Case report

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Mixed hepatoblastoma in child. Case report

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Abstract

Hepatoblastoma represents the child's most frequent malignant hepatic tumor. We present the case of a one-year old prematurely born patient with an abdominal mass. Ultrasound and CT scan demonstrated a solid hepatic tumor. Serum alpha fetoprotein level was increased. He presented thrombocytosis and a left lobe hepatectomy was performed. Pathological examination revealed complete excision of a mixed hepatoblastoma. Hepatic tumor at a child under 3 years old correlated with elevated serum alpha fetoprotein and thrombocytosis are almost patognomonic for hepatoblastoma. Complete surgery is the mainstay of therapy in hepatoblastoma.

Key words: hepatoblastoma, ultrasonography, child

Rezumat

Hepatoblastomul reprezintă cea mai frecventă tumoră hepatică malignă a copilului. Se prezintă cazul unui pacient în vârstă de un an, născut prematur, având o formaţiune tumorală abdominală. Ecografia şi tomografia computerizată au evidenţiat o tumoră hepatică solidă. Alfafetoproteina serică avea valori crescute. Asociat prezenta trombocitoză. S-a practicat hepatectomie stângă. Examenul histologic a relevat excizia în totalitate a unui hepatoblastom tip mixt. Tumora hepatică la un pacient cu vârsta sub 3 ani, având alfafetoproteina crescută şi trombocitoză sunt aproape patognomonice pentru diagnosticul de hepatoblastom. Exereza chirurgicală completă reprezintă baza terapiei unui hepatoblastom.

Cuvinte cheie: hepatoblastom, ecografie, copil

Introduction

Hepatic tumors represent 1% of the child's malignant tumors, most of them being the hepatoblastoma and hepatocarcinoma with an annual occurrence of 1.5 cases to 1 million children [1,2].

The child's hepatic tumors raise diagnosis and therapy problems, one of the reasons being their infrequency: 1-4 % of solid tumors [3].

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The suspicion of child's hepatic tumor is based on history, clinical, biological and imagistic data, correlated with the alpha-fetoprotein level and referred to the patient's age. The histological, immunohistochemical and molecular biology examinations emphasize certain mechanisms of oncogenic activation with prognosis and therapeutic implications.

Case Presentation

We present the case of a one-month-old male patient, hospitalized for the evaluation of a hepatic mass. The patient was prematurely born, at 8 months of gestation, with a weight of 2180 gr. Family history was insignificant. At the age of 3 months, during an ultrasound examination, a hepatic mass was identified, which was not investigated due to the family's lack of cooperation. At 11 months of

age the patient was hospitalized for viral meningitis, a solid hepatic mass being revealed at ultrasound. Due to the family's lack of compliance, the patient was re-examined at the age of 1 year old.

The physical examination at hospitalization in the pediatric department (July 2005) revealed a patient with good general status, no fever, weight 10.7 kg (percentile 75), height 80 cm (percentile 90), pallor, good appetite, normal intestinal transit. The following were revealed at the abdomen examination: palpable liver at 2 cm under the rib border, spleen at 1 cm under the rib border as well as an tumoral mass without pain palpable in the epigastric area, of 5/4 cm with relatively smooth surface.

The lab investigations revealed anemia (Hb 8.9 g/dl; Ht 28 %), thrombocytosis (platelets 825 000/mm^3), normal liver tests (ALAT 11 u/l, ASAT 23 u/l), normal inflammatory tests.

The abdominal ultrasound emphasized a homogeneous hepatomegaly as well as a well defined tumoral mass with non-homogeneous, hypoecogeneous parenchymatous structure, with areas intratumorally more ecogeneous, vascularized, dimensions of 5/5/5 cm placed in the III-IV hepatic segments (fig 1). No splenomegaly was found. The portal and hepatic veins as well as the inferior vena cava did not show tumoral invasion. The computerized tomography showed a well defined tumoral mass of 5/6 cm, with inhomogeneous structure, situated near the ligament fissure (fig 2).

The serum alpha-fetoprotein (AFP) showed high values: 138.2 ng/ml (normal values < 20 ng/ml). We excluded the infection with B and C hepatitis viruses, the HIV test was negative.

The patient's age, clinical-imagistic data, high value of alpha-fetoprotein and thrombocytosis raised the suspicion of a hepatoblastoma.

An aspiration punction was performed from the hepatic tumor, the cytological examination showing groups of cohesive cells with malignant character.

