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Case Report

Primitive neuroectodermal tumor of the liver: a case report of a rare case in pediatrics ☆,☆☆

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ABSTRACT

Primitive neuroectodermal tumors (PNETs) belong to the Ewing sarcoma family of tumors. These lesions are highly aggressive and are usually found in paravertebral regions, lower limbs, and thorax. However, abdominal PNETs are extremely rare, and only 3 cases of pediatric PNET of the liver have been previously reported. Most patients exhibit symptoms associated with mass effect, due to rapid tumor growth and dissemination. Therefore, an appropriate differential diagnosis is of pivotal importance in order to initiate the corresponding treatment. Here we report the case of a 4-year-old female patient who was diagnosed with PNET of the liver, and we discuss the analysis of focal liver lesions and differential diagnosis in pediatric patients.

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Introduction

Primitive neuroectodermal tumors (PNETs) are members of the Ewing sarcoma family of tumors, as are the Askin's and peripheral neuroepithelioma tumors, the great majority of which are associated with translocation t(11,22)(q24;q12) [1]. While these highly aggressive lesions are usually found in

paravertebral regions, lower limbs, and thorax, abdominal PNETs represent < 1% of cases reported in the literature, and specifically of pediatric PNET of the liver only 3 cases have been previously reported [1]. In pediatric patients, imaging study findings of focal hepatic lesions may be variable and non-specific, and additionally require histopathologic evaluation and immune biomarkers in order to reach a diagnosis. Here we report the case of a pediatric PNET of the liver and

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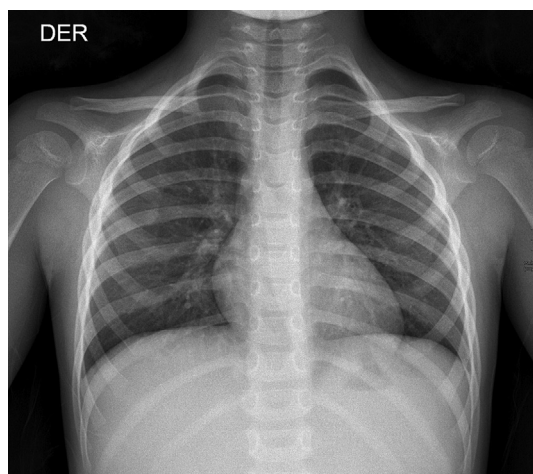


Fig. 1 – Anterior-Posterior chest X-ray shows well-defined, radiopaque nodules in both hemithorax (arrows).

a review of the current literature available for this type of tumor. We discuss the approach to a focal hepatic lesion in pediatric patients and differential diagnosis.

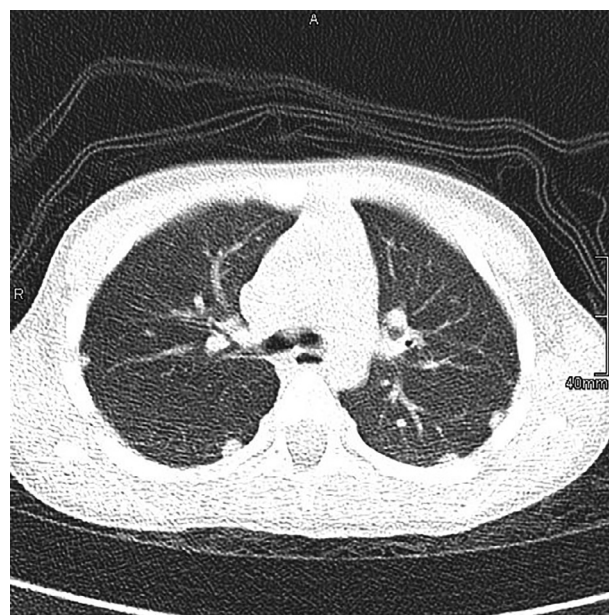


Fig. 3 – Non-contrast low-dose chest CT protocol showing multiple subpleural, up to 10-mm lung nodules compromising both lung fields (arrows).

