World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v6.i7.486

World J Hepatol 2014 July 27; 6(7): 486-495
ISSN 1948-5182 (online)

REVIEW

Differential diagnosis and management of liver tumors in infants

Israel Fernandez-Pineda, Rosa Cabello-Laureano

Israel Fernandez-Pineda, Rosa Cabello-Laureano, Department of Pediatric Surgery, Virgen del Rocio Children's Hospital, Sevilla 41013, Spain
Author contributions: Fernandez-Pineda I and Cabello-Laureano R designed the review article and wrote the manuscript.
Correspondence to: Israel Fernandez-Pineda, MD, Department of Pediatric Surgery, Virgen del Rocio Children's Hospital, Av. Manuel Siurot s/n, t. 0034 955012924, Sevilla 41013, Spain. israfdez@hotmail.com
Telephone: +34-955-012924 Fax: +34-955-012805
Received: January 21, 2014 Revised: March 21, 2014
Accepted: May 31, 2014
Published online: July 27, 2014

Abstract

During the first year of life, most of the liver neoplasms are benign in origin, but some of these histologically benign lesions may be challenging in their management. Although most hepatic hemangiomas can be safely observed until involution is documented, some patients will need treatment due to progressive hepatomegaly, hypothyroidism and/or cardiac failure. Large mesenchymal hamartomas may require extensive hepatic resection and an appropriate surgical plan is critical to obtain good results. For malignant neoplasms such as hepatoblastoma, complete surgical resection is the mainstay of curative therapy. The decision about whether to perform an upfront or delayed resection of a primary liver malignant tumor is based on many considerations, including the ease of resection, surgical expertise, tumor histology and stage, and the likely chemosensitivity of the tumor. This article reviews the initial management of the more common hepatic tumors of infancy, focusing on the differential diagnosis and treatment options.

Key words: Hepatoblastoma; Hepatic hemangioma; Mesenchymal hamartoma; Undifferentiated embryonal sarcoma of the liver; Focal nodular hyperplasia

Core tip: Management of liver neoplasms during the first year of life may be challenging. Some of these tumors may be observed but others require extensive surgical resection and adjuvant therapies. Differential diagnosis and treatment options are discussed in our article.

Fernandez-Pineda I, Cabello-Laureano R. Differential diagnosis and management of liver tumors in infants. *World J Hepatol* 2014; 6(7): 486-495 Available from: URL: http://www.wjgnet.com/1948-5182/full/v6/i7/486.htm DOI: http://dx.doi.org/10.4254/wjh.v6.i7.486

INTRODUCTION

The management of infants with liver tumors may be challenging and it may require a complete work-up because of symptoms or concern about malignancy. Initial evaluation should be focused on patient history, pregnancy evaluation, gestational age at birth, weight and findings on physical exam. Diagnostic imaging modalities may facilitate the identification of benign and malignant liver tumors, however biopsy or resection for histological diagnosis sometimes becomes necessary. Some of these infantile hepatic neoplasms are highly vascularized and surgical interventions are at high risk of bleeding. Certain tumor markers may be helpful in the initial work-up and evaluation of response to therapy. Alpha-fetoprotein (AFP) level may be elevated in children with malignant lesions such as hepatoblastoma and hepatocellular carcinoma, but cautious interpretation is warranted as AFP level is frequently elevated in infants up to 6 mo of age and may be slightly elevated with benign tumors and with hepatic insult or regeneration. Therapy must be tailored according to the nature of the lesion. Observation is recommended for asymptomatic hepatic hemangioma,

Table 1 Hepatic tumors characterisctics

	Clinical findings	Laboratory findings	Biopsy findings	Therapy	Outcome
Hepatic hemangioma	Cutaneous hemangiomas	Decreased T3, T4	Glut-1 positive/negative	Observation Propranolol Embolization	Favourable
Focal nodular hyperplasia	Bleeding Torsion	-	Glutamine synthetase	Observation Surgery	Favourable
Mesenchymal hamartoma	Hepatomegaly	-	Vimentin, desmin, a-1 antitrypsin, actin, cytokeratins	Surgery	Favourable
Hepatoblastoma	Hepatomegaly	Elevated AFP	Small cells Embryonal epithelial cells	Chemotherapy Surgery	EFS 30%-90%
Billiary tract rhabdomyosarcoma	Jaundice Hilum of the liver	Cholestasis	Embryonal or botryoid subtype	Chemotherapy Radiation therapy Surgery	EFS 60%-90%
Angiosarcoma	Metastatic disease	-	Glut-1 negative	Chemotherapy Radiation therapy Surgery	Unfavourable
Malignant rhabdoid tumor	Metastatic disease	-	INI1/BAF 47	Chemotherapy Surgery	Unfavourable
Undifferentiated embryonal sarcoma	Right lobe of the liver	-	SMA, a-ACT, desmin, vimentin	Chemotherapy Surgery	Unfavourable
Metastatic hepatic disease from NB	Hepatomegaly	Elevated catecholamines	MYC-N	Chemotherapy Radiation therapy Surgery	EFS 50%-90%

AFP: Alpha-fetoprotein; MYC-N: MYC-N proto-oncogene protein; EFS: Event free survival; SMA: Smooth muscle actin; ACT: Actin; INI1/BAF: INI1/BAF protein; NB: Neuroblastoma.

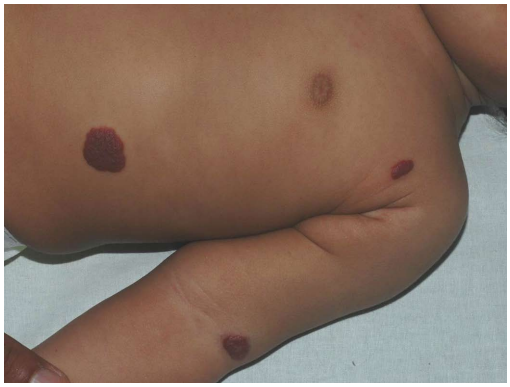

Figure 1 Cutaneous hemangiomatosis.

whereas complete surgical resection in the mainstay of treatment in hepatoblastoma. Benign primary liver tumors described in infants include hemangioma, focal nodular hyperplasia and mesenchymal hamartomas. Hepatic adenoma is almost exclusively a disease of older children. Malignant lesions include hepatoblastoma, biliary tract rhabdomyosarcoma, angiosarcoma, rhabdoid tumor, undifferentiated embryonal sarcoma and metastatic neuroblastoma (Table 1). The aim of this article is to review the clinical features and management of infants diagnosed with a liver tumor.

