

## History of the infantile hepatic hemangioma: From imaging to generating a differential diagnosis

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**Author contributions:** All authors contribute to the final manuscript.

**Conflict-of-interest statement:** All the authors declare that they have no competing interests.

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**Manuscript source:** Invited manuscript

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**Received:** January 19, 2016

**Peer-review started:** January 19, 2016

**First decision:** March 24, 2016

**Revised:** April 6, 2016

**Accepted:** June 1, 2016

**Article in press:** June 3, 2016

**Published online:** August 8, 2016

### Abstract

We aim to provide an up-to-date summary of infantile hepatic hemangioma (IHH) and its misnomers and to dialectically present the differential diagnosis of these rare entities of the liver. Eligible peer-reviewed articles on hepatic infantile hemangiomas, published between 2000 and 2015, were reviewed for this study. IHH is the most common hepatic vascular tumor in children. Once a liver mass is identified in an infant, the differential diagnosis ranges from vascular malformations to benign and malignant tumors including mesenchymal hamartoma, hepatoblastoma, metastatic neuroblastoma, so careful physical examination, imaging studies, and, if indicated, tumor markers and biopsy, are of pivotal importance to ascertain the correct diagnosis. Despite the benign nature of IHHs, some of these lesions may demand medical and/or surgical intervention, especially for multiple and diffuse IHH. Complications can include hepatomegaly, hypothyroidism and cardiac failure. Therefore, a close follow-up is required until complete

involution of the lesions. We propose an algorithm to guide the physicians towards the proper management of hepatic lesions.

**Key words:** Hepatic hemangiomas; Infant; Children; Vascular tumors

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**Core tip:** Differential diagnosis of pediatric liver lesions ranges from vascular malformations to benign and malignant tumors. Infantile hepatic hemangioma (IHH) is the most common, benign, hepatic vascular tumor in infants. They are sub-classified in focal, multiple and diffuse lesions, based on degree of unaffected liver parenchyma. Despite the benign nature of IHHs, multiple and diffuse lesions can present with life-threatening complications including severe hypothyroidism and cardiac failure, requiring prompt medical intervention. Therefore, a proper diagnosis is of pivotal importance. Including severe hypothyroidism and cardiac failure, requiring prompt medical intervention, therefore, a proper diagnosis is of pivotal importance.

Gnarra M, Behr G, Kitajewski A, Wu JK, Anupindi SA, Shawber CJ, Zavras N, Schizas D, Salakos C, Economopoulos KP. History of the infantile hepatic hemangioma: From imaging to generating a differential diagnosis. *World J Clin Pediatr* 2016; 5(3): 273-280 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v5/i3/273.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v5.i3.273>

## INTRODUCTION

Infantile hemangiomas (IHs) are the most common benign tumor of infancy, affecting up to 10% of the pediatric population with a higher incidence in female (3:1), preterm infants, and Caucasian population. Most IHs are not present at birth but become apparent a few days to a few weeks after birth. IHs are characterized by a rapid proliferative phase in the first 6-10 mo, followed by a slow involution, which can last up to 10 years<sup>[1]</sup>.

Despite their benign nature, IHs can cause severe morbidities and therefore sometimes require medical intervention<sup>[2]</sup>. IHs can range from asymptomatic to life threatening. Vital functions such as breathing, vision, and feeding can be impaired, depending on the location of the lesion.

IHs are confirmed by positive immunostaining for glucose transporter-1 (GLUT-1), which is pathognomonic for the diagnosis of IHs, and therefore helps to distinguish IHs from other vascular anomalies<sup>[3]</sup>. While most IHs are present in the skin, IHs can occur in the viscera, with or without cutaneous manifestations. The liver is the most common site of visceral IHs, followed by the gastrointestinal system<sup>[4]</sup>.

Screening for liver IHs (IHH) by ultrasonography

(USG) is recommended when 5 or more cutaneous IHs are noted. However, the majority of IHHs are discovered as incidental findings during routine imaging.

IHHs are classified in three different subtypes, focal, multifocal and diffuse IHH, based on the remaining unaffected liver parenchyma.

Singular or focal lesions will often involute rapidly after birth without any complications. Multifocal lesions tend to involute in a similar pattern to cutaneous IHs, over a 6-10 year period. Diffuse lesions tend to replace almost the entire liver parenchyma, with severe complications.

