Unresectable Multifocal Hepatoblastoma With Cardiac Extension: Excellent Response With HB-94 Chemotherapy Protocol

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Summary: A 10-month-old white infant presented with abdominal distention and bilateral scrotal hernia. Imaging studies of the abdomen and thorax showed a huge liver with multiple tumor masses and calcification involving all the segments. There was thrombosis in the inferior vena cava and right atrium. α-Fetoprotein was 246,000 IU/mL. HB-94 chemotherapy protocol was started at once due to rapid deterioration of the patient. Surgical biopsy performed after the first IPA (ifosfamide, cisplatin, doxorubicin) course showed hepatoblastoma with macrotrabecular variant. After a second IPA course and 2 courses of carboplatin and etoposide, the boy’s clinical condition was excellent with normal α-fetoprotein but minimal regression and increased calcification in the tumor mass. Hepatic tumor was unresectable and no surgical intervention was performed. Transplantation could not be performed because of high morbidity and mortality. Despite general agreement that complete surgical resection is the cornerstone of treatment for patients with hepatoblastoma, the patient is in remission with 100% Karnofsky score in the 43 months of diagnosis.

Key Words: hepatoblastoma, cardiac extension, macrotrabecluar, HB-94 protocol

In the early years, surgery was the only modality of treatment in hepatoblastoma (HB). Before the development of effective chemotherapy, even after a successful surgery, most of the children died. Early postoperative mortality was high and appearance of metastases was very frequent.1 The contemporary approach is to avoid heroic primary resections with a high probability of leaving a residual tumor. In the HB-94 study, only 30% (21/69) of the patients underwent resection before chemotherapy; 28% (20/69) underwent resection after chemotherapy, and 39% (27/69) of these were complete resections and stage I tumors. Eight percent (6/69) of the patients had metastatic disease with unresectable liver tumors. Complete resection was achieved after second-look or third-look surgery in 54 of 63 patients (86%). Seventy-seven percent of the patients remained alive. Some patients also benefit from resection of lung metastasis. In this study, 2 children with multifocal disease without distant metastasis survived after liver transplantation.²

In the HB-99 study, 25% (10/40 children) of the patients underwent primary resection. Others had neoadjuvant chemotherapy and if possible tumor resection or transplantation.³ Although chemotherapy may shrink a nonresectable tumor to a resectable size, multicenter trials show that cytotoxic drugs alone cannot eradicate HB. Complete resectability remains the most important prognostic factor.²

Although rare, HB may invade the right atrium by direct extension of the tumor from inferior vena cava (IVC).⁴,⁵ The prognostic significance of the presence of macroscopic vascular tumor invasion is controversial. In some studies, it is a poor prognostic factor for survival.²,⁷ In the HB-94 study, the pretreatment prognostic value of vascular tumor invasion was high (P = 0.0039).² However, in the SIOPEL 1 study, no correlation was found between outcome and vascular invasion.⁸

In the final report of SIOPEL 2 (135 children) for standard-risk patients (confined to the liver and involving no more than 3 hepatic sectors), 3-year progression-free and overall survivals were 89% and 91% and for high-risk patients (HB extending into all 4 sectors and/or with lung metastases or intra-abdominal extra hepatic spreads) 48% and 53%, respectively. In this protocol, even standard-risk patients had delayed surgery after 2 courses of chemotherapy. In the high-risk group, the resection rate was 67% including several children undergoing liver transplantation.⁹

In the present report, our patient had high-risk features with an advanced tumor invading 4 sectors of the liver (German tumor study stage III and SIOPEL high-risk Pretex IV V.P) in addition to thrombosis in the right hepatic vena, vena porta, IVC, and right atrium. To our
surprise, after 4 courses of HB-94 chemotherapy, the patient remained in remission in the 43 months of diagnosis without any resection or liver transplantation.

