A RARE CASE OF HEPATOCELLULAR CARCINOMA IN A 6 YEAR-OLD FEMALE

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Introduction

Hepatocellular carcinoma (HCC) is quite rare in children. Hepatoblastoma is the most common liver malignancy in pediatric patients and should always be considered as a differential diagnosis in a case such as this. While the etiology of HCC in adults in generally secondary to chronic disease, the etiology in children is typically related to Hepatitis B or congenital disease. HCC is generally diagnosed between age 12 and 14 in pediatric patients, and rarely is it diagnosed in those younger then 5.

The symptoms of hepatocellular carcinoma are quite non-specific, and include abdominal pain and distension, nausea, vomiting, weight loss, and fever. This leads to a diagnostic delay as well as a delay in treatment. Only those who have advanced disease have symptoms such as jaundice and cachexia. Ultrasound can be used initially, however further analysis requires the use of CT or MRI. Elevated levels of serum AFP are specific but not very sensitive for detecting hepatocellular carcinoma in those who are at increased risk. For lesions without known cirrhosis, biopsy is recommended to confirm the diagnosis. There are no specific recommendations in children about when to biopsy, however it is recommended that in children without cirrhosis, histological evaluation be done, due to the implication of different histological subtypes on the prognosis and response to treatment.

When deciding treatment for pediatric patients with HCC it is important to consider four factors: 1) liver function status including ascites, albumin, alkaline phosphatase, bilirubin, portal vein thrombosis, and Child-Turcotte-Pugh scores; 2) tumor characteristics – including size, number of nodules, vascular invasion, TNM staging, distant metastasis, and AFP levels; 3) presence of portal hypertension and 4) the overall status of the patient. The option that provides the highest success rate is complete resection for non-metastatic HCC or liver transplantation. It should be noted that there has been a dramatic improvement in the 5-year survival rates of children with HCC. This is likely attributed to improvement in surveillance and surgical techniques, specifically liver transplantation. For children in whom liver transplantation or resection is not an option, systemic neoadjuvant chemotherapy (including regiments of PLADO – cisplatin and doxorubicin or super-PLADO – cisplatin, carboplatin, and doxorubicin) can be used and can serve as a bridge to transplantation re-evaluation at a later time. Other treatment options include targeted therapies based on certain pathological mechanisms of cell proliferation involved in the oncological process.

Sorafenib is a novel multikinase inhibitor against RAF kinase and VEGF along with anti-proliferative and anti-angiogenic properties. Many trials have shown that use of sorafenib, in comparison to placebo has improved time to tumor progression and overall survival. Additionally, the combination of doxorubicin with sorafenib has shown better outcomes than either agent alone. From the German GPOH group, sorafenib when used in combination with PLADO in children with hepatocellular carcinoma showed tumor regression in 4 out of 7 unresectable tumors.

Case Presentation

A 6 year-old female patient with past medical history of seasonal asthma presented to the primary care with the chief complaint of abdominal pain and abdominal distension for about 2 weeks. The patient was otherwise healthy, very active, a diligent student with minimal absences and good grades, no recent travel history, and no sick contacts. No family history of liver diseases, cancers, or autoimmune diseases. The following sequence of events are mentioned with dates for proper orientation.

Timeline	Incident/Results
Day 1 of Sxm Onset	• Patient complains of "increased abdominal pain, decreased oral intake, increased lethargy". No fevers, vomiting, diarrhea, cough, nasal congestion, or bleeding. • She was taken to the urgent care as later patient complained of "her heart beating too fast". • At urgent care, blood pressure was elevated, strep and mono test were negative, and negative for UTI. • She was discharged home with a diagnosis of a "stomach bug".
Day 14	• Follow up with PCP and again told she had a "stomach bug". • No vomiting, fever, or diarrhea. Only symptoms were ongoing abdominal pain and decreased energy. • Labs showed slightly elevated liver enzymes (AST 114 & ALT 46) but normal BP at this visit.
Day 24	• ED visit for abdominal swelling. • Vitals showed: T:100F, other vitals normal, AST 153, ALT 51, CRP 1.13. • KUB showed hepatosplenomegaly with downward displacement of bowel loops. • Diagnosis of constipation and viral hepatitis made, patient discharged home.
Day 25	• Follow up with PCP, ultrasound ordered for July 18th.
Day 26	• Patient taken to the ED for hypoglycemia – glucose 37, AST 182, ALT 39, bilirubin normal, albumin 2.7, uric acid 1.7, LDH 442, BUN/Cr 6/0.33. Repeat POC glucose in ER was 29 with undetectable insulin levels at <1. Cortisol 14.57 and GH level at 0.46. • Admitted to Children's Hospital and remained inpatient with extensive workup.
Day 28	• MRA/MRCP/MRV for further imaging of liver.
Day 29 (*Day 1 dx*)	• Open liver biopsy, showing concern for Hepatoblastoma vs. Hepatocellular Carcinoma. • Pathology was sent to Pittsburg for a second opinion and after review, diagnosed with Hepatocellular Carcinoma Stage 3.
Day 35, *(Day 1 Tx)*	• Thorough imaging including CT chest, abdomen, and pelvis showed no pulmonary metastasis. • Started on broad spectrum chemo of Carboplatin on D1 and D2, Vincristine on D1, and Etopside D1 and D2. • Noted to have pancytopenia. • After her first cycle of chemo, AFP increased from 491 (July 23) to 894 (August 1). • Required Neulsta for pancytopenia and neutropenia. • Has also required intermittent O2 for respiratory support, increased WOB, and tachypnea due to abdominal ascites, tumor burden, and pain.
Day 35 – Day 50	• Hypoglycemia attributed to HCC and Cirrhosis. • Failed evaluation for liver transplant due to concern of lung lesions and metastatic pulmonary disease. Additionally, large tumor thrombus in IVC. • Ascites improved, nutrition worsened with significant weight loss. • Started on NG tube feeds. • Sent back for chemo directed therapy as liver transplantation not an option without first receiving systemic chemotherapy at the time.
Day 51	• Received her first cycle of systemic chemotherapy for HCC that consisted of cisplatin 80mg/m2 IV x1; dexrazoxane 300 mg/m2 IV prior to Doxorubicin 30 mg/m2 IV on days 1 and 2. • Tolerated chemotherapy well.
Day 54	• Started on Sorafenib at the low dose of 100 mg daily; increased to full dose (150 mg/m2) 200 mg last night. • The patient received sorafenib x 19 total doses (days 4-22).
Day 54 - NOW	• After receiving a complete course of chemotherapy as per the treatment plan, the patient was approved for liver transplantation as there were no longer any concerning metastatic lesions. • The patient underwent liver transplantation and is currently doing well.

