CASE REPORT

Hepatocellular Carcinoma: An Unusual Presentation of this Rare Clinical Entity in Children

Marta Martins[1], Maria Filomena Cardosa[1], Paulo Calhau[1], Gabriela Caldas[2], Rui Alves[3]

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Abstract

Malignant hepatic tumors are rare in children and hepatocellular carcinomas only represent 20% of cases. A previously healthy 10 year-old male was admitted for sudden abdominal pain. Ultrasound imaging showed an ileo-ileal intussusception with spontaneous resolution, but in the face of worsening pain, fever, and a palpable epigastric mass, abdominal magnetic resonance imaging was performed, showing a liver lesion. Laboratory tests presented elevated liver enzymes and C-reactive protein, so a liver abscess was considered and treated with metronidazole plus ceftriaxone. All of the microbiology tests as well as tumoral markers were negative. Despite clinical and laboratory improvement, the lesion persisted in the imaging. A liver biopsy confirmed a hepatocellular carcinoma, and the patient was submitted to surgical resection and chemotherapy. Contrarily to adults in whom most cases are secondary to chronic liver disease, children may not have risk factors for the disease, which makes it harder to make a prompt diagnosis.

Keywords: Abdominal Pain/etiology; Carcinoma, Hepatocellular/diagnosis; Carcinoma, Hepatocellular/pathology; Child

Introduction

Liver tumors are rare in children, accounting for 0.5%-1.5% of all pediatric malignancies.[1-3] Hepatoblastoma constitutes about 80% of the cases, with the remaining 20% being hepatocellular carcinomas.[3,4] A hepatocellular carcinoma in children can be sporadic or secondary to an underlying disease, such as viral infection or a metabolic or vascular disease.[1,2] Adult cases are mainly associated with chronic inflammation and/or cirrhosis secondary to alcohol, viral, or non-alcoholic fatty liver disease.[5] On the other hand, in children, sporadic cases without underlying liver disease are much more frequent, reaching as high as 50% of all cases in areas with a low endemicity of hepatitis B virus (HBV) infection.[6]

The most common symptoms of hepatocellular carcinomas in children are abdominal mass and pain,[2,3] but up to one third of the tumors are found incidentally on imaging.[7,8] In a child with cirrhosis or an underlying liver disease, the presence of an abnormal hepatic mass on ultrasound with the elevation of tumoral markers (alpha fetoprotein) should increase the concern about the possibility of an hepatocellular carcinoma.[2,3] Usually, contrast-enhanced computerized tomography (CT) or magnetic resonance imaging (MRI) is needed for the further characterization of the mass.[2,3] A biopsy is recommended to confirm the diagnosis, especially in children without cirrhosis.[2,3]

The classical management of hepatocellular carcinoma consists of a combination of chemotherapy and surgery[9] with the highest cure rates seen in those submitted to complete surgical resection.[3,10] However, only 10%-30% of the tumors are fully resectable and there is still not a chemotherapy combination effective for the remaining cases of inoperable tumors.[3,6,11-13] The localized and fully resectable tumors have a good prognosis with five-year survival rates of 80%-90%.[3,12] Even in these patients submitted to surgery, there are still doubts about the chemotherapy regimens, including its additional benefit over clinical observation only.

This case demonstrates an unusual presentation of hepatocellular carcinoma presumably complicated by an infection in a previously healthy child, without any known risk factors for a liver tumor and illustrates the difficulty on the differential diagnosis of hepatocellular carcinomas in children, the importance of taking into consideration all the clinical, laboratorial, and imaging elements and the crucial role of the histological exam.

1. Department of Pediatrics, Hospital Garcia de Orta, Almada, Portugal
2. Department of Pediatrics, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon, Portugal
3. Pediatric Surgery Department, Hospital de Dona Estefânia, Centro Hospitalar Universitário Lisboa Central, Lisbon, Portugal
Corresponding Author
Marta Esteves Martins
https://orcid.org/0000-0002-9793-0284
marta.martins@campus.ul.pt
Serviço de Pediatria, Hospital Garcia de Orta, Av. Torrado da Silva, 2805-267 Almada, Portugal
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Case Report

We report the case of a 10 year-old male, admitted to the pediatric emergency room for sudden abdominal pain. No family history was known for gastrointestinal disease or malignancies. He was previously healthy, with regular growth, and had no history of surgical interventions. The immunization schedule was updated, including three doses of hepatitis B virus vaccine.

