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Case Report

Malignant degeneration of hepatic adenomas to hepatocellular carcinoma

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Abbreviations:
HA, hepatic adenoma
HCC, hepatocellular carcinoma
PCP, primary care physician
RUQ, right upper quadrant
CT A/P, abdomen/pelvis computed tomography
IV, intravenous
MRI, magnetic resonance imaging
FNA, fine needle aspiration
US, ultrasound
CEA, carcinoembryonic antigen
AFP, alpha-fetoprotein
FLR, future liver remnant
HPT, hypothalamic-pituitary-thyroid
OC, oral contraceptive
FNH, focal nodular hyperplasia

ABSTRACT

Background

Hepatic adenomas (HA) are rare, benign proliferations of hepatocytes with high glycogen and fat content that lack normal hepatic architecture. In general, the long-term incidence of malignant degeneration to HCC has not been well characterized. This case report discusses a 37 male with a 10-year history of weekly anabolic steroid abuse who presented with bilobar hepatic adenomas with subsequent malignant degeneration to hepatocellular carcinoma (HCC).

Case Presentation

Our patient is a 37 old male with a 10-year history of weekly anabolic steroid abuse who presented to his primary care physician (PCP) in July 2013 with intermittent right upper quadrant (RUQ) pain. He was subsequently referred to our cancer center after abdomen/pelvis computed tomography (CT A/P) with oral and intravenous (IV) contrast at an outside hospital revealed two large hepatic masses. The larger mass in segment 2 measured 6.5 x 9.1 cm, while the segment 6/7 mass measured 7.5 x 7.6 cm. Abdomen magnetic resonance imaging (MRI) with and without IV contrast performed at our institution on July 23, 2013 confirmed the presence of the two above noted masses, which were felt to be consistent with probable HA, although HCC could not be definitely ruled out. Of note, his carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP) were within normal limits. Percutaneous, ultrasound-guided (US) biopsy of the left lobe mass was consistent with probable HA, although HCC could not be definitely ruled out.

Conclusion

We present the case of a 37-year-old male 10-year history of weekly anabolic steroid abuse who presented to us in 2013 with HA which had malignant degeneration to HCC while on surveillance over a 2-year period. This case report stresses the importance of having a high clinical suspicion for HA in patients with a history of anabolic steroid abuse and liver masses. Additionally, it reiterates that it can be difficult to differentiate HA from well-differentiated HCC on imaging and/or with a limited biopsy. Furthermore, it is important to keep in mind that the growth of a mass, especially off steroids is highly concerning for malignancy (and masses that fail to regress completely can harbor occult HCC).

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Background

HAs are rare, benign proliferations of hepatocytes with high glycogen and fat content that lack normal hepatic architecture. They have an estimated prevalence of 1-3 per 100,000 young women with a long-standing history of oral contraceptive (OC) use, with a female/male ratio up to 11:1 [1, 2]. This case report discusses a 37 male with a 10-year history of weekly anabolic steroid abuse who presented with bilobar hepatic adenomas with subsequent malignant degeneration to HCC.

