

## Giant hepatocellular adenoma in a previously obese thirteen-year-old boy

Richard A. Rosencrantz,<sup>\*,\*\*</sup> Youmin Wu,<sup>\*\*</sup> Pierre-Yves Sonke,<sup>\*\*\*</sup> Yasmin Yusuf<sup>\*\*\*\*</sup>

<sup>\*</sup> Department of Pediatrics, Section of Gastroenterology and Hepatobiliary Diseases. <sup>\*\*</sup> Center for Transplantation. <sup>\*\*\*</sup> Department of Radiology.  
<sup>\*\*\*\*</sup> Department of Pathology, New York Medical College, Maria Fareri Children's Hospital at Westchester Medical Center, Valhalla, New York, USA.

### ABSTRACT

Hepatocellular adenoma is an uncommon neoplasm, especially in the childhood age group. We describe a previously obese 13-year-old male with a giant hepatocellular adenoma requiring an extensive hepatic resection. The related pediatric tumor literature, diagnosis and clinical management is discussed.

**Key words.** Pediatrics. Obesity. Liver resection.

### CASE REPORT

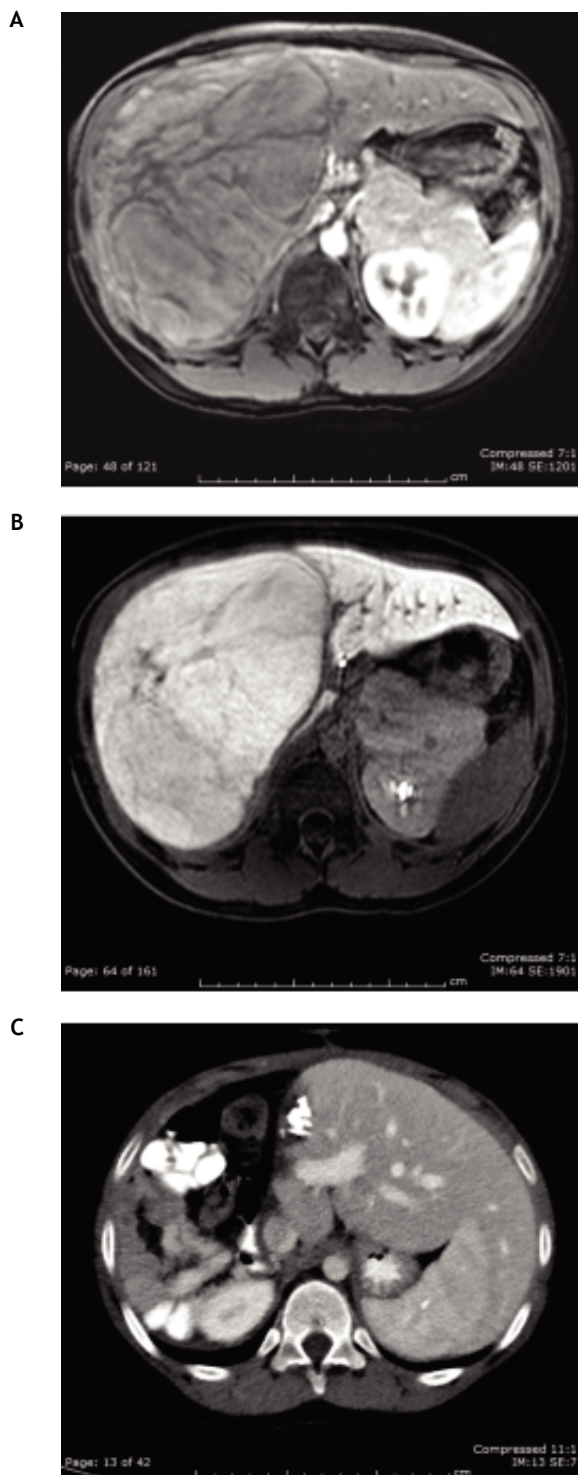
A 13-year-old African-American male presented with a 1-year history of nighttime enuresis occurring approximately 5 times per week. The patient was referred by his pediatrician after palpating a right upper quadrant mass which was revealed by ultrasound to originate in the liver. Past medical history was significant for mild intermittent asthma, hypertension and a 15 lb. weight loss over the last 1 year. He was developmentally appropriate for age. There was no history of hormonal or estrogen use. He denied any jaundice, bruising, bleeding, pruritis or any abdominal complaints including abdominal pain, nausea, diarrhea or constipation. On physical exam his weight, height and body mass index were in the 50th, 5th and 75th percentiles, respectively. Vital signs were: T 36.1 °C, HR 74 bpm, BP142/89, RR16, O2 saturation 100%. His exam was significant for a non-tender firm right upper quadrant mass palpated approximately 3 finger breadths below the right costal margin. Laboratory evaluation showed a WBC 6.7 X 10<sup>9</sup>/L, Hgb 13.1 g/dL, platelets 461 x 10<sup>9</sup>/L, AST 33 U/L, ALT 23 U/L,