The patient presented with a six-hour history of abdominal pain, localized to the left quadrants and peri-umbilical region without any other symptoms, including vomiting, diarrhea, or fever. He denied any change of the intestinal pattern or of urine and feces coloration. He also denied any respiratory symptoms, anorexia, fatigue, or weight loss. No epidemiological risk factors were identified, namely recent travels, contact with animals, ingestion of non-pasteurized products, or non-potable water.

Physical examination revealed abdominal pain on epigastric and peri-umbilical regions, with rebound tenderness. Laboratory data showed an elevation of C-reactive protein (CRP) (31 mg/dL) and liver enzymes, with alanine aminotransferase (ALT) 424 UI/L, aspartate aminotransferase (AST) 297 UI/L, and alkaline phosphatase (ALP) 293 UI/L, but a normal white blood cell count, bilirubin, gamma glutamyl transferase, and amylase.

Abdominal ultrasound showed an ileo-ileal intussusception with spontaneous resolution during the exam (Fig. 1). After an initial improvement, the symptoms reaggravated with worsening abdominal pain, fever, and a painful 4 x 5 cm epigastric mass. In an ultrasound reevaluation, a focal hepatic lesion, measuring 5.8 x 4.0 cm, was identified. Abdominal MRI was performed for further characterization, presenting a heterogeneous lesion in the segment III of the left liver lobe (Fig. 2), formed by a hyperintense T2 imaging component, with no enhancement within in both vascular phases, suggesting a non-pure fluid content, and a rim enhancement, in favor of a capsulated lesion. Adjacently, there was a solid component, slightly hypointense in T1 and hyperintense in T2. It was also hypointense in diffusion-weighted imaging, indicating a high cellularity nature.

A hepatic abscess was assumed, and the patient was treated with a six-week trial of intravenous ceftriaxone 100 mg/kg/day and metronidazole 40 mg/kg/day with the resolution of fever in six days, decrease of CRP and normalization of liver enzymes in two weeks.

Etiological investigation was inconclusive as viral serologies, *Entamoeba* spp and *Equinoccoccus* spp as well as cultures and tumoral markers were negative (Table 1). Four weeks later, the lesion persisted with reduced inflammatory reaction. In an MRI, the solid component presented an early contrast enhancement, a late washout, diffuse restriction, and no hepatocytes specific contrast enhancement suggesting the absence of functional hepatocytes.

Given the imaging characteristics, an aspiration cytology was performed, revealing atypical hepatocytes. The diagnosis of hepatocellular carcinoma was confirmed through a liver biopsy. The PRETEXT staging was complemented with a thoracic computed tomography