BENIGN LIVER TUMORS IN INFANTS

Hepatic hemangioma

Hepatic hemangioma (HH) is the most common benign liver tumor of infancy and it must be differentiated from misnamed hepatic hemangiomas seen in adults, which correspond actually to hepatic venous malformations[1,2]. These adult cases are histologically described as cavernous hemangiomas with large, dilated, blood-filled vessels lined by flattened endothelium, whereas HH are true vascular tumors composed of proliferating endothelial cells. A great variety of pediatric vascular lesions is incorrectly referred to as "hemangiomas" in the medical literature and a significant number of patients receive ineffective and potentially harmful treatment based on misclassification. In 2007, Christison-Lagay *et al*[3] from Vascular Anomalies Center in Boston Children's Hospital postulated three principal categories of HH (focal, multifocal, and diffuse) and a clinical practice algorithm. These lesions share the same patterns of growth, histological findings and involution as their cutaneous counterparts, the infantile hemangioma (IH) and the Rapidly Involuting Congenital Hemangioma (RICH)[4-6]. Focal hemangioma seems to correspond with a RICH, a vascular tumor completed formed at birth with no postnatal growth in which involution is normally observed in the first 12-18 mo after birth. Multifocal and diffuse HH correspond with IH, the most common vascular tumor in children that shows a rapid postnatal growth (0-12 mo) followed by slow involution (1-5 years). It is probable that most HH remain undiagnosed since they are asymptomatic self-limiting lesions, although they often come to clinical attention while screening for visceral hemangioma based on the presence of multiple cutaneous IH (Figure 1), since the liver is the most commonly involved organ[3,7,8]. Some patients may develop a congestive heart failure associated with high-volume vascular shunting and treatment is warranted. Unresponsive patients to therapy may develop a severe cardiac failure with hypothyroidism (IH express type 3

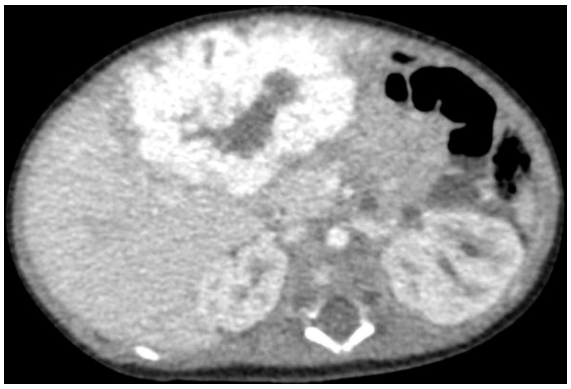

Figure 2 Abdominal computed tomography-contrast. Focal hepatic hemangioma that shows centripetal enhancement and central sparing because of thrombosis, necrosis and/or intralesional hemorrhage.

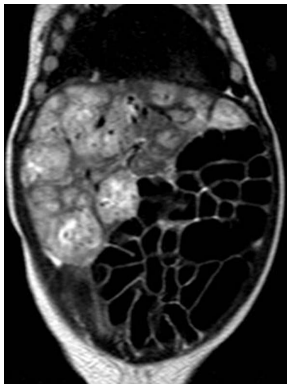

Figure 3 Abdominal magnetic resonance imaging-contrast. Diffuse hepatic hemangioma that nearly totally replaces the liver.

iodothyronine deiodinase that converts thyroid hormone to its inactive form, resulting in an acquired hypothyroidism), abdominal compartment syndrome, and death[9-12].

Differential diagnosis with malignant liver tumors should be performed and AFP should be included in the initial lab work. Focal HH (Figure 2) shows centripetal enhancement and central sparing because of thrombosis, necrosis, or intralesional hemorrhage on computed tomography (CT) or gadolinium magnetic resonance imaging (MRI). Multifocal HH shows multiple well-defined, spherical lesions with intervening areas of normal hepatic parenchyma, whereas diffuse lesions (Figure 3) nearly totally replace the liver. On CT, lesions are hypodense relative to liver without contrast but enhance centripetally with contrast. Central sparing, thrombosis, or necrosis is not seen in multifocal and diffuse HH. Radiologists who are very specialized in looking at vascular lesions feel comfortable in many cases saying that something is an hemangioma *vs* another tumor based upon its radiographic presentation. Hepatoblastomas tend to be heterogeneous on T2-weighted imaging and angiosarcomas seem to have central enhancement rather than centrifugal enhancement, but if there is any question about the diagnosis, a biopsy is recommended, although this procedure is at high risk of bleeding[13-16].

Most of the diagnosed HH may be observed closely with serial abdominal ultrasonography until involution is documented. If the lesions become symptomatic (hemodynamically significant shunting), medical therapy is firstly recommended. Recently, propranolol has been introduced as an effective treatment for cutaneous IH and several recent cases have been reported showing excellent response of diffuse HH to propranolol, even in patients with associated hypothyroidism. Corticosteroids have been first line treatment of infantile hemangioma, but the use of propranolol is emerging as the treatment of choice for high-risk infantile hemangiomas[17,18]. Other therapeutic options include arterial embolization, hepatic artery ligation, resection, or liver transplantation[3].

Focal nodular hyperplasia

Focal nodular hyperplasia (FNH) of the liver is a rare benign lesion, usually seen in older children rather than infants. Girls are more affected than boys. An asymptomatic incidental finding on a diagnostic study is commonly observed[19,20]. A cumulative incidence is reported in oncologic pediatric patients after completion of therapy and differential diagnosis to other focal hepatic lesions, such as metastasis, is often challenging. Infants with neuroblastoma and metastatic hepatic disease seem to be a specific risk-group for FNH development, especially if they underwent chemotherapy and/or radiation therapy to the liver during treatment[21-23]. Gutweiler *et al*[24] reported a hepatoblastoma case presenting with FNH after treatment of neuroblastoma. FNH should be considered in patients with persistent late imaging changes. Classical CT-contrast picture is a lesion enhanced when compared with normal liver and a central scar that becomes hyperintense owing to concentration of the contrast. Currently, liver ultrasound (US) and MRI are the recommended diagnostic imaging tools for characterizing the lesion and subsequent follow-up. Glutamine synthetase is a nitrogen metabolism enzyme with a distribution in the human liver characterized by its strict pericentrolobular localization[25]. It has emerged as a good marker for identification of resected FNH and for differentiating FNH from all other types of hepatocellular nodules developed on normal liver[26]. Acute abdominal pain may develop owing to torsion or rupture of the lesion with bleeding. Although FNH is a benign lesion that is typically managed conservatively in adults, most children with FNH undergo biopsy or resection because of increasing size, concerning symptoms or inability to rule out malignancy, especially in pediatric cancer survivors[27].

Mesenchymal hamartoma

After hemangiomas, mesenchymal hamartoma of the liver (MHL) is the second commonest benign hepatic tumor in childhood, but these tumors are relatively rare. Most MHLs are large benign multicystic masses that present in the first 2 years of life[28]. Prenatal diagnosis of MHL has been reported, most often in the last trimester of pregnancy and it may be a cause of severe hydrops. An early prenatal diagnosis and a subsequent follow-up could help to establish the best time for delivery. Fetal intervention

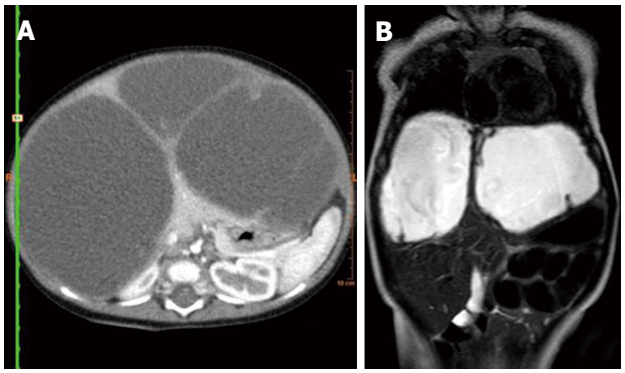

Figure 4 Abdominal computed tomography and magnetic resonance imaging. A: Abdominal computed tomography-contrast shows enhancement of the solid component, septate, and the peripheral rim; B: Abdominal magnetic resonance imaging-contrast shows a high signal intensity on T2-weighted magnetic resonance sequences.

may be beneficial in selected cases. If the fetus is becoming hydropic, early delivery or fetal treatment (particularly if the tumor is composed of a few large cysts) should be considered. Most affected fetuses have been successfully delivered vaginally[29].

