Case Report

A Case Report and a Review of Pediatric Hepatoblastoma

Anthony D DeRenzi, DO1,2; Audrey Bowen, MD3

Abstract

Introduction
Hepatoblastoma is a rare pediatric cancer. Approximately 100 cases of hepatoblastoma are reported per year. Due to the limited incidence of this disorder an internationally agreed-upon criteria was developed to classify patients as standard or high-risk. Studies involving chemotherapeutic agents, surgery, and liver transplants have been demonstrated to improve the disease-free survival rate. The combination of chemotherapeutic agents and surgery demonstrated the ability of these regimens to downgrade the initial diagnostic staging of tumors and transform previously unresectable tumors into resectable tumors.

Case Presentation
The following case of hepatoblastoma presents a 4-year-old male who presented to the emergency department with an upper respiratory infection symptom and was found to have hepatomegaly. The patient was later classified as high-risk, unresectable hepatoblastoma.

Conclusion
Hepatoblastoma is a rare liver cancer in children with an annual incidence of 1.5 cases per million. With PRETEXT staging criterion, therapeutic options such as cisplatin/doxorubicin combination, radiotherapy, and lobectomy, have become the standard of care for this condition. Many trials have demonstrated these therapeutic options to successfully improve the survival rate of patients affected by hepatoblastoma, downgrading tumors from advanced PRETEXT stages and enabling previously unresectable tumors to be considered resectable.

Keywords
hepatoblastoma; pediatric cancer; chemotherapy; doxorubicin; lung metastasis; liver neoplasm; PRETEXT; rare tumor; staging

Introduction
Hepatoblastoma is the most common primary liver tumor in children, accounting for just over 1% of pediatric cancers. Hepatoblastoma primarily affects children from infancy to about 5 years of age. It is the most common malignant liver tumor in early childhood. Hepatoblastoma accounts for 79% of all liver tumors in children and almost two-thirds of primary malignant liver tumors in the pediatric population. Approximately 100 cases of hepatoblastoma are reported per year. The annual incidence of hepatoblastoma in infants younger than 1 year is 11.2 cases per million. Between 1990-1995, the annual incidence in children was 1.5 cases per million.1

Most hepatoblastoma tumors begin in the right lobe of the liver. The most common site of metastasis with hepatoblastoma is the lungs. Hepatoblastoma affects White children more often than Black children and is more common in boys than girls up to about age 5, which is when the gender difference disappears.1

Although the exact cause of hepatoblastoma is unknown, several conditions are associated with an increased risk of developing hepato-
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2 toblastoma. These conditions include Beckwith-Wiedemann syndrome, familial adenomatous polyposis, hemihypertrophy, and biliary atresia. Children exposed to hepatitis B infection at an early age have a significantly higher rate of hepatoblastomas, as well as premature children with low birth weight and very low birth weight.2

The following case of hepatoblastoma discusses a 4-year-old male who presented to the emergency department (ED) with upper respiratory infection (URI) symptoms and was found to have hepatomegaly during his physical exam at his return visit.

Case Presentation
A 4-year-old male, accompanied by his mother, presented to the ED on August 2, 2019, and was treated for URI symptoms. The patient’s medical history included being born prematurely at 25 weeks and weighing 750 grams. He was discharged from the ED with instructions for supportive care. The patient returned to the ED 1 week later, on August 12, 2019, with vomiting and a fever. The history taken during this encounter described the patient as being asymptomatic for 2 days and having a recurrence of symptoms for 5 consecutive days. The patient’s physical exam was abnormal due to the liver edge being palpable 8 cm below the costal margin and the epigastric area. Lab results during this visit included a white blood cell count of 13.7 x 10^9/L, an absolute neutrophil count of 10.3, and a platelet count of 486 x 10^9/L. An abdominal x-ray was performed due to pain and vomiting, which revealed hepatomegaly with multiple radio densities projecting over the liver. The right upper quadrant ultrasound demonstrated a large, ill-defined left hepatic lobe mass with extension into the right lobe as well as splenomegaly. A computed tomography (CT) scan showed an unresectable liver mass measuring 179 mm, suspicious for hepatoblastoma, primary bilateral effusions, and ascites (Figure 1).

