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A FIRST CASE OF HEPATOCELLULAR CARCINOMA IN THE BABOON (*Papio spp.*) PLACENTA

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Abstract

We present a case of hepatocellular carcinoma (HCC) in the placenta of healthy baboon (*Papio spp.*). Grossly, the fetal, maternal and placental tissues were unremarkable. Histologically, the placenta contained an unencapsulated, poorly demarcated, infiltrative, solidly cellular neoplasm composed of cells that resembled hepatocytes. The neoplastic cells were diffusely positive for vimentin and focally positive for Ael/Ae3, Arginase –1, glutamine synthetase, and CD10, and negative for ER, vascular markers (CD31 and D240), S100, glypican, C-reactive protein, FABP, desmin, and beta-catenin; INI1 positivity was similar to non-neoplastic tissues. The case likely represents a unique subtype of HCC.

Keywords

Non-Human Primates; Baboon; placenta; hepatocellular carcinoma

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most prevalent form of cancer, the most common liver malignancy and the second most common cause of death from cancer worldwide [1, 2]. The increase in frequency of HCC has been associated with the rise of non-alcoholic fatty liver disease (NAFLD) through activation of glutamine synthetase [3]. Extrahepatic cases of primary and secondary HCC are rare and include abdominal and thoracic wall, diaphragm [4] and metastases in different organs [5] [6, 7]. While hepatocellular carcinoma is common, finding this type of cancer within the placenta is a rare

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occurrence in humans with only few cases reported worldwide [8–15]. There are no cases of primary placental HCC reported in non-human primates. Here we describe the incidental finding of a hepatocellular carcinoma in the placenta of a baboon (*Papio spp.*).

DESCRIPTION

Animal info.

A 16-year-old, captive born female baboon (*Papio spp*) had a history of one stillbirth and six live births (total of seven offspring during an eight year reproductive period). Placental histopathology from the previous stillbirth was not remarkable. The animal was enrolled into an IACUC approved protocol after completing a health check and received high fat diet at least six months prior to and throughout pregnancy. The pregnancy was not remarkable. All biochemical and CBC parameters were within the normal limits for this species during pregnancy. A cesarean section was performed close to term (165 days of gestation) according to the experimental protocol; maternal weight prior to conception was 21.99 kg, which is above the normal published range at late gestation [16, 17]. Fetal (female fetus) and placental weights were 709.32 g and 186.4 g respectively, which is within the published range for this species [16]. The gross appearance of fetal and maternal hepatic tissues was unremarkable at necropsy. Microscopic evaluation showed that the fetal liver had diffuse marked hepatocyte glycogenosis (normal in a fetus). The maternal liver was also unremarkable microscopically.

Tissue Fixation.

Specimens were fixed in 10% neutral buffered formalin, processed conventionally, embedded in paraffin, cut at 5 micrometers, stained with hematoxylin and eosin and evaluated by both a board-certified veterinary pathologist and human perinatal pathologist.

Histology: The placenta contained an unencapsulated, poorly demarcated neoplasm that infiltrated into the villous tissue, cell islands and placental septa. The neoplastic cells were arranged in a generally solid pattern, supported by scant to inapparent fibrovascular stroma and inconspicuous intra-tumoral capillaries. The neoplastic cells resembled hepatocytes, with some loss of cohesiveness, vesicular nuclei with open reticular chromatin, occasionally slightly irregular contours, distinct nucleoli and a mitotic rate up to 2 per 10 high power fields (Figure 1a). Focally, the cells had a spindle cell pattern (Figure 1b). There was a focal necrosis and hemorrhage. No bile production or pale bodies were observed.

Immunohistochemistry.