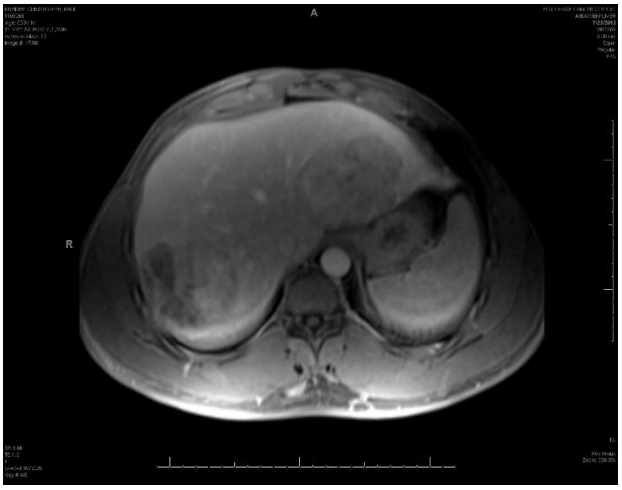
Case Description

We report a case of malignant degeneration of HA to HCC. Our patient is a 37 old male with a 10-year history of weekly anabolic steroid abuse who presented to his PCP in July 2013 with intermittent RUQ pain. In particular, for the first 8 years, he would cycle on and off of testosterone derivatives for 3 months at a time but for the last 2 years he constantly injected 250 mg enanthate or cypionate per week. He also used growth hormone (2 IU a day) and tried other agents such as boldenone undecylenate. He was subsequently referred to our cancer center after a CT A/P with oral and IV contrast revealed two large hepatic masses. The larger mass in segment 2 measured 6.5 x 9.1 cm, while the segment 6/7 mass measured 7.5 x 7.6 cm. Both had enhancement heterogeneously in the arterial phase which slightly washed out in the delayed phase. Both masses did fill in completely on late delayed phase images. Abdomen MRI with and without IV contrast performed at our institution on July 23, 2013 confirmed the presence of the above noted masses;one in segment 2 measuring approximately 7.3 x 9.1 cm and the other in segments 6/7 measuring approximately 7.9 x 7.9 cm. The mass in segment 2 was isointense on the short echo time images and mildly hyperintense on the long echo time images. The mass in segments 6/7 was hypointense with areas of isointensity on the short-echo time images and hyperintense on the long-echo time images. These masses did not restrict diffusion and demonstrated early arterial enhancement with delayed washout. They also had central areas that did not demonstrate early enhancement but demonstrated enhancement on the delayed images. Given these results and his history of anabolic steroid use, percutaneous, US-guided biopsy of the left lobe mass was consistent with probable HA, although HCC could not be definitely ruled out. He was advised to discontinue anabolic steroids, and that if the masses fail to regress off anabolic steroids, grew, or bled, surgical resection would be indicated. He was also referred to endocrinology for advice regarding restoration of hypothalamic-pituitary-thyroid (HPT) axis off of anabolic steroids. The patient discontinued anabolic steroids and underwent a repeat abdomen MRI and right lobe mass biopsy 6 weeks later; MRI revealed partial regression of both liver masses, and right lobe mass biopsy was consistent with HA. The decision was made to continue close surveillance with serial abdomen MRIs every 6 months.

Follow-up abdomen MRI in April 2014 revealed continued partial regression of the masses off steroids. In particular, his segment 2 mass was 6.7 x 4.4 cm and his segment 6/7 mass were 5.5 x 5.7 cm. Follow-up abdomen MRI in October 2014 also revealed continued regression with the segment 2 mass measuring 4.7 x 4.3 cm and the segment 6/7 mass measuring 4.8 x 4.8 cm. Unfortunately, his repeat abdomen MRI in July 2015 revealed mild increase in size and heterogeneity of the segment 6/7 mass from 5.5x5.7 cm to 6.4 x 6.2cm, concerning for possible malignant degeneration. The segment 2 mass remained stable. Given the interval growth, worrisome imaging characteristics, and concern for potential tumor seeding with repeat percutaneous biopsy, the patient was discussed at our multidisciplinary gastrointestinal/hepatico-pancreatico-biliary tumor board, and the decision was made to proceed with attempted surgical resection of the enlarging right lobe mass. Due to the proximity of the left hepatic lobe mass to the left hepatic vein (and risk of damage resulting in insufficient venous drainage of the future liver remnant [FLR]), the decision was made to proceed with staged resection at a later time.

