

CASE REPORT

Primary Hepatic Neuroblastoma in a 19-month-old Child: A Case Report

✉ Jovana Dimic¹, Dejan Skoric^{1,2}, Aleksandar Sretenovic^{2,3}, Slavisa Djuricic ^{4,5}¹ Department of Hematology and Oncology, University Children's Hospital, Belgrade, Serbia² School of Medicine, University of Belgrade, Belgrade, Serbia³ Department of Surgery, University Children's Hospital, Belgrade, Serbia⁴ Department of Clinical Pathology, Mother and Child Health Care Institute of Serbia "Dr. Vukan Cupic", Belgrade, Serbia⁵ School of Medicine, University of Banjaluka, Banjaluka, Bosnia and Herzegovina**Received:** 27 May 2022**Revised:** 22 June 2022**Accepted:** 29 June 2022

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✉ **Correspondence to:**

Dr. Jovana Dimic, MD, Department of Hematology and Oncology,
University Children's Hospital, 10 Tirsova Str.,
11000 Belgrade, Serbia
E-mail: jovana.dimic87@gmail.com

Summary

Introduction. Neuroblastoma in solid organs other than the sympathetic nervous system is extremely rare. The most common site of neuroblastoma is the adrenal medulla. Liver neuroblastomas are usually metastatic lesions, particularly from stage 4S adrenal neuroblastoma. **Patient review.** We report the first case of primary hepatic high-risk neuroblastoma diagnosed in a child older than 12 months. The patient received multimodal oncology treatment, including chemotherapy, surgery, bone marrow transplantation, radiotherapy, and immunotherapy, as well as deep regional hyperthermia. Despite the timely diagnosis, the tumor was refractory to intensive treatment, and the patient died 2.5 years after the diagnosis. **Conclusion.** The differential diagnosis of primary malignant liver tumors in pediatric patients should include neuroblastoma, especially in tumors with atypical clinical presentation. The reports of similar cases in the future may contribute to better tumor biology understanding and facilitate clinical management.

Keywords: liver, hepatic, neuroblastoma, pediatrics.

INTRODUCTION

Neuroblastoma is the most common extracranial solid malignant tumor in children. It arises from primitive neural crest cells. Neuroblastoma is characterized by biological heterogeneity and various clinical presentations. The most common neuroblastoma sites are the adrenal gland, retroperitoneum, posterior mediastinum, and neck, although theoretically, neuroblastomas could arise anywhere where sympathetic nerves are spread (1). Neuroblastoma arising in solid organs other than the sympathetic nervous system is extremely rare. Here we report on a child with primary hepatic neuroblastoma.

CASE PRESENTATION

A 19-month-old boy was admitted to our hospital with jaundice and acholic stools. He had a 1-month history of itching without apparent skin changes. His previous medical history was uneventful, and the boy was developmentally normal. The family history of cancer predisposition syndrome was unremarkable. He was the second child of healthy unrelated parents.

On physical examination, a tumor mass was palpable in the upper abdomen, and jaundice was noticeable. Initial laboratory findings were as follows: total bilirubin levels 188 $\mu\text{mol/L}$ (ref. $<17.1 \mu\text{mol/L}$), conjugated bilirubin levels 161 $\mu\text{mol/L}$ (ref. $<3.0 \mu\text{mol/L}$), ALT 262 U/L (ref. 19–59 U/L), AST 214 U/L (ref. 16–57 U/L), alkaline phosphatase 862 U/L (ref. 103–349 U/L), GGT 685 U/L (ref. $<50 \text{ U/L}$).

Abdominal MRI revealed a large, two-component tumor lesion in the liver and pancreatic head (**Figure 1**). Both adrenal glands were normal in size and appearance.

Secondary metastases were not detectable on the chest CT scan.

Regarding tumor markers, serum α -fetoprotein level (AFP) was performed before the biopsy, and it was within the normal range for age. Serum lactate dehydrogenase (LDH) was 2076 U/L (ref. 85–227 U/L).

Histopathological analysis of liver tumor biopsy showed undifferentiated neuroblastoma with *N-Myc* oncogene amplification. Histopathological analysis of bone marrow biopsy revealed no malignant cells. Molecular cytogenetic karyotype analysis from bone marrow cell culture and fluorescence in situ hybridization (FISH) showed a normal male karyotype.