Immunohistochemistry was performed on tissue samples collected from the placenta with antibodies listed in Table 1. Staining was performed using an automated IHC/ISH slide staining system BenchMark ULTRA (Ventana Medical systems Inc., Tuscon, AR, USA) with pre-treatments according to manufacturers' instructions either with Cell Conditioning Solution (CC1) (cat# 950–124), Protease 1 (cat# 760–2018) or no pre-treatment. The tumor was strongly vimentin positive (cytoplasmic) (Figure 1c), focally strongly Ae1/Ae3 positive (cytoplasmic) (Figure 1d), focally arginase positive (cytoplasmic and nuclear) (Figure 1e), focally glutamine synthetase positive (cytoplasmic) (Figure 1f), focally CD10 positive

(membranous) (Figure 1g), and showed nuclear INI1 positivity similar to non-neoplastic tissues (Figure 1h). The tumor was ER negative; vascular markers (CD31 and D240), S100, glypican, C-reactive protein, FABP, desmin, and beta-catenin were negative (Table 1, Figure 1, Supplementary material Figure 1S). The cross reactivity of the antibodies with the baboon tissues has been published for the majority of used antibodies (Table 1) and intact placental tissue from the same specimen was used as an internal control (Supplementary material Figure 1S).

DISCUSSION

To our knowledge this is the first report of primary HCC in a nonhuman primate placenta. Baboons have been extensively described as a model of obesity [17, 59, 60] in which a high fat diet induces a phenotype similar to humans, including atherosclerosis [61] and NAFLD [62]. However, very few cases of primary liver cancer have been described in this species [63, 64]. In the case presented here, the animal was on a high fat diet for six months prior to and during pregnancy. Interestingly, maternal dietary quality is positively correlated with glutamine synthetase expression [65]. Association between high fat diet and HCC is underlined by the fact, that glutamine synthetase is the part of the central mechanism of obesity-induced NAFLD to HCC transformation. Glutamine synthetase is an early marker of HCC [50], and was positive in this case. Another protein, influenced by maternal high fat diet is a Fatty Acid Binding Protein –1 (FABP-1). In the rodent model of maternal HFD, liver expression of FABP1 was decreased in male offspring [66]. In general, FABP1 plays critical roles in tumor initiation and progression in several types of cancer. FABP1 expression is down-regulated in cell lines and tissues in HCC, and decreased expression of FABP1 correlates with lower survival rates and a higher tumor recurrence through mechanism of increased aerobic glycolysis [67]. In line with these observations, FABP was negative in the presented case, which is also in agreement with the recent reports about the association of HCC with lack of FABP-1 staining [44]. Another marker of HCC is Arginase –1 [68] with high expression in well differentiated tumors. This enzyme is expressed in the cytoplasm and nucleus and responsible for hydrolyses of arginine in the urea cycle [69]. Integrase interactor 1 (Ini-1), part of the pathway of chromatin remodeling in cancer [46, 47], was strongly positive in the present case. CD10 has been reported within the battery of tissue markers, used to confirm a diagnosis of HCC [69, 70]. The tumor was ER negative, indicating hormonal independence. The cases of hepatic neoplasia described in human placenta [12, 13] are benign lesions – hepatocellular adenomas (HA). It has been suggested, that these neoplasms arise from displaced yolk sac elements with hepatocytic differentiation [12]. In the presented case, low molecular weight cytokeratin (CAM 5.2) antibody staining was negative, pointing out earlier origin of the neoplasm, since CAM 5.2 is a marker of mature hepatocytes [71]. CD31, a common endothelial marker with cross-reactivity in *Papio spp* [30], did not show immunoreactivity with the tumor tissue in our study as well. This, with the negative D240 staining, used for recognition of lymphatic endothelium, excluded a lymphatic origin of the tumor. CRP is up-regulated in inflammation and specifically in inflammatory hepatocellular adenomas. CRP was negative in the tumor, thus excluding an inflammatory origin of neoplasia. Vimentin is an intermediate filament protein expressed in mesenchymal cells, which have been shown to promote metastasis and tumor growth in

