

Hepatoblastoma requiring liver transplantation. A case report

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ABSTRACT

Hepatoblastoma is a rare pathology in pediatric patients, occurring in 5-10/one million children. A two year old patient was admitted to our clinic for intense abdominal pain. On examination he presented a large mass in the right hypochondrium. Abdominal ultrasound and computer tomography (CT) revealed a large, solid hepatic tumor with thrombosis of the right portal vein. Serum alpha fetoprotein (AFP) level and thrombocyte number were increased. Liver biopsy was performed and the histopathological aspect was specific for an epithelial hepatoblastoma. Chemotherapy was initiated, followed by surgery in two steps: right portal branch ligation and subsequent tumor resection. Six months after surgery a relapse was suspected, confirmed by CT and elevated AFP levels. A „rescue” liver transplantation was performed and the patient is disease-free for three years. Elevated AFP and thrombocyte levels point to the diagnosis of hepatoblastoma. Liver transplantation is the final option for extensive, inoperable or relapsing tumors.

Keywords: hepatoblastoma, chemotherapy, relapse, liver transplantation

Abbreviation list

CT: Computer tomography

AFP: Alpha-fetoprotein

Hgb: Haemoglobin

AST: Aspartate-aminotransferase

ALT: Alanine-aminotransferase

LDH: lactate dehydrogenase

CRP: C-reactive protein

ESR: erythrocyte sedimentation rate

HIV: Human immunodeficiency virus

INTRODUCTION

Hepatoblastoma is a rare malignancy, accounting for just over 1% of total pediatric cancers (1) and occurs in 5-10/one million children per year (2).

The etiology of the disease is unknown. Several genetic alterations have been found to be associated with hepatoblastoma, the most common are trisomy 2, 8 and 20 (3). Whole-genome DNA analysis led to the detection of many altered genomic regions, of which gain of material on chromosome 2q 13-22, 2q 36-37 and deletions of 2p and 4q were associated with advanced tumors and poor prognosis (3,4).

The diagnosis of hepatoblastoma is suspected in the patient aged between 6 months and 3 years, in the presence of a hepatic tumor, thrombocytosis and a high level of serum alpha-fetoprotein (AFP) (3). A high serum level of AFP should be interpreted according to age, very high values indicating hepatoblastoma. Moderately high values of serum AFP can be detected in yolk sack tumors, hepatocarcinoma as well as in certain benign tumors (mesenchymal hamartoma, focal nodular hyperplasia and infantile hemangioendothelioma)(4).

The hepatoblastoma histological classification comprises of six types grouped into two large categories: 1) epithelial hepatoblastoma and 2) epithelioid

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lial and mesenchymal mixed hepatoblastoma. Pure epithelial tumors account for approximately 56% of cases; they contain varying amounts of fetal cells, embryonal cells, or both. Within this group, purely fetal tumors account for 31% of hepatoblastomas and embryonal tumors account for 19% of hepatoblastomas (5).

The hepatoblastoma treatment is relatively standardized, the only controversy matter between the European and American study groups remains the time of the surgical intervention. The International Childhood Liver Tumors Strategy Group (SIOPEL) recommends pre-surgical chemotherapy followed by tumor excision and then a short period of post-surgical chemotherapy (6). The American study group recommends surgical intervention at the moment of diagnosis (applicable in 50% of patients) followed by post-surgical chemotherapy (7).

We report a case of hepatoblastoma with an unfavourable evolution and highlight the importance of liver transplantation for the management of such cases.

Informed written consent was obtained from the patient's mother before the publication of this case report.

PATIENT PRESENTATION

Presenting concerns

A two-year old male patient was admitted to our clinic for the investigation of an abdominal mass. The patient did not have any significant personal or family medical history prior to presentation.

Clinical findings

Physical examination on admission revealed an influenced general state, constitutional growth delay (Weight = 7.9 kg < 3rd percentile, Height = 75 cm < 3rd percentile), marked skin pallor. The abdomen was painful, distended, with a firm mass in the right flank.

Diagnostic focus and assessment

Blood results showed anemia (Hgb: 9.5 g/dl), leukocytosis (24,900/mm³), neutrophilia (16,000/mm³), thrombocytosis (994,000/mm³), abnormal liver tests (AST- 240 U/l, ALT- within normal limits), elevated LDH (618 U/l) and high inflammatory markers (CRP- 104.56 mg/dl, ESR- 65 mm/h).