Postnatal presentation is more common with abdominal distension and/or an upper abdominal mass. Liver function tests are usually normal. AFP is occasionally elevated though not to the degree that occurs in hepatoblastoma. About 75% of MHL occur in the right lobe of the liver. In the newborn, the tumor may expand rapidly and cause life-threatening abdominal distension with respiratory distress[30]. Diagnostic imaging studies demonstrate a multiloculated cystic tumor with a variable amount of solid tissue[31]. This may be seen in undifferentiated embryonal sarcoma of the liver (UESL), but rarely in hepatoblastoma. Intratumor calcification, which can be frequently detected in hepatoblastoma or hepatic hemangioma, has been reported very rarely for a MHL.

Ultrasound demonstrates the presence of thin mobile septate and/or round hyperechoic parietal nodules within the cysts, but rarely containing debris. The hepatic architecture is normal beyond the outer rim of compressed liver. On CT-contrast the solid component, septate, and the peripheral rim may enhance. On MRI, MHL has a low signal intensity on T1-weighted magnetic resonance sequences and a variable signal intensity on T2-weighted sequences (Figure 4)[32]. In most patients, the diagnosis of MHL is suggested by imaging and confirmed by histological examination of the resected specimen. If radiological diagnosis is not clear, a percutaneous or open tumor biopsy can be performed[33].

Although a laparoscopic or open surgical biopsy is considered by some authors, SIOPEL (International Childhood Liver Tumor Study Group of the International Society of Paediatric Oncology) currently recommends image-guided coaxial plugged needle biopsy for liver tumors (obtaining numerous cores)[34]. Fine needle aspiration cytology is of limited value because hepatoblastoma or a malignant mesenchymal tumor is difficult to exclude. MHL has been considered a focal tumor, but small satellite lesions at the tumor margin have been described, which could explain tumor recurrence after apparent complete resection. Clinical and histological evidence suggest that UESL can develop within a preexisting MHL[28,30]. Both tumors share similar features on gross pathology (cystic and solid components, sometimes pedunculated), histology (mesenchymal elements with benign bile duct epithelial structures), and immunohistochemistry (positive staining for vimentin, desmin, a-1-antitrypsin, actin, cytokeratins). Flow cytometry studies have shown that although most MHLs are diploid, some are aneuploid and cytogenetic studies have demonstrated a balanced translocation involving the same breakpoint on chromosome 19 (band 19q13.4) and chromosome 11. These abnormalities have been found in both, UESL and MHL[28].

The management of MHL remains still controversial. MHL has the potential to involute spontaneously, especially for those tumors with a prominent angiomatous component. Nonoperative management may be appropriate in selected cases (*e.g.*, infants with a biopsy-proven MHL and a prominent vascular component). Percutaneous aspiration or drainage of larger cysts may temporarily control tumor size in life-threatening lesions and it may helpful for the definitive surgical resection. The standard of care is complete resection with the goal of achieving negative margins to avoid the risks of local recurrence and long-term malignant transformation. Enucleation may be adequate in case of very large tumors that replace most of the liver parenchyma. Liver infiltration by MHL is rarely seen and a surgical plain is normally found for resection (Figure 5). Pedunculated lesions are amenable to laparoscopic resection. Marsupialization or partial resection are suboptimal because of the risk of tumor recurrence. Liver transplantation can be considered for unresectable tumors[28,30].

MALIGNANT LIVER TUMORS IN INFANTS

Hepatoblastoma

Hepatoblastoma (HB) is the most common malignant liver tumor in infancy and early childhood, accounting for over 65% of all liver cancer diagnosed in children under 15 years of age. Recent publications indicate that the incidence rates for HB have increased in the last decades[34,35]. Maternal smoking, parental occupation and genetic susceptibility (gene *MPO*, *NQ01*, *SULT*, *IGF-2* and so on) have been associated with HB and recent studies provide support for an increased risk of HB in low (1500-2500 g) and very low (< 1500 g), birth weight infants, in which HB is diagnosed at older ages and in more advanced stages than HB cases of normal birth weight. Neonatal therapies including supplemental oxygen, phototherapy, administration of numerous drugs, total parenteral nutrition and blood transfusions may play a role in the development of HB[36]. An infant with HB usually presents with an abdominal mass often detected by a parent.

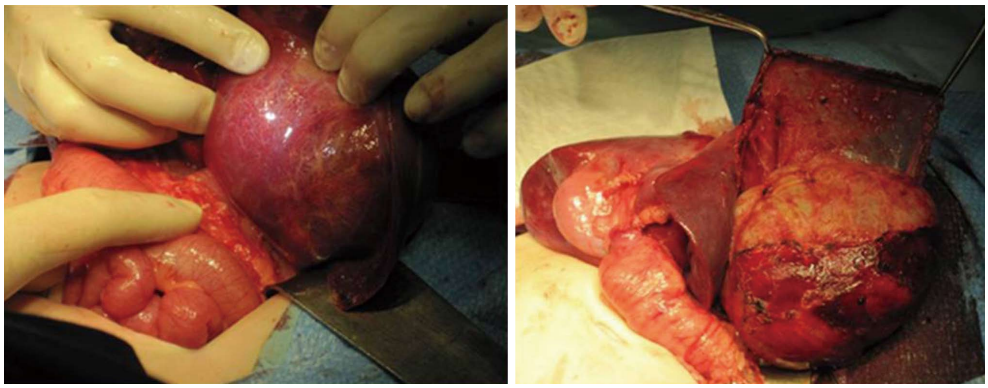

Figure 5 Surgical resection of mesenchymal hamartoma of the liver.

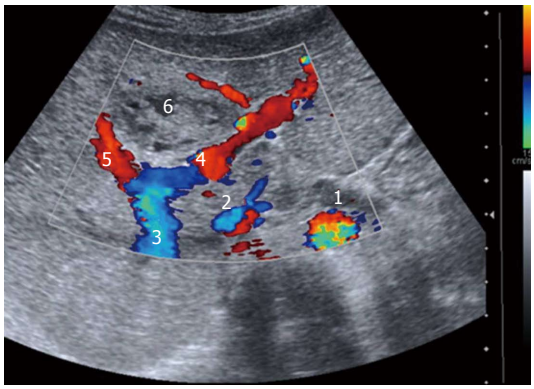

Figure 6 Doppler-US of the liver allows to investigate the relation between the tumor and the hepatic vessels. 1: Aorta; 2: Inferior vena cava; 3: Hepatic portal vein; 4: Left portal vein; 5: Right portal vein; 6 Tumor.