HCC [32]. Based on immunophenotype (positive Arginase-1), the HCC in the described case can be called “conventional” as opposed to the fibrolamellar type (FL-HCC) [72, 73], primary HCC. FL-HCC is characterized by the presence of well differentiated tumor cells, organized in cords, separated by fibrous lamellae [74] and comprises 1–9% of HCCs, affecting younger adults as compared to conventional HCC, which affects an older population [75–77]. However, the lack of clinical associations, e.g. presence of the chronic liver injury, typically seen in patients with conventional HCC and the lack of positivity of other markers of conventional HCC, suggest the possibility of a unique, not yet described HCC type in this case.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Balogh J, Victor D, 3rd, Asham EH, Burroughs SG, Boktour M, Saharia A, Li X, Ghobrial RM, Monsour HP, Jr.: Hepatocellular carcinoma: a review. *Journal of hepatocellular carcinoma* 2016; 3:41–53. [PubMed: 27785449]
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F: Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International journal of cancer* 2015; 136:E359–386. [PubMed: 25220842]
3. Teilhet C, Morvan D, Joubert-Zakeyh J, Biesse AS, Pereira B, Massoulier S, Dechelotte P, Pezet D, Buc E, Lamblin G, Peoc’h M, Porcheron J, Vasson MP, Abergel A, Demidem A: Specificities of Human Hepatocellular Carcinoma Developed on Non-Alcoholic Fatty Liver Disease in Absence of Cirrhosis Revealed by Tissue Extracts (1)H-NMR Spectroscopy. *Metabolites* 2017; 7.
4. Shirai K, Tamai H, Shingaki N, Mori Y, Moribata K, Enomoto S, Deguchi H, Ueda K, Maekita T, Inoue I, Iguchi M, Yanaoka K, Oka M, Ichinose M: Clinical features and risk factors of extrahepatic seeding after percutaneous radiofrequency ablation for hepatocellular carcinoma. *Hepatology research : the official journal of the Japan Society of Hepatology* 2011; 41:738–745. [PubMed: 21699637]
5. Li Q, Shi X, Fan C: A metastasized hepatocellular carcinoma in the capsule of an undescended testis in the right inguinal area: report of a rare case. *World journal of surgical oncology* 2018; 16:12. [PubMed: 29351804]
6. Hsu CY, Liu PH, Ho SY, Huang YH, Lee YH, Lee RC, Nagaria TS, Hou MC, Huo TI: Metastasis in patients with hepatocellular carcinoma: Prevalence, determinants, prognostic impact and ability to improve the BCLC system. *Liver international : official journal of the International Association for the Study of the Liver* 2018.
7. Gong LI, Zhang WD, Mu XR, Han XJ, Yao LI, Zhu SJ, Zhang FQ, Li YH, Zhang W: Hepatocellular carcinoma metastasis to the gingival soft tissues: A case report and review of the literature. *Oncology letters* 2015; 10:1565–1568. [PubMed: 26622710]
8. Saluja R, Faye-Petersen O, Heller DS: Ectopic Liver Within the Placental Parenchyma of a Stillborn Fetus. *Pediatric and developmental pathology : the official journal of the Society for Pediatric Pathology and the Paediatric Pathology Society* 2017:1093526617712640.
9. Yee EU, Hale G, Liu X, Lin DI: Hepatocellular Adenoma of the Placenta With Updated Immunohistochemical and Molecular Markers: A Case Report. *Int J Surg Pathol* 2016; 24:640–643. [PubMed: 27106781]