These can include cardiac failure<sup>[5]</sup>, high volume arteriovenous shunting<sup>[6]</sup>, hypothyroidism secondary to overproduction of type III iodothyronine deiodinase<sup>[7]</sup>, bleeding and abdominal compartment syndrome<sup>[8]</sup>.

Therefore, once diagnosed, patients with IHHs usually require close monitoring until complete involution of the lesions.

Before the modern classification system developed by Mulliken in 1982<sup>[9]</sup>, and the more recent subtyping of liver IHs by Christison-Lagay *et al*<sup>[10]</sup> in 2007, there was widespread confusion. Terminology for IHHs has been varied, a fact which can propagate the confusion and delay in the correct diagnosis and proper treatment of the affected patients. Moreover, there are several other hepatic lesions that may mimic different types of IHHs. Solitary hepatic lesions in an infant can also include, hepatoblastoma, mesenchymal hamartoma, congenital cysts (such as ciliated foregut duplication cysts) or kaposiform hemangioendotheliomas (KHEs). IHHs have also been historically called "hemangio-maendothelioma", regardless of the type of lesion.

It is therefore imperative to distinguish all 3 subtypes of true IHHs from other benign and malignant liver lesions, as this can deeply impact the management of these conditions. For this reason, we systematically review the literature in order to provide an up-to-date understanding of IHHs and their misnomers and to dialectically present the differential diagnosis of these rare entities of the liver.

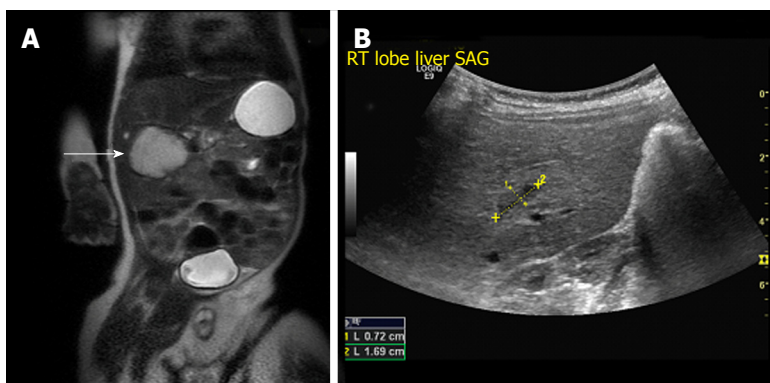
## RESEARCH AND LITERATURE

Eligible articles were identified thorough search of the PubMed bibliographical database extending from January 2000 to 2015. Two investigators working independently executed the search using the following keywords in all the possible combinations: Hepatic hemangioma, infantile hepatic hemangioma, liver hemangioma and visceral hemangioma. In addition, we checked all the references of relevant reviews and eligible articles that our search retrieved. Search of the literature was restricted to those articles published in English, based on the following criteria: (1) original clinical series and case reports describe infants with hepatic hemangiomas; and (2) reviews of the literature on infantile hepatic hemangiomas. The selection-process excluded at the same time: (1) studies that

**Table 1** Description of the clinical, radiological, histological findings of the different subtypes of infantile hepatic hemangiomas and recommended treatment for the three different subgroups of infantile hepatic hemangiomas

IHH	Focal	Multifocal	Diffuse
Onset	Prenatal development	Postnatal (few weeks after birth)	Postnatal (few weeks after birth)
Association with cutaneous IH	Rarely	Frequently	Frequently
MRI	Solitary tumor; robust enhancement; often with Ca <sup>2+</sup> and central cystic change	Hypointense to liver on T1, hyperintense on T2. Rapid enhancement. May have central flow voids on T2 spin echo sequence	Near-total replacement of the hepatic parenchyma with many lesions
CT	Rapid enhancement. Often with Ca <sup>2+</sup> and central cystic changes	Homogenously; uniform or centripetal	Innumerable centripetally but rapidly enhancing lesions
Glut-1 staining	Negative	Positive	Positive
Comorbidities	Possible anemia and relatively mild thrombocytopenia; AV shunting; High-output cardiac state	High-flow shunting resulting in high-output; Cardiac failure	High-output cardiac failure; Abdominal compartment syndrome; Severe hypothyroidism
Treatment	Observation; embolization for problematic shunting	Observation; propranolol/embolization for problematic shunting, possibly propranolol; hypothyroidism	Propranolol, thyroid hormone replacement, embolization in the cases of severe arteriovenous shunting (rare in diffuse IHHs), transplantation evaluation for the most extreme cases

IHH: Infantile hepatic hemangioma; CT: Computed tomography; MRI: Magnetic resonance imaging.



