Liver Tumors in Children

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Mohamed Rela and Mettu Srinivas Reddy

Introduction

Liver tumors are uncommon in the pediatric age group and constitute 1–2 % of all solid tumors in children. About 60 % of all liver tumors in children are malignant [1]. Hepatoblastoma (HB) is by far the most common constituting over 50–60 % of all liver tumors in this age group. Hepatocellular carcinoma (HCC), undifferentiated embryonal carcinoma and biliary rhabdomyosarcoma are other malignant liver tumors in children. Benign tumors include hemangiomas (HMGs), mesenchymal hamartoma, and focal nodular hyperplasia (FNH). Secondary tumors to the liver can spread from a host of primary tumors including lymphomas, Wilms' tumor, neuroblastoma, osteosarcoma, etc. (Table 69.1). Several congenital and environmental risk factors have been reported to increase the predilection for liver tumors (Table 69.2).

There is a striking age-related variation in the frequency of different tumor types (Table 69.3). Over 90 % of liver tumors in children below 5 years are HB, while 87 % of tumors in the 15–19-year age group are HCC. A gradual increase in the incidence of liver tumors in children over the past 3–4 decades has been reported. This is particularly evident in the case of HB where the incidence has increased from 0.6 to 1.2 per million population between 1973–1977 and 1993–1997. On the contrary, incidence of HCC has decreased from 0.45 to 0.29 per million population during the same period [2].

Tumor Markers in Childhood Liver Tumors

Alpha-fetoprotein (AFP) is the most recognized tumor marker in liver tumors. AFP is a glycoprotein similar in physical and chemical characteristics to albumin. It is secreted by the fetal liver and yolk sac until 13 weeks' gestation and then primarily by the fetal liver [3]. AFP levels at birth are very high with Bader et al. reporting a median level of over 40,000 ng/ml in cord blood samples [4]. These levels rapidly drop during the first year of life at a rate primarily dictated by the half-life of AFP of 5–6 days [5]. AFP levels at birth in the preterm babies are higher than full-term babies. Similarly, a decrease in at-birth AFP for every week of prolonged gestation has been reported [4]. The high levels of AFP in the infant should be kept in mind by the clinician when AFP levels are used for the diagnosis and monitoring of pediatric liver tumors.

Several tumors are associated with elevated AFP. HB is the commonest cause in infants though HCCs and germ cell tumors are also associated with elevated AFP. Nonneoplastic conditions, such as tyrosinemia and neonatal hepatitis, can also cause elevated AFP levels.

Malignant Tumors

Hepatoblastoma

HB is the most common liver tumor in children. It is almost always seen in the first 4 years of life with median age at diagnosis of 18 months. It can present at birth and has been diagnosed in the intrauterine period on antenatal scans. Prematurity and very small birth weight have been identified as risk factors. HB developing in these children is also reported to have a worse prognosis [6, 7].

HB is a tumor of immature hepatocyte progenitor cells. It is an embryonal tumor, which recapitulates various stages of liver development. Histologically, these tumors are heterogeneous and comprise combinations of epithelial, mes-

M. Rela (✉) · M. S. Reddy
Institute of Liver Disease and Transplantation, National Foundation for Liver Research, Global Health City, Cheran Nagar, Chennai, India
e-mail: mohamed.rela@gmail.com

M. Rela
Institute of Liver Studies, King's College Hospital, London, UK

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Table 69.1 Types of liver tumors in children

Benign	Hemangioma: focal, multiple, diffuse
	Mesenchymal hamartoma
	Hepatic adenoma
	Focal nodular hyperplasia
	Inflammatory myofibroblastic tumor (may be locally invasive)
Malignant	
Primary	Hepatoblastoma
	Hepatocellular carcinoma, fibrolamellar HCC
	Transitional tumors
	Embryonal sarcoma
	Biliary rhabdomyosarcoma
	Calcifying nested stromal–epithelial tumor
	Angiosarcoma
Secondary	Lymphomas, leukemia, Wilms' tumor, neuroblastoma, osteosarcoma, colon cancer

Table 69.2 Risk factors and premalignant conditions for childhood liver tumors

Tumor	Risk factors	Premalignant lesions
Hepatoblastoma	Beckwith–Wiedemann syndrome,familial adenomatous polyposis, Li–Fraumeni syndrome, trisomy 18, preterm birth and very low birth weight	–
Hepatocellular carcinoma	Glycogen storage disease, tyrosinemia, Alagille syndrome, biliary atresia, PFIC, Ataxia-telangiectasia, hepatitis B infection, hepatitis C infection	Hepatic adenoma
Embryonal sarcoma	–	Mesenchymal hamartoma
Angiosarcoma	–	Hemangioma