Table 2 Pre-treatment evaluation system of tumor extension staging system

PRETEXT Ⅰ	One section is involved and three adjoining sections are free
PRETEXT Ⅱ	One or two sections are involved, but two adjoining sections are free
PRETEXT Ⅲ	Two or three sections are involved, and no two adjoining sections are free
PRETEXT Ⅳ	All four sectors involved, any involvement of caudate lobe indicates a minimum of PRETEXT Ⅱ

PRETEXT: Pre-treatment evaluation system of tumor extension.

Other frequent presenting findings include anorexia, failure to thrive, abdominal pain, and abdominal distension. Jaundice is rarely seen since the liver function is otherwise normal. The presence of jaundice in a pediatric patient with a liver mass is most commonly seen in biliary rhabdomyosarcoma and undifferentiated sarcoma of the liver. Marked thrombocytosis is a typical finding in the laboratory work of a HB patient due to a paraneoplastic effect related to the tumor production of interleukin-6, a potent growth factor for megakaryocytes. The measurement of the serum AFP level is an useful test in infants with a liver mass and is elevated in at least 70% of children with HB. Moreover, patients with low AFP level at diagnosis (< 100 ng/mL) tend to have a more aggressive biological tumor behaviour and ultimately an unfavourable clinical outcome[37]. AFP is also an extremely useful marker of the tumor response to therapy and in the early detection of tumor recurrence. Attention must be paid to the correction of residual fetal.

AFP in infants under 6 mo of age. Elevation of AFP may also be seen in infants with yolk-sac tumors, sarcomas and hamartomas.

Abdominal ultrasonography-Doppler should be the first imaging modality in an infant with suspicion of a liver tumor and provides information about the origin of the mass, the extention of the lesion, and discerns whether the lesion is solid or cystic and whether it is a solitary or a multifocal tumor. It represents a valuable tool of resectability assessment as it allows to investigate the relation between the tumor and the hepatic vessels (Figure 6). It can be also used intraoperatively. On CT, HB shows heterogenous, low attenuation mass which enhance during arterial phase and hypoattenuates during portal phase. MRI shows HB as hypointense in comparison to normal liver in T1-weighted sequences and hyperintense in T2-weighted sequences, while dynamic imaging with gadolinium shows early enhancement with rapid washout. Chest CT should be performed to investigate pulmonary metastatic disease[34].

The pre-treatment evaluation system of tumor extension was developed by the SIOPEL and aims to define tumor extension before any therapeutic intervention. This system divides the liver into four sectors, an anterior and a posterior sector on the right and a medial and a lateral sector on the left (Table 2). The Children's Oncology Group (COG) adopted a different system based mostly on surgical findings[38-40].

In SIOPEL protocol, a tumor biopsy is required to confirm diagnosis before starting chemotherapy and this does not upstage a patient if a subsequent complete resection is performed. Biopsy can be done with open or laparoscopic surgical technique, but a percutaneous approach ultrasound-guided is preferred. Tumor seeding should be prevented by advancing the needle through a short depth of normal liver tissue (a portion that will be resected at future surgery)[41,42]. COG protocol allows

a primary tumor resection without a biopsy if it seems feasible. Patients with negative margin and microscopic positive margin will receive a less intensive chemotherapy regimen compared with those patients with gross residual disease or initial biopsy only. Patients with negative margin and pure fetal histology are observed and will receive no adjuvant chemotherapy in the COG protocol[43].

For both protocols, surgical resection is the mainstay of curative therapy, but only one-third to one-half of newly diagnosed patients with HB will have resectable disease at diagnosis. The combination of cisplatin-based chemotherapy and surgery has improved survival in patients with unresectable HB by increasing the number of patients whose tumors can be resected. Patients whose tumor may not be resectable even after neoadjuvant chemotherapy should be referred to a liver transplant center[44-48].

Biliary tract rhabdomyosarcoma

Rhabdomyosarcoma (RMS) of the biliary tree is a rare mesenchymal neoplasm that arises as an intraluminal biliary mass or cluster of grape-like masses and it typically presents with features of obstructive jaundice[49]. Median age at presentation is 3 years, but it should be included in the differential diagnosis of an infant presenting with jaundice and a mass in the porta hepatis. Other diagnostic possibilities include undifferentiated sarcoma of the liver, pancreateoblastoma, papillary cystic tumor of the pancreas, metastatic lesions and more rarely, hepatoblastoma[50,51]. Additionally, a RMS in this location can mimic the radiological appearance of a choledochal cyst because of its combined cystic and solid component[52]. Once the radiological diagnosis is performed by US, CT or MRI, an endoscopic retrograde cholangio-pancreatography can be performed to relieve biliary obstruction, visualize the biliary tree and obtain a biopsy[53,54]. This procedure may be challenging in an infant and an open, laparoscopic or needle biopsy may be required to confirm the diagnosis. Outcome in RMS appears to have improved over the last several decades secondary to the tumor chemosensitivity. Multiagent neoadjuvant chemotherapy following the biopsy may avoid important complications associated to a massive primary resection. Even after chemotherapy, gross total resection is rarely possible but outcome is good despite residual disease after second-look surgery[48,51].

Angiosarcoma

Most of the vascular liver neoplasms in infants are benign and correspond to infantile hemangioma (multifocal and diffuse hepatic hemangioma) and rapidly involuting congentinal hemangioma (focal hepatic hemangioma). If an hepatic hemangioma shows an unusual progression, malignancy should be suspected and a tumor biopsy is warranted. Hepatic angiosarcoma is a rare and high-grade malignant neoplasm that accounts for 2% of liver tumors in children[55-57]. Early metastatic disease to the lungs is commonly seen. Diagnosis may be challenging and an open wedge biopsy may be a good choice to avoid potential bleeding and obtain an accurate histological diagnosis. Prognosis is poor, even after multiagent chemotherapy, surgical resection, radiation, and liver transplantation[58,59].

Malignant rhabdoid tumor

Malignant rhabdoid tumor of the liver (MRTL) is a rare and aggressive neoplasm that share clinical features with HB such as male predominance, thrombocytosis, anemia, and only moderate derangement of overall liver function at presentation[60,61]. However, patients at diagnosis are younger compared with HB patients and LDH is typically elevated. Accurate diagnosis of MRTL may be challenging due to extensive tumor necrosis and immunohistochemistry studies for INI1/BAF 47 protein (which is abnormally lost in all rhabdoid tumors) has emerged as an useful tool for diagnosis[62]. For infants with liver tumors and normal AFP level at diagnosis, detailed cytogenetic, immunohistochemical and/ or molecular analysis of INI1/BAF 47 protein may be helpful in distinguishing MRTL from HB[63]. Hepatoblastomas of small cell undifferentiated histology can mimic MRTL but do not have *INI1* mutations[63,64]. Outcomes for patients with MRTL are very poor. Multiagent chemotherapy including vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide in combination with complete surgical resection is the mainstay of treatment[65].