During a subsequent admission, the alpha fetal protein (AFP) levels were 648 600 nl/ml, and a biopsy demonstrated hepatoblastoma, showing a predominately embryonal pattern on the pathology report. The patient was classified as high-risk due to the metastasis, a PRETEXT 4 with (see staging below) metastatic lung lesions, and hepatoblastoma.

The patient underwent cisplatin and doxorubicin/zinecard therapy. A repeat CT scan was performed to assess the tumor response to chemotherapy, which demonstrated pulmonary nodules reflective of metastatic liver cancer and liver size had increased by 1.9 cm. The lung nodules did not clear post-chemotherapy. A repeat AFP lab was 349 200 nl/ml 3 days later, but it trended up to 423 100 nl/ml 4 days later. It was unclear whether the increase in AFP was

Figure 1. A computed tomography (CT) scan showed an unresectable liver mass measuring 179 mm, suspicious for hepatoblastoma, primary bilateral effusions, and ascites.
due to tumor resistance to chemotherapy or an expected lab finding associated with chemotherapy.

The patient was referred to a hospital in Miami for transplant consultation. However, he did not meet the transplant criteria. The patient returned to our facility on June 21, 2020, for fever, vomiting, and diarrhea. He was discharged after several days. He was later evaluated at All Children's Hospital/Johns Hopkins for experimental chemotherapy. Despite the experimental chemotherapy, the AFP levels continued to rise, and the patient unfortunately passed away on June 30, 2020.

**Discussion**

**Symptomatology**

Most patients with hepatoblastoma present with an enlarging abdominal mass. The right lobe is involved 3 times more commonly than the left, with bilobar involvement seen in 20-30% of cases and multicentric involvement in 15%. Less common symptoms are anorexia, weight loss, and pain. Association with precocious puberty has been reported. The serum AFP level is almost always elevated. Bilirubin and liver enzymes are usually normal. Anemia and platelet abnormalities have been reported. Although low platelet counts can occur in hepatoblastoma, and thrombocytosis is commonly reported, the etiology of this finding is unclear. The platelet count decreasing could indicate toxicity from chemotherapy, and Absolute Neutrophil Counts are less important for prognostication.¹

There is no clear correlation between AFP and clinical outcome. However, the persistence or recurrence of elevated AFP is a sensitive marker of the disease. There is a correlation between AFP and the extent of disease for all stages, and the rate of decline in AFP with treatment is prognostic. Low AFP levels are associated with anaplastic histology and poor outcome.

Metastases at diagnosis occur in 10-20% of patients, with the lung being the predominant site of metastases at presentation and relapse. Other sites of distant metastases, including brain and bone, are rare and usually occur in the setting of relapsed disease.¹

**Staging**

A biopsy is required to confirm the diagnosis, assist with a treatment plan, and develop a prognosis. The PRETEXT group (I, II, III, IV) reflects hepatic parenchymal tumor involvement.² The PRETEXT annotation factors denote the following extra parenchymal tumor characteristics:³

- V: Involvement of vena cava, all 3 hepatic veins, or both
- P: Involvement of portal bifurcation, both right and left portal veins, or both
- E: Extrahepatic contiguous tumor extension
- F: Multifocal liver tumor
- R: Tumor rupture at diagnosis
- M: Metastatic

As the PRETEXT stage increases from 1 to 4, the prognosis decreases. The following stages correlate with the number of liver sections radiologically involved with the tumor:⁴

- Stage I: Complete surgical resection
- Stage Ila: Complete macroscopic surgical resection, intrahepatic residual microscopic disease
- Stage IIb: Complete macroscopic surgical resection, extrahepatic residual microscopic disease
- Stage IIIa: Incomplete surgical resection with macroscopic residual and/or significant tumor spill and/or positive lymph node disease
- Stage IIIb: Tumor not resectable
- Stage Iva: Distant metastatic disease, primary tumor completely resected
- Stage IVb: Distant metastatic disease, primary tumor incompletely resected

**Therapy**

Chemotherapy: Chemotherapy treatment depends on standard versus high-risk patients as well as early versus delayed tumor resection. Typically, 5 to 6 chemotherapy treatments are standard for high-risk patients. Cisplatin is the most active single agent used to treat hepatoblastoma.⁴ The cisplatin/5-fluorouracil (5-FU)/vincristine (VCR) combination is regarded as a standard chemotherapeutic treatment in hepatoblastoma. Preoperative chemotherapy can completely eradicate metastatic pulmonary disease and multinodular liver disease. Postoperatively, chemotherapy is usually started.
approximately 4 weeks after surgery to allow liver regeneration.