PFIC progressive familial intrahepatic cholestasis

Table 69.3 Age-wise distribution of childhood liver tumors

Age group	Benign tumors	Malignant tumors
Neonatal period	Hemangioma, mesenchymal hamartoma	Hepatoblastoma
0–5 years	–	Hepatoblastoma, biliary rhabdomyosarcoma
5–15 years	–	Hepatocellular carcinoma, embryonal sarcoma
>15 years	Hepatic adenoma	Fibrolamellar carcinoma

enchymal, and occasionally teratoid components in varying proportions (Table 69.4, Fig. 69.1). Majority of tumors have a primarily epithelial component containing hepatoblasts at varying stages of differentiation. The histological type has an impact on behavior with well-differentiated fetal epithelial type having the best prognosis. The small-cell undifferentiated type of HB has the worst prognosis with very poor survival. Mixed tumors contain both epithelial and mesenchymal components, are more resistant to chemotherapy, and have a worse prognosis. Post-chemotherapy residual tumors and metastatic tumors may demonstrate a pleomorphic pattern with pleomorphic nuclei having coarse chromatin and prominent nucleoli. This pattern may resemble HCC.

Diagnosis

The usual presentation is with an abdominal lump identified by the parent or the clinician. Pain, failure to thrive, or jaundice are uncommon modes of presentation. Investigations reveal an elevated AFP level in over 90 % of cases. The AFP levels are extremely high (in the order of 10^5 ng/ml) and are usually a log higher than those seen with HCC. AFP level has been identified as a prognostic marker in HB with both very high levels and low levels (<100 ng/ml) predicting poor biology [8]. Thrombocytosis is a recognized laboratory finding in HB and is probably related to production of thrombopoietic cytokines including thrombopoietin in the tumor tissues.

Imaging with computed tomography (CT) is necessary to confirm the diagnosis, stage the extent of liver disease, identify vascular invasion, extrahepatic disease, and lung metastases. HB appears as a heterogeneously enhancing well-circumscribed lesion with occasional calcifications. A biopsy is usually required to confirm diagnosis before start of neoadjuvant chemotherapy and for prognostication.

Staging and Prognostication

Several staging systems have been developed to tailor treatment for HB. The preoperative extent of tumor (PRETEXT) system based on preoperative imaging, which was devel-

Table 69.4 Histological types of hepatoblastoma

Histological type	Description
Epithelial	Primarily containing immature hepatocytes
Fetal	Commonest variant of epithelial HB. Composed of polygonal cells resembling fetal hepatocytes arranged in one- to two-cell thick cords, trabeculae or sheets
Embryonal, well differentiated	Tumor resembles the liver at 6–8 weeks of gestation. Demonstrates organized tubular or acinar formation. Hematopoietic elements are commonly admixed with epithelial component
Cholangioblastic	Tumour cells differentiate as cholangiocytes and form small ducts. This component expresses cholangiocyte lineage markers (cytokeratins 7 and 19)
Macrotrabecular	Cells arranged in thick trabecular pattern (>5 cells thick)
Small cell undifferentiated	Sheets of small cells with large hyperchromatic nuclei similar to neuroblastoma
Mixed epithelial–mesenchymal type	Mixture of epithelial and mesenchymal cell types
Teratoid	Contains heterologous components such as stratified squamous epithelium, mucus-producing cells, neuroectodermal derivatives
Non-teratoid	Contains stromal derivatives including spindle fibroblastic cells, osteoid, skeletal muscle, and cartilage

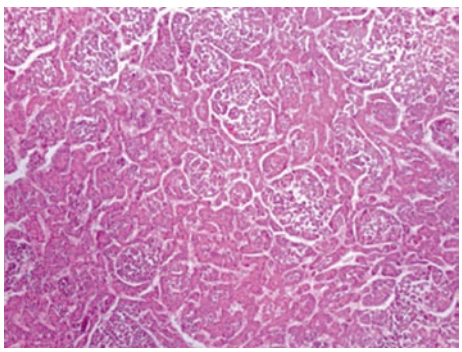

Fig. 69.1 Hepatoblastoma, epithelial type with fetal and embryonal epithelium.

oped and popularized by the International Childhood Liver Tumors Strategy (SIOPEL) Group, is commonly used in Europe (Table 69.5, Fig. 69.2). This is an anatomical classification focusing on the extent of tumor and the amount of liver that can be spared during resection [9]. Modifications to the PRETEXT scoring system have included additional subclassifications to identify high-risk factors such as vascular involvement, caudate lobe involvement, etc. (Table 69.6) [10].