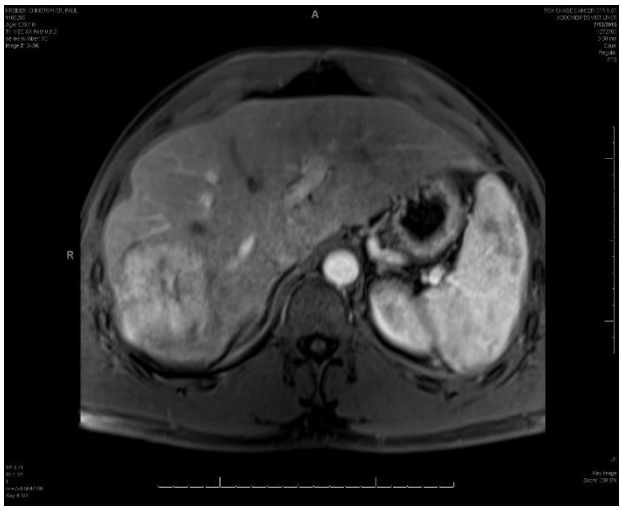
On August 14, 2015 the patient underwent an exploratory laparotomy, intraoperative ultrasound, open cholecystectomy, right hepatic lobectomy, and tru-cut needle biopsy of the left hepatic lobe mass. Surgical pathology of the right lobe mass revealed an 8 cm well-circumscribed hepatocellular carcinoma, grade I, 8.0 cm (pT3aN0; stage IIIA] with no tumor seen at inked resection margin. Needle biopsy of the left lobe mass was also consistent with well differentiated HCC.

Follow-up imaging 6 weeks postoperatively revealed compensatory left lobe hypertrophy; as a result, the segment 2 mass encroached, but no longer abutted the left hepatic vein. As such, the patient underwent exploratory laparotomy, extensive lysis of adhesions, intraoperative ultrasound, and partial left hepatic lobectomy on October 14, 2015. Surgical pathology was consistent with a 4.5 cm grade I HCC (pT1bNx, stage IB) with no tumor seen at inked resection margin.



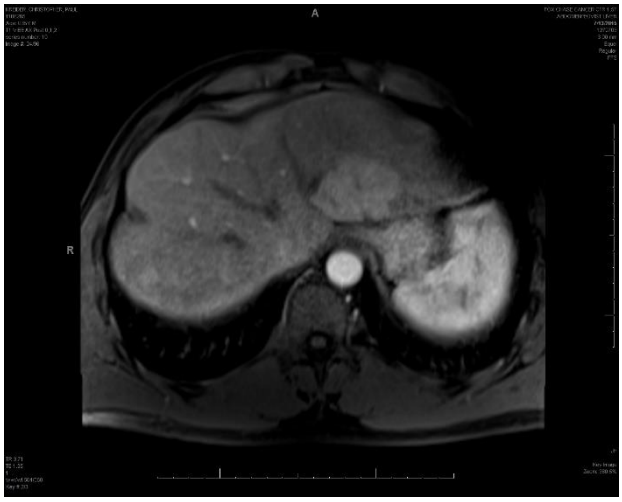
This T1 image reveals two large hepatic masses. The larger mass in segment 2 measures approximately 7.3 x 9.1 cm. The other mass straddling segment 6/7 measures approximately 7.9 x 7.9 cm. The mass in segment 2 is isointense on the short echo time images and mildly hyperintense on the long echo time images. The mass straddling segment 6/7 is hypointense with areas of isointensity on the short echo time images and hyperintense on the long echo time images. They do not demonstrate restricted diffusion and demonstrate early arterial enhancement with delayed washout. They also have central areas that do not demonstrate early enhancement but demonstrate enhancement on the delayed images.

Figure 1: Initial Abdomen MRI (July 23, 2013).



This T1 image shows that the larger mass straddling segment 6/7 has enlarged in size and now measures 6.4 x 6.2 cm (compared to 5.6 x 5.3 cm previously).

Figure 2: Surveillance Abdomen MRI (July 13, 2015)



This T1 image shows that the mass in segment 2 measures 6.1 x 4.2 cm (stable from previous imaging).