Radiotherapy: Radiotherapy is not the standard treatment in hepatoblastoma. It is more commonly used in palliative cases. Doses used for treatment of hepatoblastoma are usually 1200-2000 centigray (cGy). Radiotherapy may be used when microscopic disease is seen at the resection margins. Adjuvant radiotherapy may have a role in the treatment of chemoresistant pulmonary metastases.

**Resection and Transplantation**

Initial resection of operable primary tumors by lobectomy is the standard of care in hepatoblastoma. Liver transplantation has increased in children with nonresectable tumors or those who show chemotherapy resistance. Some patients have long-term, disease-free survival when aggressive attempts are made to eradicate all areas of disease surgically.

For a tumor to be deemed unresectable, it must be large and may lead to excessive bleeding, have involvement of both the right and left lobes, have involvement of major hepatic veins or the inferior vena cava, and present as a diffuse multifocal disease. After initial chemotherapy, tumor shrinkage allows for easier resection with less blood loss and morbidity. Prior to the use of preoperative chemotherapy, about half of newly diagnosed hepatoblastomas are considered unresectable. In cases of unresectable tumors, transplant is curable and only performed when there is no extrahepatic disease.

Due to the regenerative capacity of the liver, up to 85% of the liver can be safely resected. Elevated AFP levels immediately following surgery are common. However, failure of AFP to return to normal or rising levels after stabilization of post-resection AFP levels should prompt aggressive evaluation for local recurrence and metastatic disease.

**Imaging**

In terms of imaging modalities for a patient with hepatoblastoma, ultrasound and CT scans have been helpful. An ultrasound with a color doppler has been used to define the tumor's relationship to the portal vein. A CT scan has been used to assess the initial staging, assess resectability, and monitor tumor response to chemotherapy.

**Benefits of Chemotherapy**

A retrospective study of 20 pediatric patients with grade III and IV surgically unresectable hepatoblastomas by Venkatramani et al found that 16 out of 20 cases were resectable after just 2 cycles of neoadjuvant chemotherapy.

International Childhood Liver Tumors Strategy Group Study (SIOPEL 3): The SIOPEL-3 study compared cisplatin alone with cisplatin and doxorubicin in patients with PRETEXT II-III tumors. The study found that the survivability rates were similar for the cisplatin (95%) and cisplatin/doxorubicin (93%) groups.

SIOPEL-3HR Study: In a pilot study, SIOPEL-3 High Risk (HR), cisplatin alternating with carboplatin/doxorubicin was administered in a dose-intensive fashion to high-risk patients with hepatoblastoma. Of 74 patients with PRETEXT IV tumors, 22 of whom also had metastases, 31 became resectable, and 26 underwent transplants. The 3-year Overall Survival (OS) of this group was 69% (± 11%). Of the 70 patients with metastases enrolled in the trial, the 3-year event-free survival (EFS) rate was 56%, and the OS rate was 62%. Of patients with lung metastases, 50% were able to achieve complete remission of metastases with chemotherapy alone.

SIOPEL-4 Study: SIOPEL-4 was a cisplatin/doxorubicin chemotherapy trial and radical surgery for children with high-risk hepatoblastoma. The primary tumor masses were identified as PRETEXT II (27%), III (44%), and IV (26%). Of the 16 PRETEXT IV patients, 11 were downstaged after chemotherapy: 6 to PRETEXT III, 4 to PRETEXT II, and 1 patient to PRETEXT I. Twelve tumors became resectable; of these twelve tumor patients, 4 patients underwent a partial hepatectomy, and 8 underwent liver transplants. For patients who presented with PRETEXT IV disease, the 3-year disease-free survival was 73% (95% confidence interval [CI], 51%-96%), and the 3-year OS was 80% (95% CI, 60-100%).
**Benefits of Chemotherapy in Combination With Surgery**

