Focal Liver Lesions in Children

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Summary

Focal hepatic lesions in children include tumors, metastasis, inflammatory and cystic (both benign and acquired) lesions. Primary hepatic tumors, both benign and malignant, constitute 1-2% of all pediatric neoplasms. The majority of children with benign or malignant hepatic tumors have a palpable mass at physical examination. Imaging evaluation includes multiple modalities such as ultrasound, computed tomography, magnetic resonance, angiography and nuclear medicine. Since surgical resection is the main therapeutic option in many of these lesions, a

detailed description of the extension and anatomic relations of the mass is essential. In this article we review the imaging characteristics of focal hepatic lesions in children.

Key words (MeSH)

Hemangioendothelioma

Hepatocellular carcinoma

Focal nodular hyperplasia

Hepatoblastoma

Inflammatory pseudotumor

Lesiones focales hepáticas en niños

Resumen

Las lesiones focales del hígado en niños incluyen neoplasias, lesiones metastásicas, masas inflamatorias y quistes (congénitos o adquiridos); las neoplasias primarias —tanto benignas como malignas— representan del 1% al 2% de todos los tumores pediátricos. La mayoría de niños con tumores hepáticos benignos o malignos se presentan al examen físico con masa palpable. Dentro del estudio por imágenes de ésta se encuentran incluidas múltiples modalidades, como ultrasonido, tomografía computarizada, resonancia magnética, angiografía y medicina nuclear. Debido a que la resección quirúrgica es la principal opción de tratamiento para muchas de dichas lesiones, la descripción detallada de la extensión de la masa y sus relaciones anatómicas es esencial. En este artículo realizamos una revisión de las características imaginológicas de algunas lesiones focales hepáticas en niños.

Palabras clave (DeCS)

Hemangioendotelioma

Carcinoma hepatocelular

Hiperplasia nodular focal

Hepatoblastoma

Pseudotumor inflamatorio

Introduction

Focal liver lesions in children include neoplasms, metastatic lesions, inflammatory masses and cysts (congenital or acquired); primary neoplasms – both benign and malignant – are 1%-2% of all tumors in children (1).

Many studies suggest that benign neoplasms are less frequent than malignant tumors (1). Primary liver neoplasms are in third place, in order of frequency, among malignant intraabdominal masses in the pediatric population, after Wilms tumors and neuroblastomas, with an incidence of 5-6% (3). In spite of the fact that liver tumors are the most frequent malignant GI tumors, they are less than 2% of all malignant processes.

Most children with benign or malignant liver masses come into physical exam with palpable masses. Other symptoms include pain, anorexia, jaundice, paraneoplastic syndromes, hemorrhages and congestive heart failure (3). Several factors help when making a differential diagnosis, such as age of the child, characteristics of the images taken, clinical presentation, levels of alpha-fetoprotein and whether it is a single or multiple lesions (5).

Among the most common liver tumors in children less than 5 years of age are hepatoblastoma, infantile hemagioendothelioma and metastasis. In children over 5 years of age,

in whom the aforementioned tumors are not very frequent, we can find hepatocellular carcinoma, undifferentiated sarcoma, hepatocellular adenoma and metastatic disease.

Liver tumors associated with high serum levels of alpha-fetoprotein include hepatoblastoma and hepatocellular carcinoma. Infantile hemangioendothelioma may have high levels in a minority of lesions (< 3%).

The presence of multiple lesions suggests metastatic disease, infantile hemangioendothelioma, abscesses, cat scratch disease. adenomas or lymphoproliferative diseases in predisposing conditions, such as Fanconi's anemia or Gaucher's disease. Clinical presentation may suggest a specific diagnosis.

Many techniques have been used to study these liver masses by means of images: ultrasound (US), computed tomography (CT), magnetic resonance (MR), angiography and nuclear medicine techniques. Malignant liver lesions do not have pathopneumonic image characteristics. The main aim of images is to define precisely the extension of the lesion and its anatomical relationships, since the definitive diagnosis is based on pathology findings, and surgery is the main treatment option for many of these lesions.

Malignant Focal Lesions

Hepatoblastoma (Fig. 1)

Hepatoblastoma is the most common malignant primary tumor of the liver in children; it constitutes up to 48% of cases (6). Most patients present before 3 years of age, with a fast-growing abdominal mass, hepatomegaly, pain, fever, anorexia and weight loss. It is more frequent in males, with a ratio of 2:1. There is alfa-fetoprotein elevation in 90% of cases. The appearance of a hepatoblastoma on US varies according to the different histological types. Usually they are multilobar, septate, with well-defined borders. The epithelial variety frequently

appear as a homogeneous mass, hypoechoic, whereas the mixed variety appear as a heterogeneous mass, with hyperechoic foci, due to calcifications, and with hypo or anechoic areas, due to liquefaction necrosis (7).