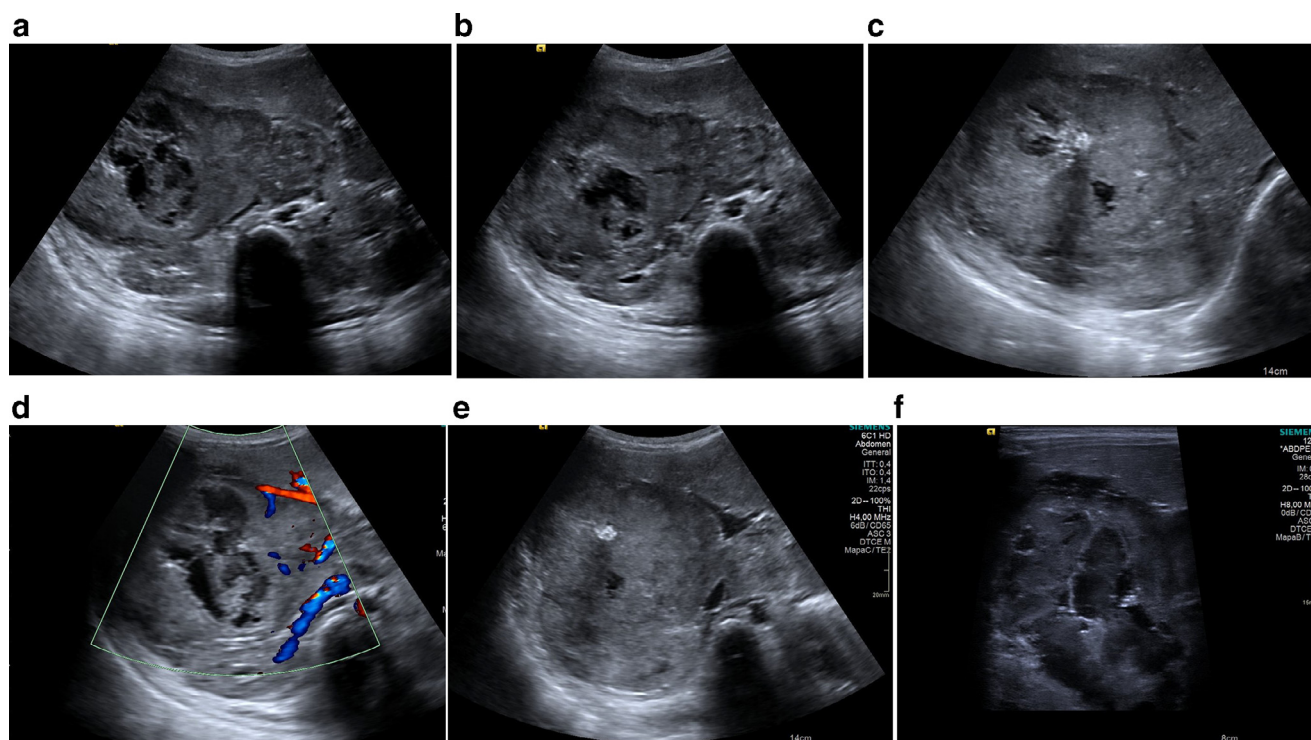


Fig. 2 – Total abdominal ultrasound shows: (A) and (B) hepatomegaly secondary to a large intrahepatic, heterogenous mass with calcification, cystic, and necrotic components, as well as irregular, lobulated borders extending into the hepatic hilum, compression of right kidney, and a greater than 50% compressed inferior vena cava; (C) and (E) multiple intratumoral calcifications; (D) tumor blood flow on Doppler ultrasound, and (F) locoregional enlarged lymph nodes in hepatic hilum.