**CASE REPORT**

A 10-month-old white infant presented with abdominal distention and bilateral scrotal hernia. His birth weight was 2700 g and the family reported a bulge in the left inguinal region in the postnatal 20 days. In the last 2 months, bilateral enlargement of the scrotum and abdomen were noticed. The infant had constipation and progressive irritability and he could drink small volumes of cow’s milk, and black tea with biscuits.

On physical examination, his general condition was poor, with extreme paleness and abdominal distention. Respiratory rate was 26/min, heart rate was 148/min, and blood pressure was 100/60 mm Hg. He had normal body weight, height, head circumference, and good features. A huge and hard mass with lobulated surface was palpated 18 and 15 cm below the right and left costal margins, respectively. The spleen was also palpated 4 cm below the left costal margin. Neuromotor development was normal.

Blood counts were hemoglobin: 2.5 g/dL, white blood cell count: 7800/mm³, absolute neutrophil count: 1800/mm³, platelet count: 212,000/mm³, mean corpuscular volume: 50 fl, RDW: 21.2, and reticulocyte index: 1%, and there were microcytic hypochromic red blood cells on the blood smear.

Blood biochemistry: alanine aminotransferase: 131 U/L, aspartate aminotransferase: 55 U/L, urea: 12 mg/dL, creatinine: 0.4 mg/dL, T-bilirubin: 5.3 g/dL, D-bilirubin: 2.4 g/dL, alkaline phosphatase: 116 U/L, γ-glutamyl transpeptidase: 201 U/L, lactate dehydrogenase: 1514 U/L, total protein: 5.4 g/dL, albumin: 2.9 g/dL, hepatitis B surface antigen negative, prothrombin time: 15.2 seconds, activated partial thromboplastin time: 32.2 seconds, international normalized ratio: 1.3, α-fetoprotein (AFP): 246,000 IU/mL.

Abdominal ultrasonography revealed hepatomegaly, splenomegaly, and ascites. Liver parenchyma was heterogenous with multiple tumor masses and calcification. Paranchyma of the spleen and kidneys were normal. Abdominal magnetic resonance imaging (MRI) also confirmed hepatomegaly and multifocal tumor invasion involving all segments of the liver. The right kidney was displaced to inferior by the liver. There was thrombosis in the IVC. Thorax computed tomography revealed no lung metastasis, but there was a mass filling the right atrial cavity. Transthoracic echocardiography (TTE) also revealed a 51 × 45 mm right atrial mass with minimal pericardial effusion. Ejection fraction was 85%. Two packed red cell transfusions in 5 mL/kg portions every 12 hours were performed with the administration of diuretics. The patient’s general condition rapidly deteriorated because of portal hypertension, ascites, severe abdominal distention, and anemia. He had dyspnea, tachypnea, edema, and decreased oxygen saturation (SPO₂: 92).

HB-94 chemotherapy protocol was started at once without histologic confirmation. Oxygen therapy with nasal prongs was started. Two courses of IPA (ifosfamide 3 g/m², cisplatin 100 mg/m², and doxorubicin 60 mg/m²) were administered. During the first course of therapy, close monitoring, a reduction in hydration, and aggressive furosemid therapy were required. Mesna doses were increased due to hemorrhagic cystitis. Moderate elevations in blood urea, uric acid, and transaminases were observed. Nutrition was maintained via a nasogastric tube with frequent small volumes. He also experienced a febrile neutropenia episode. After the first course of chemotherapy, the patient’s condition improved, with a decrease in the abdominal distention and disappearance of the edema and allowed incisional biopsy with mini laparatomy and central venous port catheter insertion. Although mini laparatomy did not give the surgeon the chance of visualizing all the hepatic mass, 3 cores of tissue samples were obtained from different tumor nodules. Histopathology revealed HB with macrotrabecules consisting of hepatoid cells and sinusoidal vessels. Silver staining demonstrated reticulin fibers surrounding trabecules that had 2-cell thickness. The tumor had less than 2 mitoses/10 high-power fields (Fig. 1). All the sections obtained from the samples showed the same histologic pattern except 1 sample with hemorrhagic necrosis and no tumor tissue. After the second course of IPA, AFP decreased to 584 IU/mL, and bilirubin decreased to normal level. TTE revealed minimal decrease in the dimensions of the right atrial mass (50.7 × 37.9 mm). Abdominal computed tomography also showed minimal tumor regression. Two more courses of chemotherapy (carboplatin 800 mg/m² and etoposide 400 mg/m²) were planned because of stable disease. The patient had short myelosuppression and granulocyte colony-stimulating factor 5 μg/kg was administered. After the second course of carboplatin/etoposide, TTE showed minimal regression and calcification in the right atrial mass. There was also minimal shrinkage in the liver but calcification of the tumor masses were increased. AFP decreased to 55 IU/mL. The patient tolerated the last 2 courses without any severe infection except balanitis. During discharge, the liver was palpable 10 and 9 cm below the right and left costal margins, respectively. His