The CT image is variable. In the simple phase, the epithelial tumor appears as a homogeneous hypodense mass, whereas the mixed type has a heterogeneous appearance. There can be calcifications in both types: small and thin in the epithelial, thick and large in the mixed type. After the injection of intravenous contrast media some uptake can be seen, usually less than in healthy liver tissue. The uptake pattern is heterogeneous, it is possible to see uptake in ring form, mainly if acquired during the early arterial phase. If this type of uptake is found, later series must be obtained to differentiate the lesion from a hemangioendothelioma (8).

When MR is used, the behavior of the hepatoblastoma is very similar to what was observed with CT. The epithelial type is hypointense in T1 and hyperintense in T2. The mixed type is heterogeneous, depending on the presence of necrosis, calcifications, hemorrhages, septa and fibrosis. With MRI, gradient echo or angio-MR, vascular invasion is seen more clearly, these can also be used to assess vascularization and anatomical variations, so as to facilitate the resection procedure (9).

Mortality due to this neoplasm depends on whether it is completely removable surgically, since if resection is not complete, even with chemotherapy, survival is less than 20% at 2 years. This tumor presents metastasis mainly in the liver hilum and lung and, less frequently, in brain and bones.

Hepatocellular Carcinoma (Fig. 2)

It presents, mainly, in children from 12 to 14 years of age, and less frequently in children less than 4 to 5 years of age. Approximately 50% of these children have a pre-existing liver

condition, such as hepatitis, glycogenosis, tyrosinemia, cirrhosis, hemochromatosis or alpha-1-antitrypsin deficiency (10). Clinically, hepatocellular carcinoma presents with a palpable mass and elevation of alpha-fetoprotein serum levels, it is rare to find alteration of liver tests, such as alanine-aminotransferase, total bilirubin, albumin and alkaline phosphatase (11). It can be a single or multiple lesion and vascular invasion is common. The appearance on CT or MR is similar to that of hepatoblastoma and the right lobe is affected twice as frequently as the left (12). Using US the echogenicity is variable, calcifications are rare and the adjacent parenchyma may be abnormal. Complete resection of this tumor is possible in 30-40% of cases. The prognosis is poor, only 30% of children survive in the long term (13).

Undifferentiated Embryonal Sarcoma (UES) (Fig. 3)

The UES is an infrequent malignant liver tumor (5% of liver tumors in children). In almost 90% of cases it is seen in children (6-10 years of age) and adolescents, with no predilection as to sex (9). Its clinical manifestations are not very specific, presentation symptoms vary from acute abdominal pain, fever, anorexia and diarrhea, to the incidental finding of a solitary liver cyst (14). Typically, alpha-fetoprotein and liver function tests are normal. The UES is a neoplasm with a primitive mesenchymal fenotype. The size of the tumor frequently is >10 cm and can be up to 30 cm. It is a single mass, large, predominantly solid; the remainder have cystic contents (15).

The appearance of an UES on US varies form a cystic hypoechoic mass, with echogenic septa of variable thickness, to an echogenic mass with multiple cystic spaces. On CT, the tumor usually appears as a large mass, hypoattenuated, with multiple septa. Occasionally it is possible to identify large areas of solid tissue within the mass (16). On MR, the tumor is mainly hypointense in comparison with the liver in T1, heterogeneous, with areas of greater signal intensity, which probably represent hemorrhagic foci. In T2 images a hyperintense mass is seen

that has hypointense septa. If gadolinium is injected it is possible to see late and moderate heterogeneous uptake by areas, with absence of uptake in the greater part of the mass, consistent with cystic changes and necrosis (17).

Benign Focal Lesions

Infantile Hemangioendothelioma (Fig. 4)

This is the third most common type of tumor in children (12% of all liver tumors of children); it has a predilection for the female sex, with a 2:1 ratio; it is the most common vascular liver tumor in children and the first symptomatic liver tumor during the first 6 months of life (85% of patients) (18). Of these patients, between 45-50% present associated skin hemangiomas (19). Clinical manifestations are variable, they can by asymptomatic and be an incidental finding or, more frequently, be large tumors that are manifested by hepatomegaly, abdominal distension or as a palpable mass. There may be extensive arteriovenous formations within the lesion which cause a decrease in peripheral vascular resistance: this requires an increase of blood volume and cardiac output, which leads to congestive heart failure in up to 50-60% of patients (20). Hematological anomalies have been seen, such as anemia and especially thrombocytopenia, caused by thrombocyte entrapment with consumptive coagulopathy (Kasabach-Merrit syndrome).