albumin 3.8 g/dL, total bilirubin 0.4 mg/dL, prothrombin time INR 0.92, blood urea nitrogen (BUN) 10 mg/dL, creatinine 0.67 mg/dL, uric acid 4.7 mg/dL, lactate 1.6 mmol/L, ferritin 105.7 µg/L, cholesterol 54 mg/dL, triglycerides 34 mg/dL, alpha-fetoprotein 1.54 ng/mL. Serologies were negative for viral hepatitis A, B, and C. Serum amino acids, plasma acylcarnitine profiles, urine organic acids, 24 h urine collection for porphobilinogen showed no abnormalities. MRI with Eovist on T1-weighted images showed a large heterogenous mass measuring approximately 16.8 cm x 12.7 cm x 16.6 cm with sparing of segment 5 arising from the right lobe of the liver and inferiorly displacing the right kidney; and predominantly hypo-intense enhancement in the hepatobiliary phase (Figure 1 A, B). A liver biopsy of the mass showed features consistent with a hepatocellular adenoma (see below). The patient underwent an extended right lobe resection and hepatectomy removing completely the tumor in its entirety. Post-operative course was marked by mild fluid third-spacing responsive to diuresis and a transient ileus that resolved by post-operative day 5. Prothrombin time and bilirubin remaining normal throughout, however, serum ALT peaked at 525 U/L on post-op day 5, decreased to almost normal by post-op day 13 and was discharged home. A follow-up CT scan with IV contrast 2.5 months after surgery showed a hypertrophied left liver lobe extending to the left lateral abdominal wall without residual tumor (Figure 1 C). The patient is clinically well, normotensive and has normal hepatic synthetic function four months after surgery.

**Correspondence and reprint request:** Richard A. Rosencrantz, M.D.  
Maria Fareri Children's Hospital at Westchester Medical Center  
Pediatric GI & Hepatobiliary Diseases, 503 Grasslands Road, Suite 201,  
Valhalla, NY 10595  
E-mail: richard\_rosencrantz@nymc.edu

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**Figure 1.** A. T1-weighted image showing a large 16.8 cm well-defined heterogeneous right liver lobe mass with arterial enhancement. B. T1-weighted image in delayed hepatobiliary phase showing the heterogeneous right liver lobe mass with predominantly hypo-intense signal relative to the liver. C. CT scan 2.5 months after resection showing a hypertrophied left liver lobe without tumor recurrence.

### Pathologic diagnosis

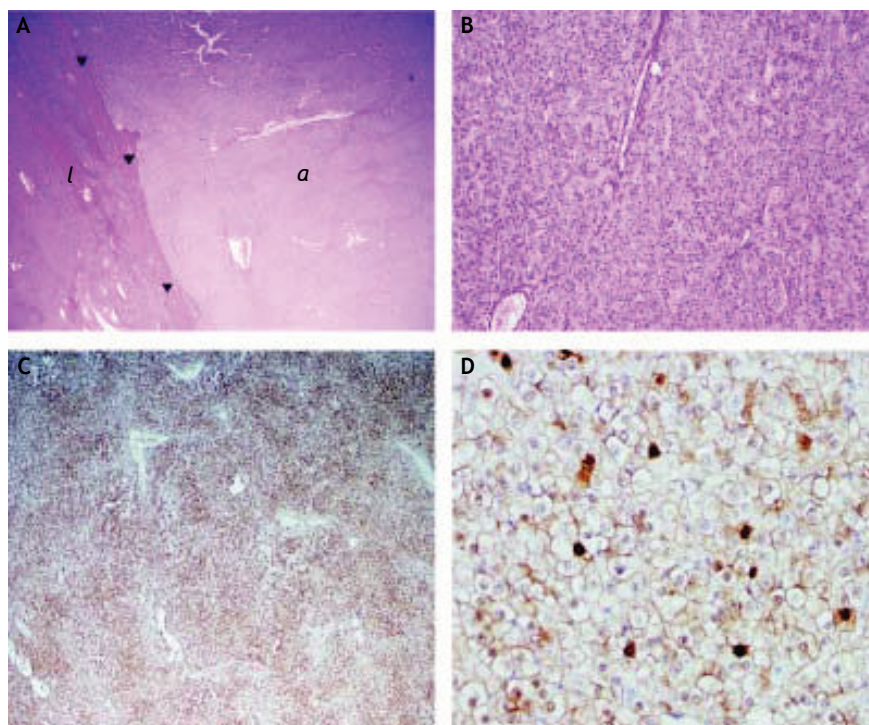
Specimen (Figure 2 A-D) showed a well-delineated, non-encapsulated 16 cm x 14 cm x 6 cm brown mass. Microscopically, the mass was composed of benign-appearing hepatocytes without cytologic atypia arranged in one to two cell thick plates (reticulin stain) with occasional acini. There were no portal or portal triad-like areas seen. Traversing the mass were unpaired arterioles. No cytologic features such as trabecular or acinar structures were present. No peliosis, sinusoidal dilatation, inflammatory infiltrate or steatosis was seen. The uninvolved surrounding liver was normal. Immunohistochemical stains revealed that the tumor was diffusely positive for glutamine synthetase and showed diffuse membranous and patchy focal nuclear  $\beta$ -catenin positivity supporting the diagnosis of  $\beta$ -catenin activated hepatocellular adenoma. Immunostains for serum amyloid A (SAA), and C-reactive protein were negative (CRP).