**FIGURE 1.** HB with macrotrabecular pattern with irregularly formed by hepatoid cells and sinusoidal vessels (hematoxylin-eosin × 200).
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**DISCUSSION**

HBs comprise over two-thirds of the malignant tumors of the liver in childhood. Others include hepatocellular carcinoma and much less common tumors such as malignant mesenchymoma, rabdomyosarcoma, angiosarcoma, germ cell tumors, and undifferentiated sarcoma. HB occurs primarily in young children and 80% of the reported cases are less than 3 years of age. In the German Cooperative Pediatric Liver Tumor studies and in SIOP studies, patients 6 months to 3 years with elevated AFP and tumor in both liver lobes or primary stage IV underwent chemotherapy without a biopsy. In HB-89, 6 of the 26 infants under 3 months were initially treated under a wrong assumption. Neither tumor markers nor imaging techniques were always reliable.

Karnofsky score was 100%. AFP decreased to 6 IU/mL in the following month. He is in the 43rd month of diagnosis without any clinical abnormality except persisting hepatomegaly and scrotal hernia. His growth and neuromotor development are normal. Although right atrial mass (31 x 37 mm) with central hypoechogenicity also persists, ejection fraction is 67% and there is only minimal tricuspid regurgitation. Complete blood counts, blood biochemistry, and AFP are all normal. Abdominal and thorax MRI revealed hepatomegaly with heterogenous paranchyma and a 7 x 6 x 7 cm mass in segments V and VI. There was thrombosis in the right hepatic vena, vena porta, IVC, and right atrium (Fig. 2). There was no pulmonary metastasis. Thrombophilia evaluation showed no protein C, protein S, antithrombin deficiency, factor V Leiden mutation and activated protein C resistance. There was no family history of thrombophilia and no new thrombosis in the follow-up period.

Serum AFP may be elevated in hemangiendothelioma and mesenchimal hamartoma and may be mistaken for HB in infants. In hemangiendothelioma, the AFP level is usually normal or moderately elevated, but a highly elevated level (3490 ng/mL) was reported in the 3-month-old infant. In mesenchymal hamartoma of the liver also, a markedly elevated AFP level is rarely reported (7500 µg/L in a 2-month old infant); AFP elevations are generally below 1000 µg/L in these tumors, whereas concentrations greater than 500,000 ng/mL are not unusual in HB. Elevation to the degree seen in the present case is not expected in hemangiendothelioma and hamartoma. Five of the 28 hepatocarcinomas in the large US Intergroup report occurred in children younger than 5 years, whereas 20 of HBs (11%) were in children older than 10 years. Finegold suggests that all hepatic masses in children should be primarily resected if the extent of the tumor permits. Our patient’s poor condition did not permit a surgical biopsy at diagnosis.