Abdominal ultrasound showed a large, solid hepatic tumor. A CT scan was performed, which described a large 59/69/55 mm tumor located in segment 6 with heterogeneous structure and areas of necrosis, adherent to the external oblique muscle

and with thrombosis of the right portal vein, no pulmonary metastatic lesions, horseshoe kidneys (Fig. 1).



FIGURE 1. Abdominal CT scan showing large hepatic tumor

We excluded an infection with hepatitis B, C, HIV, *Toxoplasma gondii*, Epstein-Barr virus or cytomegalovirus. Vanil-mandelic levels in the urine were determined in order to exclude the diagnosis of neuroblastoma, with a normal value: 1.11 mg/24 h.

AFP levels were highly elevated - 174200 UI/ml (Normal: 0.92-6.73).

Taking into account the patient's age, elevated AFP levels, thrombocytosis, and imaging data the suspicion of a hepatoblastoma was raised. A biopsy was performed and the histopathological examination showed a histological aspect of an embryonic epithelial hepatoblastoma (Fig. 2).

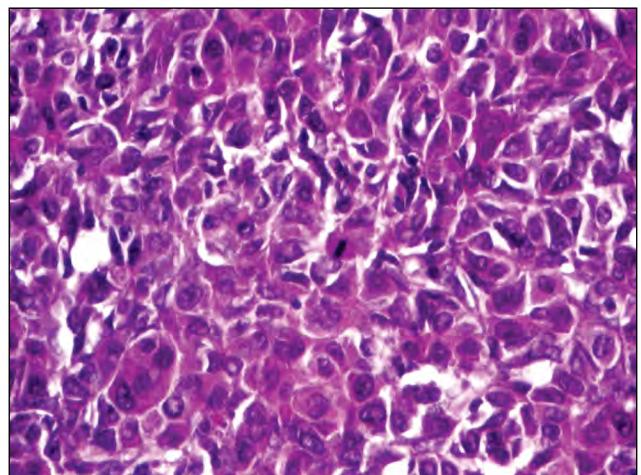


FIGURE 2. Hepatoblastoma. Hematoxylin-eosin

Therapeutic focus and assessment

Once the diagnosis of neuroblastoma – High Risk (due to the portal vein involvement) was con-

firmed, chemotherapy was initiated, according to the International Childhood Liver Tumors Strategy Group 3HR trial, which involved 4 cycles of Cisplatin and 4 cycles of Carboplatin-Doxorubicin. Following chemotherapy the patient developed medullary aplasia requiring blood transfusion and granulocyte colony-stimulating factors.

AFP values decreased to 29.9 ng/ml and the abdominal CT scan showed a small reduction in tumor size, 60/32/54 mm.

First surgery involved right portal branch ligation, followed by a cycle of Cisplatin. Step two of the surgical procedure (tumor resection) was performed five months later followed by a final cycle of Cisplatin.

Follow-up and outcome

Six months after the second surgery a relapse was suspected due to hepatomegaly, confirmed by very high levels of alpha-feto protein (56,8163 UI/ml) and abdominal CT scan which showed multiple lesions in the right and left liver lobes. Chemotherapy was resumed, with 3 cycles of Carboplatin-Doxorubicin and 4 cycles of Cisplatin/Vincristin/5-Fluorouracil. A bone scintigraphy and a thoracic CT scan were performed in order to exclude bone or pulmonary metastases, both negative.

Following the guidelines for relapses after surgery and chemotherapy, a liver orthotopic transplantation with segments 2-3 from a living related donor was performed. Postoperative evolution of the graft was favorable and the patient is disease-free for three years.

In order to evaluate the degree of fibrosis of the transplanted liver we performed liver elastography and Fibrotest®, both of the investigations were in normal range,

DISCUSSION

A large number of congenital syndromes and malformations have been described in patients with hepatoblastoma, such as Beckwith-Wiedemann syndrome, familial adenomatous polyposis and renal malformations. It was found to be more frequent in low-birth weight and premature infants (8,9). Our patient did not have any of the above-mentioned clinico-pathological risk factors associated with higher incidence of hepatoblastoma. In terms of possible associated conditions, he presented horseshoe kidneys with hypoplasia of the right kidney. Chan et al. proposed a new association be-

tween hepatoblastoma and hypoplastic kidneys, in a retrospective study performed in the Los Angeles Childhood Oncology Department and reported three such cases (10).