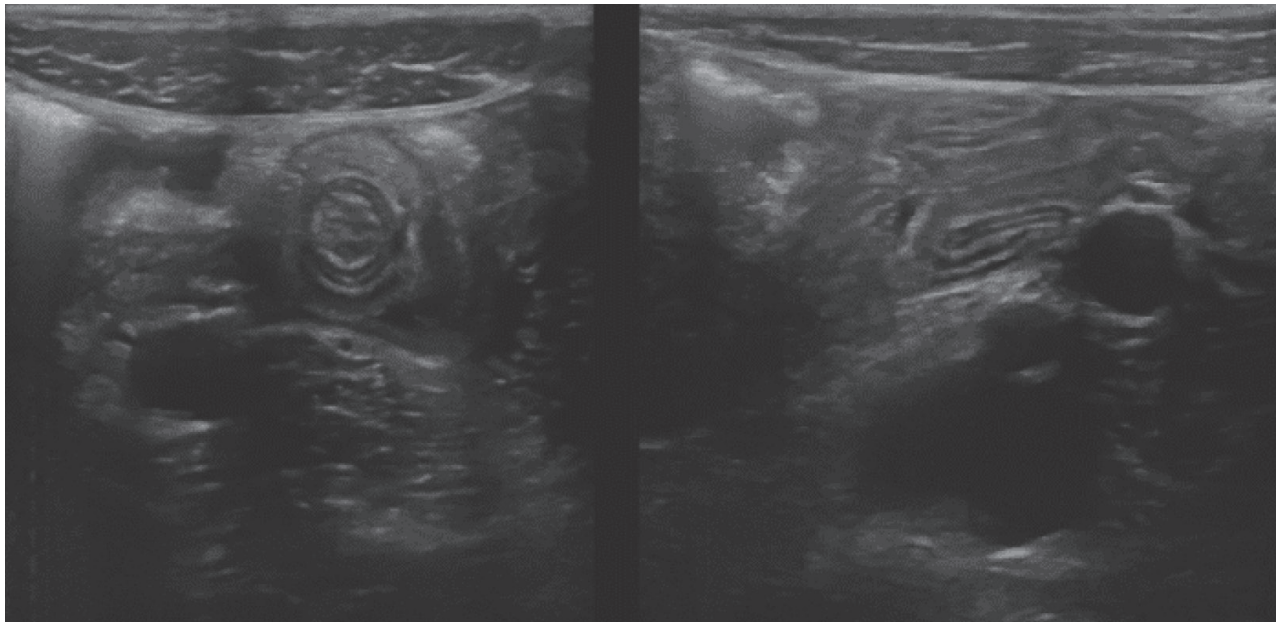

Figure 1. Ultrasound image of intussusception in cross-section (left side), doughnut/target sign, and in the longitudinal view (right side), 15 mm in length.

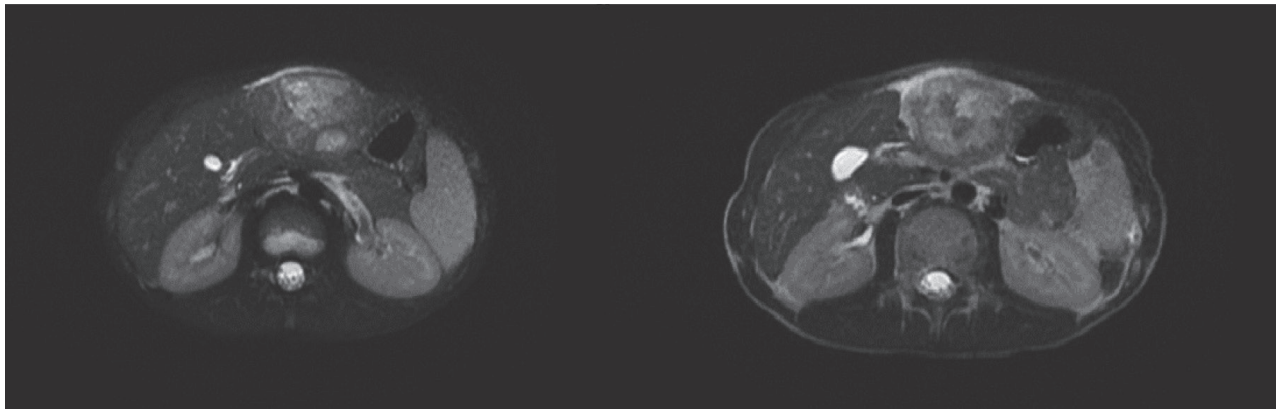

Figure 2. Magnetic resonance image showing a hepatic lesion on segment III of the left liver lobe (6.6 x 4.5 x 5.8 cm) with a hyperintense component on T2 weighted sequence and no contrast enhancement, suggestive of non-pure liquid content and a solid component, hypointense on T1 weighted sequence, and hyperintense on T2 weighted sequence.

Table 1. Results of the laboratory tests

Tests	Results
Viral serologies (HAV, HBV, HCV, CMV, EBV, *Herpes simplex* virus, HIV)	IgG negative/IgM negative for HAV, HCV, CMV, HSV and HIV
	Anti-HBs e anti-HBc negative, HBsAg negative
	IgG positive/IgM negative for EBV
Bacterial serologies (*Mycoplasma pneumoniae*, *Brucella*, *Bartonella*)	IgG positive/IgM negative for *Mycoplasma pneumoniae*
	Negative for *Bartonella* and *Brucella*
Parasitic serologies (*Entamoeba histolyitica*, *Equinoccoccus* spp, *Toxocara* spp)	Negative
Blood culture	Sterile
Stool culture	No pathogenic agents
Stool ova and parasites test	Negative
IGRA	Negative
Tumoral markers	
Alpha-fetoprotein	1 ng/mL (normal range < 10 ng/mL)
Human chorionic gonadotropin hormone	< 0.6 UI/L (normal range < 5 UI/L)

Anti-HBs - hepatitis B surface antibody; Anti-HBc - hepatitis B core antibody; CMV - cytomegalovirus; EBV - Ebstein-Barr virus; HAV - hepatitis A virus; HBsAg - hepatitis B surface antigen; HBV - hepatitis B virus; HCV - hepatitis C virus; HIV - human immunodeficiency virus; HSV - **Herpes simplex** virus; Ig - immunoglobulin; IGRA - interferon gamma release assays.