Undifferentiated embryonal sarcoma

Undifferentiated embryonal sarcoma of the liver (UESL) is an uncommon malignant hepatic neoplasm that occurs more frequently in older children but has also been described in infancy[66,67]. Malignant transformation from mesenchymal hamartoma or a solitary liver cyst to UESL has been reported. It is generally considered to be a highly invasive malignant tumor with lung, peritoneum and pleura as the typical sites for distant metastasis. The diagnosis may be challenging and relies on postoperative pathology and immunostaining analysis (positive expression of SMA, a-ACT, desmin, vimentin). If the tumor is not suitable to primary resection, a biopsy should be obtained followed by chemoradiation. Survival rates have significantly improved in the last decades and long-term survival cases have been reported[68,69]. In an Italian-German soft tissue sarcoma study[70], 12 of 17 children with UESL achieved remission following treatment with chemoradiation and surgery. Patients whose tumor is not able to be resected or who have postoperative local recurrence of the tumor without distant metastasis may be candidates for liver transplantation.

Metastatic neuroblastoma

Neuroblastoma (NB) is the most common extracranial solid tumor in the pediatric population, accounting for 6%-10% of all childhood cancers and 15% of all cancer related mortalities in children. Common sites for metastasis are bone marrow, bone and liver. Stage 4S or MS represents 5% of NB cases and it is defined as disease with a localized primary adrenal or extra-adrenal tumor

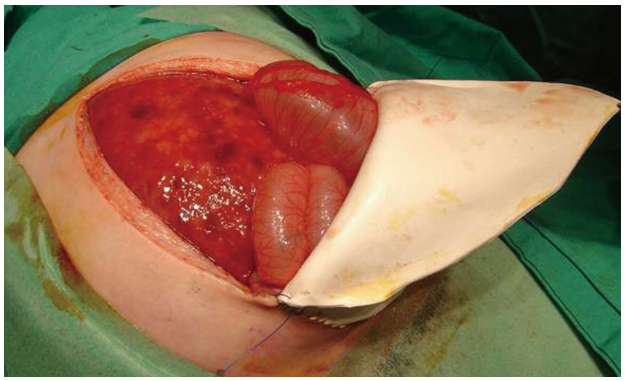

Figure 7 Extensive hepatic infiltration by neuroblastoma. Surgical abdominal decompression by patch placement.

and metastasis restricted to the liver, skin, and bone marrow involvement less than 10%[71,72]. Although, it is associated with survival rates of 70%-97% due to the possibility of regression and spontaneous tumor maturation, some of these young patients may present with extensive and diffuse liver involvement (Figure 7) that can cause respiratory compromise and symptoms of abdominal compartment syndrome with decreased venous return, renal impairment and coagulation disorders secondary to extensive hepatic infiltration. Chemotherapy and liver radiation have been advocated as therapeutical options for those infants who present with progressive disease and life-threatening symptoms[73,74]. Surgical management by abdominal decompression may be necessary in case an abdominal compartment syndrome is present[75,76]. However, the decision of when and how to treat remains controversial.

Our experience

Benign hepatic tumors: we have evolved from corticosteroids treatment to oral propranolol in the last 5 years for the management of symptomatic hepatic hemangiomas. We have observed a more rapid response to propranolol on ultrasound follow-up compared with steroids. Oral propranolol is discontinued until lesion involution is documented which it normally occurs after the first year of age. Patients with asymptomatic lesions have been observed with good results.

Most of our FNH patients underwent incisional biopsy to rule out malignancy. We have observed FNH as a residual lesion of primary vascular anomalies.

In our experience, a surgical plain may lead the resection of MHL with good residual liver parenchyma. All our patients have a normal liver function on follow-up.

Malignant hepatic tumors: at our institution, we follow the SIOP protocol for the management of hepatoblastoma with an initial incisional biopsy at presentation followed by cisplatin-based chemotherapy and surgical resection. Our overall survival is 70% and it does not differ from the results published by other groups.

As for RMS in other locations, our experience in the management of biliary tract RMS has evolved from primary tumor resection in the last decades to initial biopsy followed by neoadjuvant chemotherapy and non-massive second look surgery for tumor resection and evaluation of tumor response.

We have anecdotal cases of infants with tumors other than hepatoblastoma (angiosarcoma, malignant rhabdoid tumor, undifferentiated embryonal sarcoma) and conclusions are difficult to be drawn.

We have successfully managed liver infiltration by neuroblastoma with standard protocols based on chemotherapy and radiation therapy. We have only performed one surgical abdominal decompression by patch placement in a patient with an abdominal compartment syndrome (Figure 7) who finally died.

REFERENCES

1 **MullikenJB**, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. *Plast Reconstr Surg* 1982; **69**: 412-422 [PMID:7063565]

2 **Mulliken JB**, Fishman SJ, Burrows PE. Vascular anomalies. *Curr Probl Surg* 2000; **37**: 17-84 [DOI: 10.1016/S0011-3840(00)80013-1]

3 **Christison-Lagay ER**, Burrows PE, Alomari A, Dubois J, Kozakewich HP, Lane TS, Paltiel HJ, Klement G, Mulliken JB, Fishman SJ. Hepatic hemangiomas: subtype classification and development of a clinical practice algorithm and registry. *J Pediatr Surg* 2007; **42**: 62-67; discussion 67-68 [PMID: 17208542 DOI: 10.1016/j.jpedsurg.2006.09.041]

4 **Drut RM**, Drut R. Extracutaneous infantile haemangioma is also Glut1 positive. *J Clin Pathol* 2004; **57**: 1197-1200 [PMID: 15509684 DOI: 10.1136/jcp.2003.012682]

5 **Mo JQ**, Dimashkieh HH, Bove KE. GLUT1 endothelial reactivity distinguishes hepatic infantile hemangioma from congenital hepatic vascular malformation with associated capillary proliferation. *Hum Pathol* 2004; **35**: 200-209 [DOI: 10.1016/j.humpath.2003.09.017]

6 **Hernández F**, Navarro M, Encinas JL, López Gutiérrez JC, López Santamaría M, Leal N, Martínez L, Patrón M, Tovar JA. The role of GLUT1 immunostaining in the diagnosis and classification of liver vascular tumors in children. *J Pediatr Surg* 2005; **40**: 801-804 [PMID: 15937818 DOI: 10.1016/j.jpedsurg.2005.01.046]

7 **Metry DW**, Hawrot A, Altman C, Frieden IJ. Association of solitary, segmental hemangiomas of the skin with visceral hemangiomatosis. *Arch Dermatol* 2004; **140**: 591-596 [PMID: 15148105 DOI: 10.1001/archderm.140.5.591]

8 **Mulliken JB**, Enjolras O. Congenital hemangiomas and infantile hemangioma: missing links. *J Am Acad Dermatol* 2004; **50**: 875-882 [PMID: 15153887 DOI: 10.1016/j.jaad.2003.10.670]

9 **Güven A**, Aygun C, Ince H, Aydin M, Pinarli FG, Baysal K, Küçüködük S. Severe hypothyroidism caused by hepatic hemangioendothelioma in an infant of a diabetic mother. *Horm Res* 2005; **63**: 86-89 [PMID: 15711094 DOI: 10.1159/000083879]

10 **Konrad D**, Ellis G, Perlman K. Spontaneous regression of severe acquired infantile hypothyroidism associated with multiple liver hemangiomas. *Pediatrics* 2003; **112**: 1424-1426 [PMID: 14654623 DOI: 10.1542/peds.112.6.1424]