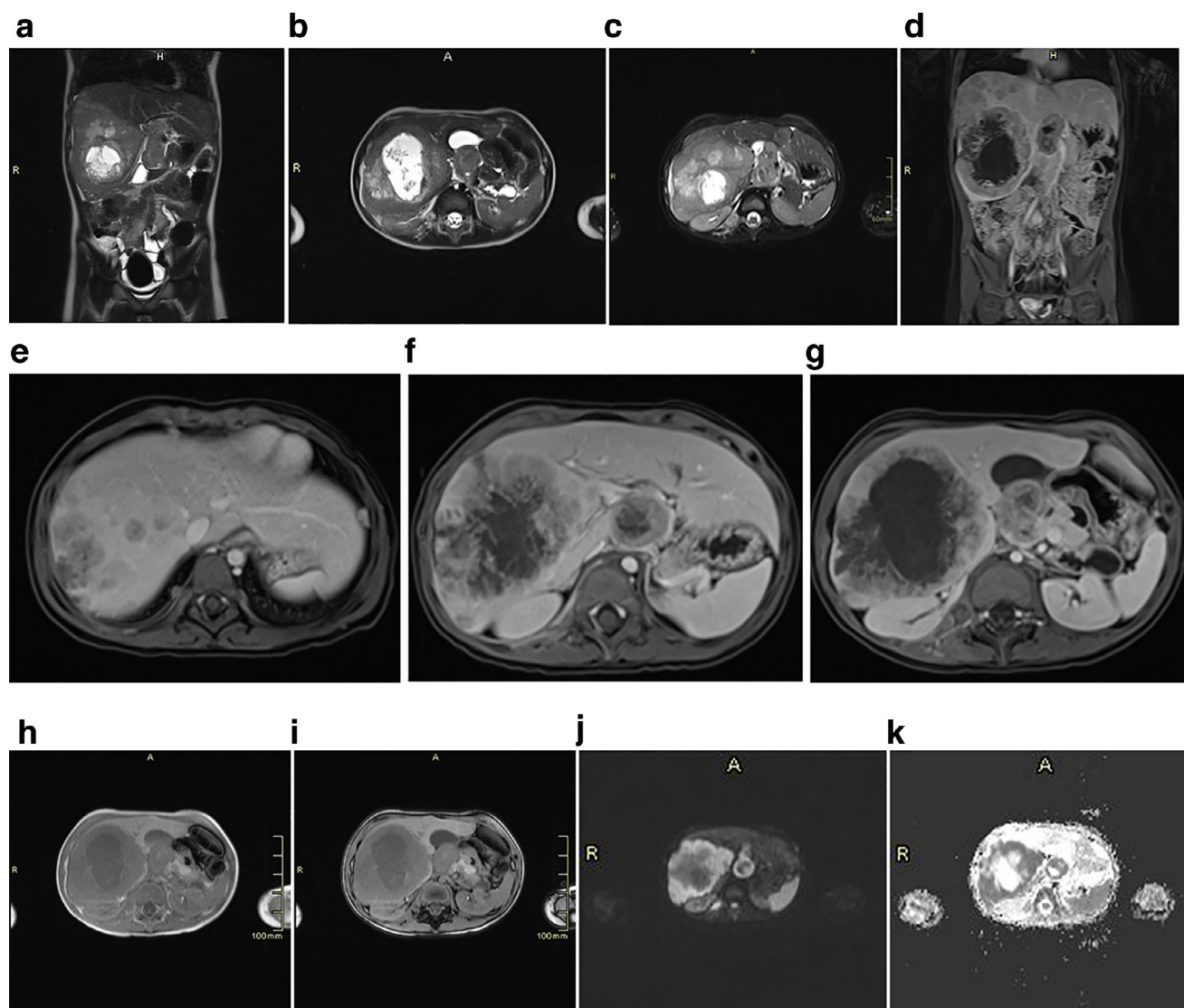


Fig. 4 – Abdominal contrast MR: (A) and (B) sequential coronal and axial T2 sequences showing diffuse hepatomegaly secondary to a intrahepatic, heterogeneous mass with necrotic areas, entire right lobe, and in addition involvement of the hepatic hilum. Smaller satellite lesions with a similar behavior were also observed. (C) Axial T2 with fat saturation showing a mass localized posterior to the right diaphragmatic crus at the costovertebral junction extending to the vertebral foramen, and psoas muscle edema (arrow). (D) Post-contrast T1 coronal sequences; (E-G) Post-contrast T1 axial sequences. (H, I) In-phase and out-of-phase T1 sequences showing no intralesional fat component. (J, K) b800 diffusion sequence and on the ADC map peripheral diffusion restriction was observed at the hepatic hilum and the above-described lesion posterior to the diaphragmatic crus.

Case report

A 4 year and 3-month-old girl presented with fever and abdominal pain in right hypochondriac region associated with weight loss, nocturnal diaphoresis, and decreased appetite. She had past medical history of bacterial sinusitis 2 weeks before. Upon physical examination she presented pale mucous membranes, multiple enlarged lymph nodes, and hepatomegaly. Differential diagnosis included lymphoproliferative syndrome and additional diagnostic imaging studies were requested. Initial lab studies showed increased lactate

Dehydrogenase 1374 UI/l (105–333 UI/l), Alanine aminotransferase 114 UI/l (5–60 UI/l, Aspartate aminotransferase 68 UI/l (10–34 UI/l). the alpha-fetoprotein was normal 1.19 ng/ml (1–10 ng/ml) and normocytic normochromic anemia with Hemoglobin: 11 gr/dl (11.5–14.5 gr/dl) and hematocrit: 34,5% (35%–45%).