Although the surgery was recommended, the parents refused it and came back to our clinic 6 months later (January 2006).

The objective examination at that time revealed an unfeverish, 11 kg weight patient, with extremely pale teguments, hepatomegaly at 5 cm under the rib margin, an epigastric tumoral mass of 8/7 cm, splenomegaly at 3 cm under the rib margin, good appetite, and normal intestinal transit. Biologically, he had severe regenerative anemia (Hb 6.1 g/dl; Ht 19.3%; MCV 69.6fl; MCH 19.6pg; RDW 19,5%, reticulocytes 11‰) and severe thrombocytosis (platelets 1 371 000/mm^3). Neither hepatocytolisis syndrome (TGP 17 u/l; TGO 21 u/l) nor hepatopriv or biliary retention syndromes were emphasized.

The AFP reexamination, 5 months after the first detection, showed higher values: 556 ng/ml, in accordance with hepatic tumor enlargement. The abdominal ultrasound revealed the increase of the hepatic tumor 8/7/6 cm, the mass being intensely non-homogeneous, vascularized and well-defined compared to the adjacent hepatic parenchyma, pushing the hepatic vessels without invading them (fig 3, fig 4). The splenomegaly was confirmed by ultrasound. The abdominal ultrasound and chest X-ray did not show metastases.

The patient was operated in February 2006 in a general surgery department. A well-defined mass of 8/8 cm without vascular invasion was detected in the hepatic segments III-IV. A left hepatectomy with sub hepatic drainage was performed. The macroscopic examination of the partial hepatectomy piece revealed a massive tu-

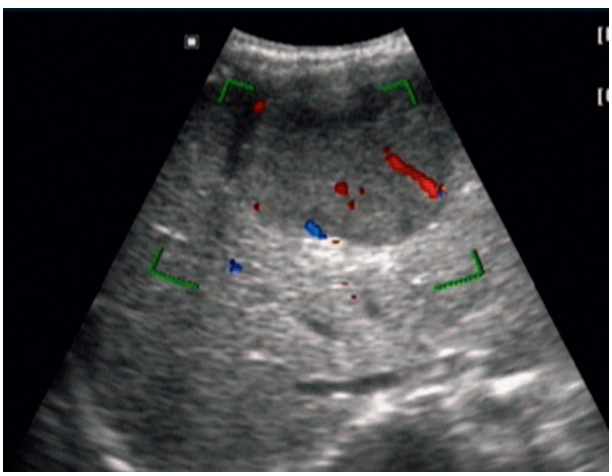


Fig 1. Abdominal ultrasound - hepatic tumor with vascularisation

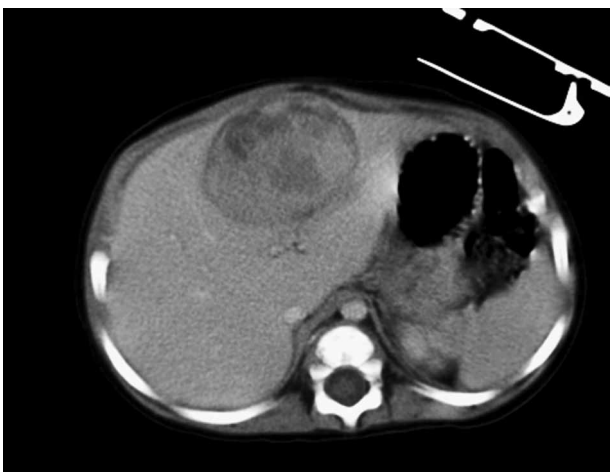


Fig 2. Abdominal computed tomography with contrast agent – inhomogeneous hepatic tumor