11 **Ho J**, Kendrick V, Dewey D, Pacaud D. New insight into the pathophysiology of severe hypothyroidism in an infant with multiple hepatic hemangiomas. *J Pediatr Endocrinol Metab* 2005; **18**: 511-514 [PMID: 15921182 DOI: 10.1515/-JPEM.2005.18.5.511]

12 **Huang SA**, Tu HM, Harney JW, Venihaki M, Butte AJ, Kozakewich HP, Fishman SJ, Larsen PR. Severe hypothyroidism caused by type 3 iodothyronine deiodinase in infantile hem-

angiomas. *N Engl J Med* 2000; **343**: 185-189 [PMID: 10900278 DOI: 10.1056/NEJM200007203430305]
13 **Kassarjian A**, Dubois J, Burrows PE. Angiographic classification of hepatic hemangiomas in infants. *Radiology* 2002; **222**: 693-698 [PMID: 11867787]
14 **Kassarjian A**, Zurakowski D, Dubois J, Paltiel HJ, Fishman SJ, Burrows PE. Infantile hepatic hemangiomas: clinical and imaging findings and their correlation with therapy. *AJR Am J Roentgenol* 2004; **182**: 785-795 [PMID: 14975986 DOI: 10.2214/ajr.182.3.1820785]
15 **Regier TS**, Ramji FG. Pediatric hepatic hemangioma. *Radiographics* 2004; **24**: 1719-1724 [PMID: 15537980 DOI: 10.1148/rg.246035188]
16 **Hughes JA**, Hill V, Patel K, Syed S, Harper J, De Bruyn R. Cutaneous haemangioma: prevalence and sonographic characteristics of associated hepatic haemangioma. *Clin Radiol* 2004; **59**: 273-80 [DOI: 10.1016/S0009-9260(03)00267-8]
17 **Léauté-Labrèze C**, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taïeb A. Propranolol for severe hemangiomas of infancy. *N Engl J Med* 2008; **358**: 2649-2651 [PMID: 18550886 DOI: 10.1056/NEJMc0708819]
18 **Marsciani A**, Pericoli R, Alaggio R, Brisigotti M, Vergine G. Massive response of severe infantile hepatic hemangioma to propanolol. *Pediatr Blood Cancer* 2010; **54**: 176 [PMID: 19743301 DOI: 10.1002/pbc.22262]
19 **Stocker JT**, Ishak KG. Focal nodular hyperplasia of the liver: A study of 21 pediatric cases. *Cancer* 1981; **48**: 336
20 **Whelan TJ**, Baugh JH, Chandor S. Focal nodular hyperplasia of the liver. *Ann Surg* 1973; **177**: 150-158 [PMID: 4698535 DOI: 10.1097/00000658-197302000-00004]
21 **Sugito K**, Uekusa S, Kawashima H, Furuya T, Ohashi K, Inoue M, Ikeda T, Koshinaga T, Tomita R, Mugishima H, Maebayashi T. The clinical course in pediatric solid tumor patients with focal nodular hyperplasia of the liver. *Int J Clin Oncol* 2011; **16**: 482-487 [PMID: 21455626 DOI: 10.1007/s10147-011-0210-x]
22 **French AE**, Irwin MS, Navarro OM, Greenberg M, Nathan PC. Long-term hepatic outcomes in survivors of stage 4S and 4 neuroblastoma in infancy. *Pediatr Blood Cancer* 2012; **58**: 283-288 [PMID: 21370436 DOI: 10.1002/pbc.23077]
23 **Benz-Bohm G**, Hero B, Gossmann A, Simon T, Körber F, Berthold F. Focal nodular hyperplasia of the liver in long-term survivors of neuroblastoma: how much diagnostic imaging is necessary? *Eur J Radiol* 2010; **74**: e1-e5 [PMID: 19369017 DOI: 10.1016/j.ejrad.2009.05.002]
24 **Gutweiler JR**, Yu DC, Kim HB, Kozakewich HP, Marcus KJ, Shamberger RC, Weldon CB. Hepatoblastoma presenting with focal nodular hyperplasia after treatment of neuroblastoma. *J Pediatr Surg* 2008; **43**: 2297-2300 [PMID: 19040959 DOI: 10.1016/j.jpedsurg.2008.08.069]
25 **Bioulac-Sage P**, Cubel G, Taouji S, Scoazec JY, Leteurtre E, Paradis V, Sturm N, Nhieu JT, Wendum D, Bancel B, Ramos J, Paraf F, Saint Paul MC, Michalak S, Fabre M, Guettier C, Le Bail B, Zucman-Rossi J, Balabaud C. Immunohistochemical markers on needle biopsies are helpful for the diagnosis of focal nodular hyperplasia and hepatocellular adenoma subtypes. *Am J Surg Pathol* 2012; **36**: 1691-1699 [PMID: 23060349 DOI: 10.1097/PAS.0b013e3182653ece]
26 **Shafizadeh N**, Kakar S. Diagnosis of well-differentiated hepatocellular lesions: role of immunohistochemistry and other ancillary techniques. *Adv Anat Pathol* 2011; **18**: 438-445 [PMID: 21993269 DOI: 10.1097/PAP.0b013e318234abb4]
27 **Meyers RL**, Scaife ER. Benign liver and biliary tract masses in infants and toddlers. *Semin Pediatr Surg* 2000; **9**: 146-155 [PMID: 10949425 DOI: 10.1053/spsu.2000.7562]
28 **Stringer MD**, Alizai NK. Mesenchymal hamartoma of the liver: a systematic review. *J Pediatr Surg* 2005; **40**: 1681-1690 [PMID: 16291152 DOI: 10.1016/j.jpedsurg.2005.07.052]
29 **Cignini P**, Coco C, Giorlandino M, Bagolan P, Morini F, Giorlandino C. Fetal hepatic mesenchymal hamartoma: a case report. *J Prenat Med* 2007; **1**: 45-46 [PMID: 22470828]
30 **Thompson PA**, Chintagumpala M. Renal and hepatic tumors in the neonatal period. *Semin Fetal Neonatal Med* 2012; **17**: 216-221 [PMID: 22595862 DOI: 10.1016/j.siny.2012.04.002]
31 **Kim SH**, Kim WS, Cheon JE, Yoon HK, Kang GH, Kim IO, Yeon KM. Radiological spectrum of hepatic mesenchymal hamartoma in children. *Korean J Radiol* 2007; **8**: 498-505 [PMID: 18071280 DOI: 10.3348/kjr.2007.8.6.498]
32 **Anil G**, Fortier M, Low Y. Cystic hepatic mesenchymal hamartoma: the role of radiology in diagnosis and perioperative management. *Br J Radiol* 2011; **84**: e91-e94 [PMID: 21511744 DOI: 10.1259/bjr/41579091]
33 **Millard J**, Fraser N, Stewart RJ. Mesenchymal hamartoma of the liver: is biopsy always necessary? *Pediatr Surg Int* 2006; **22**: 622-625 [PMID: 16807720 DOI: 10.1007/s00383-006-1702-z]
34 **Roebuck DJ**. Assessment of malignant liver tumors in children. *Cancer Imaging* 2009; **9**: S98-S103 [PMID: 19965302 DOI: 10.1102/1470-7330.2009.9041]
35 **Siegel MJ**. Pediatric liver imaging. *Semin Liver Dis* 2001; **21**: 251-269 [PMID: 11436576 DOI: 10.1055/s-2001-15339]
36 **Mann JR**, Kasthuri N, Raafat F, Pincott JR, Parkes SE, Muir KR, Ingram LC, Cameron AH. Malignant hepatic tumours in children: incidence, clinical features and aetiology. *Paediatr Perinat Epidemiol* 1990; **4**: 276-289 [PMID: 2374747 DOI: 10.1111/j.1365-3016.1990.tb00651.x]
37 **Maruyama K**, Ikeda H, Koizumi T, Tsuchida Y. Prenatal and postnatal histories of very low birthweight infants who developed hepatoblastoma. *Pediatr Int* 1999; **41**: 82-89 [PMID: 10200142]
38 **De Ioris M**, Brugieres L, Zimmermann A, Keeling J, Brock P, Maibach R, Pritchard J, Shafford L, Zsiros J, Czaudzerna P, Perilongo G. Hepatoblastoma with a low serum alpha-fetoprotein level at diagnosis: the SIOPEL group experience. *Eur J Cancer* 2008; **44**: 545-550 [PMID: 18166449 DOI: 10.1016/j.ejca.2007.11.022]
39 **Aronson DC**, Schnater JM, Staalman CR, Weverling GJ, Plaschkes J, Perilongo G, Brown J, Phillips A, Otte JB, Czauderna P, MacKinlay G, Vos A. Predictive value of the pretreatment extent of disease system in hepatoblastoma: results from the International Society of Pediatric Oncology Liver Tumor Study Group SIOPEL-1 study. *J Clin Oncol* 2005; **23**: 1245-1252 [PMID: 15718322 DOI: 10.1200/JCO.2005.07.145]
40 **Roebuck DJ**, Aronson D, Clapuyt P, Czauderna P, de Ville de Goyet J, Gauthier F, Mackinlay G, Maibach R, McHugh K, Olsen OE, Otte JB, Pariente D, Plaschkes J, Childs M, Perilongo G. 2005 PRETEXT: a revised staging system for primary malignant liver tumours of childhood developed by the SIOPEL group. *Pediatr Radiol* 2007; **37**: 123-132; quiz 249-250 [PMID: 17186233 DOI: 10.1007/s00247-006-0361-5]
41 **Czauderna P**, Otte JB, Aronson DC, Gauthier F, Mackinlay G, Roebuck D, Plaschkes J, Perilongo G. Guidelines for surgical treatment of hepatoblastoma in the modern era--recommendations from the Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL). *Eur J Cancer* 2005; **41**: 1031-1036 [PMID: 15862752 DOI: 10.1016/j.ejca.2005.02.004]
42 **Hoffer FA**. Liver biopsy methods for pediatric oncology patients. *Pediatr Radiol* 2000; **30**: 481-488 [PMID: 10929368 DOI: 10.1007/s002470000244]
43 **Maturen KE**, Nghiem HV, Marrero JA, Hussain HK, Higgins EG, Fox GA, Francis IR. Lack of tumor seeding after percutaneous biopsy of hepatocellular carcinoma using coaxial cutting needle technique. *AJR Am J Roentgenol* 2005; **184**: 37
44 **Davidoff AM**, Fernandez-Pineda I, Santana VM, Shochat SJ. The role of neoadjuvant chemotherapy in children with malignant solid tumors. *Semin Pediatr Surg* 2012; **21**: 88-99 [PMID: 22248974 DOI: 10.1053/j.sempedsurg.2011.10.010]
45 **Brown J**, Perilongo G, Shafford E, Keeling J, Pritchard J, Brock P, Dicks-Mireaux C, Philips A, Vos A, Plaschkes J.