10. DeNapoli TS: Coexistent Chorangioma and Hepatic Adenoma in One Twin Placenta: A Case Report and Review of the Literature. *Pediatric and developmental pathology : the official journal of the Society for Pediatric Pathology and the Paediatric Pathology Society* 2015; 18:422–425.
11. Dargent JL, Verdebout JM, Barlow P, Thomas D, Hoorens A, Goossens A: Hepatocellular adenoma of the placenta: report of a case associated with maternal bicornuate uterus and fetal renal dysplasia. *Histopathology* 2000; 37:287–289. [PubMed: 10971709]
12. Khalifa MA, Gersell DJ, Hansen CH, Lage JM: Hepatic (hepatocellular) adenoma of the placenta: a study of four cases. *Int J Gynecol Pathol* 1998; 17:241–244. [PubMed: 9656120]
13. Vesoulis Z, Agamanolis D: Benign hepatocellular tumor of the placenta. *Am J Surg Pathol* 1998; 22:355–359. [PubMed: 9500778]
14. Fiutowski M, Pawelski A: [Primary nontrophoblastic tumors of the placenta]. *Ginekologia polska* 1996; 67:515–519. [PubMed: 9289433]
15. Chen KT, Ma CK, Kassel SH: Hepatocellular adenoma of the placenta. *Am J Surg Pathol* 1986; 10:436–440. [PubMed: 3013034]
16. Schlabritz-Loutsevitch NE, Dudley CJ, Gomez JJ, Nevill CH, Smith BK, Jenkins SL, McDonald TJ, Bartlett TQ, Nathanielsz PW, Nijland MJ: Metabolic adjustments to moderate maternal nutrient restriction. *The British journal of nutrition* 2007; 98:276–284. [PubMed: 17391566]
17. Comuzzie AG, Cole SA, Martin L, Carey KD, Mahaney MC, Blangero J, VandeBerg JL: The baboon as a nonhuman primate model for the study of the genetics of obesity. *Obesity research* 2003; 11:75–80. [PubMed: 12529488]
18. Listrom MB, Dalton LW: Comparison of keratin monoclonal antibodies MAK-6, AE1:AE3, and CAM-5.2. *Am J Clin Pathol* 1987; 88:297–301. [PubMed: 2443001]
19. Wee A: Diagnostic utility of immunohistochemistry in hepatocellular carcinoma, its variants and their mimics. *Applied immunohistochemistry & molecular morphology : AIMM* 2006; 14:266–272. [PubMed: 16932016]
20. Jones CJ, Fazleabas AT: Ultrastructure of epithelial plaque formation and stromal cell transformation by post-ovulatory chorionic gonadotrophin treatment in the baboon (*Papio anubis*). *Human reproduction (Oxford, England)* 2001; 16:2680–2690.
21. Durkes A, Garner M, Juan-Salles C, Ramos-Vara J: Immunohistochemical characterization of nonhuman primate ovarian sex cord-stromal tumors. *Veterinary pathology* 2012; 49:834–838. [PubMed: 22273575]
22. Mishra D, Singh S, Narayan G: Role of B Cell Development Marker CD10 in Cancer Progression and Prognosis. *Mol Biol Int* 2016; 2016:4328697. [PubMed: 27965895]
23. Kaneko T, Stearns-Kurosawa DJ, Taylor F, Jr., Twigg M, Osaki K, Kinasewitz GT, Peer G, Kurosawa S: Reduced neutrophil CD10 expression in nonhuman primates and humans after in vivo challenge with *E. coli* or lipopolysaccharide. *Shock (Augusta, Ga)* 2003; 20:130–137.
24. Baldissera VD, Alves AF, Almeida S, Porawski M, Giovenardi M: Hepatocellular carcinoma and estrogen receptors: Polymorphisms and isoforms relations and implications. *Medical hypotheses* 2016; 86:67–70. [PubMed: 26804600]
25. Pepe GJ, Billiar RB, Leavitt MG, Zachos NC, Gustafsson JA, Albrecht ED: Expression of estrogen receptors alpha and beta in the baboon fetal ovary. *Biology of reproduction* 2002; 66:1054–1060. [PubMed: 11906925]
26. Dias P, Kumar P, Marsden HB, Morris-Jones PH, Birch J, Swindell R, Kumar S: Evaluation of desmin as a diagnostic and prognostic marker of childhood rhabdomyosarcomas and embryonal sarcomas. *Br J Cancer* 1987; 56:361–365. [PubMed: 3311112]
27. Jain D, Mittal S, Gupta M: Hepatocellular carcinoma arising in a testicular teratoma: a distinct and unrecognized secondary somatic malignancy. *Annals of diagnostic pathology* 2013; 17:367–371. [PubMed: 22763193]
28. Garcia N, Ramis G, Pallares FJ, Seva JI, Martinez CM, Quereda JJ, Munoz A: Clinical, histologic, and immunohistochemical features of an undifferentiated renal tubular carcinoma in a juvenile olive baboon (*Papio anubis*). *Journal of veterinary diagnostic investigation : official publication of the American Association of Veterinary Laboratory Diagnosticians, Inc* 2009; 21:535–539.
29. Cioca A, Ceausu AR, Marin I, Raica M, Cimpean AM: The multifaceted role of podoplanin expression in hepatocellular carcinoma. *Eur J Histochem* 2017; 61:2707. [PubMed: 28348421]