SIOPEL also classifies HB into standard risk, high risk, and very-high-risk groups based on the PRETEXT staging and additional factors to tailor management (Table 69.7) [11]. Other staging systems include the Children's Oncology Group (COG) classification, which is based on intraoperative findings, and presence of residual tumor have been used more commonly in the USA.

Management

Early results of HB with surgical resection alone were poor due to the advanced stage at which these tumors usually present. Only 5% of all tumors at presentation can be staged as PRETEXT I, and over 50% are unresectable at initial presentation (Table 69.5). Metastatic disease in the lungs at presentation is not uncommon. However, this should not dissuade the clinician from aiming for cure as resection of lung metastases along with treatment of primary has been shown to improve long-term survival [12].

HB are highly chemosensitive tumors and respond well to platinum-compound-based chemotherapy. Use of chemotherapy in conjunction with surgery has radically altered the outcomes of these tumors. Today, multimodality treatment with surgery and chemotherapy is the mainstay of treatment for HB.

Ideal treatment strategy for PRETEXT I tumors is controversial. Some authors have suggested complete resection alone without chemotherapy as an option. This is especially true for the low-risk tumors with fetal histology where complete surgical resection with follow-up has been shown to be effective in providing long-term disease control [13]. Ad-

Table 69.5 PRETEXT staging and frequency of various PRETEXT stages at initial presentation [8]. Refer to Fig. 69.2

PRETEXT staging	Definition	Frequency at presentation (%)
I	One section is involved and three adjoining sections are free	4.8
II	One or two sections are involved, but two adjoining sections are free	36.6
III	Two or three sections are involved and no two adjoining sections are free	38.8
IV	All four sections are involved	19.8

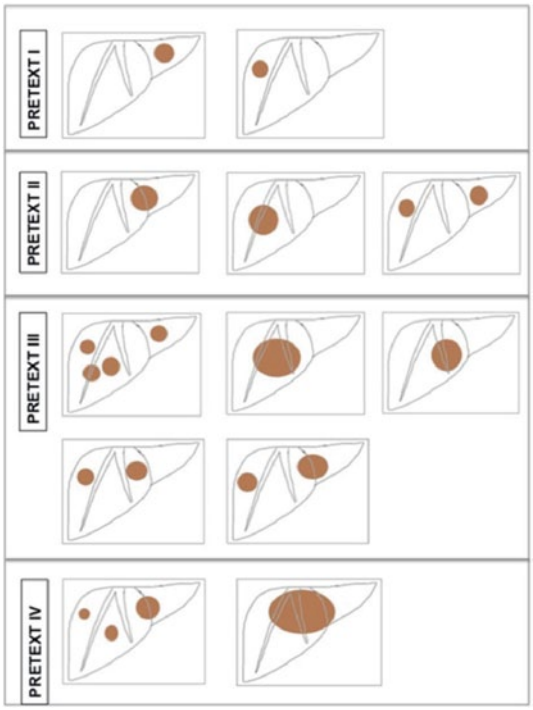

Fig. 69.2 PRETEXT staging: The PRETEXT system is based on the preoperative imaging and is an assessment of the liver that is free of tumor. The liver is divided into four sectors by the right and middle hepatic veins and the falciform ligament. The four sectors are the left lateral, left medial, right medial, and right lateral sectors. The number of contiguous sectors that are free of tumor is the key to the staging. Tumor may be single or multiple. **a** PRETEXT 1, three contiguous sectors are tumor free, **b** PRETEXT 2, two contiguous sectors are free of disease, **c** PRETEXT 3, only one sector is free, **d** PRETEXT 4, all four sectors are involved

vocates for this approach highlight the fact that these children are spared the adverse effects of chemotherapy such as ototoxicity [14]. The SIOPEL group advocates neoadjuvant chemotherapy for all HB. The purported advantages of this approach are that it shrinks the tumor, and clearly demarcates the tumors making resection more straightforward. Tumors also become more fibrotic and hence intraoperative handling is easier.

The current protocol for PRETEXT II and III is to give up to four cycles of neoadjuvant chemotherapy, followed by assessment for resection (Fig. 69.3).

If the tumor becomes resectable, then surgery is followed by two more cycles of chemotherapy. If the tumor remains unresectable, two further cycles of chemotherapy may be considered before a decision is made regarding attempted resection or primary transplantation. Monitoring the fall in AFP level after beginning chemotherapy and after surgery is an excellent means of predicting tumor response. The chemotherapy regimen advised by the SIOPEL group varies for the standard risk and high-risk HB (Table 69.7)[11].

Surgical resection for HB should be carefully planned and is best carried out in units with expertise in pediatric hepatobiliary surgery and liver transplantation (LT). This is particularly true in children with large tumors and borderline resectability. Children can tolerate extensive liver resections better than adults, and up to 85% of liver can be resected safely. More aggressive liver resection techniques such as total vascular exclusion and caval resection may be required to achieve complete disease clearance.

