CLINICAL VIGNETTE

Large Hepatic Adenoma in a Pregnant Patient

Laura McEnerney, MD[1] and Simon Beaven, MD, PhD[1,2]

[1]Vatche & Tamar Manoukian Division of Digestive Diseases
[2]Pfleger Liver Institute, David Geffen School of Medicine at University of California, Los Angeles, CA 90095

Description of the Case

An asymptomatic 32-year-old woman presented for evaluation of incidentally noted elevation of the alkaline phosphatase to 414 U/L (reference range 37-113 U/L). A subsequent gamma glutamyl transferase (GGT) was elevated at 216 U/L (reference range 7-68 U/L), suggesting a hepatic origin for the elevated alkaline phosphatase. The patient had been on continuous oral contraceptives for the past fifteen years but recently stopped them because of her desire to become pregnant. She had no known prior liver disease, did not drink alcohol in any significant amount, did not have diabetes, obesity, or evidence of metabolic syndrome, and had no known risk factors for viral hepatitis. Her personal and family history was unremarkable for autoimmune and genetic/metabolic liver diseases. The physical exam was unremarkable.

An abdominal ultrasound showed multiple hepatic lesions scattered throughout the liver, thought to represent hepatic adenomas. A follow-up MRI confirmed multiple arterially enhancing liver lesions, with many of them lacking Eovist uptake, but without definitive venous washout. The largest lesion was in the hepatic dome, splaying the right and middle hepatic veins. It measured 58 x 60 x 73 mm (Figure 1), with smaller lesions measuring 47 x 19 x 33 mm, 27 x 23 x 26 mm and 37 x 28 x 35 mm. These lesions were thought to represent a combination of hepatic adenomas and focal nodular hyperplasia. The patient was advised to defer her pregnancy plans and to remain off oral contraceptives. A blood pregnancy test was negative.

She met with a hepatobiliary surgeon two weeks later, who noted that the lesions were likely to be benign, but that the largest lesion (measuring greater than 5 cm) did have increased risk for hemorrhage or malignant degeneration. However, the location of the large lesion between the right and middle hepatic veins was not amenable to surgical resection. It was recommended that the patient continue to defer conception, with plans to repeat an MRI in the next three to six months to document stability or regression of the lesions off of oral contraceptives. The following day, the patient took a home pregnancy test and discovered that she was pregnant. Subsequent b-HCG confirmed the pregnancy.

The patient established care with a maternal-fetal medicine specialist. It was recommended that she undergo right upper quadrant ultrasounds every two weeks for the duration of the pregnancy to monitor interval growth of the hepatic lesions, with plan for potential embolization lesion grew too large. The lesions remained relatively stable in size until her 28 week ultrasound which showed two lesions increased by 1 cm in size compared to the initial ultrasound. On the 30 week ultrasound, one liver lesion continued to marginally increase in size. A multi-disciplinary conference was held with hepatology, hepatobiliary surgery, maternal-fetal medicine and interventional radiology, concluding with a plan to defer any treatment in the absence of adenoma hemorrhage until after delivery of the fetus. Fortunately, subsequent ultrasounds did not show any further significant increases in liver lesion size, and a scheduled Caesarian section performed at 37 weeks gestation resulted in the delivery of a healthy baby boy without complications.

The patient was advised to avoid future pregnancies until adenoma regression is documented or embolization of the larger adenomas can be performed. In the meantime, she will use non-hormonal contraception. After discussion with her obstetrician, she will have a copper intrauterine device placed for prevention of future pregnancies.

Discussion

Hepatocellular adenoma (HCA) is a benign liver tumor occurring mostly in reproductive aged women. Liver adenomatosis is defined as at least 3-10 adenomas noted within the liver, which occurs in a third of patients with HCA.[1] These tumors are thought to be hormone responsive, although the mechanism by which estrogen induces growth of hepatic adenomas is unclear. Long term oral contraceptive use is a risk factor for developing HCA, as much as 34 times more likely than for non-users of oral contraceptives.[2] HCA tends to regress in size after oral contraceptives are discontinued.

High quality imaging with contrast enhanced, multi-phase MRI or CT generally allows for accurate diagnosis of HCA. Percutaneous core needle biopsy is not usually necessary to confirm a diagnosis.[1] More recent literature suggests molecular

markers obtained from core biopsies may be useful in predicting the clinical course of adenomas.[3] Hepatic adenomas can be classified into three sub-types: 1) Inflammatory HCA (40-55%); 2) HCA with HNF-1a mutation (35-50%) , and 3) HCA with b-catenin activation (10-15%). Sub-types 1 and 2 are virtually always found in women, while sub-type 3 is more frequent in men.[1] Sub-type 3 carries the highest risk for malignant transformation, while subtype 2 is the least aggressive or complicated form.[1] Subtype 1 lesions, which are common, are the most likely to result in spontaneous hemorrhage.[1] In this case, the patient most likely had HCA subtype 1 with intense arterial enhancement persisting into the portal venous and delayed phases (Figure 1). Most hepatic adenomas are asymptomatic and are discovered incidentally on imaging or liver tests; however, on occasion they can present with symptoms of right upper quadrant pain, discomfort related to bleeding within the adenoma itself, or with life threatening hemorrhage into the peritoneal cavity. Hemorrhage occurs mostly in HCA tumors greater than 5 centimeters in size. Malignant transformation of HCAs has been reported at a frequency of 4.2%,[4] primarily occurring in those tumors measuring greater than 5 centimeters in size.[1]

During pregnancy, the hyperdynamic circulation, increased liver vascularity, and increased circulating estrogens increase the risk of HCA growth and consequently HCA rupture. HCA rupture threatens the well-being of both mother and fetus. Rupture risk is highest during the third trimester, although the exact risk is unknown. For women desiring pregnancy, it is recommended that interventions be performed prior to conception for HCAs that exceed 5 centimeters in size. Surgery is the preferred intervention, but embolization can be pursued if the lesion is not amenable to surgery.[2-5] HCAs under 5 centimeters in size do not present a contraindication to pregnancy.

