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The WJH is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database. The 2021 edition of Journal Citation Reports® cites the 2020 Journal Citation Indicator (JCI) for WJH as 0.61. The WJH’s CiteScore for 2020 is 5.6 and Scopus CiteScore rank 2020: Hepatology is 24/62.

RESPONSIBLE EDITORS FOR THIS ISSUE
Production Editor: Xu Guo; Production Department Director: Xiang Li; Editorial Office Director: Xiang Li.

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Nikolaos Pyrropoulos, Ke-Qin Hu, Koo Jeong Kang

EDITORIAL BOARD MEMBERS

PUBLICATION DATE
October 27, 2021

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ONLINE SUBMISSION
https://www.f6publishing.com

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E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com
Pediatric vascular tumors of the liver: Review from the pathologist’s point of view

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Author contributions: Cordier F performed the writing of the paper; Creytens D, Hoorens A, and Van Dorpe J performed the study concept, design and review of the paper; All authors read and approved the final paper.

Conflict-of-interest statement: The authors state that there are no conflicts of interest to disclose.

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Manuscript source: Invited manuscript

Specialty type: Anatomy and

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Abstract

Differential diagnosis of pediatric vascular liver tumors can be challenging due to inconsistent nomenclature, histologic overlap and the rarity of some entities. Here we give an up-to-date overview of the most important entities. We discuss the clinic, histology and pathophysiology of hepatic congenital and infantile hemangioma, hepatic epithelioid hemangioendothelioma and hepatic angio-sarcoma.

Key Words: Hepatic congenital hemangioma; Hepatic infantile hemangioma; Hepatic epithelioid hemangioendothelioma; Hepatic angiosarcoma; Hepatic vascular tumors of infancy; Hepatic hemangiomas

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Core Tip: Overview of the most important pediatric hepatic vascular tumors from the point of view of the pathologist, including hepatic hemangiomas, hepatic epithelioid hemangioendothelioma and hepatic angiosarcoma.

Citation: Cordier F, Hoorens A, Van Dorpe J, Creytens D. Pediatric vascular tumors of the liver: Review from the pathologist’s point of view. World J Hepatol 2021; 13(10): 1316-1327
URL: https://www.wjgnet.com/1948-5182/full/v13/i10/1316.htm
DOI: https://dx.doi.org/10.4254/wjh.v13.i10.1316

INTRODUCTION

Through the years the classification of vascular anomalies in the liver has evolved due to better biological understanding with substantial contribution of molecular genetics
Hepatic hemangiomas belong to the group of benign vascular tumors. The term “hemangioma” has been used through the years for a variety of vascular malformations of the liver. In 2018, the ISSVA reserved this term for vascular lesions that match the definition of congenital or infantile hemangiomas. These benign endothelial neoplasms can occur in the liver and belong to the histologic group of “hepatic hemangioendothelioma, type 1” (Figure 1). However, the term ‘hemangioendothelioma’ has to be used with caution, due to the terminology overlap with epithelioid hemangioendothelioma (which is considered as a malignant vascular entity) and should be avoided in absence of histologic evaluation. Further, histologic confirmation of hemangiomas is often not required, since the diagnosis can easily be made with physical examination, imaging and review of patient’s history. Still, a biopsy can be performed when the history or clinical/radiological features are atypical. Hemangiomas are characterized by a proliferation, plateau and involution phase. They occur due to an imbalance in angiogenesis, resulting in an uncontrolled proliferation of vascular elements. Involvement of the lesions is characterized by a decrease in angio-genic factors, endothelial cell apoptosis and high levels of angio-genic inhibitors, replacing the endothelial cells by loose stromal tissue.

Hepatic congenital hemangioma

Hepatic congenital hemangiomas (HCH) are benign high-flow vascular tumors that proliferate in utero and are fully grown at birth with no postnatal increase in size. They are less common than hepatic infantile hemangioma (HIIH) and present mostly as a solitary lesion. Diagnosis can be made on prenatal imaging showing a large mass with extensive central infarction, hemorrhage, calcifications and sometimes large abnormal vessels, suggestive for arteriovenous malformation. They can be asymptomatic or can cause intratumoral bleeding, thrombocytopenia, hypofibrinogenemia (Kasabach-Merritt syndrome, occasionally associated with large hepatic hemangiomas) and high-output cardiac failure.