Seen on images, the lesions can by single or multiple, and the calcifications are seen by histopathological analysis in 50% of cases (21, 22). Most tumors are benign, grow during the first year of life, and later undergo involution, probably due to thrombosis and fibrosis. On a simple CTs hemangoendotheliomas are usually seen as a well defined hypoattenuated mass in a normal liver (8). In 16-40% of cases, the lesion is heterogeneous, with areas of high attenuation, secondary to bleeding or calcification. They can, furthermore, present as multiple lesions, hyperdense, in simple phases, and with contrast uptake similar to that of hemangiomas (nodular

and peripheral, in the early phase). In large tumors there may be a lack of central uptake secondary to necrosis or scar formation. In MR without contrast, lesions have a low intensity signal in potentiated images in T1, and a high signal in potentiated images in T2. After the intravenous administration of gadolinium, enhancement is similar to what was described for CTs. Histopathologically this is a mesenchymal tumor, with a network of small caliber vascular channels (23). Two types of infantile hemangioendothelioma have been identified according to their size and blood vessel supply (3). The most important differential diagnosis in this age group is with hepatoblastoma.

Patients with infantile hemangioendothelioma have an excellent prognosis. Treatment is necessary according to size and severity of symptoms; and can be medical or surgical. Surgical treatment is necessary if the symptoms are life-threatening or if the tumor cannot be differentiated by imaging from a malignant tumor. Medical therapy includes steroids, interferon, radio and chemotherapy.

Focal Nodular Hyperplasia (FNH) (Fig. 5)

FNH is the second most frequent tumor seen in the liver in adults after hemangioma, but it is infrequent in children (8). It is thought to be the result of a normal hepatocyte localized response to an underlying congenital arteriovenous malformation. It is a hyperplastic process, in which all the liver constituents are present, but in a disordered manner in the context of a liver which is otherwise healthy or almost healthy (24). Usually, patients are asymptomatic and this is an incidental finding. The main complaints are: abdominal mass and pain, when due to size or bleeding the live capsule is distended. Usually liver function tests are normal (25).

On CT imaging, FNH is seen as a tumor with a lobular outline. In the simple phase the lesion or lesions are iso or hypoattenuated in comparison with the adjacent liver. In the arterial

phase they are hyperattenuated, except in the central scar. In the portal and subsequent phases, the lesion once more becomes isoattenuated, except in the central scar, which may show uptake. The need for acquisitions in several phases and the consequent high dose of radiation makes us question whether this is an appropriate diagnostic method in children (9). In MR, 94-100% of the patients with FNH show iso or hypointense lesions on T1 images and hyper or isointense lesions on T2 images in the same proportion. The central scar is hypointense on T1, with variable findings on T2; 75% hyperintense and 25% hypointense. After the application of gadolinium, behavior is the same as the phases seen on CT, with dense uptake in the arterial phase and isointensity in the portal and late phases (26). Usually, FNH do not require treatment, since this lesion has no risk of becoming malignant, and can be followed-up with US.

Inflammatory Pseudotumor (Fig. 6)

This is a rare benign process, which histologically corresponds to a mass of chronic inflammatory infiltrate and fibrous stroma without anaplasia (5). It has been reported in several organs in the abdomen, including the liver, spleen, pancreas, adrenal glands, kidneys, retroperitoneum, diaphragm, mesentery, and gastrointestinal and urinary tracts (27). Liver involvement was described initially by Pack and Baker, in 1953 (28). Most inflammatory liver pseudotumors are seen in children and young adults. Clinically, most are solitary solid tumors, located in the right liver lobe. A few involve the liver hilum or the biliary tract, which causes obstructive jaundice. Other symptoms include abdominal pain and loss of weight (29,30).

Typically, on CT a solitary mass is seen of 1-20 cm, or less frequently, multiple nodules with low attenuation (16% of cases), with variable contrast uptake patterns. Ring form uptake may be seen in the portal phase or in late phases (31). The lesion is hypointense or minimally hyperintense, in comparison with adjacent liver parenchyma, on MR images potentiated in T1

and iso or hyperintense in T2 potentiated sequences. A hyperintense ring corresponding to a fibrous capsule can be seen in images potentiated in T2 (32).