### DISCUSSION

Hepatocellular adenoma (HCA) is a benign epithelial liver tumor that has malignant potential. HCA represents 3.8% of all hepatic tumors from birth to 20 years. It is the eighth most common pediatric hepatic tumor following hepatoblastoma, hepatocellular carcinoma (HCC), infantile hemangioendothelioma, focal nodular hyperplasia, mesenchymal hamartoma, undifferentiated embryonal sarcoma and nodular regenerative hyperplasia.<sup>1</sup>

Childhood HCA is seen sporadically usually in adolescent girls, but has been diagnosed as early as in the third trimester of pregnancy by prenatal ultrasonography in a male fetus.<sup>2</sup> High-risk groups for HCA development include those with a history of anabolic steroid intake<sup>3</sup> or estrogen oral contraceptive use.<sup>4</sup> In addition, de novo HCA formation may be seen in glycogen storage diseases (GSD) types 1a (glucose-6-phosphatase deficiency – von Gierke disease) and 3 (amylo-1-6-glucosidase deficiency – Cori disease), hereditary tyrosinemia, galactosemia, hereditary hemochromatosis, androgen-treated Fanconi's anemia, familial adenomatous polyposis coli, alcohol consumption, congenital or surgical portosystemic shunts and obesity.<sup>5-8</sup>

Hepatic tumors in children commonly present as an asymptomatic abdominal mass; however, at least half exhibit acute or chronic abdominal pain, hypertension due to right kidney compression, hematuria



**Figure 2.** A. Normal liver parenchyma (l) and hepatocellular adenoma (a), interface (arrowheads) (H&E 2x). B. HCA. One to two cell layers thick hepatic plates without cytologic atypia, unpaired arterioles without portal triads (H&E 10x). C. HCA. Immunohistochemical stain for glutamine synthetase showing diffuse cytoplasmic positivity (4x). D. HCA. Immunohistochemical stain for  $\beta$ -catenin, showing diffuse membranous and patchy focal nuclear positivity (40x).

or elevated liver function tests.<sup>9</sup> HCA usually appears in non-cirrhotic liver as a solitary well-delineated, non-encapsulated mass with a predilection for the right lobe, but bilobar and multiple adenomas (adenomatosis) may be seen in patients with obesity and GSD.<sup>10,11</sup> In a series of children with type 1 GSD, HCA developed in 15% of patients by 15 years of age and occurred more commonly in those who had poor metabolic control as measured by serum triglyceride levels greater than 500 mg/dL.<sup>12</sup>

HCAs can be classified by genotype into three subtypes using immunohistochemical methods, although, up to 10% display no distinguishing molecular characteristics.<sup>13</sup> Inflammatory HCA (SAA and/or CRP positive), occurring in approximately 50%, is more associated with obesity, carries the highest risk of nodular peliosis and non-tumor liver macrovesicular steatosis; HNF-1  $\alpha$  inactivated HCA (liver fatty acid binding protein negative), occurring in about 35%, is more frequently found in adenomatosis (> 10 nodules), has more tumor steatosis and has the lowest risk of HCC; and  $\beta$ -catenin activated HCA, found in approximately 12%, of which slightly more than half are also SAA/CRP positive, has the highest overall risk of HCC.