LT for unresectable HB is a well-defined indication [15]. These could be PRETEXT IV tumors (solitary or multifo-

Table 69.6 Additional criteria for PRETEXT staging [10]

Caudate lobe involvement	C1—tumor involving caudate lobe	–
	C0—all other patients	
Extrahepatic abdominal disease	E0—no evidence of tumor spread in abdomen (except M or N)	Add suffix "a" if ascites is present
	E1—direct extension of tumor into adjacent organs or diaphragm	
	E2—peritoneal nodules	
Tumor focality	F0—solitary tumor	–
	F1—two or more discrete tumors	
Tumor rupture	H1	–
Distant metastases	M1	–
Lymph node metastasis	N0—no nodal metastases	–
	N1—abdominal lymph node metastases only	
	N2—extra-abdominal lymph node metastases	
Portal vein involvement	P1—involvement of left or right branch of portal vein	Add suffix "a" if intravascular tumor present
	P2—involvement of main portal vein	
IVC or hepatic vein involvement	V1—involvement of one hepatic vein, IVC free	Add suffix "a" if intravascular tumor present
	V2—involvement of two hepatic veins, IVC free	
	V3—involvement of all three hepatic veins and/or IVC	

IVC inferior vena cava

Table 69.7 Risk stratification and treatment of hepatoblastoma (SIOPEL guidelines). (Available at www.siopel.org [11])

Risk status	Definition	SIOPEL guideline for treatment
Standard risk	PRETEXT I, II, III without any other risk factors as defined below[a]	*SIOPEL 3, Cisplatin alone arm*
		Cisplatin X 4 cycles
		Surgical resection
		Cisplatin X 2cycles
High risk	PRETEXT IV or any PRETEXT stage with vascular involvement (P2 or V3), extrahepatic disease (E1, E2), tumor rupture (H1)	*SIOPEL 3, SUPERPLADO arm*
		Alternating cycles of Cisplatin and carboplatin + doxorubicin X 7 cycles
		Resection/Transplantation
		Alternating cycles of Cisplatin and carboplatin + doxorubicin X 3 cycles
Very high tisk	Any tumor with metastases or very low AFP (< 100 ng/ml)	SIOPEL 4, dose-dense cisplatin-based chemotherapy or enrolment in clinical trial

[a] PRETEXT I with fetal histology may be considered for surgical resection alone and observation
AFP alpha-fetoprotein, *PRETEXT* preoperative extent of tumor

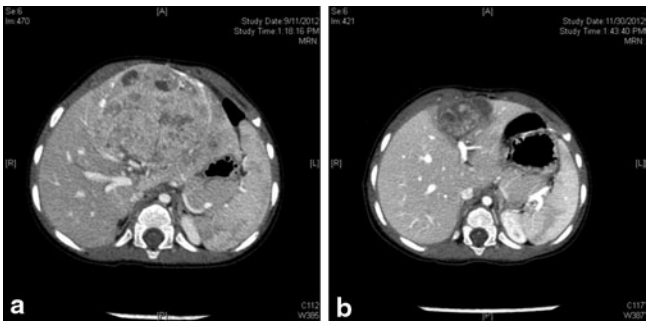

Fig. 69.3 CT images of Hepatoblastoma in a 1-year-child. **a** CT at presentation showed a PRETEXT 2 disease with tumor involving the two left sectors. **b** CT following four cycles of chemotherapy prior to resection. Note the significant shrinkage in tumor size. The CT appearance of the tumor has also changed and the demarcation between the tumor and healthy liver tissue is much more clear

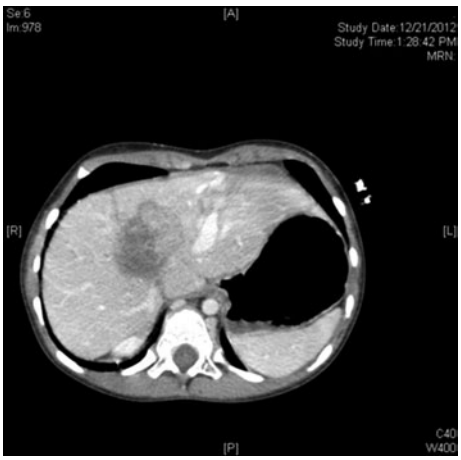

Fig. 69.4 CT image of a hepatoblastoma in a 6-year child. This child had persistent PRETEXT III tumor after six cycles of chemotherapy. The tumor was closely approximated to the cava. She underwent primary living donor liver transplantation

cal), centrally located PRETEXT II or III, or tumors with portal or caval involvement (Fig. 69.4). In children where surgical resection is not feasible, early referral for LT assessment is the best approach. Primary LT in high-risk cases has better outcomes than rescue transplantation after resection, and the latter should be considered a relative contraindication [16]. A recent US study reported that over the past 20 years, the percentage of HB receiving transplantation has increased from 5 to 20%, and the number of transplantations for HB has increased almost 20-fold [17]. This could be a reflection of the increasing confidence among clinicians for this radical modality of treatment.