The most important clinical differential diagnoses of a liver mass in infants include hepatic infantile hemangioma (HIIH), epithelioid hemangioendothelioma, hepatoblastoma, germ cell tumors, (metastatic) neuroblastoma, mesenchymal hamartoma, cysts and abscesses. There are 3 clinical subtypes depending on the pattern of evolution: rapidly involuting congenital hemangioma (RICH), partially involuting congenital hemangioma (PICH) and noninvoluting congenital hemangioma (NICI). These subtypes share common histopathologic features and have to be seen as a single entity with differences in their clinical behavior.

Histologically (Figure 2), HCHs are usually well-demarcated vascular lesions which can show entrapment of hepatocytes and bile ducts in interface areas. RICH is composed of lobules of variable sized, mostly small thin-walled vessels lined by plump endothelium without cytonuclear atypia. There may be evidence of thrombosis and the central part (i.e., the first area of involution) may contain necrotic and hemorrhagic areas, fibrosis and focal dystrophic calcifications. Extramedullary hematopoiesis can also be observed. At the periphery of the lesion abundant larger vessels occur, sometimes associated with aneurysmal changes. In contrast to RICH, NICI shows lobules of small vessels with interlobular fibrosis but without signs of involution. Arteriovenous microfistulae with large irregular vessels in the center can occur. PICH shows histologic overlap between RICH and NICI and cannot be distinguished histologically. Endothelial cells show immunoreactivity for Wilms’ Tumor 1 (WT-1), CD34, CD31, factor VIII and Erythroblast transformation.
specific [ETS]-related gene (ERG)[13-15]. Triana et al[16] showed there was no expression of podoplanin (D2-40) in HCH. However, El Zein et al showed focal positivity for podoplanin in congenital hemangiomas of the skin, mainly in abnormal extralobular lymphatic vessels or in patients with concomitant thrombocytopenia (with decrease of intensity when platelet count normalized)[13]. The endothelial cells of HCH do not stain for glucose transporter-1 (GLUT-1), which is an important hallmark in the differentiation of HCH with HIH (Figure 2)[5,10].

Genetic studies revealed that almost all HCHs have mutually exclusive, missense mutations that alter glutamine at amino acid 209 (Gln209) in the alleles which code for guanine nucleotide-binding protein G(q)alpha (GNAQ) and guanine nucleotide-binding protein subunit alpha-11 (GNA11), regardless of subtype. This implies that also other genetic, epigenetic and/or environmental factors may influence the behaviour of these lesions[10,17]. A subset shows missense mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) (c.3140A > T; p.His1047Leu)[16].

**Hepatic infantile hemangioma**

HIH is the most common benign hepatic tumor in infancy, with female predominance[7]. It proliferates rapid after birth, reaching a maximal size at 6 to 12 mo, and then it gradually involutes until 3 to 9 years[5,6]. Most hemangiomas are asymptomatic and remain undetected or are incidental findings on postnatal imaging. Still, a subset can be symptomatic due to their size, location or hemodynamic effects[8]. The high flow within the tumor or presence of shunts can cause cardiac failure. Also, thrombocytopenia and anemia can be observed when intralesional thrombosis occurs[5,8,18,19]. Due to high expression of type 3 iodothyronine deiodinase in these vascular lesions, which inactivates thyroid hormone, acquired consumptive hypothyroidism occurs. All of these complications are detected after birth during the proliferation phase and can be missed initially on newborn screening[5]. Further, HIH can occur in association with Beckwith-Wiedemann syndrome[6].

The clinical differential diagnosis of HIH is broad and includes arteriovenous malformations, arteriportal fistula, mesenchymal hamartoma, hepatoblastoma, angiosarcoma and (metastatic) neuroblastoma[8].

