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PEDIATRIC LIVER MASSES

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DEDICATION

To the spirit of my mother,

Spirit of My father,

My brother Shaban,

My sisters Mervate and Alliaa,

And to all of my family,

I dedicate this work

Mohammad Ghalwash

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Abbreviations

AFP	alpha-fetoprotein
APC	adenomatous polyposis coli
CFTR	cystic fibrosis transmembrane conductance regulator
CK19	cytokeratin 19
CML	Chronic myeloid leukemia
CT	computed tomography
DFS	Disease free survival
EFS	event free survival
FAP	familial adenomatosis polypi
FNA	fine needle aspiration
FNH	Focal nodular hyperplasia
G-CSF	Granulocyte colony stimulating factor
HA	Hepatic artery
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HCC	hepatocellular carcinoma
HD	hydatid disease
HB	hepatoblastoma
ICAM-1	intercellular adhesion molecule 1
IF-α2A	interferon-α2A
IGF2	insulin like growth factor 2
IPA	ifosfamide / cisplatin / doxorubicin
IPT	Inflammatory pseudotumor
IVC	Inferior vena cava
LDH	lactate dehydrogenase
MDCT	multidetector CT
MHL	Mesenchymal hamartoma of the liver
MR	magnetic resonance
MRI	magnetic resonance imaging
NHL	Non Hodgkin Lymphoma
NK	natural killer
NRH	Nodular regenerative hyperplasia
OLT	orthotopic liver transplantation
OS	overall survival
PAS	periodic acid-Schiff
PECAM-1	platelet endothelial cell adhesion molecule 1
PLA	Pyogenic liver abscess
PLS	Papillon-Lefèvre syndrome
PV	portal vein
SGOT	Serum glutamic-oxaloacetic transaminase

SIOP	International Society of Pediatric Oncology
SNPCL	solitary nonparasitic cyst of the liver
TNM	tumor, node, metastases
UES	Undifferentiated embryonal sarcoma
US	Ultrasound
U.S.	United States
VP	ventriculoperitoneal

Introduction

Hepatic masses are increasingly being diagnosed, often as a result of more frequent and sophisticated imaging. Lesions can be detected during screening for primary or metastatic tumors, or as an incidental finding. Although some have distinctive radiological appearances allowing for a confident diagnosis, histological assessment of biopsy and resection specimens remains the cornerstone for the correct identification of many lesions ***(Clouston, 2004).*** The list of differential diagnosis, when meeting a child suffering from a hepatic mass, is long (table 1). It includes benign and malignant primary tumors, vascular tumors, metastases, cysts and abscesses. When hepatic masses are symptomatic, they most commonly manifest as a palpable mass with abdominal distention. Other signs and symptoms may include pain, anorexia, weight loss, fever, jaundice, and congestive heart failure (***Siegel, 2001***).

There are several benign and malignant processes in the liver, which are different from the normal and diffuse pathological alterations in smaller or bigger forms of hepatic nodules. Some of them are benign alterations having no clinical significance, but they have some difficulties in the differential diagnosis (***Palko, 2004***). In children, **benign** tumors constitute only 30% of liver tumors and most are vascular in origin (***Reynolds, 1999***). There is a remarkable diversity of conditions encompassed by benign liver masses in infants and toddlers. The most common **benign hepatic tumor** in this age group is infantile hepatic hemangio-endothelioma. It has no morphologic counterpart in the adult liver if one allows for the difficulty in the differential diagnosis in some cases with angiosarcoma (***Chandra, 1992***). The differential diagnosis of

benign hepatic tumors includes nonneoplastic cystic masses including biliary and simple hepatic cysts, hematoma, parasitic cysts, and pyogenic and amebic liver abscess (***Meyers and Scaife, 2000***).

Table (1): Classification of Liver Masses.