The serum level of neuron-specific enolase (NSE) was greater than 370 ng/mL (ref. 0–16.3 ng/mL). The urine catecholamine levels were within the normal range (the level of urinary vanillylmandelic acid (VMA) was 6.5 mg/g creatinine, and the level of urinary homovanillic acid (HVA) was 31 mg/g creatinine). The ferritin level was normal.

Iodine 123-meta-iodobenzylguanidine (123I-mIBG) scintigraphy showed increased radiopharmaceutical uptake only in the liver.

Based on the tumor site, the boy was classified as stage III (according to the International neuroblastoma staging system (INSS) or stage L2 (according to the International neuroblastoma risk group staging system (INRGSS)), but considering *N-Myc* amplification, he was defined as high-risk neuroblastoma. Soon after the diagnosis, chemotherapy was started according to the International Society of Pediatric Oncology Europe Neuroblastoma (SIOPEN) HR-NBL-1 protocol. Abdominal CT scan after induction chemotherapy showed that the intrahepatic tumor component had shrunk by 50%, and that the extrahepatic component had shrunk by 40%. Having completed the in-

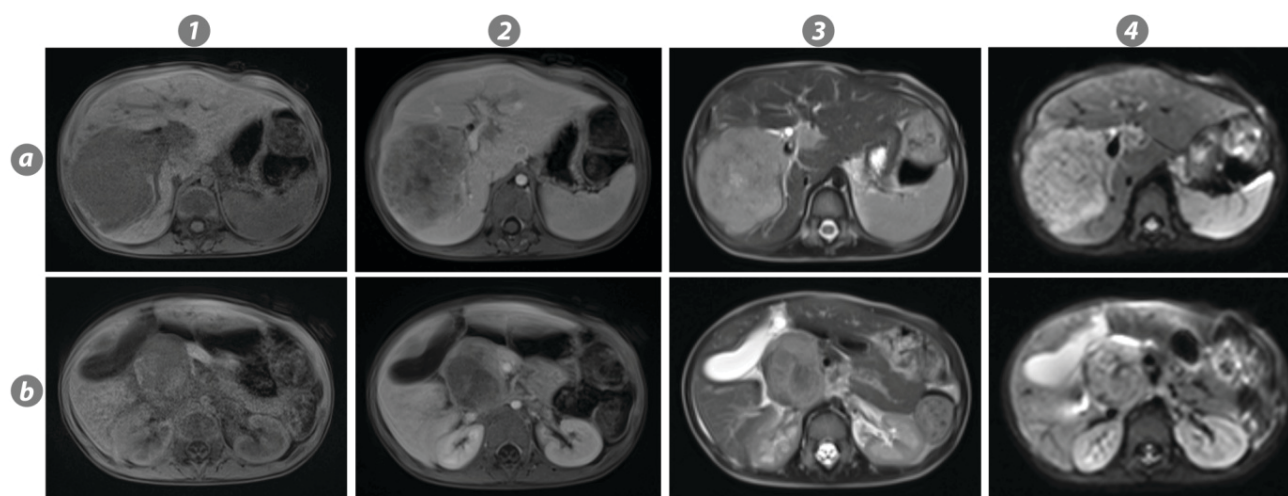


Figure 1. 1) The two-component tumor mass showed hypointense signal to the surrounding liver on T1W MR images, 2) heterogeneous hypervascularity on Gd contrast-enhanced images, 3) moderate signal hyperintensity on T2W, and 4) diffusion restriction on diffusion-weighted images (DWI); a) The first tumor component occupied V, VI, and VIII liver segments measuring 7.8 cm x 7.35 cm x 7 cm; b) The second tumor component had the caudal spread from porta hepatis, between the hepatoduodenal ligament and the pancreatic head, with dimensions 4.5 cm x 5 cm x 5 cm. It exerted pressure on the surrounding anatomic structures, including the common bile duct, duodenum, and inferior vena cava.