Radiology/Imaging

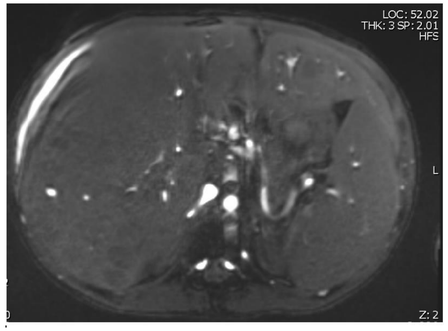

Figure 1: MRI Abdomen MRCP with and without contrast – Initial Evaluation (Day 28)

The liver is markedly abnormal and enlarged with the craniocaudal dimension of the right lobe reaching almost 18 cm. There are innumerable lesions throughout the liver, that are nodular. There are large conglomerate area of coalescent lesions rather than a large single mass, involving the right and left lobes. This area is difficult to measure precisely but is on the order of 7.6 x 12.7 x 12.2 cm. There are scattered innumerable other lesions throughout all hepatic segments.

There is extensive portal vein involvement with expanded irregular main, right and left portions of the portal vein with abnormal high signal material showing some enhancement. There is high suspicion that this is very likely a tumor thrombus. Some changes shown are compatible with cavernous transformation near the main portal vein where it becomes occluded. There is no evidence of occlusion or thrombosis of the IVC or of the middle, right, or left hepatic veins. These veins are in extensive contact with the tumor and in places are suspected to be encased by tumor. The IVC is compressed and quite narrowed but not occluded as it comes up into the liver. The lesions in question enhance but less so than the liver. Enhancement increases on the later/portal venous phases. There is some arterial phase enhancement in the periphery of the main lesion right lobe.

There is abnormal lymph node enlargement. One example lymph node, in front of the aorta displacing the celiac trunk to the left measures 1.9 x 2.9 x 2 cm. The kidneys, adrenal glands, and pancreas appear normal. The spleen is enlarged without focal lesions. The craniocaudal dimension of the spleen measures 14 cm. The gallbladder wall appears thickened and edematous. There may be some pericholecystic fluid as well. There appears to be no discernible biliary dilation. There is mild ascites present in both upper quadrants including fluid around the liver and adjacent to the spleen. No organized fluid collection is evident. There is trace bilateral pleural effusions.

Final Impression:
Overall the findings are that of neoplasm with evidence of nodal metastasis. There is evidence of Portal vein tumor thrombus and Hepatic vein positive disease. The present splenomegaly and ascites are likely related to portal venous hypertension.

CT Chest w/o contrast (Day 40)
1. Scattered pulmonary nodules are present measuring approximately 2-4 mm. The right middle lobe nodules also seen on the prior exams have the most suspicious appearance and could represent pulmonary metastatic disease. The right upper lobe and lingular pulmonary nodules are more nonspecific in appearance and may represent intrapulmonary nodules, but the possibility of pulmonary metastatic disease cannot be excluded.
2. Pleural parenchymal bands in the lingula and lower lobes bilaterally are favored to represent subsegmental atelectasis rather than pleural parenchymal scarring and have improved relative to prior studies.

Conclusions

HCC is a rare diagnosis in the pediatric population. There was 4 weeks of delay between the initial presentation seen by PCP and definitive diagnosis in our patient. This case highlights the challenge of the PCP not keeping cancer in their differential for abdominal distension in pediatric patients because of its rarity, and rather attributing symptoms and even physical findings to more benign diagnosis such as constipation. In this case, this occurred even at the subspecialist levels (GI and oncology).

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