**Figure 1** Focal infantile hepatic hemangiomas. A: Coronal T2 weighted MRI image through the abdomen of an 8-wk-old boy revealing a large hyperintense mass arising from the liver (arrow); B: Abdominal USG of the same patient at 17-mo-old shows a minimal residual scar (demarcated by calipers). USG: Ultrasonography; MRI: Magnetic resonance imaging.

describe malignant lesions alone; (2) lesions that are mistakenly categorized under the definition of infantile hepatic hemangiomas; (3) studies that do not contain the main outcomes of interest as described below.

In addition, historical evaluations of the failings of certain clinical treatments from beyond that timeline have been considered and included in order to present the story of IHHs as it has evolved.

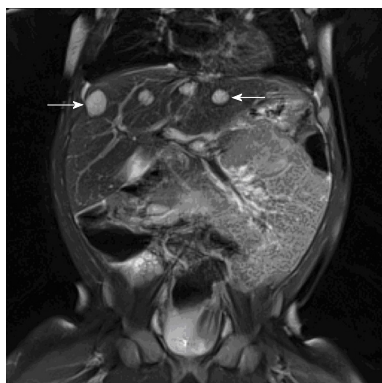
## CLINICAL PRESENTATION

A complete description of the clinical, radiological, histological findings of the different subtypes of IHH, and recommended treatment, can be found in Table 1. IHH lesions typically present and evolve in three different categorized patterns: Focal lesions, multifocal lesions, and diffuse lesions<sup>[11]</sup>.

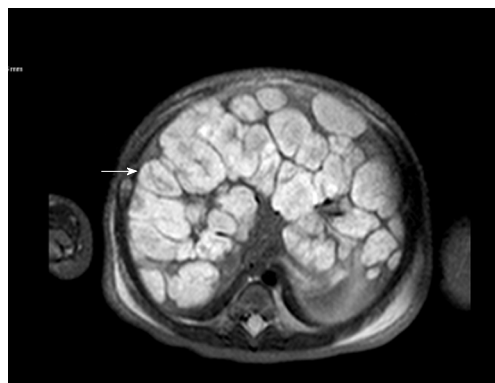
### Focal lesions

Focal lesions are completely formed at birth and are mainly detected prenatally during routine USG. They fully involute soon after birth, sharing a similar evolution of their cutaneous counterpart, rapidly involuting

congenital hemangiomas (RICHs)<sup>[10]</sup>. Similar to RICHs, focal hepatic hemangiomas stain negative for GLUT-1. Magnetic resonance imaging (MRI) shows these lesions as single hypointense areas relative to the surrounding liver parenchyma on T1-weighted sequences, and hyperintense on T2-weighted sequences (Figure 1)<sup>[12]</sup>. They often demonstrate central cystic areas that may be interpreted as central necrosis. In over 15% of cases, focal liver lesions are associated with cutaneous IHs<sup>[13]</sup>. Despite being usually asymptomatic, focal lesions can be accompanied by mild thrombocytopenia and arteriovenous shunting, which may require medical intervention if present after involution of the IHH. The presence of mild thrombocytopenia has to be distinguished from Kasabach Merritt Phenomenon (KMP) in which the symptoms of severe thrombocytopenia and coagulopathy are seen in combination with a rapidly growing vascular lesion. KMP is associated with KHE and Tufted Angiomas, rare and locally aggressive vascular infantile tumors which are part of the same neoplastic spectrum<sup>[14]</sup>. Mild coagulopathy can also occur in venous malformations and can be defined as Localized Intravascular Coagulopathy.



**Figure 2 Multiple infantile hepatic hemangiomas.** Coronal T2 weighted MRI image through the upper abdomen in a 5-mo-old girl depicts multiple well-defined, T2 hyperintense masses in the liver (arrows). This was consistent with multifocal infantile hepatic hemangiomas. MRI: Magnetic resonance imaging.