duction chemotherapy, the patient underwent trisegmentectomy (segments V, VI, and VIII) to remove the residual hepatic tumor. A separate tumor mass between the hepatoduodenal ligament and the pancreatic head was also completely removed. The resected liver specimen measuring 6.5 x 5 x 4.8 cm contained a vaguely demarcated tumor nodule of irregular shape, which was firmer on the periphery and softer in the central part. The extrahepatic tumor component was resected in two pieces with a maximal size of 2.35 cm and in the form of crumbly granular calcified tissue. The histopathological analysis of the intrahepatic tumor component showed poorly differentiated neuroblastoma with low mitosis-karyorrhexis index (MKI). In the reactive fibrous tumor background, neuroblastoma islets focally showed anaplastic characteristics focally. Lymphovascular invasion was also observed (Figure 2a, b, c). The extrahepatic tumor component also had histology of a poorly differentiated neuroblastoma with infiltration elements into the lymph nodes (Figure 2d).

After surgery, the boy received high-dose chemotherapy with busulphane and melphalan, followed by autolo-

gous bone marrow transplantation (BMT). The patient subsequently underwent radiation therapy at the tumor site (21 Gy in 14 fractions).

After irradiation, the boy received immunotherapy with chimeric anti-GD2 monoclonal antibody ch14.18/CHO combined with isotretinoin. After two courses of immunotherapy, the patient developed obstructive jaundice and acholic stools. The boy underwent a surgery, which revealed an obstructing mass surrounding and infiltrating the pancreatic head and common bile duct, leading to a resection of the gallbladder and common bile duct, followed by Roux-en-Y hepaticojejunal anastomosis. Jaundice resolved after surgery, but one month after surgery, tumor relapse was detected on abdominal MRI, and the second line therapy with topotecan, vincristine, and doxorubicin started. Because of further tumor progression, the boy received four courses of hyper-PEI regimen: cisplatin, etoposide, and ifosfamide plus simultaneous 1-h regional deep hyperthermia (41–43°C). After the fourth course of the hyper-PEI regimen, abdominal MRI showed tumor rest in the liver, and 123I-mIBG scintigra-