Pretreatment prognostic factors for children with hepatoblastoma - results from the International Society of Paediatric Oncology (SIOP) study SIOPEL 1. *Eur J Cancer* 2000; **36**: 1418-1425 [DOI: 10.1016/S0959-8049(00)00074-5]

46 **Perilongo G**, Shafford E, Maibach R, Aronson D, Brugières L, Brock P, Childs M, Czauderna P, MacKinlay G, Otte JB, Pritchard J, Rondelli R, Scopinaro M, Staalman C, Plaschkes J. Risk-adapted treatment for childhood hepatoblastoma. final report of the second study of the International Society of Paediatric Oncology--SIOPEL 2. *Eur J Cancer* 2004; **40**: 411-421 [PMID: 14746860 DOI: 10.1016/j.ejca.2003.06.003]

47 **Katzenstein HM**, London WB, Douglass EC, Reynolds M, Plaschkes J, Finegold MJ, Bowman LC. Treatment of unresectable and metastatic hepatoblastoma: a pediatric oncology group phase II study. *J Clin Oncol* 2002; **20**: 3438-3444 [PMID: 12177104 DOI: 10.1200/JCO.2002.07.400]

48 **Pritchard J**, Brown J, Shafford E, Perilongo G, Brock P, Dicks-Mireaux C, Keeling J, Phillips A, Vos A, Plaschkes J. Cisplatin, doxorubicin, and delayed surgery for childhood hepatoblastoma: a successful approach--results of the first prospective study of the International Society of Pediatric Oncology. *J Clin Oncol* 2000; **18**: 3819-3828 [PMID: 11078495]

49 **Spunt S**, Lobe T, Pappo A, Parham DS, Wharam MD Jr, Arndt C, Andersen JR, Crist WM, Paidas C, Wiener E, Andrassy RJ, Schwartz CL. Aggressive surgery is unwarranted for biliary tract rhabdomyosarcoma. *J Pediatr Surg* 2000; **35**: 309-316 [DOI: 10.1016/S0022-3468(00)90030-7]

50 **Zampieri N**, Camoglio F, Corroppolo M, Cecchetto M, Ornis S, Ottolenghi A. Botryoid rhabdomyosarcoma of the biliary tract in children: a unique case report. *Eur J Cancer Care* (Engl) 2006; **15**: 463-466 [PMID: 17177904 DOI: 10.1111/j.1365-2354.2006.00683.x]

51 **Perera MT**, McKiernan PJ, Brundler MA, Hobin DA, Mayer DA, Mirza DF, Sharif K. Embryonal rhabdomyosarcoma of the ampulla of Vater in early childhood: report of a case and review of literature. *J Pediatr Surg* 2009; **44**: e9-e11 [PMID: 19231522 DOI: 10.1016/j.jpedsurg.2008.10.113]

52 **Pollono DG**, Tomarchio S, Berghoff R, Drut R, Urrutia A, Cedola J. Rhabdomyosarcoma of extrahepatic biliary tree: initial treatment with chemotherapy and conservative surgery. *Med Pediatr Oncol* 1998; **30**: 290-293

53 **Tireli GA**, Sander S, Dervisoglu S, Demirali O, Unal M. Embryonal rhabdomyosarcoma of the common bile duct mimicking choledochal cyst. *J Hepatobiliary Pancreat Surg* 2005; **12**: 263-265 [PMID: 15995817 DOI: 10.1007/s00534-004-0959-7]