HIH presents clinically/macroscopically as white-tan nodules with occasionally degenerative changes in the centre[9]. They can be divided into 3 categories based on degree of unaffected liver parenchyma: focal, multifocal or diffuse disease. Focal HIH shows overlap with RICH, as it does not express GLUT-1 and can be found on prenatal imaging[8,18,19]. Therefore, focal HIH is not considered as a true HIH[8]. Multifocal HIH presents as areas of hemangioma with intervening segments of normal hepatic parenchyma, whereas a diffuse pattern is defined as innumerable tumors with nearly
Figure 2 Hepatic congenital hemangioma. A: A relatively well-demarcated vascular lesion; B: Lobules of variable sized, mostly small thin-walled vascular spaces and more abundant larger vessels at the periphery; C: Necrotic and hemorrhagic areas in the central part (area of involution); D: Entrapment of hepatocytes and bile ducts in interface areas.

Figure 3 Hepatic congenital hemangioma. A: Erythroblast transformation-specific-related gene expression of endothelial cells; B: No GLUT1 expression of endothelial cells.

complete hepatic parenchymal replacement\cite{5}. Diffuse HIH shows a higher risk of complications, e.g., abdominal compartment syndrome, heart failure, profound hypothyroidism, and even mortality\cite{5,8}. Associated cutaneous infantile hemangioma is often present in patients with multifocal or diffuse HIH and increases with prematurity. Screening for HIH is therefore advised when multiple cutaneous infantile...
heman-giomas occur (mostly 5 or more), as the liver is the most common visceral site [8,18].

Histologically (Figure 4), HIH are well-demarcated, non-encapsulated vascular lesions composed of lobular, mostly small-sized vessels (capillary-like) with a pericytic cuff, highlighted by the immunohistochemical staining smooth muscle actin (SMA) (Figure 4)[6,9,11,20]. The periphery of these vascular lesions is cellular and mitotic active, with plump endothelial cells (suggesting active growth). Involution is particularly prominent in the center of the lesion and is characterized by reduced cellularity and enlarged vascular spaces lined by flat, mitotically inactive endothelium. The interstitium is fibrotic or fibromyxoid[9]. Bile ducts and hepatocytes are often entrapped within the advancing edge of the tumor. Areas of extra-medullary hematopoiesis may be present[11]. Central infarction, hemorrhage, calcification and abnormally enlarged vessels or arteriovenous malformation (AVM) can be observed[9].

Rarely, these vascular lesions show irregular anastomosing vascular spaces with prominent papillary formation lined by plump, pleomorphic endothelial cells with hyperchromatic nuclei [also known as hepatic hemangioendothelioma type 2 with intermediate histologic characteristics, by some reports considered as a low-grade angiosarcoma (Figure 1)] [5,9,11,21]. The interstitium of these lesions can contain nests of epithelioid endothelial cells, entrapped nests of liver cells, and bile duct epithelium [9]. When these atypical features are seen or when a lesion is persistent or present in an older child, follow-up is indicated, because of the potential of malignant transformation[6,9].

Multifocal and diffuse HIH show positive staining for GLUT-1, which correlates with a high cell-proliferation and distinguish them from other types of vascular liver tumors (Figure 5)[5,10,22]. The endothelial cells are also positive for ERG, CD31, CD34 and factor VIII but do not express the lymphatic marker podoplanin [D2-40 (Figure 5)] [5,15,21].