Liver Cysts (Fig. 7)

Liver cysts are rare in children, they can be congenital or acquired. Congenital cysts arise from alterations in the development of the intrahepatic bile ducts. Acquired cysts are the result of inflammation, trauma or parasite infections. They can be multiple or solitary; multiple cysts are seen in association with dominant polycystic autosomic disease, most are detected incidentally in imaging studies; however, very big ones can present as abdominal masses or hepatomegaly. The classic image of a simple cyst is a that of a lesion with well-defined margins, unilocular, round or oval with thin walls. On US they are anechoic with posterior acoustic enhancement, on CT they are seen as hypodense, with no uptake of contrast media, and on MR they are hypo and hyperintense in T1 and T2, respectively. Findings such as a thick and irregular wall, internal septa or a density greater than 20 UTH on CT suggest a complex cyst, and in this case a biopsy may be necessary for specific diagnosis (8).

Conclusion

Liver neoplasms are third in order of frequency among malignant tumors seen in infancy; malignant liver tumors are more frequent than benign ones. Due to the similarities in clinical symptoms both of benign and malignant liver neoplasm evaluation by means of images is important to determine the diagnosis, but, mainly, to define treatment and prognosis. These lesions do not have pathopneumonic imaging characteristics, therefore, in most cases, diagnosis is based on a surgical specimen. The main object of images is to clearly establish the lesion’s characteristics, extension and relationship with adjacent anatomical structures.

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Received for assessment: February 20, 2009

Accepted for publication: April 4, 2009

Figures

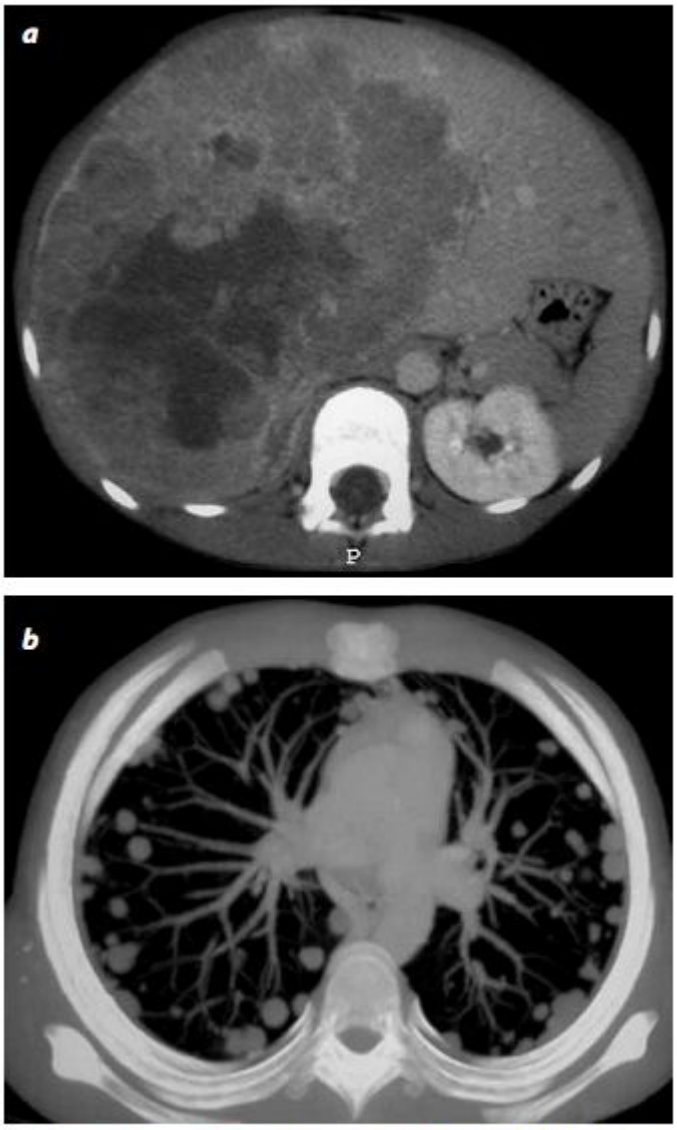

Fig. 1. Hepatoblastoma: (a) Imagen de TC contrastada en fase portal. Muestra una gran lesión en el lóbulo hepático derecho y en el segmento medial del izquierdo. Esta lesión es de densidad heterogénea y realza periféricamente con el medio de contraste en grado menor que el parénquima sano adyacente. Tiene área central hipodensa por necrosis. (b) Metástasis pulmonares.