(CT) scan that did not reveal any pulmonary metastases. As a single lesion limited to the segment III, without vascular involvement nor metastatic disease, it was classified as PRETEXT I. The patient was then submitted to a segmentectomy of the III and IVb liver segments. The histological findings confirmed a moderately differentiated hepatocellular carcinoma with a trabecular pattern, 6 mm tumor free margins, and no evidence of lymphatic or vascular invasion.

This case was presented to the international childhood liver tumors strategy group (SIOPEL) and accepted for the multicentric clinical trial pediatric hepatic international tumor trial (PHITT). According to the trial protocol, the patient was included in the fully resectable tumor group and submitted to a four-course treatment with cisplatin and doxorubicin (PLADO). After a 24 month follow-up, there were no clinical or imaging signs of recurrence.

Discussion

Hepatocellular carcinoma is a rare malignancy in children and in about half of the cases there are no risk factors or known underlying liver disease,[1-3] which makes it difficult to make a prompt diagnosis.

The clinical presentation of this case with an acute onset of symptoms is atypical. The initial evidence of intussusception on the abdominal ultrasound was puzzling and made it harder to make the diagnosis. There is a previous report of a 10 year-old child with a liver abscess initially mistaken for an intussusception on ultrasound.[14] However, stool, psoas muscle, edematous bowel, and bowel with intramural hematoma have also been reported to sonographically mimic intussusception.[15] In our case, it is not obvious if there was a real intussusception associated to the hepatic mass or if the image already corresponded to the liver lesion.

Despite the atypical presentation with sudden fever and acute abdominal pain, the hypothesis of liver abscess seemed the most probable at the time, especially as it was concerning a previously healthy child. The high value of CRP and, particularly, the clinical and laboratory response to the antibiotic treatment contributed to maintaining this diagnosis, even if no microbiological identification was available to confirm it. Liver abscess is nowadays an uncommon pathology in developed countries.[16] It occurs mostly in children with an underlying disease such as an immunodeficiency, abdominal trauma or infection, abnormality of the biliary tract, or tumor.[16] A hepatocellular carcinoma can be manifested as an abscess due to either spontaneous liquefied necrosis of the tumor or biliary obstruction by a tumor fragment. This is a condition rarely reported in the literature. In a series of cases of hepatocellular carcinoma in adults (n = 906), only 0.99% presented with abscess.[17]

For a differential diagnosis of liver lesions, careful imaging and its characteristics are essential as clinical history and laboratory exams are frequently nonspecific. Alpha fetoprotein elevation is associated with malignant tumors, but the levels can be normal in 30%-50% of patients with hepatocellular carcinoma.[2,12]

On ultrasound imaging, a liver abscess may present in an early phase as a mixed-echoic lesion, with irregular margins and without signs of tissue liquefaction, mimicking a solid lesion.[17] Only in a later phase with the course of inflammation, ultrasound reveals a low-echoic and well-defined lesion.[17] At the same time, hepatocellular carcinoma, especially those with necrotic content, may appear in an ultrasound as hypoechoic and without posterior enhancement making it to be possibly confused with liver abscesses.[17] For a better characterization of the lesion, a dynamic imaging is needed and the MRI is the modality of choice.[18,19]

A liver abscess on MRI exhibits hypointense T1 signal and hyperintense T2 signal within and rim and septal enhancement on post-contrast T1 images.[20] An hepatocellular carcinoma typically presents as a mass heterogeneously hyperintense on the T2 and hypointense on T1.[20,21] The tumor usually has an intense enhancement in the arterial phase and a contrast washout in the subsequent venous contrast phase, which is a typical pattern essential for an accurate diagnosis.[20,21] Occasionally associated with an abscess, there is enhancement in the surrounding liver parenchyma, suggesting perilesional edema/inflammation, which can be hard to distinguish from tumoral tissue.[20] A hepatic specific contrast-enhanced imaging study can help in this matter[20], but a liver biopsy may be needed to exclude the presence of tumoral cells.[2,3]

Distinguishing between a tumor with liquefied necrosis *versus* one complicated by an abscess may also be difficult, for which clinical presentation, serologies, and imaging studies are commonly insufficient. In that matter, an aspiration of the liquid content and culture is usually necessary.[17] In our case, that could have helped to confirm the diagnosis, but unfortunately, it was not performed since the radiology team considered it technically difficult and risky.