Hepatoblastoma prognosis depends on the tumor extension at the moment of diagnosis, on its excisability and on the histological type (11,12). In our case, the involvement of the portal vein and the large dimensions of the tumor led to the inclusion of the case in stage III, unresectable neuroblastoma. In terms of histology, pure fetal type confers the best prognosis (13). Our patient's tumor presented an epithelial, embryonal and fetal mixed histology, with a less favorable prognosis.

Hepatoblastoma treatment combines preoperative chemotherapy with surgical excision, allowing a survival rate of over 70% (14). Complete surgical resection is the cornerstone of treatment; however less than 40% of patients have resectable disease at diagnosis (15). If the tumor is considered unresectable and the patient is at high risk for complications, a biopsy is taken and preresection chemotherapy is indicated (5).

Asmar and Rassi described the case of a 8 months old female infant with a mixed mesenchymal and epithelial type hepatoblastoma who did not respond to chemotherapy, but was treated successfully via surgical resection, with no recurrent disease after 15 years (16).

Hepatoblastoma is considered to be non-surgical when: the tumor is extremely large, involving the risk of severe hemorrhage; both hepatic lobes are affected, the hepatic vein or the inferior vena cava is involved (17). In our case we performed a two-step procedure: during the first step, the right portal vein was ligated. This maneuver produced fibrosis of the right hepatic lobe and an enlargement of the left hepatic lobe. In these conditions, during the second step, a resection of the tumor in fibrous tissue was easier to perform and the risk of hemorrhage was decreased. This technique was first described in a pediatric patient by Chan et al., who performed a liver partition and portal vein ligation followed by tumoral resection in a patient aged 6 with a large hepatoblastoma. The patient had a favorable evolution, unlike our case who presented a relapse 6 months after surgery (18). Another study by Qazi et al. described an early tumoral recurrence in an infant with hepatoblastoma, who developed a relapse within the first month after the two-step surgery (portal vein ligation and subsequent tumoral resection) (19).

Despite the aggressive chemotherapy regimen and the complete resection of the tumor, our patient presented a recurrence 6 months after surgery, with multiple lesions in the right and left liver lobes. A “salvage” liver transplantation was the only viable option for the patient. A liver orthotopic transplantation with segments 2-3 from a living related donor (the mother) was performed, with favorable post-operative and long-term evolution. Fernandez et al. reported a case of a chemoresistant hepatoblastoma in a patient with trisomy 18, who developed recurrent disease after surgery and aggressive chemotherapy with cisplatin, vincristine, and 5 fluorouracil. Similar to our case, the patient underwent rescue orthotopic liver transplantation with a good long-term outcome (20).

Primary liver transplantation is indicated in the case of multifocal or solitary hepatoblastomas invading all four liver sectors or in centrally located tumors with close proximity to the major veins. Liver transplantation appears to have a better outcome when performed as a primary procedure rather than a salvage procedure for recurrent disease. Otte et al. reported 85% survival for 7 children un-

dergoing primary liver transplantation and only 40% for 5 children who underwent “rescue” transplantation (21).

Liver elastography can be used to non-invasively detect the development of fibrosis in the transplanted liver, with good accuracy (22). We performed shear-wave elastography in order to evaluate the degree of liver fibrosis in our patient and compared it with the result of Fibrotest® (an algorithm developed by Biopredictive as an alternative to liver biopsy, which uses the serum levels of alpha-2 macroglobulin, haptoglobin, apolipoprotein A1, total bilirubin, gamma-glutamyltranspeptidase). Both of the investigations were in normal range, indicating no liver fibrosis.

CONCLUSION

Hepatoblastoma is a very rare pathology in children. Elevated AFP and thrombocyte levels point to the diagnosis of hepatoblastoma. For patients with extensive, non-resectable tumors or disease relapse after chemotherapy and surgery, liver transplantation remains the final, salvaging option.

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