Fig. 1 Hepatoblastoma: (a) CT image with contrast in portal phase. It is possible to see a large lesion in the right liver lobe and in the medial segment of the left lobe. This lesion is heterogeneous in density and is less enhanced peripherally by the contrast media than the healthy adjacent parenchyma. It has a central hypodense area due to necrosis. (b) Lung metastasis.

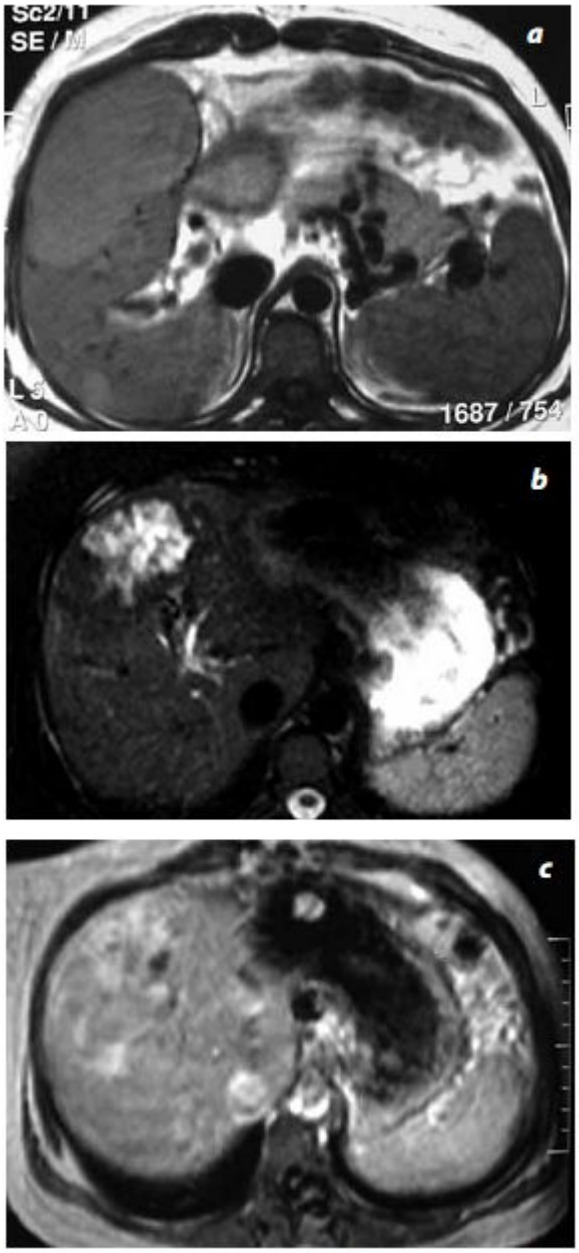

Fig 2. Hepatocarcinoma: (a)IRM con información en T1: lesión biendefinida, ligeramente

Fig. 2. Hepatocarcinoma: (a) MRI with information in T1: well defined lesion, slightly hyperintense compared with the liver parenchyma, with a capsule with lower signal intensity. (b) Behaves hyperintensively in the T2FS sequence. (c) Is heterogeneously enhanced by the contrast media, with a limiting capsule seen in the late phase.