The options are either split-liver deceased donor LT (DDLT) or living donor LT (LDLT) and both have comparable results. Children planned for DDLT usually complete neoadjuvant chemotherapy and are placed on the waiting list with some form of prioritization to enable timely transplantation. Where LDLT is an option, transplantation can be planned to follow the planned course of neoadjuvant chemotherapy. Transplantation should be followed by adjuvant chemotherapy. Presence of lung metastases increases the risk of posttransplant recurrence but is not a contraindication for LT as long as they can be resected [18]. Close follow-up in the posttransplantation period is essential and usually involves periodic AFP estimation and imaging studies.

Results of HB have significantly improved over the past 2–3 decades. Overall disease-free survival has improved to over 70% for all HB. Low-risk tumors have a 90% 5-year survival, while high-risk tumors have a survival of around 50%. Histological subtype has an impact on survival. Fetal types of HB have the best outcomes, while the small-cell undifferentiated type of tumors have worse prognosis. Relapse after initial complete response occurs in 11% of children. Liver and lungs are the commonest sites of relapse. Positron emission tomography/computed tomography (PET/CT) has been reported to be better at identifying relapse when compared to CT or MRI [19]. Combination of surgery and chemotherapy provide the best chance of achieving a second complete response in these children with reported 3-year overall survival of over 40% [20].

Hepatocellular Carcinoma

HCC is the second commonest liver tumor in children. It forms 15 % of all malignant liver tumors in children but constitutes over 75 % of all liver tumors in adolescents. HCC in children can occur in a background of chronic liver disease secondary to hepatitis B or metabolic disorders though non-cirrhotic HCC is more common than in adults. With increasing use of universal hepatitis B immunization, the incidence of HCC in children has decreased [2, 21]. HCC in children may be the standard type as seen in adults or the fibrolamellar variant seen in children and young adults.

HCC usually presents as an abdominal lump. Occasional presentation may be with abdominal pain or jaundice due to biliary compression or tumor ingrowth into the biliary tree. Rarely, these tumors may present as an emergency due to bleeding or rupture. HCCs are usually associated with an elevated AFP level though the elevation is not as high as that seen in HB. Liver function tests should be evaluated to assess the severity of any underlying liver disease. Metabolic screen is important to identify underlying liver disease which may impact management. Triphasic CT or MRI with contrast can help in characterizing the lesion, presence of chronic liver disease, any vascular involvement, and the presence of metastases.

HCC are chemoresistant tumors. Complete surgical excision provides these children with the best chance of long-term cure. However, the feasibility of resection depends on the size and extent of the tumor and the presence of underlying liver disease. In patients with underlying chronic liver disease, LT has the benefit of treating the underlying liver disease and providing adequate tumor clearance.

In the adult setting, the option of LT is available only for HCC within strict size and number criteria [22]. It is unclear if these criteria are appropriate in the pediatric setting, as most children will present with large tumors. Studies have shown good results in children transplanted for HCC beyond Milan criteria [23]. Hence, unless there is major vascular invasion or extrahepatic disease, unresectable HCC in children should be considered for LT. Presence of lung metastases is a contraindication for LT in pediatric HCC unlike HB due to the high risk of posttransplant progression of metastatic disease. Use of sorafenib in combination with cisplatin-based chemotherapy has also been reported in the management of pediatric HCC [24].

Outcomes of pediatric HCC are inferior to HB. The average 5-year survival is around 70 %. Recurrent disease is the most common cause of death in these children and usually occurs in the lungs or bones.

Fibrolamellar Hepatocellular Carcinoma

This is an uncommon form of primary liver tumor seen in children greater than 5 years and young adults. The median age at presentation is 21 years. It is less common than standard HCC and occurs on a background of a non-cirrhotic liver. An elevated AFP is only seen in around 10 % of these tumors. They are detected incidentally when they become symptomatic and are hence large at presentation. In a systematic review of available literature of fibrolamellar HCC (FL-HCC), the mean size of tumor at surgery was 12 cm [25]. On CT imaging, they appear as large well-circumscribed lesions which enhance strongly in arterial and portal venous phases becoming isodense in delayed scans. A poorly enhancing central scar may be seen. These tumors spread by both lymph node and blood borne systemic metastases.