Tumor histology and grade have prognostic significance in HB. Low mitotic activity is associated with good prognosis in all histologic forms. Pure fetal histology with low mitotic activity behaved better than all histotypes. Tumors with small cell undifferentiated histology have the worst prognosis. Fetal and embryonal tumors have intermediate prognosis. Small cell undifferentiated histology may be missed if only small biopsies are performed and these tumors generally do not have elevated AFP. We preferred incisional biopsy instead of multiple needle biopsies to obtain adequate tumor tissue and to control any tumor bleeding. Macrotrabecular pattern is a hepatocytic proliferation in trabeculae 10, 20, or more cells thick. The macrotrabecular cells can be fetal or embryonal hepatocytes. Occasionally, the cell size exceeds that of normal uninvolved liver tissue. In the HB-89 study, no macrotrabecular HBs were described. In the present case, mitotic activity was low, which is an independent variable associated with improved survival in all stages. In the literature, there is limited experience about the macrotrabecular pattern and its significance on prognosis. Conran et al. reported that macrotrabecular pattern appears to have a worse prognosis. Rowland suggests that the criteria for this histology is not being applied uniformly in the studies. We cannot suggest that macrotrabecular histology may have a role in the survival of the presented patient.

There was extensive calcification in the tumor tissue, which suggests bleeding and necrosis. Calcifications are seen in some HBs but the significance of this finding is not reported. It may show spontaneous or chemotherapy-induced necrosis and sensitivity to chemotherapy. There was a considerable delay in the diagnosis of the present case probably due to the poor social and economic status of the family. The left inguinal bulge noticed by the family in the neonatal period must be due to inguinal hernia caused by increased abdominal distention related to HB. On presenting to our hospital when the patient was 10 months old, the tumor gained an

**FIGURE 2.** Thorax and abdominal MRI show hepatomegaly with heterogenous paranchyma, 7 x 6 x 7 cm mass in segments V and VI. There is tumor thrombus in the right hepatic vena, vena porta, IVC, and right atrium.

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enormous size and the patient had severe microcytic anemia, which is not usual in HB. In addition to increased intravascular volume due to tumor tissue, impaired nutrition of the patient probably contributed to anemia. The infant’s diet was mainly composed of cow’s milk and black tea, which cause iron deficiency.

Malignancy itself is a risk factor for coagulability and the pressure of the tumor mass on the vessels cause stasis. There was no lung metastases despite atrial thrombosis but venous involvement does not always involve lung metastasis in HB. But even if the thrombosis in the venous system and right atrium were not tumor thrombosis, but a clot, the tumor stage would be still III or PRETEX IV invading all 4 sectors. Anyway, the patient has an unexpected prognosis for an unresected HB being in remission in the 43rd month of diagnosis with only chemotherapy. Sensitivity to chemotherapy either due to the histologic type or individual factors determining drug metabolism may be effective in the present case. In the literature, we could not find a report about a similar patient with advanced disease achieving good disease control after chemotherapy without tumor resection. The results of many studies were disappointing for these patients. In the Japanese Study Group of Pediatric Liver Tumor Protocol-I enrolling 145 patients with HB, patients with advanced tumors who underwent no operation were even excluded from the study. The Children’s Cancer Study Group and Pediatric Oncology Group found that a 2-year disease-free survival rate was only 12% in patients with unresectable hepatic tumors in spite of chemotherapy. Some patients with unresectable multifocal disease and vascular invasion are alive and disease free after liver transplantation.

During courses of chemotherapy, despite a dramatic fall in the AFP, tumor images did not change. Some of the mass probably was not composed of active tumor, or chemotherapy-induced maturation of the tumor is achieved.

Orthotopic living donor transplants or cadavreic transplants are effective treatments for unresectable unifocal and multifocal HB confined to the liver. All recipients receive preoperative chemotherapy and majority also postoperative chemotherapy. Response to chemotherapy is considered as an important factor influencing survival. In the world experience, 147 transplantations for HB are reported. The overall survival rate at 6 years after liver transplantation was 82% for 106 patients who received primary transplantation, whereas it was 30% for 41 patients who underwent a rescue transplantation. Macroscopic venous invasion had a significant impact on overall survival. In a series of 14 HBs, transplanted from living donors, the 1-year survival rate of patients with macroscopic venous invasion was poor (33%). However, macroscopic venous invasion is considered as a relative contraindication for liver transplantation in HB. These patients can be transplanted if clearance can be achieved by chemotherapy or surgery.

