothelioma

Infantile hemangioendothelioma is the most common mesenchymal tumor in infancy, occurring in children younger than 6 months of age. This tumor is more common in female children. Patients present with abdominal distention, hepatomegaly and failure to thrive; high output cardiac failure due to AV shunting and Kassabach-Merritt syndrome with consumptive coagulopathy and thrombocytopenia has been reported. The tumor tends to be multifocal or diffuse. The cut surface is red-brown and spongy and may show areas of scarring. Microscopically, the tumor consists of numerous interconnecting vascular channels lined by a single layer of endothelial cells. Bile ducts are seen throughout the tumor. Thrombosis, scarring and extramedullary hematopoiesis are common. The tumor tends to show microscopic extension into the surrounding hepatic parenchyma. These tumors have been classified into Type I and Type II, distinguished by atypia, papillary projections, multilayering, mitoses or solid areas in the latter. These tumors may involute after several months but the cardiac function needs to be supported. Surgical resection is curative, Type II is more likely to recur and there are anecdotal reports of transformation to a more malignant phenotype.

Embryonal sarcoma

Embryonal sarcoma occurs in children between 6 and 10 years of age with an approximately equal gender distribution. The tumor presents with abdominal distension, abdominal mass and weight loss. The tumor appears solid on ultrasound, but may show a misleading cystic appearance on CT and MRI, leading to misguided attempts at aspiration or delay in treatment. Grossly, the tumor has a variegated, soft cut surface that may be cystic or solid with areas of necrosis and hemorrhage. Microscopically, the tumor is an undifferentiated sarcoma consisting of stellate, spindle or pleomorphic cells. The cells are either arranged loosely in a myxoid stroma or as more compact fascicles and bundles of spindle cells. Abundant matrix of acid mucopolysaccharides, extramedullary hematopoiesis, PAS positive diastase resistant globules and benign bile ducts are prominently present in most tumors. p53 mutations have been reported in these tumors and may represent the major carcinogenic pathway. This is a very aggressive tumor with poor prognosis, although the Soft Tissue Sarcoma Italian and German Co-operative groups have recently shown almost 60% 5-year survival following multimodal therapy.
**Rhabdomyosarcoma (sarcoma botyroides)**
This tumor occurs in children under 5 years of age and has also been reported in adults. Patients present with obstructive jaundice, fever and weight loss. This tumor arises in large hilar bile ducts, and like sarcoma botyroides in other parts of the body, appears as soft intraluminal grape-like masses. The tumor is covered by biliary epithelium and has an abundant myxoid stroma. There is a submucosal cambium layer that contains dark, round to oval tumor cells. Immunocytochemistry and electron microscopy show evidence of rhabdomyoblastic differentiation: actin, myosin, myoglobin, thick and thin myofilaments and Z bands. The treatment and prognosis parallels that of embryonal sarcoma.

**Epithelioid hemangioendothelioma**
Epithelioid hemangioendothelioma occurs over a wide age range, but the average patient is a woman in her fifties. Patients present with an abdominal mass, pain or nonspecific symptoms such as weight loss and malaise. Some patients may present with features of veno-occlusive disease or Budd-Chiari syndrome due to vascular occlusion. Imaging shows either a single mass, but more commonly, multifocal masses that are avascular and calcified. Grossly, the tumors are white, firm with central calcification and/or ossification. The microscopic appearance is distinctive with a centrally fibrotic, calcified or ossified tumor. Tumor cells are more abundant at the periphery and consist of epithelioid cells, many of which have a signet ring appearance with an intracytoplasmic lumen; pathognomonic cells contain red blood cells within these lumina. The tumor infiltrates the liver along the sinusoids, using them as scaffolding. Typically, adjacent portal tracts show invasion of vascular structures by papillary or glomeruloid tufts of malignant cells. The tumor demonstrates evidence of endothelial differentiation by immunohistochemistry and electron microscopy. Epithelioid hemangioendothelioma is a low-grade malignancy with 5-year survival of almost 50%. Complete surgical resection is the treatment of choice. In patients with multifocal disease, liver transplantation offers long-term disease-free survival. Metastases occur in 30-45% of cases but are also conducive to long-term survival if the lesions are resectable. There are anecdotal instances of recurrence of a more malignant, angiosarcoma-like tumor in the transplanted liver. A translocation, t(1;3)(p36.3;q25) has been described in 2 cases.

**Angiosarcoma**
A rare tumor, angiosarcoma is nonetheless the most common sarcoma arising in the liver. The peak incidence is in the 6th and 7th decades of life, with a M:F ratio of 3:1. Although the etiology of angiosarcoma is unknown in the majority of cases, the most common associations are exposure to vinyl chloride monomer, arsenic, pesticides and thorium dioxide; the last mentioned was a radioactive contrast medium used from the 1920s to the 1950s. The tumor presents with abdominal enlargement, pain, hepatomegaly, jaundice, hemorrhage and portal hypertension. Grossly, the liver shows multifocal or diffuse spongy, hemorrhagic, ill-defined lesions. The tumor infiltrates extensively along the hepatic sinusoids causing gradual atrophy and effacement of the liver cell plates. The tumor cells may be spindle-shaped or epithelioid, and are pleomorphic with malignant nuclear features. Diagnosis is made by immunohistochemical or electron microscopic demonstration of endothelial differentiation. This is a highly aggressive tumor with no
genuinely effective therapy. Metastases occur frequently and rapidly to the spleen, lymph nodes, lungs, bone and adrenals.

**Angiomyolipoma**
Angiomyolipoma in the liver resembles its counterpart in the kidney. When present in the context of tuberous sclerosis, liver tumors are always associated with renal tumors. Patients are usually middle-aged females. The tumors are usually solitary and contain a variable amount of fat, vessels and smooth muscle cells. Diagnostic confusion arises when the fat cell component is inconspicuous and the smooth muscle component assumes an unusual morphologic phenotype; smooth muscle cells may be epithelioid, clear cell, oncocytic, or spindle cell in nature. The pathognomonic feature is positivity for HMB-45 along with positivity for muscle markers; the expression of melanocytic and muscle markers places this tumor in the category of PEComas, or tumors of perivascular epithelioid cells. CD117 is also positive in angiomyolipomas. These tumors are benign and surgical resection is curative.

**Inflammatory (myofibroblastic) tumor**
This lesion is characterized by the presence of infection-like symptoms that include fever, abdominal pain, vomiting, diarrhea and jaundice. Laboratory work-up may show leucocytosis, eosinophilia, high ESR and hyperglobulinemia. A history of travel or gallstones may be elicited. Most patients are young and there is a male predominance. Imaging may show a single mass or multiple lesions, the latter may arouse suspicion of malignancy. The lesion can assume massive size. Microscopically, there are chronic inflammatory cells that include numerous polyclonal plasma cells, lymphocytes and eosinophils. A spindle cell component that shows evidence of fibroblastic or myofibroblastic differentiation is present in variable proportion. No microorganisms are found in the lesion. The most frequent association is with an autoimmune pancreatitis with or without sclerosing cholangitis; rare cases have been reported with Crohn’s disease and primary biliary cirrhosis. The lesion may regress spontaneously or reduce in size over a relatively short time of observation along with the clinical symptoms; thus surgery is not uniformly recommended for these lesions.

**References**
**Pediatric tumors**


**Hepatoblastoma**


**Mesenchymal hamartoma**


**Infantile hemangioendothelioma**

**Embryonal sarcoma**


**Epithelioid hemangioendothelioma**


**Angiosarcoma**


**Angiomyolipoma**


**Inflammatory pseudotumor**

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