**Figure 3 Diffuse infantile hepatic hemangiomas.** T2 weighted axial MRI image of a 7-d-old with diffuse hemangiomas. Note the innumerable T2 hyperintense masses throughout the liver with central hypo-intense central regions (arrow). MRI: Magnetic resonance imaging.

### Multifocal lesions

Multifocal lesions share a similar clinical course with cutaneous IHS. As for the cutaneous counterpart, multiple IHHs develop postnatally and exhibit a proliferating phase of around 9-12 mo in length, followed by a slow involution phase. They are more prevalent in females and Caucasians, and stain positive for GLUT-1. Multifocal IHHs can be detected on MRI as intensely enhancing spherical masses that are hypointense relative to the liver on T1-weighted sequences and hyperintense on T2-weighted sequences. They often present with a stellate (star shaped) central flow void on T2 spin echo sequences (Figure 2). Unlike focal lesions, multifocal IHHs can lead, in some cases, to moderate cardiomegaly and high-output heart failure due to arteriovenous and portovenous shunting. In over 60% of the cases, multifocal lesions are accompanied by cutaneous counterparts<sup>[5]</sup>.

### Diffuse lesions

Diffuse lesions are characterized by massive replacement of the hepatic parenchyma with various proliferating lesions with hyper enhancement on MRI (Figure 3). They have similar demographics with multifocal lesions, and also stain positive for GLUT-1. Association of cutaneous IH, may be present. Aortovenous, aortoportal, and venoportal shunting lead to high output cardiac failure<sup>[15]</sup>. Severe hepatomegaly may lead to compression of the systemic veins and thoracic cavity, leading to respiratory distress, abdominal compartment syndrome and multi-organ system failure. Diffuse lesions may also lead to severe hypothyroidism due to massive overproduction of type III iodothyronine deiodinase<sup>[7]</sup> (an enzyme involved in converting thyroxine into an inactive form) and leads to acquired hypothyroidism. Therefore, it is mandatory that when diffuse lesions are suspected, thyroid hormone levels be closely monitored, as undetected hypothyroidism can cause permanent neurologic damage, impaired hemostasis, and low-flow cardiac depression<sup>[16]</sup>.