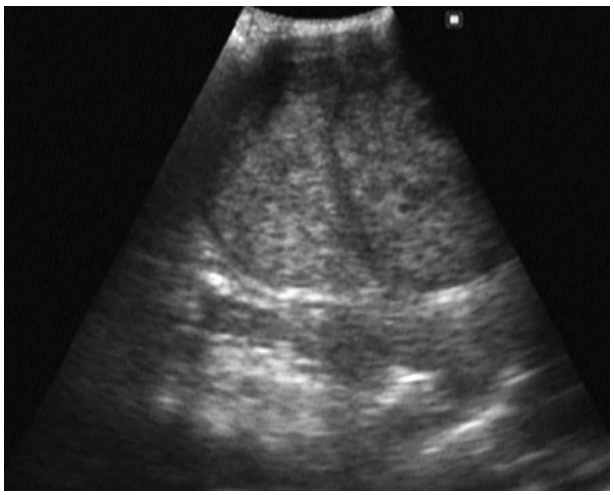


Fig 3. Abdominal ultrasound - hepatic tumor with vessel displacement

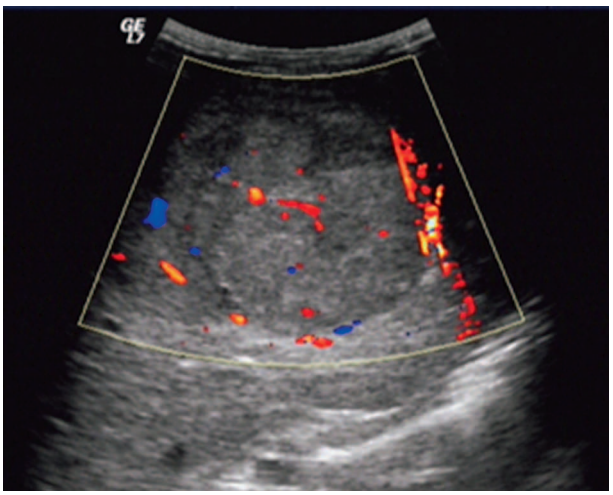


Fig 4. Abdominal ultrasound - hepatic tumor – Doppler color examination

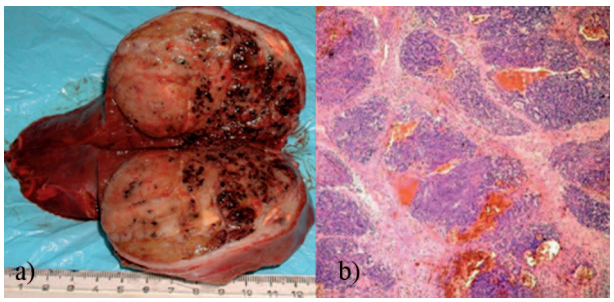


Fig 5. a) Macroscopic aspect in section of the hepatic tumor; b) Microscopic aspect – nodular aspect with haemorrhages, 40x enlargement

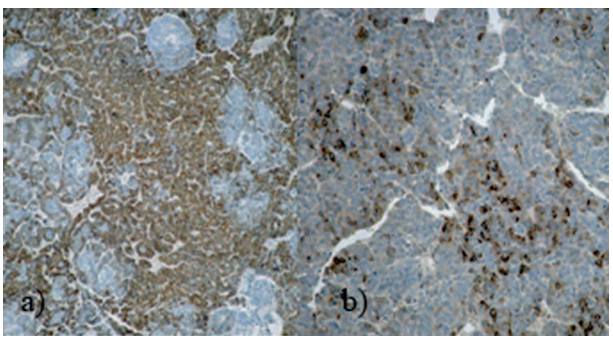


Fig 6. Microscopic aspect a) Hep par 1 shows islands of positive tumoral cells close to an area of negative tumoral cells, 100x enlargement; b) positive alpha-fetoprotein in some of the tumoral cells, 100x enlargement

mor with a maximum diameter of 9 cm, well-defined, apparently separated from the hepatic parenchyma by a pseudo capsule. The section showed an inhomogeneous, white aspect, with vascularized and hemorrhagic areas, a softener consistency compared to the non-tumoral liver (fig 5a). The microscopic examination demonstrated the histological aspect of a mixed hepatoblastoma with fetal and embryonic epithelial hepatocytic elements and immature mesenchyma foci (osteoid and "fibroblast" stroma), hematopoiesis, areas of tumor necrosis (<10%) and mitotic activity existent in the embryonic component (fig 5b). The tumoral cells showed positive immunolabel grouped into parcels for Hep par 1 and focally for AFP (fig 6). The anatomopathological diagnosis was of mixed hepatoblastoma without mature teratoid elements, totally removed.

The post surgical evolution was favorable, with the healing of the surgical wound and remission of splenomegaly. However, the thrombocytosis persisted precociously post surgery (platelets 974 000/mm^3) and the AFP registered high values: 700 ng/ml.

The patient was later transferred to the Oncology Hospital, where he tolerated well treatment with Cisplatine (CDDP) 80 mg/m^2 i.v., administered according to the SIOPEL 3 protocol (hepatoblastoma therapeutic strategy according to the standard risk).