The therapeutic approach to these patients is still a challenge since complete surgical resection is essential for a better prognosis, but only 10%-30% are eligible for initial surgical intervention.[3,9,10] The localized and fully resectable tumors have a good prognosis with five-year survival rates of 80%-90%.[3,12,22] However, there are many questions to be answered about the therapeutic options for these patients, including those submitted to surgery. The classical treatment consists of a combination of surgery followed by chemotherapy, even if it remains unclear which regimen has a better outcome or even if postoperative chemotherapy has a survival benefit over clinical observation only.[22]

The pediatric oncology group and children cancer group conducted a clinical trial including children with hepatocellular carcinoma postoperatively treated with a combination of cisplatin, 5-fluorouracil, and vincristine *versus* cisplatin and doxorubicin. The five-year survival rate was 88% for stage I hepatocellular carcinoma patients (n = 8), without any difference between treatment groups.[12] Other authors also reported on their study with carboplatin/etoposide postoperatively, a five-year survival of 89% (n = 14).[22] Thus, there seems to be no difference in survival based on the chemotherapy used. However, given the absence of a control group, without chemotherapy, there is still no evidence that adjuvant chemotherapy offers additional benefit in resectable localized hepatocellular carcinoma. A retrospective study found that from 12 upfront fully resected hepatocellular carcinoma, 10 did not receive any adjuvant chemotherapy and all of them are alive without evidence of disease (median follow-up 54.1 months).[23]

Another controversial issue is the role of a liver transplant on the treatment of hepatocellular carcinoma. Liver transplant in children has been an option mainly for unresectable tumors, contrarily to adults in whom the transplant is the first line treatment when the Milan criteria are met (single tumor < 5 cm or less than three foci with < 3 cm each), since it has better survival and recurrence rates.[3] The less frequent cases associated with cirrhosis in children, and consequent better hepatic

reserve in face of a liver resection, has contributed to prioritizing this surgical approach. However, some series reported a better survival after a transplant. It was shown that children undergoing resection had a worse survival rate compared to those submitted to liver transplant (40% *vs.* 72%)[24] and more recently in a retrospective study (n = 80) a five-year survival rate of 85.3% in a liver transplant group against 53.4% in a resection group.[25] The heterogeneity of patients and tumor characteristics included in these studies make it harder to take any conclusions, but these outcomes from liver transplant should be further studied. Large prospective and randomized controlled trials are lacking to evaluate all of these questions and help to define the best treatment.

In our case, we hope for a good prognosis given the localized and single lesion disease and the surgical free tumor margins, but the follow up is still insufficient for reliable prognostic considerations.

WHAT THIS CASE REPORT ADDS

- Hepatocellular carcinomas are a rare clinical entity in children and can arise in patients with no risk factors for liver cancer.
- For the differential diagnosis of liver lesions, careful imaging and its characteristics are essential as clinical history and laboratory exams are frequently nonspecific.
- Negative tumoral markers do not exclude the diagnosis, so in the face of a suspicious lesion in a previous healthy child, with no chronic liver disease, a liver biopsy should be considered.
- The therapeutic approach to these patients is still a challenge and full of controversial questions.
- A complete surgical resection is essential for a better prognosis, but it is still not certain which chemotherapy regimen has a better outcome or even if postoperative chemotherapy has a survival benefit.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Consent for publication was obtained.

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

Awards and presentations

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Carcinoma Hepatocelular: Uma Apresentação Rara desta Entidade Pouco Comum em Crianças

Resumo

Os tumores hepáticos malignos são raros em crianças e os carcinomas hepatocelulares representam apenas 20% dos casos. Um rapaz de 10 anos de idade, previamente saudável, foi admitido por dor abdominal repentina. Foi feita uma ecografia que evidenciou intussuscepção íleo-ileal com resolução espontânea. No entanto, perante o agravamento da dor, febre e identificação de uma massa epigástrica palpável, foi realizada uma ressonância magnética que evidenciou uma lesão hepática. Os exames laboratoriais revelaram um aumento dos valores das enzimas hepáticas e proteína C reativa. Foi considerada a possibilidade de ser um abscesso hepático, que foi tratado com metronidazol mais ceftriaxona. Todos os exames microbiológicos foram negativos, bem como os marcadores tumorais. Apesar da melhora clínica e laboratorial, a lesão manteve-se nos exames de imagem. Uma biópsia hepática confirmou tratar-se de um carcinoma hepatocelular, e o doente foi submetido a excisão cirúrgica e quimioterapia. Ao contrário dos adultos, em que a maioria dos casos é secundária a uma doença hepática crónica, as crianças podem não ter fatores de risco para a doença, o que dificulta o diagnóstico.

Palavras-Chave: Carcinoma Hepatocelular/diagnóstico; Carcinoma Hepatocelular/patologia; Criança; Dor Abdominal/etiologia