30. Shi Q, Cox LA, Hodara V, Wang XL, VandeBerg JL: Repertoire of endothelial progenitor cells mobilized by femoral artery ligation: a nonhuman primate study. *Journal of cellular and molecular medicine* 2012; 16:2060–2073. [PubMed: 22128816]
31. Maletzki C, Bodammer P, Breitruck A, Kerkhoff C: S100 proteins as diagnostic and prognostic markers in colorectal and hepatocellular carcinoma. *Hepat Mon* 2012; 12:e7240. [PubMed: 23166536]
32. Satelli A, Li S: Vimentin in cancer and its potential as a molecular target for cancer therapy. *Cell Mol Life Sci* 2011; 68:3033–3046. [PubMed: 21637948]
33. Timek DT, Shi J, Liu H, Lin F: Arginase-1, HepPar-1, and Glypican-3 are the most effective panel of markers in distinguishing hepatocellular carcinoma from metastatic tumor on fine-needle aspiration specimens. *Am J Clin Pathol* 2012; 138:203–210. [PubMed: 22904131]
34. Yamamoto S, Sakai Y: Ovarian Sertoli-Leydig Cell Tumor With Heterologous Hepatocytes and a Hepatocellular Carcinomatous Element. *Int J Gynecol Pathol* 2018.
35. Mitra S, Gupta S, Dahiya D, Saikia UN: A Rare Case of Primary Sarcomatous Hepatocellular Carcinoma Without Previous Anticancer Therapy. *Journal of clinical and experimental hepatology* 2017; 7:378–384. [PubMed: 29234205]
36. Clark I, Shah SS, Moreira R, Graham RP, Wu TT, Torbenson MS, Chandan V: A subset of well-differentiated hepatocellular carcinomas are Arginase-1 negative. *Human pathology* 2017; 69:90–95. [PubMed: 28970136]
37. Grant WF, Gillingham MB, Batra AK, Fewkes NM, Comstock SM, Takahashi D, Braun TP, Grove KL, Friedman JE, Marks DL: Maternal high fat diet is associated with decreased plasma n-3 fatty acids and fetal hepatic apoptosis in nonhuman primates. *PloS one* 2011; 6:e17261. [PubMed: 21364873]
38. Morin PJ: beta-catenin signaling and cancer. *Bioessays* 1999; 21:1021–1030. [PubMed: 10580987]
39. Ding Z, Shi C, Jiang L, Tolstykh T, Cao H, Bangari DS, Ryan S, Levit M, Jin T, Mamat K, Yu Q, Qu H, Hopke J, Cindhuchao M, Hoffmann D, Sun F, Helms MW, Jahn-Hofmann K, Scheidler S, Schweizer L, Fang DD, Pollard J, Winter C, Wiederschain D: Oncogenic dependency on beta-catenin in liver cancer cell lines correlates with pathway activation. *Oncotarget* 2017; 8:114526–114539. [PubMed: 29383099]
40. Khan-Dawood FS, Yang J, Ozigi AA, Dawood MY: Immunocytochemical localization and expression of E-cadherin, beta-catenin, and plakoglobin in the baboon (*Papio anubis*) corpus luteum. *Biology of reproduction* 1996; 55:246–253. [PubMed: 8828826]
41. Zheng Z, Zhou L, Gao S, Yang Z, Yao J, Zheng S: Prognostic role of C-reactive protein in hepatocellular carcinoma: a systematic review and meta-analysis. *Int J Med Sci* 2013; 10:653–664. [PubMed: 23569429]
42. Rosenblatt RE, Tafesh ZH, Halazun KJ: Role of inflammatory markers as hepatocellular cancer selection tool in the setting of liver transplantation. *Translational gastroenterology and hepatology* 2017; 2:95. [PubMed: 29264433]
43. Shi Q, Vandeberg JF, Jett C, Rice K, Leland MM, Talley L, Kushwaha RS, Rainwater DL, Vandeberg JL, Wang XL: Arterial endothelial dysfunction in baboons fed a high-cholesterol, high-fat diet. *The American journal of clinical nutrition* 2005; 82:751–759. [PubMed: 16210703]
44. Cho SJ, Ferrell LD, Gill RM: Expression of liver fatty acid binding protein in hepatocellular carcinoma. *Human pathology* 2016; 50:135–139. [PubMed: 26997447]
45. Inoue M, Takahashi Y, Fujii T, Kitagawa M, Fukusato T: Significance of downregulation of liver fatty acid-binding protein in hepatocellular carcinoma. *World journal of gastroenterology* 2014; 20:17541–17551. [PubMed: 25516669]
46. Fukuoka J, Fujii T, Shih JH, Dracheva T, Meerzaman D, Player A, Hong K, Settnik S, Gupta A, Buetow K, Hewitt S, Travis WD, Jen J: Chromatin remodeling factors and BRM/BRG1 expression as prognostic indicators in non-small cell lung cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2004; 10:4314–4324. [PubMed: 15240517]
47. Chen Z, Lu X, Jia D, Jing Y, Chen D, Wang Q, Zhao F, Li J, Yao M, Cong W, He X: Hepatic SMARCA4 predicts HCC recurrence and promotes tumour cell proliferation by regulating SMAD6 expression. *Cell death & disease* 2018; 9:59. [PubMed: 29352111]