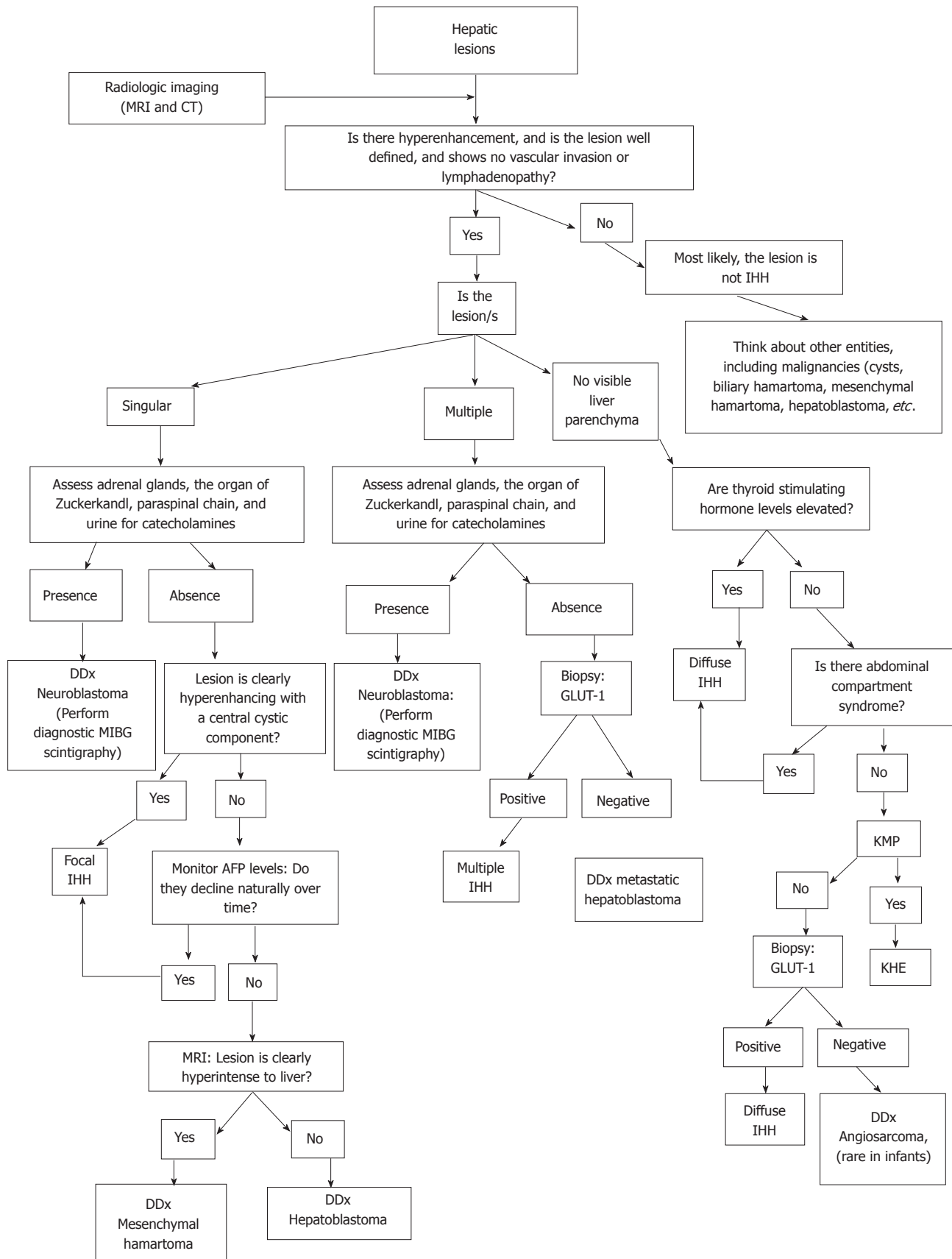
## DIFFERENTIAL DIAGNOSIS

Since IHHs are benign lesions, more aggressive liver malignancies need to be excluded at the time of diagnosis that at times may be challenging. Radiological imaging should be the first-line diagnostic analysis for physicians. A schematic algorithm to guide physicians through correct diagnosis and management of hepatic lesion can be seen in Figure 4.

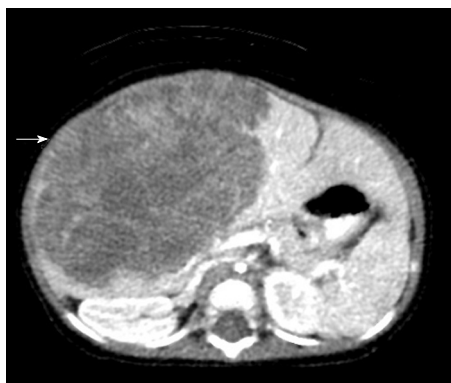
### Single lesions

Focal hepatic hemangiomas have been shown to be biologically identical to RICH. They may present with central calcifications, a finding amenable to detection by ultrasound or CT scan. Posterior acoustic shadowing and high density are the hallmarks of calcification on ultrasound and CT scan, respectively. The primary differential diagnoses include metastatic neuroblastoma, hepatoblastoma (Figure 5) and mesenchymal hamartoma (Figure 6). Primary sites of neuroblastoma (adrenal glands, organ of Zuckerkandel and paraspinal chain) should be evaluated and the urine samples should be screened for the presence of catecholamines. If the above results are unremarkable, the lesion demonstrates hyper enhancement (either on multiphase CT with iodinated contrast or MRI with gadolinium based contrast material) and there is no invasion of other structures, then a presumptive focal IHHs may be diagnosed but should still be monitored to ensure there is no further growth.

Unlike IHHs, hepatoblastomas typically demonstrate a more heterogenic signal on T2 weighted MRI. The enhancement pattern is variable after the administration of contrast. Hepatoblastomas often enhance less than the surrounding hepatic parenchyma, as opposed to the typical hyper enhancement of IHHs. When hepatoblastoma is considered in the differential diagnosis of IHH,  $\alpha$ -fetoprotein (AFP) levels should be monitored over time. AFP is a major plasma protein produced by the yolk sac and later on from the liver during fetal



**Figure 4** A schematic algorithm to guide physicians through correct diagnosis and management of hepatic lesions. IHH: Infantile hepatic hemangioma; CT: Computed tomography; MRI: Magnetic resonance imaging; DDx: Differential diagnosis; GLUT-1: Glucose transporter-1; AFP:  $\alpha$ -fetoprotein; KHE: Kaposiform Hemangioendothelioma.