54 **Himes RW**, Raijman I, Finegold MJ, Russell HV, Fishman DS. Diagnostic and therapeutic role of endoscopic retrograde cholangiopancreatography in biliary rhabdomyosarcoma. *World J Gastroenterol* 2008; **14**: 4823-4825 [PMID: 18720547 DOI: 10.3748/wjg.14.4823]

55 **Awan S**, Davenport M, Portmann B, Howard ER. Angiosarcoma of liver in children. *J Pediatr Surg* 1996; **31**: 1729-32 [DOI: 10.1016/S0022-3468(96)90065-2]

56 **Noronha R**, Gonzalez-Crussi F. Hepatic angiosarcoma in childhood. A case report and review of the literature. *Am J Surg Pathol* 1984; **8**: 863-871 [PMID: 6542321 DOI: 10.1097/00000478-198411000-00007]

57 **Dimashkieh HH**, Mo JQ, Wyatt-Ashmead J, Collins MH. Pediatric hepatic angiosarcoma: case report and review of the literature. *Pediatr Dev Pathol* 2004; **7**: 527-532 [PMID: 15547777 DOI: 10.1007/s10024-004-4041-x]

58 **Ferrari A**, Casanova M, Bisogno G, Cecchetto G, Meazza C, Gandola L, Garaventa A, Mattke A, Treuner J, Carli M. Malignant vascular tumors in children and adolescents: a report from the Italian and German Soft Tissue Sarcoma Cooperative Group. *Med Pediatr Oncol* 2002; **39**: 109-114 [PMID: 12116058 DOI: 10.1002/mpo.10078]

59 **Lezama-del Valle P**, Gerald WL, Tsai J, Meyers P, La Quaglia MP. Malignant vascular tumors in young patients. *Cancer* 1998; **83**: 1634-1639

60 **Trobaugh-Lotrario AD**, Finegold MJ, Feusner JH. Rhabdoid tumors of the liver: rare, aggressive, and poorly responsive to standard cytotoxic chemotherapy. *Pediatr Blood Cancer* 2011; **57**: 423-428 [PMID: 21744471 DOI: 10.1002/pbc.22857]

61 **Wagner LM**, Garrett JK, Ballard ET, Hill DA, Perry A, Biegel JA, Collins MH. Malignant rhabdoid tumor mimicking hepatoblastoma: a case report and literature review. *Pediatr Dev Pathol* 2007; **10**: 409-415 [PMID: 17929989 DOI: 10.2350/06-08-0155.1]

62 **Perry A**, Fuller CE, Judkins AR, Dehner LP, Biegel JA. INI1 expression is retained in composite rhabdoid tumors, including rhabdoid meningiomas. *Mod Pathol* 2005; **18**: 951-958 [PMID: 15761491 DOI: 10.1038/modpathol.3800375]

63 **Al Nassan A**, Sughayer M, Matalka I, Ghandour K, Masarweh M, Zimmermann A, Sultan I. INI1 (BAF 47) immunohistochemistry is an essential diagnostic tool for children with hepatic tumors and low alpha fetoprotein. *J Pediatr Hematol Oncol* 2010; **32**: e79-e81 [PMID: 20048688 DOI: 10.1097/MPH.0b013e3181b79613]

64 **Trobaugh-Lotrario AD**, Tomlinson GE, Finegold MJ, Gore L, Feusner JH. Small cell undifferentiated variant of hepatoblastoma: adverse molecular and clinical features similar to rhabdoid tumors. *Pediatric Blood and Cancer* 2009; **52**: 328-334

65 **Jayaram A**, Finegold MJ, Parham DM, Jasty R. Successful management of rhabdoid tumor of the liver. *J Pediatr Hematol Oncol* 2007; **29**: 406-408 [PMID: 17551403 DOI: 10.1097/MPH.0b013e3180601011]

66 **Ismail H**, Dembowska-Bagińska B, Broniszczak D, Kaliciński P, Maruszewski P, Kluge P, Swięszkowska E, Kościesza A, Lembas A, Perek D. Treatment of undifferentiated embryonal sarcoma of the liver in children--single center experience. *J Pediatr Surg* 2013; **48**: 2202-2206 [DOI: 10.1016/j.jpedsurg.2013.05.020]

67 **Pachera S**, Nishio H, Takahashi Y, Yokoyama Y, Oda K, Ebata T, Igami T, Nagino M. Undifferentiated embryonal sarcoma of the liver: case report and literature survey. *J Hepatobiliary Pancreat Surg* 2008; **15**: 536-544 [PMID: 18836810 DOI: 10.1007/s00534-007-1265-y]

68 **Webber EM**, Morrison KB, Pritchard SL, Sorensen PH. Undifferentiated embryonal sarcoma of the liver: results of clinical management in one center. *J Pediatr Surg* 1999; **34**: 1641-1644 [DOI: 10.1016/S0022-3468(99)90634-6]

69 **Gao J**, Fei L, Li S, Cui K, Zhang J, Yu F, Zhang B. Undifferentiated embryonal sarcoma of the liver in a child: A case report and review of the literature. *Oncol Lett* 2013; **5**: 739-742 [PMID: 23426588]

70 **Bisogno G**, Pilz T, Perilongo G, Ferrari A, Harms D, Ninfo V, Treuner J, Carli M. Undifferentiated sarcoma of the liver in childhood: a curable disease. *Cancer* 2002; **94**: 252-257 [PMID: 11815984 DOI: 10.1002/cncr.10191]

71 **Stephenson SR**, Cook BA, Mease AD, Ruymann FV. The prognostic significance of age and patterns of metastasis in stage IV-S neuroblastoma. *Cancer* 1986; **58**: 372-375

72 **Evans AE**, Chatten J, D'Angio GJ, Gerson JM, Robinson J, Schnaufer L. A review of 17 IV-S neuroblastoma patients at the Children's Hospital of Philadelphia. *Cancer* 1980; **45**: 833-839

73 **Bishop MW**, Yin H, Shimada H, Towbin AJ, Miethke A, Weiss B. Management of stage 4S composite neuroblastoma with a MYCN-amplified nodule. *J Pediatr Hematol Oncol* 2014; **36**: e31-e35 [PMID: 23528904 DOI: 10.1097/MPH.0b013e3182847376]

74 **Steele M**, Jones NL, Ng V, Kamath B, Avitzur Y, Chami R, Cutz E, Fecteau A, Baruchel S. Successful liver transplantation in an infant with stage 4S(M) neuroblastoma. *Pediatr Blood Cancer* 2013; **60**: 515-517 [PMID: 23152322 DOI: 10.1002/pbc.24391]

75 **Nuchtern JG**, London WB, Barnewolt CE, Naranjo A, McGrady PW, Geiger JD, Diller L, Schmidt ML, Maris JM, Cohn SL, Shamberger RC. A prospective study of expectant

observation as primary therapy for neuroblastoma in young infants: a Children's Oncology Group study. *Ann Surg* 2012; **256**: 573-580 [PMID: 22964741]

76 **Mabrut JY**, Dubois R, Pelizzo G, Floret D, Frappaz D, Chapuis JP. Abdominal expansion using a polytetrafluoroethylene prosthesis in the treatment of Pepper syndrome. *Pediatr Surg Int* 2000; **16**: 219-221 [PMID: 10786988 DOI: 10.1007/s003830050729]

P- Reviewer: Wakiyama S **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com