Because of the patient's past medical history of sinusitis and abdominal pain, chest X-ray and total abdominal ultrasound were performed. Chest X-ray showed well-defined radiopaque nodules in both hemithorax (Fig. 1). In addition, total abdominal ultrasound showed hepatomegaly secondary to a large 14 × 7 × 9.5 cm intrahepatic, heterogeneous mass with

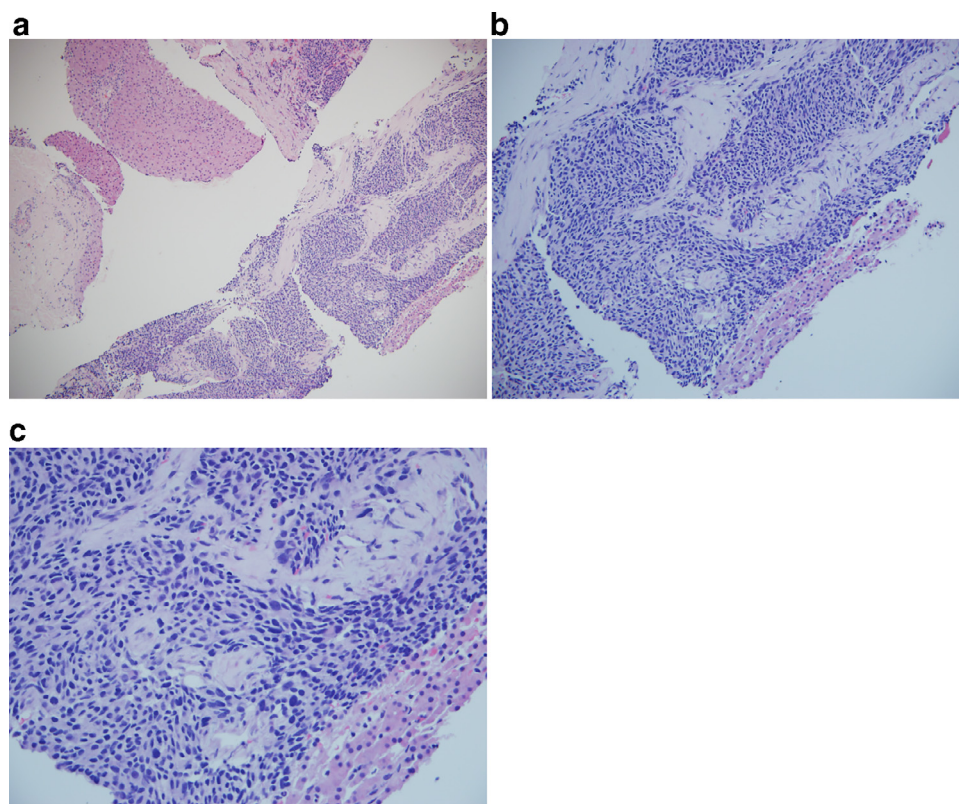


Fig. 5 – Photomicrograph of histopathologic specimen of 4-year old girl. Hematoxylin eosin stain (A) X100; (B) 200x and (C) 400x. Stain shows small, round, blue cell pattern.

calcification, cystic, and necrotic components, as well as irregular, lobulated borders extending into the hepatic hilum. Furthermore, compression of right kidney, and a greater than 50% compressed inferior vena cava were also observed. In the hepatic hilum, the tumor exhibited blood flow on Doppler and locoregional enlarged lymph nodes (Fig. 2A–F).

Following these findings, additional extension studies included non-contrast low-dose chest CT protocol (simple chest CT, 64-detector CT, tube current 239 mA, DLP 6mGy.cm, kilovolts 80, effective dose 0.2 milligray (mGy)), which showed multiple subpleural, up to 10-mm lung nodules compromising both lung fields (Fig. 3).

The distribution and characteristics of these lung nodules suggested metastatic disease, thus complementary studies with contrast abdominal magnetic resonance (MR) imaging were requested.