Malignant transformation correlates with increased tumor size and gender. A literature review of 1617 cases of HCA found that malignant transformation to HCC occurred in 4.2% and more than

95% arose in a tumor size of greater than 5 cm in diameter.<sup>14</sup> Remarkably, a French adult study reported an almost 50% greater risk of malignant transformation in males.<sup>15</sup> Evidence suggests that lipogenesis facilitates cancer cell proliferation. In fact, increased de novo fatty acids synthesis, synthetic precursors of triglycerides, may promote cell transformation by modifying oncoproteins via protein lipidation which activate oncogenes such as Ras, Src and Wnt.<sup>16</sup>

Abdominal imaging techniques such as CT scan and MRI can be used for diagnosis. One MR Eovist imaging study of 43 pathology-proven HCA lesions demonstrated that 88.4% show an inhomogenous mass with 90.7% having mild-moderate arterial phase enhancement and 93% appearing hypo-intense on hepatobiliary phase.<sup>17</sup> Similarly, this enhancement pattern was seen in our patient. Interestingly, the Bordeaux group confirmed in adults, that MRI can identify specific radiographic features associated with either HNF-1 $\alpha$  inactivated HCA or inflammatory HCA – together comprising approximately 85% of HCA subtypes.<sup>18</sup>

Other complications such as bleeding and rupture occur more commonly and frequently in HCA lesions greater than 5 cm in diameter. A literature review of 1176 patients with HCA showed complications such as hemorrhage and rupture in approximately 15.8% and 17.5%, respectively.<sup>19</sup>



The management approach for HCA should be more vigorous than that of most other benign hepatic tumors because of the higher possibility for bleeding and/or malignant progression.<sup>20,21</sup> Asymptomatic lesions less than 5 cm and having MRI features of HNF-1 $\alpha$  inactivated HCA, conservative management can be attempted such as discontinuing any hormonal therapy and if applicable treating obesity. Serial imaging every 6 months for 2 years and annual should be obtained thereafter depending on lesion stability. Lesions less than 5 cm and having IHCA MRI characteristics or those greater than 5 cm should be biopsied and categorized according to subtype.  $\beta$ -catenin activated positive nodules should undergo surgical resection particularly in men because of the increased risk of HCC. If no surgical intervention is elected, conservative management along with serial imaging every 6 months is advocated and the surgical route should be taken if the nodule is growing in size or becomes symptomatic.

In the present case, clinical risk factors for HCA development such as estrogen or androgen exposure, alcohol, and female gender were notably absent. Furthermore, metabolic disease such as Glycogen Storage Disease was excluded because the patient did not have any features consistent with the syndrome such as fasting hypoglycemia, hyperlipidemia, elevated lactate, creatine phosphokinase (CPK), or uric acid or any proteinuria. In addition, no biochemical or histologic evidence of iron overload was found. His past BMI of 28 corresponding to > 95th %ile for age (obesity) may have played a role in the development of HCA. A one year randomized control study of overweight and obese adults showed that a body weight reduction of 10% can result in significant improvement and resolution in biopsy-proven non-alcoholic steatohepatitis histology.<sup>22</sup> While IHCA is more commonly associated with obesity, our patient's weight loss was equivalent to a 15% weight reduction which similarly may have changed the histologic picture since he did not have any hepatic steatosis or display immunohistochemical features of IHCA such as SAA or CRP reactivity. Nevertheless, resection was indicated because the risk for malignant transformation was high on account of tumor size and  $\beta$ -catenin activated HCA positive histology.

## CONCLUSION

HCA is uncommon in pediatrics; however this case illustrates that development of high risk tumors may occur in pediatric patients who had a pri-

or history of obesity without other established risk factors and may present as a large hepatic mass without any specific abdominal symptoms or biochemical abnormalities.