**Figure 5 Hepatoblastoma.** Axial computed tomography scan after the injection of IV contrast material in a 7-mo-old girl demonstrates a poorly enhancing large mass within the liver (arrow).



**Figure 6 Mesenchymal hamartoma.** 15-mo-old with abdominal distention: Axial computed tomography scan after the administration of IV contrast material demonstrates a large multi-cystic mass arising from the liver (arrow). Additional mixed solid and cystic elements are present laterally in the expanded left hepatic lobe.

development. At birth, normal infants have high AFP levels that decreases to a normal range over the first year of life. A baseline measurement in an infant with a focal hepatic lesion can be useful to be certain AFP is appropriately trending down towards the normal range, especially in a patient for whom the diagnosis of focal IHHs is later questioned. In case of hepatoblastomas, AFP levels do not decline over time.

Persistent mild elevation of AFP can also be observed in mesenchymal hamartoma. Mesenchymal hamartoma lesions typically appear distinct from IHHs, as they have predominant cystic components. However, the more mass-like variants can have some imaging overlap with IHHs. Both IHHs and mesenchymal hamartomas are benign lesions. In the literature evidence of association between these two entities has been reported<sup>[17]</sup>.

### Multiple and diffuse lesions

When multiple well-demarcated hepatic lesions are present - particularly if they demonstrate avid enhancement at MRI, and all appear similar on each sequence - a multifocal IH is the most likely diagnosis, although an atypical presentation of neuroblastoma is still possible. When the hepatic parenchyma appears entirely or nearly entirely replaced with similar appearing lesions as previously described without other abdominal masses, diffuse IHH is likely. The diagnosis can be more confidently made in the context of supporting evidence such as profoundly suppressed thyroid function (or can say elevated TSH), bleeding or compartment syndrome. For a presumptive diagnosis of IHHs, regardless of the subtype, the enhancement pattern must be hyperacute (*i.e.*, arterial), the lesion(s) must be well defined and there must not be any vascular invasion or lymphadenopathy. If any of these criteria are not met, an alternative diagnosis should be considered. The lesion may warrant tissue sampling or resection.

Other rare tumors that can potentially mimic IHHs include the KHE. This tumor is more infiltrative appearing (less well-defined) and Kasabach-Merritt phenomenon often accompanies it. Undifferentiated embryonal sarco-

ma is a primary hepatic tumor, which can be included in the differential diagnosis (DDx), however it typically presents later in childhood. Though it is typically rare in infants, angiosarcoma can mimic IHH on CT and MRI. In this case of suspected malignancy, a biopsy staining for GLUT-1 positivity can rule out or confirm the diagnosis of IHHs.

Radiological imaging can prove extremely helpful to further characterize the lesion(s) and define the anatomic extent of liver involvement. For instance, radiologically IHHs can be differentiated from hepatoblastomas. Hepatoblastomas tend to appear heterogeneous on a T2 weighted MRI sequence and enhance heterogeneously as opposed to the homogeneous and rapid enhancement of IHHs. If there are atypical features, percutaneous biopsy and staining for GLUT-1 positivity is indicated, despite the high risk of bleeding<sup>[4]</sup>. DDx includes also other benign lesions such as cysts, biliary hamartomas and arteriovenous malformations. These entities, however, present imaging characteristics in the neonates that do not overlap with IHH.

## MANAGEMENT OF COMPLICATIONS

Despite the benign nature of IHHs, a careful follow-up should be planned in case of hepatic lesions. Unlike focal IHHs, multifocal and diffuse IHHs may lead to severe complications and possibly death<sup>[18]</sup>.

Multifocal and diffuse lesions are often associated with arteriovenous shunting. In this case, frequent echocardiograms and close cardiologic follow-ups should be recommended until complete regression of the lesion, due to increased risk of congestive heart failure secondary to high-cardiac output. Congestive heart failure represents the main cause of mortality in these patients.