Häberle et al demonstrated that tumor-free survival from hepatoblastoma could be improved to 75% of all patients by combining surgery with chemotherapy. Twenty-six patients with an extended but potentially resectable tumor (stage III) were preoperatively treated with 3 courses of chemotherapy followed by tumor resection and a fourth course of chemotherapy. Nine patients with high-risk hepatoblastomas (3 x stage III HR, 6 x stage IV) were treated with 2 courses of carboplatin (800 mg/m$^2$) and etoposide (400 mg/m$^2$) (CARBO/VP16).

Forty out of 45 (89%) of all hepatoblastoma patients were in remission. Thirty-four out of 36 (94%) standard-risk (SR) patients (stage I - III SR) were tumor-free; 2 died of therapy complications.

Six HR-patients were tumor-free; 1 lived but with a tumor, and 2 died. In relation to the PRETEXT grouping, a remission was achieved in 4 out of 4 patients in stage I; 14 out of 16 in stage II; 16 out of 16 in stage III; 5 out of 6 in stage I - III, V, P, E, M; and 1 out of 3 in stage IV tumors. Six out of 9 HR-hepatoblastomas were good responders to CARBO/VP16. Five of these patients were in remission. Three out of 9 tumors did not respond, and only 1 could be eradicated by liver transplantation.

In 5 of 9 HR-patients, resection was possible after chemotherapy. In an R1-resection, 1 received a liver transplant, and 2 tumors remained inoperable. In 4 out of 6 cases, lung metastases could be removed entirely, or, in 1 case, they had vanished in the CT scan under chemotherapy. These 4 patients remained in remission. The most frequent severe toxicity of CARBO/VP16 concerned leukopenia (23% of courses) and thrombocytopenia (85% of courses). Under high-dose therapy, severe infections (2 out of 7, 28%) and elevation of transaminases occurred. There was no toxic death.

A cure rate of over 90% can be reached by conventional cisplatin, doxorubicin-containing chemotherapy, and radical surgery in SR-hepatoblastoma.

**Liver Transplantation**

A study that included hepatoblastoma liver transplantation patients from 1990 and 2004 analyzed the impact on survival, including previous tumor resection, metastatic disease at diagnosis, microscopic vascular invasion, AFP levels at diagnosis and at transplant, tumor histology, and administration of post-transplantation chemotherapy.

Effectiveness of pre-transplantation chemotherapy was defined as a drop of more than 99% in peak AFP levels.

Fourteen patients were transplanted, including 9 males and 5 females whose ages ranged from 18 months to 13 years of age, and averaged transplant 4 months after diagnosis. Overall survival was 71% (10 of 14), with a mean follow-up of 46 months. All deaths were secondary to a recurrent tumor. Of 10 patients who underwent a primary liver transplant, 9 survived compared to only 1 of 4 transplanted for unresectable tumor recurrence after primary resection (90% vs 25%; \(P = .02\)). Decline in peak AFP of more than 99% was also associated with better survival rates (100% vs 56%; \(P = .08\)). Similarly, patients who received post-transplantation chemotherapy had a 100% survival rate compared with the 56% rate for those who did not receive chemotherapy (\(P = .08\)).

**Conclusion**

Hepatoblastoma is a rare liver cancer in children with an annual incidence of 1.5 cases per million. Due to the rarity of this condition, it was difficult to have internationally approved staging criteria prior to the PRETEXT staging criteria. Upon having an approved staging criterion, therapeutic options were considered following several successful trials, which concluded cisplatin/doxorubicin combination, radiotherapy, and surgical options, including lobectomy, to be the standard of care for this condition. Many trials have demonstrated these therapeutic options to successfully improve the survivability rate of patients affected by hepatoblastoma, downgrading tumors from advanced PRETEXT stages and enabling previously unresectable tumors to be considered resectable.
Conflicts of Interest
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Author Affiliations
1. HCA Florida North Florida Hospital, Gainesville, FL
2. UCF/HCA Healthcare GME Consortium of North Florida
3. Nemours Children’s Hospital, Orlando, FL

References