Figure 3: Surveillance Abdomen MRI from (July 13, 2015)

Conclusion

Although the exact pathophysiology remains uncertain, HAs typically develop when hepatocyte proliferation is stimulated by hormonal agents (e.g., oral contraceptives (OCs) and androgen-containing anabolic steroids) or metabolic abnormalities such as diabetes mellitus, beta-thalassemia, and glycogen storage disease type 1 and III [3,4]. Studies suggest that long-term use of OCs increases the annual incidence of HAs from 1 per million to 3 to 4 per 100,000 [5, 6]. This relationship between OCs and HAs is proportional to the hormonal dose and duration and is highest in women over 30 years old who have been using OCs for over 2 years. The estimated risk of developing an HA increases by a factor of 5 after 5 years and by 25 after 9 years of OC use [7]. There is a paucity of data between androgen-containing anabolic steroids and HA development. That being said, OCs and androgen-containing anabolic steroids have also been shown to increase the number and size of HAs. On the other hand, discontinuation of OCs and anabolic steroids can lead to regression of HAs [8, 9].

HAs are often diagnosed incidentally on imaging or during abdominal surgery, such as a laparoscopic cholecystectomy. It is important to note that it can be difficult to differentiate HA from HCC and focal nodular hyperplasia (FNH) on imaging [10]. Although the classical appearance of a HA on US is a well-demarcated hyper-echoic mass, they can also be iso or hypo-echoic. The hallmark feature of HCC (late arterial enhancement with washout relative to the liver parenchyma during the venous or delayed phases) is more sensitive on MRI verses CT A/P (81% vs 68%, respectively), however, their specificities are more similar (85% vs 95%, respectively) [10-12]. Nevertheless, clinical context is key as HAs are more likely to present in women with non-cirrhotic livers, while HCCs primarily occur in cirrhotic livers [10].

Patients with HA can present with symptoms of primarily RUQ or epigastric pain secondary to bleeding within the HAs. In more extreme cases, these patients may present with a surgical abdomen and life-threatening bleeding from an uncontained rupture. HAs are prone to bleeding due to numerous sinusoids filled with high pressure arterial flow and lack of soft tissue support. The risk of bleeding into or from a HA is thought to be between 20 and 40% [2]. Surgical resection is often recommended for patients with a HA greater than 5cm due to an increased risk of hemorrhage [13].

Although size greater than 5cm has also been associated with an increased risk of malignancy, the long-term incidence of malignant degeneration to HCC has not been well characterized. In the largest systematic review to date, Stoot et al. reviewed a total of 1568 reported HAs over a 40-year time period and reported that the overall frequency of malignant transformation was 4.2% among all HA cases and 4.5% among all resected HAs [3]. This study also identified several groups of patients with an increased risk of malignant degeneration. These included patients with a history of androgen or anabolic steroids, males, and patients with glycogen storage diseases [3]. Another proposed risk factor for malignant degeneration is the presence of dysplasia in HAs [3]. More recently, an analysis of 96 HAs by a French collaborative network identified four different subtypes: (i) hepatocyte nuclear factor 1α (HNF1α) mutated (30%–50%), (ii) β-catenin-activated (10–15%), (iii) inflammatory (35%), and (iv) unclassified tumors (5%–10%) [14]. HCC associated with HA, or in lesions between HCC and HA, was found in 46% of β-catenin-mutated tumors but was not seen in inflammatory tumors and rarely found in HNF1α-mutated tumors [14].

This case report stresses the importance of having a high suspicion for HA when seeing a patient with a history of anabolic steroid abuse and liver masses. Additionally, it reiterates that it can be difficult to differentiate HA from well-differentiated HCC on imaging and/or with a limited biopsy. Furthermore, it is important to keep in mind that the growth of a mass, especially off steroids is highly concerning for malignancy (and masses that fail to regress completely can harbor occult HCC).