Management of these tumors is primarily surgical. If resectable, surgical resection offers the best chance of cure for these tumors with a 5-year survival of 70 % in adults [25, 26]. However, within the pediatric age group, results of FL-HCC do not appear to be superior to standard HCC probably because of late presentation and local recurrence after resection [27]. LT for FL-HCC has been reported though the long-term results are not encouraging possibly because of large tumor size at presentation and presence of lymph nodal metastases.

Transitional Tumors

These are a special group of tumors initially described by Prokurat et al. that share characteristics of both HB and HCC [28]. They usually develop in older children and are large in size at presentation. AFP levels are elevated. Histologically, they have features intermediate between the macrotrabecular variant of HB and trabecular HCC. Most of these were initially diagnosed as HB and treated as such. However, they have been reported to have much poorer outcome.

Embryonal Sarcoma (Undifferentiated Sarcoma of Liver)

This is a rare mesenchymal tumor constituting 5 % of all liver tumors in children. The median age of presentation is between 6 and 10 years and is more common in males. There have been several reports of development of embryonal sarcoma from mesenchymal hamartomas [29]. Studies have also shown similar karyotypic abnormalities in both tumors. Presentation is with an abdominal lump. This tumor has characteristic radiological appearance. Ultrasonography

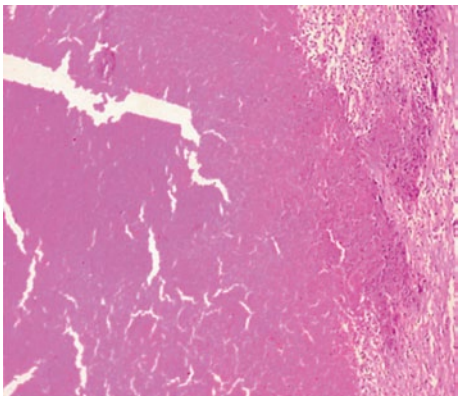

Fig. 69.5 Histology of embryonal sarcoma. Tumor shows large areas of necrosis with islands of spindle-shaped tumor cells in a myxoid matrix

(USG) shows a solid isoechoic clearly demarcated tumor. CT shows a well-circumscribed hypoattenuating lesion with multiple enhancing septations. An enhancing pseudocapsule may be present. The tumors are usually large at presentation and may be associated with lung metastases. Histologically, these tumors demonstrate large areas of necrosis with patches of viable tumor. Stellate or spindle-shaped tumor cells are loosely arranged in a myxoid matrix (Fig. 69.5).

Initial reports of this tumor described poor prognosis [30]. However, recent reports have shown that multimodality approach combining resectional surgery, chemotherapy, and transplantation can provide survival rate of up to 90 % [31, 32].

Biliary Rhabdomyosarcoma

This is the most common cause of malignant biliary obstruction in the pediatric age group. These tumors arise from any part of the intrahepatic and extrahepatic biliary tree including the gall bladder and ampulla of Vater. The median age at presentation is 3 years, and children commonly present with jaundice and abdominal pain. Preoperative diagnosis is usually a choledochal cyst [33, 34]. CT scan shows a dilated biliary tract with a hypoattenuating tumor in the bile duct [35]. Surgery helps in confirming diagnosis and enables resection of the tumor and biliary drainage in the form of a hepaticojejunostomy. Surgical excision with negative microscopic margins is rarely possible. These tumors have been found to respond well to adjuvant multi-agent chemotherapy. Spunt et al reported 25 cases of biliary rhabdomyosarcoma with a 5-year survival of 66 % for all cases and 78 % for children without systemic metastases. Death was primarily due to recurrent disease or complications of aggressive resection and/or chemotherapy [36].

Calcifying Nested Stromal-Epithelial Tumor

These are rare primary liver tumors of uncertain histogenesis that typically occur in children and young adults [37, 38]. Histologically, they have a characteristic appearance with circumscribed nests and islands of bland-appearing epithelioid cells. Focal psammoma-like calcifications with or without ossification may be present. The tumors typically have an indolent course and are considered as low-grade malignancies. Surgical resection is the treatment of choice. Some of these tumors have been reported to be associated with Cushing's syndrome which improved on resection.

Angiosarcoma

These are highly malignant tumors with poor prognosis. Malignant transformation from HMGs has been reported. Resection, if possible, should be carried out. Survival is poor due to development of systemic metastases [39, 40].