There are several hypotheses for the pathophysiology of HIH and its cutaneous counterpart. Clinical observations suggested hypoxia as a trigger for infantile hemangio (IH). Hypoxia may be due to maternal events as well as the infant’s own hypoxia-induced factors and is associated with GLUT-1, as GLUT-1 is a downstream target of hypoxia-inducible factor-1-alpha (HIF-1α), along with vascular endothelial growth factor A (VEGF-A) and insulin-like growth factor 2 (IGF-2). Also, the renin-angiotensin system (RAS) may play a role because high concentrations of angiotensin II (ATII), due to local expression of angiotensin-converting enzyme (ACE) in IH, stimulate cell proliferation. Further, IH expresses GLUT-1 and vascular antigens like Fc-gamma-receptor II, merosin, and Lewis Y antigen, which are also expressed in placental tissue. Another study found that IH endothelial cells share a similar immunophenotype (CD34 and CD133 positive) with embryonic veins, suggesting IH endothelial cells are in an early stage of vascular differentiation[23]. Further, Takahashi et al observed an imbalance of vasculogenic factors in IH. During the proliferating phase, IH shows a high expression off type IV collagenase and vascular endothelial growth factor (VEGF) and when involuting there is an increase in tissue metalloproteinases, inhibiting new vessel formation[24]. Moreover, Walter et al showed allelic loss after methylation-based and transcription-based polymerase chain reaction clonality assays, suggesting a nonrandom X-inactivation pattern and, thus, a monoclonal origin of IH. In addition, they found 2 cases of IH with a missense mutation, one in the kinase domain of the vascular endothelial growth factor receptor (VEGFR2) gene and one in the kinase insert of the VEGFR3 gene. These observations all suggest an alteration in the VEGF signaling pathway in IH[25].

### EPITHELIOID HEMANGIOENDOTHELIOMA

Epithelioid hemangioendothelioma (EHE) is a rare malignant vascular tumor, which can occur anywhere in the body but typically arises in liver and lung[4,26]. It is mostly seen in adults, but can be diagnosed in children (estimated prevalence of 1/1000000, mean age 13,8 years)[27]. Hepatic EHEs show a more aggressive course than when arising in bone/soft tissue and are mostly multifocal. Hepatic EHE presents in most cases as a tumoral mass and has an unpredictable clinical course. It may be indolent, stable or aggressive[26,27]. Size > 3 cm and high mitotic index (> 3 mitoses/50 HPF) are poor prognostic factors in elderly[26].

EHEs appear macroscopically as solid, white lesions with some hemorrhagic changes[20]. Histologically (Figure 6), EHEs are relatively distinctive from the normal liver parenchyma and are composed of nests, cords, strands or single infiltrative epithelioid cells set in a myxohyaline stroma. The cells in HEH are epithelioid with
Figure 4 Hepatic infantile hemangioma. A: A well-demarcated vascular lesion; B: Lobular, small-sized vascular spaces.

eosinophilic cytoplasm and frequently show intracytoplasmic vacuoles (so-called “blister cells”) [20,28]. Occasionally, there are tufts or papillary projections into the vessels. A subset of EHE shows histologic overlap with hepatic angiosarcoma (HA) containing necrosis or moderate to severe cytonuclear atypia (with large hyperchromatic cells), without the typical myxoid stromal component. In this setting, the distinction between EHE and HA can be difficult for a pathologist, especially in small liver biopsies. Usually EHE shows nuclear calmodulin-binding transcription activator1
Figure 6 Hepatic epithelioid hemangioendothelioma. A: Nests, cords, strands and single infiltrative epithelioid cells with intracytoplasmic vacuoles; B: Nests, cords, strands and single infiltrative epithelioid cells with intracytoplasmic vacuoles; C: Nuclear calmodulin-binding transcription activator1 (CAMTA1) expression; D: Nuclear CAMTA1 expression.

(CAMTA1) expression, which can be very helpful in the differential diagnosis with HA since this is a highly specific and sensitive marker for EHE with a CAMTA1 rearrangement (Figure 6) [28]. EHE also stains for ERG, CD31, CD34, factor VIII and podoplanin (D2-40) [15, 20, 28]. Nuclear positivity for transcription factor E3 (TFE3) is seen in most cases of EHE, irrespective of an underlying TFE3 rearrangement [20, 28]. A small subset of EHE expresses pan-cytokeratin or cytokeratin 8/18 [28].

Most of the EHEs are characterized by chromosomal translocations involving 1p36.3 and 3q25 resulting in WW domain-containing transcription regulator1 (WWTR1, also known as TAZ) – CAMTA1 fusion genes. A small subset shows Yes-associated protein 1 (YAP1)-TFE3 gene fusions [26, 28]. TAZ and YAP are transcriptional coactivators and effectors, which are downregulated by the Hippo tumor suppressor pathway. WWTR1 -CAMTA1 fusion genes therefore induce oncogenic transformation due to constitutive nuclear localization and activation of TAZ independent of the Hippo pathway [26].