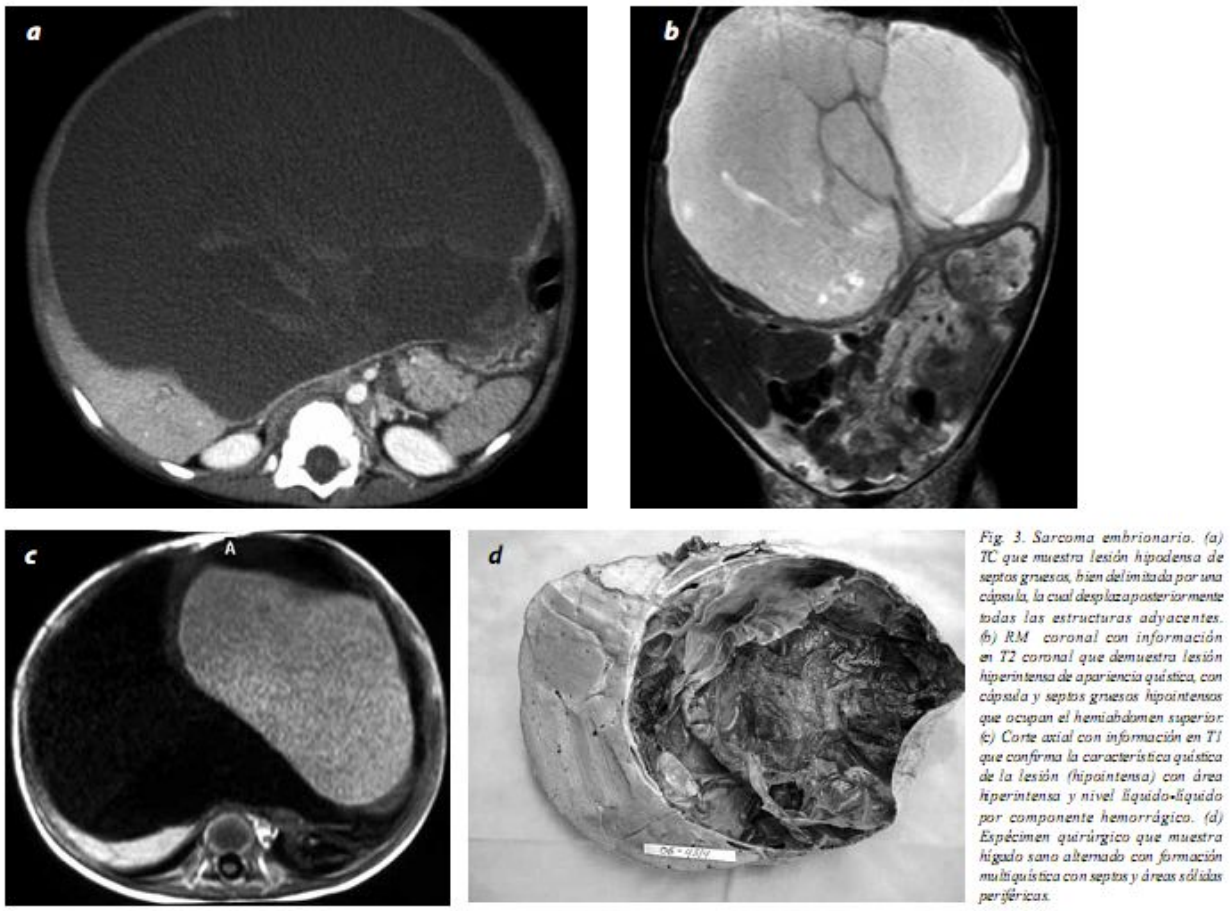

Fig. 3. Sarcoma embrionario. (a) TC que muestra lesión hipodensa de septos gruesos, bien delimitada por una cápsula, la cual desplaza posteriormente todas las estructuras adyacentes. (b) RM coronal con información en T2 coronal que demuestra lesión hiperintensa de apariencia quística, con cápsula y septos gruesos hipointensos que ocupan el hemiabdomen superior. (c) Corte axial con información en T1 que confirma la característica quística de la lesión (hipointensa) con área hiperintensa y nivel líquido-líquido por componente hemorrágico. (d) Espécimen quirúrgico que muestra hígado sano alternado con formación multiquística con septos y áreas sólidas periféricas.

Fig. 3. Embryonal Sarcoma. (a) CT that shows a hypodense lesion with thick septa, well-defined by a capsule, which to posterior displaces all adjacent structures. (b) Coronal MR with information in T2 coronal that shows a hyperintense lesion with a cyst-like appearance, with a capsule and thick hypointense septa that occupies the upper hemiabdomen. (c) Axial section with information in T1 that confirms the cystic characteristics of the lesion (hypointense) with a hyperintense area and fluid-fluid level due to a hemorrhagic component. (d) Surgical specimen that shows healthy liver alternating with multicystic formation with septa and solid peripheral areas.