Benign liver tumors	Hemangiomas & Hemangioendothelioma
	Focal nodular hyperplasia
	Hepatic adenoma & Adenomatosis
	Mesenchymal hamartomas
	Lymphangioma & Lymphangiomatosis
	Nodular regenerative hyperplasia
	Cystadenoma
	Teratoma
	Myxoma
Malignant liver tumors	Hepatoblastoma
	Hepatocellular carcinoma & fibrolamellar variant
	Undifferentiated embryonal sarcoma
	Rhabdoid tumor
	Rhabdomyosarcoma
	Angiosarcoma
	Malignant germ cell tumor
	Non-Hodgkin's lymphoma
	Metastases: neuroblastoma, Wilms' tumor, rhabdomyosarcoma, germ cell tumor, lymphoma, leukemia, Langerhans' cell histiocytosis, chriocarcinoma, pancreatoblastoma, carcinoid
Benign bile duct tumors	Granular cell tumor
	Inflammatory pseudotumor
Malignant bile duct tumors	Cholangiocarcinoma
	Adenocarcinoma
	Rhabdomyosarcoma
Non-neoplastic liver masses	Cysts: simple hepatic cyst, peliosis hepatis, parasitic Hydatid cyst
	Liver abscesses: amebic liver abscess, pyogenic liver abscess
	Hematoma & biloma
	Inflammatory pseudotumor

(Stringer, 2000)

Primary hepatic neoplasms in children are relatively infrequent, accounting for between 0.5 and 2.0% of all pediatric neoplasms. They are a diverse group of epithelial and mesenchymal tumors whose incidence can vary considerably with patient age. They are clinically relevant tumors however as two thirds of them are malignant (***Emre and McKenna, 2004***). The liver is one of the most common sites of primary abdominal neoplasm in children. **Hepatoblastoma** (HB) represents up to 85% of primary pediatric liver tumors and is followed in frequency by hepatocellular carcinoma (HCC) and infantile hemangioendothelioma. Pediatric liver masses require accurate characterization and estimation of extent relative to hepatic segmental and vascular anatomy, which have been improved with the use of multidetector CT (MDCT) and MRI. Histologic examination is still needed to characterize some benign liver tumors ***(Van Beers et al., 2003).***

Metastatic hepatic lesions such as neuroblastoma, Wilms' tumor, and lymphoma are the most common neoplasms seen in the liver. Some distinct primary liver tumors may be seen rarely, including leiomyosarcoma, rhabdoid tumor, and endodermal sinus tumor. But five of the primary hepatic neoplasms--hepatoblastoma, infantile hemangio-endothelioma, mesenchymal hamartoma, undifferentiated embryonal sarcoma, and embryonal rhabdomyosarcoma of the biliary tree--commonly occur only in children (***Stocker, 2001***). An important differentiating factor in the evaluation of pediatric hepatic masses is the age of the patient. Hemangioendotheliomas, hepatoblastomas, mesenchymal hamartomas, and metastatic disease from Wilms tumor or neuroblastoma are usually seen in the first 3 years of life, whereas HCC, focal nodular hyperplasia, hepatic adenoma, and metastases from lymphoma are more common in older children (***Siegel, 2001***).

Aim of work

The aim of this essay is to review the various aspects of liver masses in the pediatric age group. We mean to highlight the different types of masses, the most novel methods of their diagnosis and all the options of their management.

Chapter 1

Embryology, Anatomy and Histology

Embryology of the liver

The liver arises from the hepatic diverticulum of the foregut during the fourth week of gestation ***(Severn, 1971 and Couinaud, 1989)***. As the embryo develops, the blood supply to this region evolves in an elaborate manner to deliver nutrients from three different sources in the sequence: yolk sac, placenta, and gut ***(Strasberg, 1997)***. Hepatocyte precursors, the hepatoblasts, arise from endodermal cells at the advancing front of the diverticulum and invade the mesoderm of the caudal portion of the septum transversum. The vitelline veins traverse the region, bringing blood from yolk sac and digestive tube to the heart (Fig. 1). As hepatoblasts invade the mesenchyme, they disrupt the vitelline veins, tapping their blood supply. This supply is from the vitelline veins, segments of which later become the portal vein (PV). The hepatic bud is subdivided into cords by new capillaries called sinusoids. The sinusoidal flow coalesces into three major hepatic veins ***(Wanless, 2003)***.

At the time the main hepatic veins are developing, the entire liver is composed of only two lobules, and there is no artery and no left or right bile duct. As the hepatic and portal veins (PVs) begin to branch, the branches interdigitate to remain equidistant from each other, and the parenchyma is subdivided into numerous lobules, or acini ***(Ekataksin and Wake 1991)***. The hepatoblast cords develop into anastomosing tubular structures with central bile canaliculi that eventually communicate with the bile ducts. Most hepatoblasts differentiate into hepatocytes, but those adjacent to the portal mesenchyme differentiate into a layer of duct