## REFERENCES

1. Stocker JT. Hepatic Tumors in Children. *Clin Liver Dis* 2001; 5: 259-81.
2. Applegate K, Ghei M, Perez-Atayde A. Prenatal detection of a solitary liver adenoma. *Pediatr Radiol* 1999; 29: 92-4.
3. Gorayski P, Thompson CH, Subhash HS, Thomas AC. Hepatocellular carcinoma associated with recreational anabolic steroid use. *Br J Sports Med* 2008; 42: 74-5.
4. Rooks JB, Ory HW, Ishak KG. Epidemiology of hepatocellular adenoma. The role of oral contraceptive use. *JAMA* 1979; 242: 644-8.
5. Labrune P, Trioche P, Duvaltier I, Chevalier P, Odievre M. Hepatocellular Adenomas in Glycogen Storage Disease Type 1 and 3: A Series of 43 Patients and Review of the Literature. *J Pediatr Gastroenterol Nutr* 1997; 24: 276-9.
6. Paradis V, Champault A, Ronot M, Deschamps L, Valla DC, Vidaud D, Vilgrain V, et al. Telangiectatic adenoma: an entity associated with increased body mass index and inflammation. *Hepatology* 2007; 46: 140-6.
7. Bunchorntavakul C, Bahirwani R, Drazek D, Soulen MC, Siegelman ES, Furth EE, Olthoff K, et al. Clinical features and natural history of hepatocellular adenomas: the impact of obesity. *Aliment Pharmacol Ther* 2011; 34: 664-74.
8. Franchi-Abella S, Branchereau S. Benign Hepatocellular Tumors in Children: Focal Nodular Hyperplasia and Hepatocellular Adenoma. [published online ahead of print March 11 2013]. *Int J Hepatol* 2013. doi: 10.1155/2013/215064.
9. Leese T, Farges O, Bismuth H. Liver Cell Adenomas: A 12-Year Surgical Experience From a Specialist Hepato-Biliary Unit. *Ann Surgery* 1988; 208: 558-64.
10. Nichols F, van Heerden J, Weiland L. Benign Liver Tumors. *Surg Clin of North Am* 1989; 69: 297-314.
11. Labrune P, Trioche P, Duvaltier I, Chevalier P, Odievre M. Hepatocellular Adenomas in Glycogen Storage Disease Type I and III: A Series of 43 Patients and Review of The Literature. *J Pediatr Gastroenterol Nutr* 1997; 24: 276-9.
12. Wang DQ, Fiske LM, Carreras CT, Weinstein DA. Natural History of Hepatocellular Adenoma Formation in Glycogen Storage Disease Type 1. *J Pediatr* 2011; 159: 442-6.
13. Bioulac-Sage P, Laumonier H, Couchy G, Le Bail B, Sa Cunha A, Rullier A, Laurent C, et al. Hepatocellular Adenoma Management and Phenotypic Classification: the Bordeaux Experience. *Hepatology* 2009; 50: 481-9.
14. Stoot JHMB, Coelen RJS, de Jong MC, de Jong CH. Malignant transformation of hepatocellular adenomas into hepatocellular carcinomas: a systemic review including more than 1600 adenoma cases. *HPB (Oxford)* 2010; 12: 509-22.
15. Dokmak S, Paradis V, Vilgrain V, Sauvanet A, Farges O, Valla D, Bedossa P, et al. A Single-Center Surgical Experience of 122 Patients with Single and Multiple Hepatocellular Adenomas. *Gastroenterology* 2009; 137: 1698-705.
16. Fritz V, Fajas L. Metabolism and proliferation share common regulatory pathways in cancer cells. *Oncogene* 2010; 29: 4369-77.
17. Grazioli L, Bondioni MP, Haradome H, Motosugi U, Tinti R, Frittoli B, Gambarini S. Hepatocellular Adenoma and Focal Nodular Hyperplasia: Value of Gadoteric Acid-enhanced MR Imaging in Differential Diagnosis. *Radiology* 2012; 262: 520-9.

18. Laumonier H, Bioulac-Sage P, Laurent C, Zucman-Rossi J, Balabaud C, Trillaud H. Hepatocellular Adenomas: Magnetic Resonance Imaging Features As a Function of Molecular Pathological Classification. *Hepatology* 2008; 48: 808-18.
19. Van Aalten SM, de Man RA, IJzermans JN, Turkivatan T. Systematic review of haemorrhage and rupture of hepatocellular adenomas. *Br J Surg* 2012; 99: 911-16.
20. Nault JC, Bioulac-Sage P, Zucman-Rossi J. Hepatocellular Benign Tumors-From Molecular Classification to Personalized Clinical Care. *Gastroenterology* 2013; 144: 888-902.
21. Marrero JA, Ahn J, Reddy KR. ACG Clinical Guideline: The Diagnosis and Management of Focal Liver Lesions. *Am J Gastroenterol* 2014; 109: 1328-47.
22. Promrat K, Kleiner DE, Niemeier HM, Jackvony E, Kearns M, Wands JR, Fava J, et al. Randomized Control Trial Testing the Effects of Weight Loss on Nonalcoholic Steatohepatitis (NASH). *Hepatology* 2010; 51: 121-9.