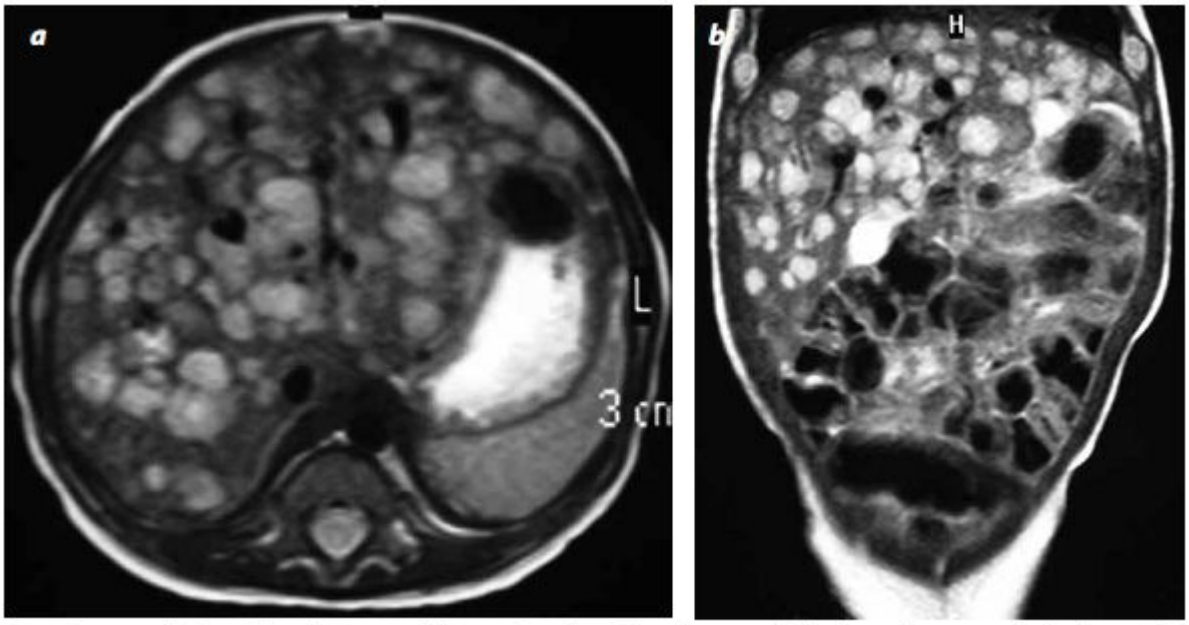

Fig. 4. Hemangioendotelioma: RM axial (a) y coronal (b) con información en T2 que demuestra múltiples lesiones hiperintensas distribuidas en todo el parénquima hepático. El paciente presentaba hemangiomas cutáneos.

Fig. 4. Hemangioendothelioma: Axial (a) and coronal (b) MR with information in T2 that shows multiple hyperintense lesions distributed throughout all the liver parenchyma. The patient presented skin hemangiomas.

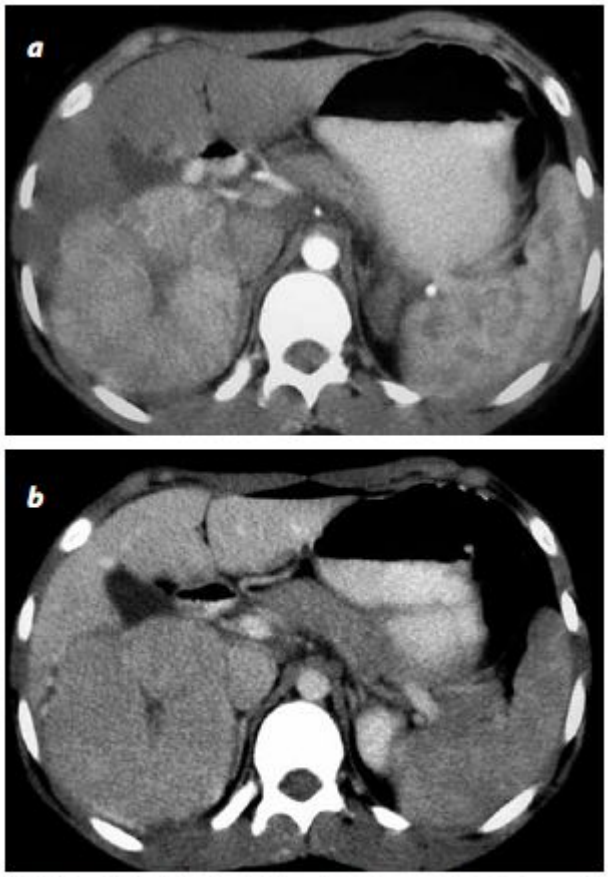

Fig. 5. Hiperplasia nodular focal. Imágenesde TC contrastada (a) enfase arterial. Lesión localizada en lóbulo hepático derecho, lobulada, bien delimitada por una cápsula; capta ávidamente el contraste en la periferia con cicatriz central hipodensa. (b) Se hace isodensa al parénquima hepático en la fase portal.

Fig. 5. Focal Nodular Hyperplasia. Contrast CT images (a) in the arterial phase. Lesion located in the right liver lobe, lobulated, well-defined by a capsule, avid peripheral uptake of contrast with a hypodense central scar. (b) The liver parenchyma is isodense in the portal phase.