HEPATIC ANGIOSARCOMA

Hepatic angiosarcoma (HA) is a rare high-grade malignant vascular tumor that occurs mostly in elderly [5, 29, 30]. Seldom they occur in children and the majority of pediatric angiosarcoma cases arises in the heart/pericardium and mediastinum [29]. When occurring in the liver angiosarcoma presents as a rapid enlargement of the liver associated with jaundice, abdominal pain, vomiting, fever, tachypnea, dyspnea and anemia [30]. Consumptive coagulopathy, disseminated intravascular coagulation and congestive heart failure are known complications [31]. In children HA has a female predominance and occurs mostly around 40 mo. It represents 1%-2% of all pediatric liver tumors and has the potential to metastasize, even at the onset of the disease. Metastasis is commonly found in the lungs [30, 32]. HA can occur in the background of
a HIH or can develop 4 to 5 years after primary diagnosis of HIH. Therefore, HIH in patients older than 1 year, should be followed carefully[30]. Also, in the past, several chemical carcinogens, including vinyl chloride monomer (VCM), thorotrast, radium and arsenic, have been associated with HA formation[33,34]. Pediatric HA has a poor
prognosis with an average survival of 16 mo and a 5-year overall survival of 20%-35% [30,32].

Diagnosis of a HA can be really challenging, as it is an extremely rare tumor and there are no specific radiographic characteristics that differentiate malignant vascular hepatic tumors from benign ones[33,35]. Histologic diagnosis can only be obtained by adequate and representative tissue biopsies, received by laparotomy[35].

Macroscopically, HA presents as a large solitary mass, or as multiple or diffuse nodules in the centre and periphery of the liver. Often sponge-like hemorrhagic areas alternate with solid gray-white nodules, surrounded by normal liver parenchyma (Figure 7)[31,36]. Commonly, both liver lobes are affected[35,36]. Histologically (Figures 8 and 9), HA shows an unencapsulated vascular tumor lesion composed of anastomosing vascular spaces and sinusoids lined by endothelial cells with marked cytological atypia and multilayering[29,31,33,35]. The cells are plump, pleomorphic with hyperchromatic nuclei and show brisk mitotic activity[33]. Focally infiltrative whorls or glomeruloid foci of sarcomatoid cells or kaposiform spindle cells with intracytoplasmic PAS positive eosinophilic globules can be seen[30,32,33,35]. Tumor necrosis can be observed[29]. Histologically, HA is classified as hepatic hemangioen-
dothelioma, type 3 (Figure 10)[5]. HA shows immunoreactivity for ERG, CD31, CD34 and factor VIII[15,28,33]. A small percentage expresses pan-cytokeratin[33]. Ki-67 shows a proliferation of more than 10%[36]. HAs are occasionally positive for GLUT-1 and podoplanin (D2-40)[15,22,32]. The spindle cell component may show cytoplasmic immunopositivity for alpha-1-antitrypsin[30].

Uptil now, little is known about the genetics of HA, due to examination of small cohorts with a selected gene panel[34]. KRAS mutations have been described in sporadic and thorotrast-induced HA, and TPS3 mutations in VCM-related HA[37,38]. Also alterations in the RAS-RAF-MAPK pathway, CDKN2A/p16 and PTEN gene have been found[34,39]. Recently a ROS1-GOCP/FIG (Fused In Glioblastome) fusion has been found in 1 case[34,37]. This fusion gene can act as a potential target for therapy. Further, upregulation of VEGF-receptor and consistent increased expression of VEGF are commonly seen[34].

CONCLUSION

Diagnosis of a pediatric hepatic vascular tumor can be challenging, not only for the clinici/radiologist, but for the pathologist as well. Throughout the years immunohistochemical markers[10] and molecular genetics have been proven very helpful in the differential diagnosis of vascular tumors. Here we gave an overview of the most important pediatric hepatic vascular tumors and their histology and pathophysiology. Still there is a lot to discover about these vascular lesions.

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