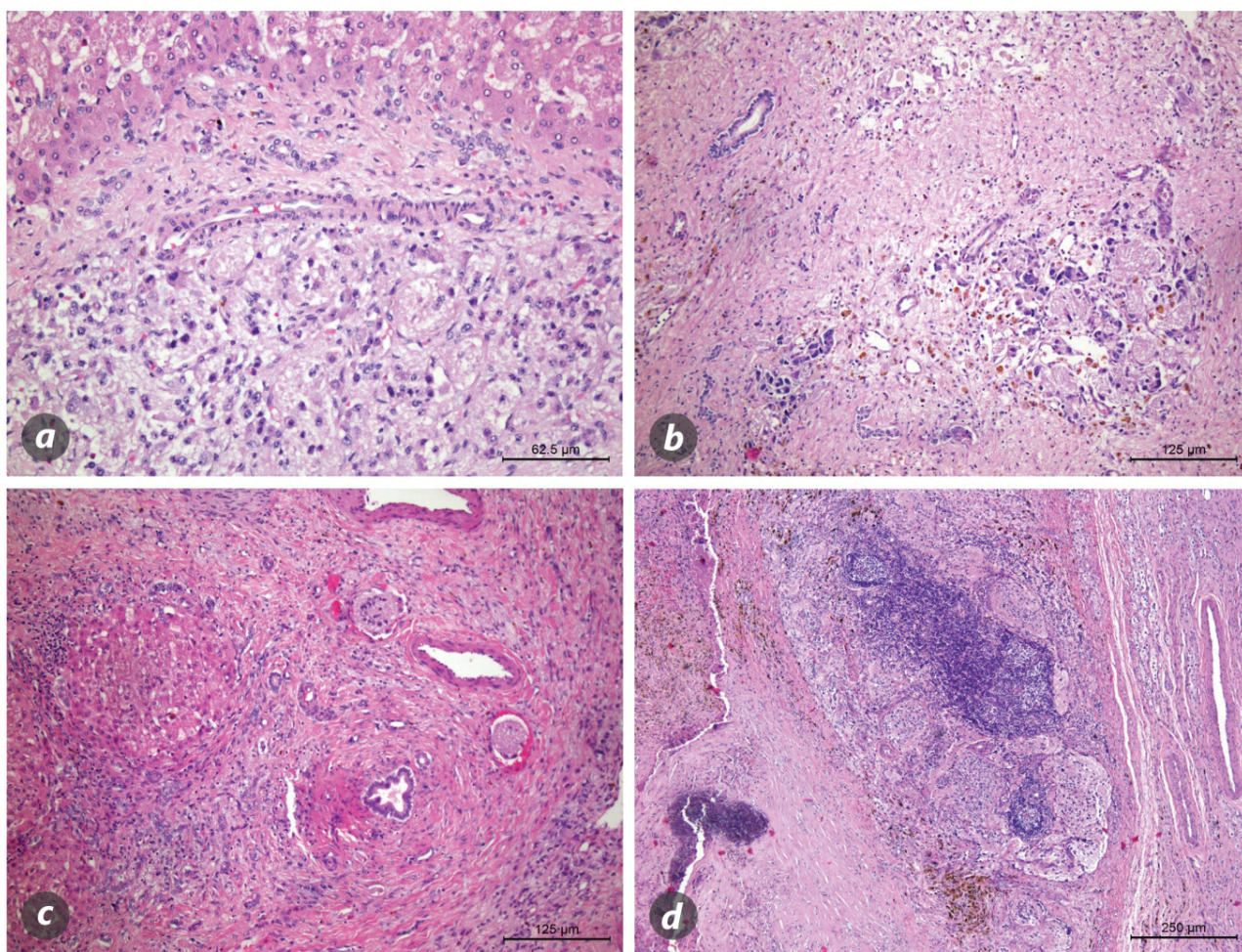


Figure 2. a) Nests of neuroblastic cells immersed in the neuropil matrix are separated from the hydropically degenerated liver parenchyma by a thick layer of reactive, fibrous tissue followed by moderately proliferated bile ducts (HE, x 200); b) In the reactive fibrous tissue, there are two tumor islets composed of non-cohesive and highly anaplastic neuroblastic cells (HE, x 100); c) Neuroblastic emboli in the lymph and venular blood vessels in the fibrous tissue of the liver around the tumor (arrows) (HE, x 100); d) In the extrahepatic part of the tumor, the infiltration of neuroblastoma tissue into the lymph node is recognizable by the partially preserved lymph follicles and accompanied by surrounding hyalinosis, foci of siderophages, and calcification (HE, x 50).

phy showed an increased radiopharmaceutical uptake in the liver and the right thoracic paravertebral space. Finally, the boy was treated with six courses of irinotecan and temozolomide, but due to further tumor progression, he passed away 2.5 years after being diagnosed with neuroblastoma.

DISCUSSION

Primary malignant liver tumors are rare in childhood, with an incidence of about 1.6 cases per million children (2). Hepatoblastoma is the most common malignant liver tumor in early childhood. Other liver malignancies in children include biliary tract rhabdomyosarcoma (BTR), undifferentiated embryonal sarcoma of the liver, rhabdoid tumor, angiosarcoma, and metastatic neuroblastoma (2). Liver neuroblastomas are usually metastatic lesions, particularly from stage 4S adrenal neuroblastoma (1).

In our case, hepatoblastoma was initially suspected because of the tumor site and the patient's age. On the other hand, our patient was admitted with jaundice, an extremely rare presentation of hepatoblastoma. Jaundice is more frequently present in BTR and undifferentiated embryonal sarcoma of the liver (3). Initial work-up included serum AFP level, which was normal. Considering clinical presentation and the fact that AFP is elevated in more than 90% of children with hepatoblastoma (2), we considered other liver malignancies in the differential diagnosis. MRI findings were the most consistent with a BTR, mainly because BTR is often located in or near the porta hepatis. Also, adjacent organ invasion and regional lymphadenopathy are frequent presentations of BTR, and similar findings were present in our case.