Abdominal contrast MR sequential coronal and axial T2 sequences without fat saturation showed diffuse hepatomegaly secondary to a intrahepatic, heterogeneous mass with necrotic areas, which in addition to the hepatic hilum was also occupying liver segments I, II, V, VI, VII, and VIII. Smaller satellite lesions with a similar behavior were also observed. Additionally, a mass localized posterior to the right diaphragmatic crus at the costovertebral junction extending to the vertebral foramen, and adjacent to the lesion psoas muscle edema were documented. In-phase and out-of-phase T1 sequences no intralesional fat component was identified. b800

diffusion sequence and on the ADC map peripheral diffusion restriction was observed at the hepatic hilum and the above-described lesion posterior to the diaphragmatic crus. Finally, on phase contrast imaging heterogeneous enhancement was observed on the described lesions (Fig. 4A–K).

The lesion was biopsied for histological analysis. Pathology report described a malignant lesion with solid nests composed of cells with oval nuclei, some cells with round, atypical, hyperchromatic nuclei, and numerous atypical mitotic figures. Some cells were multinucleated with evident nucleoli and scarce eosinophilic cytoplasm. Nest areas tend to form poorly defined rosettes, and minimal necrosis is identified. Peritumoral stroma is frankly desmoplastic with some accompanying vessels, configuring a pattern of small, round, blue cells (Fig. 5). Immunohistochemical staining was positive for chromogranin, CD99, neuron specific enolase (NSE), synaptophysin, and FLI-1. Cytoplasmic staining for beta-catenin was positive, and Ki67 index was 50% for myogenin and/or desmin negative neoplastic cells (Fig. 6A–H). Additional molecular assays ruled out neuroblastoma (Gen N myc) and Ewing tumors. Altogether, our findings supported the diagnosis of a primitive neuroectodermal tumor of the liver. Chemotherapeutic regimen (PNET/Ewing sarcoma protocol 15 days + 4, and 80 mcg/day filgrastim) was initiated. At 6-week follow up, the patient exhibited stable disease, and therefore she was scheduled to continue receiving the same chemotherapeutic regimen and for a follow-up visit at week 18.