Benign Liver Tumors

Hemangioma

HMGs are the most common benign tumors in the pediatric setting. They constitute over half of all liver tumors in the neonatal period. The Liver Hemangioma Registry of the Vascular Anomalies Center at the Children's Hospital of Boston recognizes three clinical subgroups of infantile hepatic HMG—focal, multifocal, and diffuse [41]. Focal HMGs are usually single and indolent. Their clinical presentation is based entirely on their size and usually present as a large abdominal mass. Smaller focal lesions are diagnosed only on routine imaging studies in the antenatal period or after birth and usually have no clinical relevance. Associated extrahepatic lesions are uncommon with focal HMGs.

Multifocal HMGs present as multiple lesions in one or both lobes of the liver or may involve the liver diffusely. Histologically, they may be classified as capillary or cavernous HMG and may rarely show pleomorphism, intravascular spread, necrosis, and hemorrhage. The term hemangioendothelioma has also been used to describe these lesions. Over half of these children have extrahepatic vascular lesions, most commonly in the skin but also in the brain, eye, etc. Hemangioendotheliomas have the tendency to grow in the first year of life and then involute. Status of the cutaneous lesions has been used as a marker for monitoring the involution of the liver lesions [42].

Clinical presentation is commonly as an abdominal mass. High-output cardiac failure and consumptive coagulopathy due to trapping and destruction of platelets within the lesions

are serious problems with these tumors [43]. Abnormalities in thyroid function have been reported in these children [42, 44]. A small percentage of these tumors (<5%) may be premalignant and progress to angiosarcoma if left untreated [45].

Treatment of these lesions should be tailored to individual presentation [42]. Small, asymptomatic lesions are best left alone. Symptomatic lesions have been treated with a variety of pharmacological and interventional approaches. Steroids, chemotherapeutic agents, β-blockers, hepatic artery ligation, or hepatic artery embolization have all been reported by various authors to be useful. Large symptomatic lesions are best treated by liver resection and are best managed in centers with advanced hepatobiliary and LT expertise. Liver transplantation has been reported in large symptomatic lesions not amenable to resection [42].

Mesenchymal Hamartomas

These rank second in frequency among benign liver neoplasms in children. They usually present as a large abdominal mass in the first 2 years of life. Some of these tumors may be detected incidentally or because of symptoms of abdominal pain, vomiting, or failure to thrive. Rare presentations are with respiratory distress, high output cardiac failure in the newborn and with jaundice, hemorrhage, or rupture [29, 46].

Imaging usually shows a single tumor in the right lobe with solid and cystic components. Occasionally, one cyst may be large giving it the appearance of a single cystic lesion.

Microscopic examination shows varying proportions of epithelial and loose connective tissue components arranged in a disorganized pattern. The epithelial element consists of bile ducts and hepatic parenchyma without acinar pattern. Numerous arteries and veins are scattered in the loose myxoid stroma. Cystic degeneration and foci of extramedullary hematopoiesis are also identified. Some authors have classified it as a neoplasm rather than a hamartoma. Reports that these tumors are associated with karyotype abnormalities such as aneuploidy and balanced translocations suggest a malignant potential [29].

Natural history of these tumors is variable, but the majority grows in size. There have been occasional reports of spontaneous regression or malignant transformation into undifferentiated embryonal sarcoma [47].

Treatment is primarily surgical. Complete excision is recommended and, where not possible, LT has been reported.

Hepatic Adenomas

These are diagnosed in older child and adolescents. In adults, there is a correlation between the use of oral contraception and hepatic adenomas. They are usually identified on routine screening, though bleeding and rupture of superficial adenomas may lead to a more acute presentation. Small adenomas are best followed up by serial imaging because of the small risk of malignant transformation. Larger adenomas or superficial adenomas presenting with pain are better resected to avoid complications.

Focal Nodular Hyperplasia

FNH is uncommon in children and constitutes about 5% of all pediatric liver tumors. There has been some reported association between previous liver or bone marrow cancers or the presence of congenital or surgical portosystemic shunts and the development of FNH. A possible response of the liver tissue to the cytotoxic chemotherapy has been postulated. Similarly, borderline ischemia of the liver due to the shunting has also been postulated as a possible explanation of their coexistence with shunts.

FNH is usually diagnosed on routine imaging and is identified as a slightly hypodense, discrete lesion on plain CT. On contrast images, it enhances homogeneously in the arterial phase with the lesion becoming isodense in delayed scans. A central scar is noted in 50% of cases with delayed enhancement of the central scar a characteristic finding in FNH.

Macroscopically, it appears as a well circumscribed mass with a central depression (Fig. 69.6). Cut surface shows small nodules divided by fibrous septa leading to a central scar. Microscopically, the nodules contain hyperplastic hepatocytes supported by a well-developed reticulin framework. The septa contains abundant vessels, consisting of both arteries and veins. Variable eccentric intimal fibroplasia and disruption of the elastic lamina is noted in the arteries. Inflammatory cells and numerous proliferating ductules are also identified in the septa. Chronic cholestatic features are also identified in the cells adjacent to septa.