The clinical biological evaluation, performed 2 months after the surgery, revealed a weight gain of 2 kg, absence of hepatosplenomegaly, normal platelets values. The AFP re-examination, 2 months post surgery, indicated a value of 0.7 ng/ml, fact that would represent another argument for the total excision of the hepatic tumor. The echographic re-evaluation, 2 years post surgery indicate a hepatic parenchyma without foci lesions, while the AFP value was 2.1 ng/ml, indicating the total removal of the hepatoblastoma.

Discussions

Hepatic tumors represent approximate 0.5 - 2 % of all the tumors in child, and, excluding leukemia and lymphoma, are responsible for 1-4 % of all the solid tumors [4]. Hepatoblastoma, the most frequent malignant hepatic tumor in child, 74% according to certain studies [5], is however very rare, representing less than 1 case to 100 000 births. Hepatoblastoma appears 4 - 5 times more frequently in the white race compared to the black race. There is a slight predominance of the tumor in the males (1.4-2 :1), difference detectable especially in the child under 5 years old. The diagnosis of hepatoblastoma is suspected in the patient aged between 6 months and 3 years old, in the presence of a hepatic tumor, thrombocytosis and a high level of serum AFP, this association being, in the opinion of certain authors, almost patognomonic for the diagnosis [6]. Our patient presented all these patognomonic associations.

A high serum level of AFP should be interpreted according to age, very high values indicating hepatoblastoma [7]. Moderately high values of serum AFP can be detected in certain types of hepatoblastoma, tumor of yolk sac, hepatocarcinoma as well as in certain benign tumors (mesenchymal hamartoma, focal nodular hyperplasia and infantile hemangioendothelioma).

The patients with hepatoblastoma with AFP normal, low or very high values have a modest prognosis compared to the ones with AFP averaged values. The explanation would be that certain histological variants of hepatoblastoma (the one with small cells) do not produce AFP, grow rapidly and usually do not respond to chemotherapy. The high value AFP hepatoblastoma suggests massive tumoral extension and/or the presence of metastases, thus an unfavorable prognosis. Serial measurements of AFP to our patient revealed increasing values, in accordance with tumor extension, proved clinical and by ultrasound.

Certain authors have demonstrated the existence of a correlation between hepatoblastoma and prematurity, this representing a possible risk factor [8,9].

Most of the hepatoblastoma cases are sporadic.

The hepatoblastoma occurrence is higher in patients with different anomalies: Beckwith-Wiedemann syndrome, family adenomatous polyposis, hemihipertrophy, palatoschisis, cardiac or renal malformations, Down syndrome, Wilms tumor [1]. The hepatoblastoma occurrence in children from families with family adenomatous polyposis is 200-800 times higher than in the general population.

Hepatoblastoma develops more frequently in the right hepatic lobe [10]. The left hepatic lobe receives oxygenated blood totally from the umbilical vein, while the right lobe is irrigated with blood from the portal vein, with lower oxygen saturations. The low blood pressure of the oxygen could favor the embryonic differentiation of the hepatoblastoma in certain conditions, this explaining the more frequent localization in the right hepatic lobe [11]. Our patient presented a left hepatoblastoma, less frequently seen.

Roy describes a few cases of hepatoblastoma post natal diagnosed during the first 6 weeks of life, suggesting the hepatoblastoma development during the fetal life [11].

The cytogenetic studies on patients with hepatoblastoma show multiple anomalies: trisomy of 20, 2, 8 chromosomes, recurrent translocations: deletion (4)t(1q;4q), rearrangements at the 1q12-21 level [12,13]. Certain studies emphasized frequent mutations at the level of the amino-terminal segment of β-catenine (interstitial deletions and mutations at the level of the 3 exone of β-catenine gene). The β-catenine is localized in the normal liver at the level of the hepatocytes membranes, being more present at the level of the gall duct membranes. Two isolated genes of the liver appear excessively in the hepatoblastoma: the glutamine-synthetasis gene and the LECT2 gene (*leucocyte cell-derived chemotaxin 2*). The glutamine-synthetasis is an enzyme of the glutamine metabolism that plays a critical role in the tumor growth, as energy source and in the proteic and nucleotidic synthesis. Cadoret demonstrated an accumulation of the glutamine-synthetasis in the hepatoblastoma tumoral cells [14].

The hepatoblastoma diagnosis is established according to clinical (young age), imagistic, serum (very high AFP serum level) and histological criteria.

The hepatic biopsy made to establish the diagnosis is indispensable in three circumstances: 1) infant under 3 months of age, due to the high number of tumors that can be associated to a high AFP serum level at this age; 2) child under 3 years of age, to differentiate a hepatoblastoma from a hepatocarcinoma; 3) all patients with a hepatic tumor and a normal AFP serum level [5].