Surprisingly, a liver tumor biopsy revealed undifferentiated neuroblastoma. Metastatic neuroblastoma was not initially considered because there was no sign of primary NB in the abdomen. Therefore, urine catecholamines analysis was carried out after a histopathology report was available. The most commonly used tumor markers for NB are urinary VMA and HVA levels, with combined sensitivity of 84% (4). Our patient's urinary VMA and HVA levels were within a normal range. Some studies reported the association between low VMA levels and *N-Myc* amplification (5) and the association between poor prognosis and low urinary VMA levels (6–7) and low urinary HVA levels (7). Also, the urinary VMA/HVA ratio <0.5 is associated with poor outcomes (4). Neuron-specific enolase levels above 200 ng/mL and LDH levels above 2500 IU/mL, both found in our patient, are associated with a worse outcome (5). Regarding the histopathology group, patients with poorly differentiated neuroblastoma, older than 1.5 years, with any MKI have unfavorable histology (8). Also, *N-Myc* amplification is associated with a worse prognosis (9).

There are several possible theories of developmental pathophysiology based on previously reported similar cases. The first theory is that the hepatic tumor is a metastasis of spontaneously regressed primary neuroblastoma. There is one described case of neonatal neuroblastoma 4s with diffuse hepatic metastatic involvement at presentation and without adrenal mass (10). This tumor was *N-Myc* negative, and it is well known that patients with 4s neuroblastoma have a good prognosis and even the possibility of spontaneous tumor regression. Also, there is the case of primary hepatic *N-Myc* negative neuroblastoma in a 29-year-old woman supporting the theory of spontaneously regressed primary adrenal neuroblastoma (11). Also, a possible primary tumor site could be perihepatic retroperitoneal space with *per continuitatem* spreading into the liver (12), but the tumor was not visualized in the retroperitoneal space of our patient. Having the age of our patient and *N-Myc* oncogene amplification in mind, there is a remote possibility that the hypothesis of spontaneous regression can explain the occurrence of liver neuroblastoma. The second theory is the primary pancreatic origin of the tumor because the pancreas has sympathetic innervation. Primary pancreatic neuroblastoma is exceedingly rare and was described only in several cases (13–15). However, the liver tumor component was bigger than the pancreatic component, and the first complaint of our patient was cholestasis which probably developed after the tumor spread from the liver towards the bile duct and pancreatic head. The third theory is that hepatic neuroblastoma may arise from the intrahepatic sympathetic nervous system that innervates the liver and have a role in glucose metabolism and tissue repair (16). Our opinion is that the third hypothesis is the most probable.

CONCLUSION

To the best of our knowledge, our patient is the first reported case of primary hepatic neuroblastoma in a child older than 12 months. Despite the timely diagnosis, our patient had tumor refractory to intensive multimodal oncology treatment. Similar cases should be reported and followed up to reveal clinical and biological tumor features, which should lead to the development of effective diagnostic and treatment strategies.

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PRIMARNI NEUROBLASTOM U JETRI KOD DEVETNAESTOMESEČNOG DETETA: PRIKAZ SLUČAJA

Jovana S. Dimic¹, Dejan U. Skoric^{1,2}, Aleksandar Lj. Sretenovic^{2,3}, Slavisa M. Djuricic^{4,5}

Sažetak

Uvod. Najčešća lokalizacija neuroblastoma je medula nadbubrežne žlezde. Neuroblastom koji raste u solidnim organima u kojima nema simpatičkog nervnog sistema je veoma redak. Neuroblastomi u jetri su obično metastatske lezije, uglavnom se viđaju u 4S neuroblastomu.

Prikaz pacijenta. Prikazujemo prvi slučaj visokorizičnog neuroblastoma sa primarnom lokalizacijom u jetri, koji je dijagnostikovao kod deteta starijeg od 12 meseci. Pacijent je lečen multimodalnim onkološkim pristupom, uključujući hemioterapiju, hirurgiju, transplantaciju matičnih ćelija hematopoeze, radioterapiju i imunoterapiju.

Ključne reči: jetra; neuroblastom; pedijatrija.

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Takođe, primenjena je i regionalna duboka hipertermija. I pored pravovremene dijagnoze tumor je bio refraktaran na lečenje i dečak je preminuo 2,5 godine nakon postavljanja dijagnoze. **Zaključak.** U diferencijalnu dijagnozu primarnih malignih tumora jetre u pedijatrijskom uzrastu trebalo bi uključiti i neuroblastome, posebno u slučaju atipičnih kliničkih prezentacija. Prikazi sličnih slučajeva u budućnosti bi doprineli boljem razumevanju biologije ovih tumora i poboljšali klinički pristup ovim pacijentima.