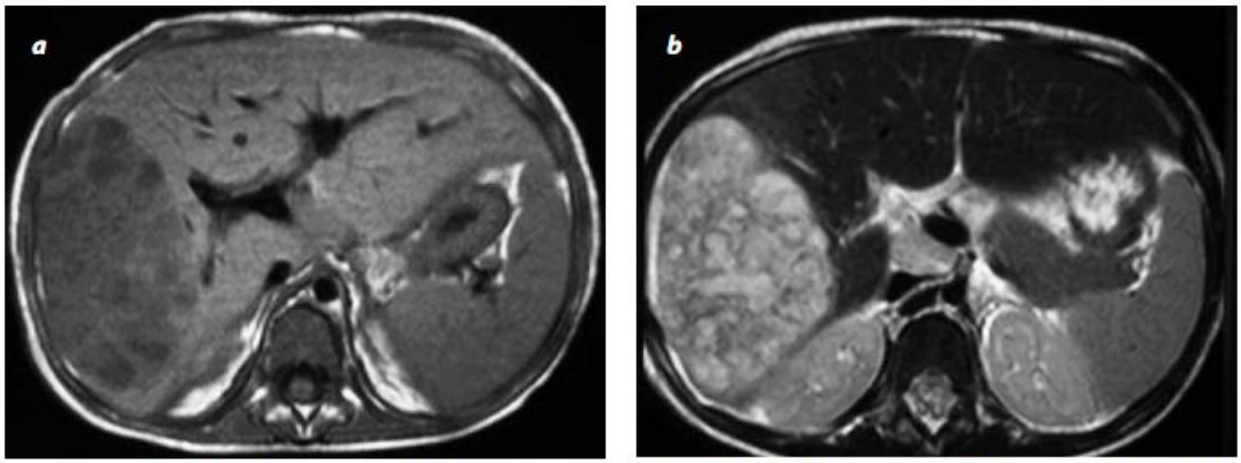

Fig. 6. Seudotumor inflamatorio. (a) RM con información en T1: se identifica lesión hipointensa en el lóbulo hepático derecho, bien delimitada, sin alteración del contorno; se comporta hiperintensa en las secuencias con información en T2. (b) El control posterior demostró un hígado sano.

Fig. 6. Inflammatory pseudotumor. (a) MR with information in T1: a hypointense lesion is identified in the right liver lobe, well-defined, with no alteration of the outline; it behaves as a hyperintense mass in sequences with information in T2. (b) Subsequent control showed a healthy liver.

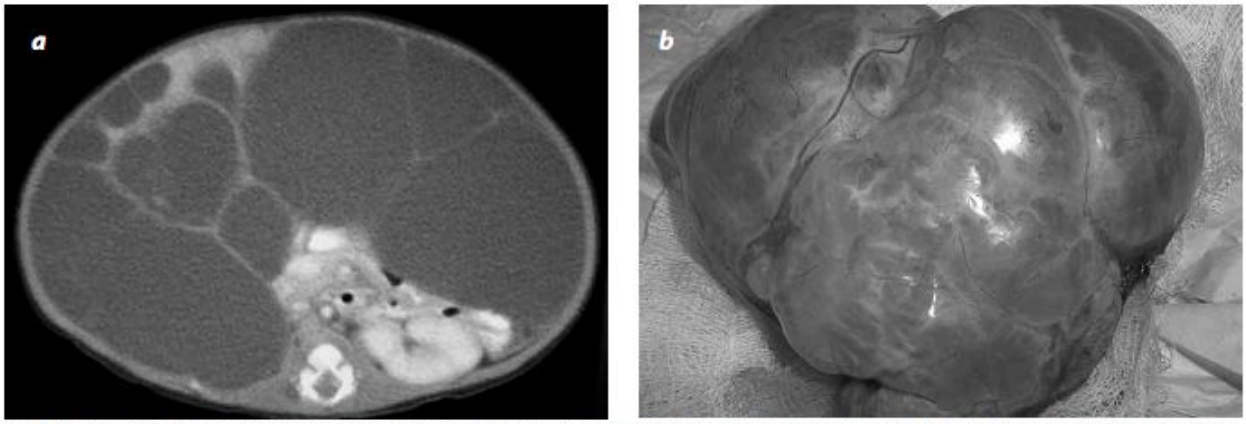

Fig. 7. Quiste hepático. Imagen por TC donde se observa una gran lesión quística (a) que ocupa el parénquima hepático casi en su totalidad, multiseptada, sin calcificaciones ni áreas de sangrado. (b) Espécimen quirúrgico que confirma las características descritas de la lesión.

Fig. 7. Liver cyst. CT image where it is possible to see a large cystic lesion (a) that occupies almost the whole liver parenchyma, multiseptated, with no calcifications or bleeding areas. (b) Surgical specimen that confirms the described lesion characteristics.