With the improvement in surgical techniques, involvement of hepatic vein and IVC by hepatic tumors are no more considered unresectable. They are resected and reconstructed with Gore-Tex interposition grafts or by using segments of the portal veins from the resected side of the liver as a graft.

To perform extended liver resection in small children, circulatory arrest and deep hypothermia techniques under cardiopulmonary bypass have been developed.

Central hepatic resection is also used for tumors that are located centrally and involve all or part of the segments IV, V, and VII. This helps avoid the use of extended hepatectomy and preserves normal hepatic substance. But this technique also could not be applied due to multifocal involvement of the presented case.

Although experiences are limited, high-dose chemotherapy with autologous transplantation is also used with success in metastatic HB.

Arterial chemoembolization in unresectable HB performed before chemotherapy is reported to provide good survival.

Although liver transplantation gave a chance for survival to patients with unresectable HB, a combination of cyclosporine and tacrolimus immunosuppression after liver transplantation and the chemotherapeutic drugs used to treat HB are nephrotoxic. Children who underwent liver transplantation had renal dysfunction before transplantation that persisted for 36 months after transplantation.

Sensorineural hearing loss is reported in 11 of 74 children (15%) after liver transplantation due to exposure to ototoxic drugs. The median age for transplantation is 12 to 18 months, which is a critical period for language acquisition. Although hearing status before liver transplantation was not assessed, posttransplant hearing impairment was found not only in patients with HB who were exposed to ototoxic drugs (cisplatinum, carboplatinum) before transplantation but also in patients with short gut syndrome who had parenteral nutrition-associated liver disease. All 3 patients with short gut syndrome and 3 of 4 patients with HB had hearing impairment. A primary diagnosis of HB was associated with a marked increase risk of hearing impairment. Posttransplant length of hospital stay correlated with risk of impairment although days of treatment with loop diuretics or aminoglycosides did not achieve significance in the study. Late effects of transplantation must be carefully monitored.

Because of the rarity of HB, children with extensive HB should be treated in centers with surgical expertise in pediatric major liver resection and liver transplantation in close collaboration with pediatric oncologists, radiologists, and histopathologists. We preferred a conservative approach for the patient due to lack of compliance of the family, high mortality of the liver transplantation and risk of resection of the atrial tumor, and construction of IVC in unexperienced centers. Besides, the cost of these very risky interventions may not be justified in a developing country.
Our patient had a good response to chemotherapy when decline of the AFP level is considered. In the German HB-94 study, there was a significant correlation between disease-free survival and response to chemotherapy ($P = 0.0003$ for patients receiving IPA and $P = 0.0013$ for patients receiving IPA + VP16/carboplatin). In the IPA group, 41 chemotherapy-responsive children had a disease-free survival above 75% and the curve made a plateau after approximately 18 months. Of 18 patients with advanced or metastatic HB who received VP16/carboplatin, 12 chemotherapy-responsive patients also had approximately 75% disease-free survival and the survival curve also made a plateau after approximately 18 months. All the nonresponders died before 4 years of diagnosis.

To explain the unexpected disease-free survival of this multifocal unresectable HB, more experience on macrotrabecular variant and extended calcification in tumor tissue may be required. The current approach in unresectable HB is chemotherapy with or without radiation followed by liver transplantation unless there is an identifiable unresectable active tumor outside the liver. The tumor of the present case is somewhat unusual in its apparent prenatal onset and fairly slow progression. At 10 months postnatal, there were still no distant metastasis that would imply a slower progression and perhaps different biology from what might be expected. It is possible that tumors presenting in the neonatal period behave differently as occurs in neuroblastoma.

REFERENCES