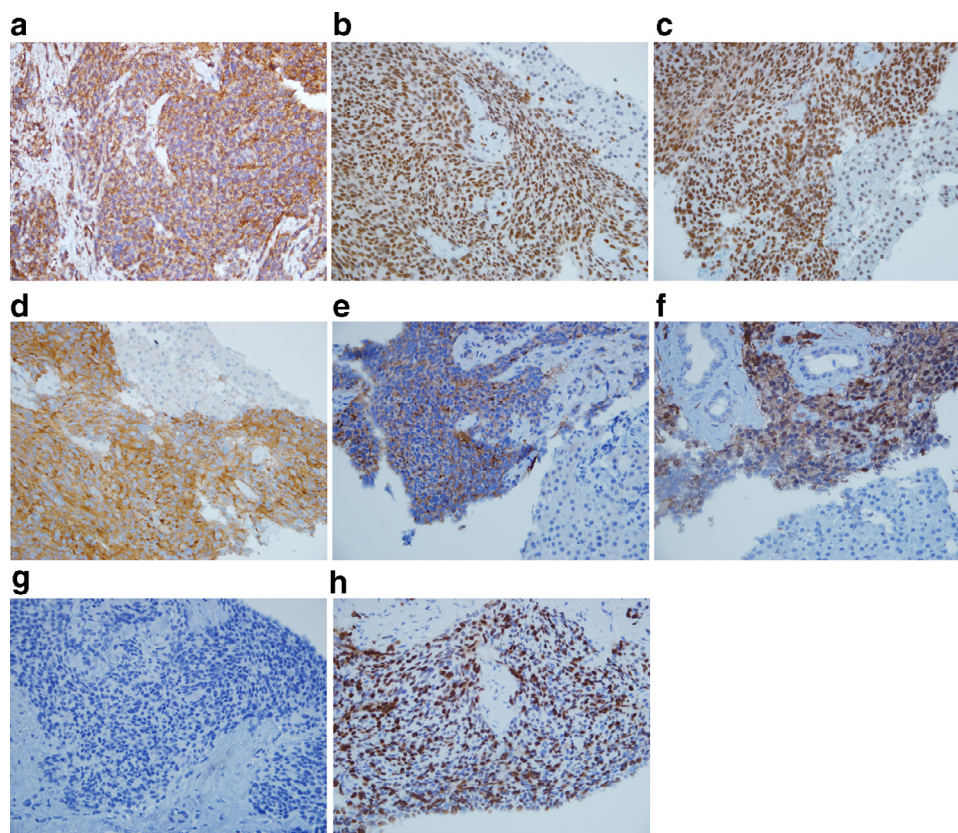


Fig. 6 – Immunohistochemical stain of histopathologic specimen of 4-year old girl for (A) CD99 (400X); (B) FLI-1 (400X); (C) INI-1 (400x); (D) synaptophysin; (E) chromogranin; (F) Neuron specific enolase; (G) glypican-3 (400x); (H) Ki67 (400x). Positive controls for neoplastic cells: chromogranin, CD99, neural specific enolase, synaptophysin, and FLI-1, and beta catenin was used as cytoplasmic staining control.

Discussion

Primitive neuroectodermal tumors (PNETs) were first described in 1918 by Staut [2]. These malignant neoplasms, as well as Askin tumors and peripheral neuroepitheliomas, belong to the Ewing sarcoma family of tumors, which carry a gene translocation at t(11; 22) (q24; q12) [1]. PNETs mostly affect young patients, most commonly compromising the paravertebral region, lower extremities, and thorax, while abdominal involvement is rare and is only observed in less than 1% of cases, usually involving pancreas, stomach, and small intestine¹. Primitive neuroectodermal tumors behave as a highly proliferating single mass, with rapid systemic dissemination. Clinically, PNETs present as abdominal pain, and mass effect and compression symptoms. The first case of a primitive neuroectodermal tumor of the liver was reported in 2010 [3], and since then, to our knowledge, only three more cases have been reported in the literature [2].

Most imaging studies of PNETs show a poorly-defined, heterogeneous mass. On Doppler ultrasound, tomography with calcifications on 25% to 30% of cases, and magnetic resonance, a well-defined pseudocapsule with necrotic, hemorrhagic and intratumoral cystic components, with heterogeneous contrast enhancement³.

Pathology reports are characterized by a round blue cell pattern, with scarce cytoplasm and round nuclei, which is identified in tumors such as neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, and desmoplastic small round cell tumors [4]. Specific positive immunohistochemical markers include CD99, neuron specific enolase, synaptophysin, among others [1].

Regarding treatment and prognosis, while a multimodal approach including chemotherapy, radiotherapy, and definitive surgery has been described, local recurrence rate can be up to 30% [5]. Poor prognostic factors described to date include metastatic disease at time of diagnosis, tumor size, extensive necrosis, and poor response to chemotherapy [1,5].

Differential diagnosis of focal hepatic lesions in pediatric patients should include malignant and benign tumors. Malignant lesions such as hepatoblastoma and undifferentiated embryonal sarcoma should be considered. Hepatoblastoma, defined as an embryonic tumor affecting patients younger than 4 years of age, exhibits elevated alpha-fetoprotein in 90% of the cases, and should be considered as first choice. In addition, undifferentiated embryonal sarcoma, which occurs in children between 6 and 10 years old, and presents with normal levels of alpha fetoprotein and liver function tests, shows as a hepatic lesion with solid-cystic component that has a solid

appearance on ultrasound, and mostly cystic on computed tomography and magnetic resonance [4-5].

On the other hand, benign hepatic lesions such as hepatic hemangioma, inflammatory pseudotumor of the liver, and hamartomas should also be included in the differential diagnosis. Hepatic hemangioma is the most common vascular liver tumor, diagnosed mainly in infants as these tumors tend to regress after the first year of life, and have an excellent prognosis. Inflammatory pseudotumor of the liver is a mass with fibrous stroma and chronic inflammatory infiltrate, benign, rare, and of unknown etiology, which usually requires biopsy for its diagnosis. Finally, mesenchymal hamartomas are benign hepatic lesions found in children younger than 2 years of age, and are characterized by a predominantly cystic component [6].

In our case, differential diagnosis included neuroblastoma -since immunohistochemical staining was positive for neuron specific enolase (NSE)-, and hepatoblastoma -due to the elevated alpha-fetoprotein, since up to 90% of these tumors present with elevated AFP. Desmoplastic small round cell tumor is a rare, highly aggressive, peritoneal tumor usually found in retrovesical and retrouterine space of young adolescents [7]. Finally, rhabdomyosarcoma, which affects children younger than 10 years of age, and is positive for desmin and MyoD1 immunohistochemical markers was also considered [8].

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