In the patient presented above, pregnancy was established before the adenomas could be monitored and/or treated. The identification of HCAs was particularly concerning given that the largest lesion measured more than 5 centimeters, increasing the risk for lesion growth and rupture. Important considerations for her included avoidance of embolization before 26 weeks if possible, as the fetus is most sensitive to radiation during this time period.[2-5]

Now that she has completed her pregnancy, trans-arterial embolization (TAE) may be necessary should her largest HCA lesion fail to spontaneously regress in size within 12 months.[3] Should TAE prove necessary, it is minimally invasive and may result in regression or complete involution of up to 80% of HCA lesions.[3] Percutaneous radiofrequency ablation seems most useful for HCAs smaller than 5 centimeters.[6] After pregnancy, the recommendation is to monitor HCA growth with repeat CT or MRI every 6 months for the first two years, and then annually after that.[2] Some authors recommend continued follow-up evaluation until menopause.[1]

Conclusion

Pregnancy should be discouraged when an HCA greater than 5 centimeters is identified, at least until regression of the lesion is established, or it can be treated via surgery or other interventional procedure. When an HCA measuring more than 5 centimeters is encountered during pregnancy, it is important to obtain regular imaging throughout the course of the pregnancy to assess for growth of the HCA that might place a patient at risk for rupture of the lesion.

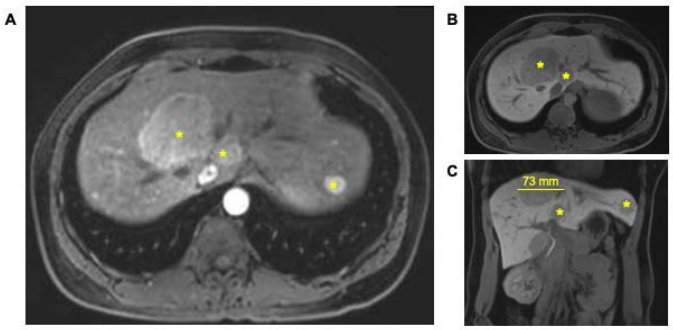

Figure 1. **Multiple hepatic adenomas in a pregnant patient.** **(A)** Using contrast enhanced MRI, T1-weighted arterial phase transverse image of the patient's multiple hepatic masses (*). Also shown are delayed, 18-20 min, T1-weighted transverse **(B)** and coronal **(C)** images with the largest lesion measuring 73 mm in greatest diameter.

REFERENCES

1. **Agrawal S, Agarwal S, Arnason T, Saini S, Belghiti J**. Management of Hepatocellular Adenoma: Recent Advances. *Clin Gastroenterol Hepatol*. 2015 Jul;13(7):1221-30. doi: 10.1016/j.cgh.2014.05.023. Epub 2014 Jun 5. Review. PubMed PMID: 24909909.
2. **Marrero JA, Ahn J, Rajender Reddy K; American College of Gastroenterology**. ACG clinical guideline: the diagnosis and management of focal liver lesions. *Am J Gastroenterol*. 2014 Sep;109(9):1328-47; quiz 1348. doi: 10.1038/ajg.2014.213. Epub 2014 Aug 19. PubMed PMID: 25135008.
3. **Tsilimigras DI, Rahnemai-Azar AA, Ntanasis-Stathopoulos I, Gavriatopoulou M, Moris D, Spartalis E, Cloyd JM, Weber SM, Pawlik TM**. Current Approaches in the Management of Hepatic Adenomas. *J Gastrointest Surg*. 2019 Jan;23(1):199-209. doi: 10.1007/s11605-018-3917-4. Epub 2018 Aug 14. PubMed PMID: 30109469.
4. **van Aalten SM, Bröker ME, Busschbach JJ, de Koning HJ, de Man RA, Steegers EA, Steyerberg EW, Terkivatan T, Ijzermans JN**. Pregnancy and liver adenoma management: PALM-study. *BMC Gastroenterol*. 2012 Jun 29;12:82. doi: 10.1186/1471-230X-12-82. PubMed PMID: 22748109; PubMed Central PMCID: PMC3503786.
5. **Bröker ME, Ijzermans JN, van Aalten SM, de Man RA, Terkivatan T**. The management of pregnancy in women with hepatocellular adenoma: a plea for an individualized approach. *Int J Hepatol*. 2012;2012:725735. doi: 10.1155/2012/725735. Epub 2012 Dec 24. PubMed PMID: 23320183; PubMed Central PMCID: PMC3540741.

6. **van der Sluis FJ, Bosch JL, Terkivatan T, de Man RA, Ijzermans JN, Hunink MG**. Hepatocellular adenoma: cost-effectiveness of different treatment strategies. *Radiology*. 2009 Sep;252(3):737-46. doi: 10.1148/radiol. 2523082219. PubMed PMID: 19717753.