Macroscopically, the hepatoblastoma is usually a solitary large tumor, well-defined, multi-nodular, white-yellowish, with fibrous stripes, areas of necrosis and cavities [5]. All these aspects were present in our patient. The liver on which the tumor develops is not cirrhotic. The hepatoblastoma histological classification comprises six types grouped in two large categories: 1) the epithelial hepatoblastoma and 2) the epithelial and mesenchymal mixed hepatoblastoma [5,15].

Thrombocytosis, frequently seen in children with hepatoblastoma and other malignities, is considered a

paraneoplasic phenomenon [16,17]. Thrombocytosis would appear due to the excessive production of thrombopoietin at the level of the tumoral tissue. The human thrombopoietin, also called growth factor of the megakaryocytes, is secreted by hepatocytes, kidneys, spleen and stromal cells of the bone marrow. The level of the serum thrombopoietin stimulates the megakaryocytopoiesis and determines the increase of the thrombocytes number [18]. Hwang demonstrated in a study on adult patients with hepatocarcinoma that the thrombocytosis correlated statistically significantly with: AFP values > 140 000 ng/ml, the tumoral volume > 30 % of the total hepatic volume, the tumoral alteration of both of the hepatic lobes and tumoral thrombosis in the portal vein [18].

The hepatoblastoma treatment combines the preoperatory chemotherapy with surgical excision, allowing a survival rate over 70 %. The high risk hepatoblastoma is treated with a presurgical chemotherapy more aggressive than the standard risk hepatoblastoma.

The hepatoblastoma treatment is relatively standardized, the only controversy matter between the European and American study groups being the time of the surgical intervention. The SIOPEL Group recommends the presurgical chemotherapy followed by the tumoral excision and then a short period of post surgery chemotherapy [19]. The American study group recommends the surgical intervention when diagnosed (applicable on 50% of the patients) followed by post surgical chemotherapy [20].

The 3-year global survival of the patients with standard risk hepatoblastoma is of 91 % with the SIOPEL 2 protocol and of 53 % for the ones with high risk hepatoblastoma [19]. In Japan, the study group of the child's hepatic tumors (JPLT-1) reported a 6-year survival of 73 % [21]. Matsunaga reported a favorable evolution after surgical excision in the cases of local recurrent lesions or pulmonary lesions [22]. Some children with hepatoblastoma will evolve unfavorably, developing predominantly pulmonary metastases.

Hepatoblastoma is considered to be non-surgical when: the tumor is extremely large, involving the risk of severe hemorrhage; both hepatic lobes are altered; the hepatic vein or the inferior vena cava is affected.

The hepatic transplant is indicated either initially, for the non-excisable hepatoblastoma or after the relapse [23]. Multicentric studies demonstrated a 10-year global survival of 85 % in the case of children with a primary hepatic transplant and of 40 % in the case of those who needed a hepatic transplant after the relapse [24].

The presurgical transarterial chemoembolization applicable to all non-excisable tumors can produce a tumoral necrosis of 25-95 % and a decrease of the tumoral volume of 26 %, necessitating though a highly specialized interventional team.

The complete surgical excision represents the essence of the hepatoblastoma treatment [25]. Our case had a complete excision of the tumor, based on histological examination.

The AFP level monitoring represents a valuable marker of the response to the presurgical chemotherapy, in the evaluation of the excision result and for the precocious diagnosis of the hepatoblastoma relapse. Certain authors have reported a transitory increase of the serum AFP correlated with each session of chemotherapy, the monitoring of AFP value in dynamics being necessary [26]. The complete excision of the hepatoblastoma determines the decrease of the AFP serum level, which will be normalized after 4-6 weeks. Our patient had, 2 years postoperatory, normal values of AFP, confirming complete resection of hepatoblastoma. The persistency or secondary increase of the AFP values suggests a residual tumor, metastases or a relapse, the AFP monitorization being necessary. The AFP serum level increases very much before the imagistic demonstration of the tumor relapse.

In conclusion, this paper emphasizes some important aspects regarding hepatoblastoma:

1. In the evaluation of the tumor excisability, ultrasound can offer more relevant data than computerized tomography.
2. The hepatoblastoma prognosis depends on its extension at diagnosis, on the histological type and on its excisability.
3. The ultrasound monitoring and AFP measuring in dynamics are compulsory.

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