Declarations

Disclosure of Conflicts: Dr. Goel has no conflicts of interest or financial disclosures to report. Dr. Rhodes has no conflicts of interest. Dr. Milestone has no conflicts of interest. Dr. Esnaola has served as a consultant for Merck, Celgene, and AngioDynamics.

Ethics Approval

Not applicable

Consent for Publication

Consent was obtained from the patient for publication of this case report

Competing Interests

No competing interests to declare

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None

Authors' contributions

NG assisted in the writing, editing, and final draft of the manuscript; LR assisted in the initial writing of the manuscript, BM assisted in the radiology interpretation of the images, management of the case, and editing of the final manuscript, NE was the operating surgeon, managed the patient, and assisted in the editing of the final manuscript. All authors read and approved the edited the manuscript.

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REFERENCES

1. Buell JF, Tranchart H, Cannon R, Dagher I (2010) Management of benign hepatic tumors. *Surg Clin North Am* 4: 719-735. [Crossref]
2. Ludger Barthelmes, Iain S Tait (2005) Liver cell adenoma and liver cell adenomatosis. *HPB (Oxford)* 7: 186-196. [Crossref]
3. Jan HMB Stoot, Robert JS Coelen, Mechteld C de Jong, Cornelis HC Dejong (2010) Malignant transformation of hepatocellular adenomas into hepatocellular carcinomas: a systematic review including more than 1600 adenoma cases. *HPB (Oxford)* 12: 509-522. [Crossref]
4. Dokmak S, Paradis V, Vilgrain V, Sauvanet A, Farges O, et al. (2009) A single-center surgical experience of 122 patients with single and multiple hepatocellular adenomas. *Gastroenterology* 137: 1698-1705. [Crossref]
5. Flejou JF, Barge J, Menu Y, Degott C, Bismuth H, et al. (1985) Liver adenomatosis. An entity distinct from liver adenoma? *Gastroenterology* 89: 1132. [Crossref]
6. Horvath E, Kovacs K, Ross RC (1974) Benign hepatoma in a young woman on contraceptive steroids. *Lancet* 1: 357-358. [Crossref]
7. Rosenberg L (1991) The risk of liver neoplasia in relation to combined oral contraceptive use. *Contraception* 43: 643-652. [Crossref]
8. Edmonson HA, Henderson B, Benton B (1976) Liver cell adenomas association with use of oral contraceptives. *N Engl J Med* 294: 470-472. [Crossref]
9. Nime F, Pickren JW, Vana J, Aronoff BL, Baker HW, et al. (1979) The histology of liver tumors in oral contraceptive users observed during a national survey by the American College of Surgeons Commission on Cancer. *Cancer* 44: 1481-1489. [Crossref]
10. Park YS, Lee CH, Kim JW, Shin S, Park CM (2016) Differentiation of hepatocellular carcinoma from its various mimickers in liver magnetic resonance imaging: What are the tips when using hepatocyte-specific agents? *World J Gastroenterol* 22: 284-299. [Crossref]
11. Colli A, Fraquelli M, Casazza G, Massironi S, Colucci A, et al. (2006) Accuracy of ultrasonography, spiral CT, magnetic resonance, and alpha-fetoprotein in diagnosing hepatocellular carcinoma: a systematic review. *Am J Gastroenterol* 101: 513-523. [Crossref]
12. Bruix J, Sherman M (2011) Management of hepatocellular carcinoma: an update. *Hepatology* 53: 1020-1022. [Crossref]
13. Terkivatan T, de Wilt JH, de Man RA, van Rijn RR, Tilanus HW, et al. (2001) Treatment of ruptured hepatocellular adenoma. *Brit J Surg* 88: 207-209. [Crossref]
14. Zucman Rossi J, Jeannot E, Nhieu JT, Scoazec JY, Guettier C, et al. (2006) Genotype-phenotype correlation in hepatocellular adenoma: new classification and relationship with HCC. *Hepatology* 43: 515-524. [Crossref]