In case of severe high-flow arteriovenous shunting, embolization should be considered. Shunt embolization should be attempted however only in refractory lesions and those with a worsening clinical course. Poten-

tial complications of this procedure include hepatic infarction, necrosis, cirrhosis, and sepsis. Therefore, embolization has to be performed only when expert interventional radiologists, skilled in performing intra-hepatic infant embolization, are available.

As previously mentioned, another possible complication of multifocal and diffuse IHHs is severe consumptive hypothyroidism. For this reason, TSH, T3, and T4 levels should be closely monitored by specialized pediatric endocrinologists. Thyroid hormone replacement should be considered if thyroid hormone levels are low. These patients, however, require much higher doses of thyroxine to achieve a stabilizing euthyroid status than required in patients with congenital hypothyroidism due to continuous catabolism of the exogenous thyroid hormone by the deiodinase 3. As IHHs undergo involution, the hypothyroidism resolves<sup>[19]</sup>. Therefore, thyroid hormone levels represent excellent biomarkers of tumor response to IHHs treatment.

When the lesions occupy a significant portion of the liver parenchyma, hepatic transaminases, bilirubin and coagulation factors should also be included in the laboratory follow-up to monitor liver and coagulation function.

## TREATMENT

Following the validated treatment algorithm developed by the Fishman's group at Boston Children's Hospital<sup>[10]</sup>, focal hemangioma mostly do not require medical intervention, since they mostly involute before or soon after birth. In the rare cases associated with arterio-venous shunting, embolization should be considered. Multifocal and diffuse IHHs may require medical intervention and/or therapy. A recent study confirmed that the mortality rate is greater in patients with diffuse IHHs than in those with multifocal lesions<sup>[10]</sup>. In 2008 there was a serendipitous discovery of the effectiveness of treatment of cutaneous IH with propranolol, a non-selective  $\beta$ -blocker, revolutionizing the treatment of hemangiomas by accelerating IH involution compared to other therapies<sup>[20]</sup>.

IHHs have been shown to successfully respond to the propranolol, as well as the cutaneous counterpart<sup>[21-23]</sup>. Despite this, many studies published after 2008 still indicated interferon- $\alpha$  (INF- $\alpha$ ) and corticosteroids for the treatment of IHHs. It is estimated that 2.5% of children who received INF- $\alpha$  for the treatment of vascular anomalies developed spastic diplegia (SD), while an additional 4.1% were diagnosed with a motor developmental disturbance other than SD<sup>[24]</sup>.

Before propranolol was established as the mainstay therapy, corticosteroids were considered the gold-standard treatment for problematic multifocal or diffuse IHHs<sup>[25]</sup>. However failure rate was as high as 20%-30% and in 40% of cases there was only a stabilization of the lesion growth more than acceleration in the involution<sup>[26]</sup>. Moreover corticosteroids lead to significant side effects. These include growth retardation,

hyperglycemia, Cushingoid syndrome, hypertension and immunosuppression<sup>[27]</sup>. It has to be mentioned, however, that even propranolol is not free from side effects and include hypotension, hypoglycemia and bradycardia and exacerbation of bronchospasm, that are much less severe than the above medications<sup>[22]</sup>.

Before pharmacotherapy proved successful for the treatment of IHH lesions, and when the benign nature of IHHs had not been clearly established, surgical resection and embolization was considered the mainstay treatment<sup>[28]</sup>. Surgery for hepatic hemangiomas is rarely performed, mainly only in cases that are refractory to medical management cases. Surgery complications include internal bleeding and hepatic necrosis<sup>[29]</sup>. In rare case, patients may presents with acute IHH complications such as compartment syndrome. This represents a negative prognostic factor and if medical treatment is not effective decompressed laparotomy up to hepatic transplant should be considered.

## CONCLUSION

The literature of infantile hepatic hemangiomas has been greatly confusing in the past. Recent acceptance of IHH classification and subsequent treatment algorithms have proven an advancement in the diagnosis and management of these vascular lesions. Treatment of IHHs has evolved rapidly in the past decade, especially in the studies on the efficacy of propranolol as opposed to the efficacy and problems with long-term corticosteroid treatment. The understanding of IHHs is likely nearing the tipping point into a new revolution of clinical knowledge and treatment. Based on the new classification of IHHs, we propose an algorithm to guide the physicians towards the proper management of hepatic lesions.

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P- Reviewer: Ji Y, Sirli R S- Editor: Qiu S L- Editor: A  
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