The most common presenting symptom is pain. These lesions may be small and multiple or may be single and large. If imaging is suggestive of FNH, then close follow-up with

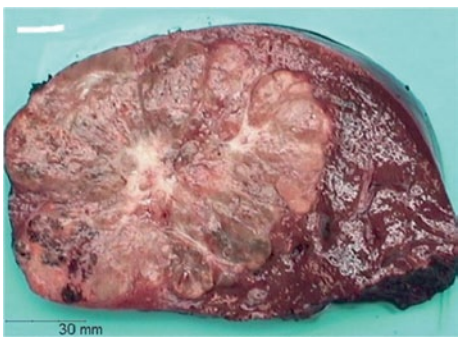

Fig. 69.6 Cut section of focal nodular hyperplasia. Note the well-circumscribed lesion with multiple nodules separated by fibrous septa joining at a central scar

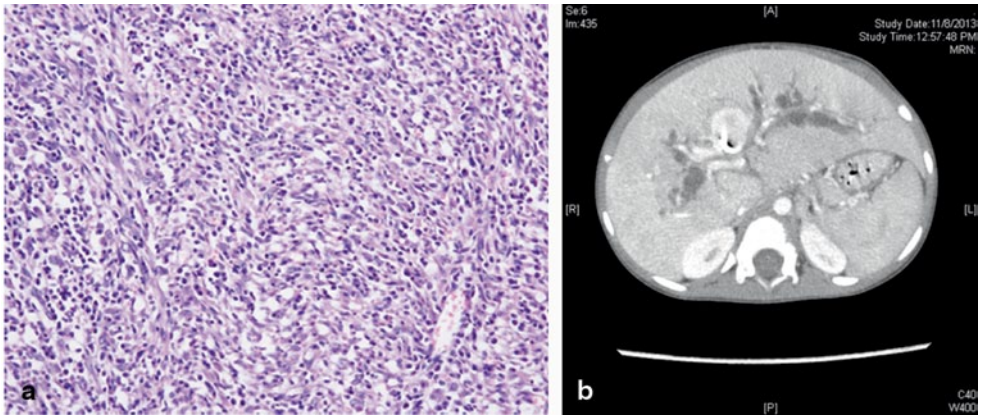

Fig. 69.7 **a** Section of an Inflammatory myofibroblastic tumor displaying interlacing bundles of fibroblasts admixed with inflammatory cells. **b** CT showing an inflammatory myofibroblastic tumor involving the hepatic hilum in a 4-year-old child. The child presented with constitutional symptoms, obstructive jaundice, and recurrent episodes of cholangitis. He underwent endoscopic stenting with no relief of symptoms. Surgical resection (extended right hepatectomy with excision of extrahepatic biliary tract) was carried out

serial imaging to detect any increase in size is recommended. Biopsy may be necessary in doubtful cases. Resection is only appropriate for large tumors or tumors with significant symptoms. Closure of the predisposing portosystemic shunts has been reported to cause shrinkage of the tumors.

Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumors (IMFT) are predominantly benign lesions of unknown origin. These tumors can occur anywhere in the body and have occasionally been reported in the liver where they may mimic liver tumors.

These lesions have a characteristic histological picture comprising a spindle-cell proliferation admixed with chronic inflammatory cell infiltrate of plasma cells, lymphocytes, and histiocytes (Fig 69.7a). Anaplastic lymphoma kinase gene rearrangements have been noticed in about half of IMFT, further supporting its neoplastic nature. Expression of anaplastic lymphoma kinase is associated with localized disease at presentation and an improved prognosis.

Presentation may be with constitutional symptoms such as fever, jaundice, and weight loss [48]. Their natural history is variable with some reports of spontaneous regression, while some children may develop recurrent episodes. Local invasion has been reported in some cases (Fig. 69.7b). Surgical resection is indicated if the lesion persists or progresses after a trial of conservative therapy, or manifests evidence of local infiltration into vital structures, or of malignant transformation. Complete resection is curative in most patients [49].

Secondary Liver Lesions

Primary tumors such as neuroblastoma and Wilms' tumor can spread to the liver and present as liver metastases. These are usually multiple and are best managed with chemotherapy. Surgical resection is rarely an option in these cases.

Conclusion

Liver tumors in children are uncommon. Most present as an abdominal lump and are usually advanced at initial presentation. HB is the most common childhood liver tumor. Evidence-based multimodality therapy using improved liver resection techniques, LT, and use of effective chemotherapeutic agents has improved outcomes in these tumors.

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