48. Court CM, Hou S, Winograd P, Segel NH, Li QW, Zhu Y, Sadeghi S, Finn RS, Ganapathy E, Song M, French SW, Naini BV, Sho S, Kaldas FM, Busuttil RW, Tomlinson JS, Tseng HR, Agopian VG: A Novel Multimarker Assay for the Phenotypic Profiling of Circulating Tumor Cells in Hepatocellular Carcinoma. *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society* 2018.
49. Ishiguro T, Sugimoto M, Kinoshita Y, Miyazaki Y, Nakano K, Tsunoda H, Sugo I, Ohizumi I, Aburatani H, Hamakubo T, Kodama T, Tsuchiya M, Yamada-Okabe H: Anti-glypican 3 antibody as a potential antitumor agent for human liver cancer. *Cancer research* 2008; 68:9832–9838. [PubMed: 19047163]
50. Long J, Lang ZW, Wang HG, Wang TL, Wang BE, Liu SQ: Glutamine synthetase as an early marker for hepatocellular carcinoma based on proteomic analysis of resected small hepatocellular carcinomas. *Hepatobiliary & pancreatic diseases international : HBPDI* 2010; 9:296–305. [PubMed: 20525558]
51. Long J, Wang H, Lang Z, Wang T, Long M, Wang B: Expression level of glutamine synthetase is increased in hepatocellular carcinoma and liver tissue with cirrhosis and chronic hepatitis B. *Hepatology international* 2011; 5:698–706. [PubMed: 21484108]
52. Burton NC, Guilarte TR: Manganese neurotoxicity: lessons learned from longitudinal studies in nonhuman primates. *Environmental health perspectives* 2009; 117:325–332. [PubMed: 19337503]
53. Chevinsky AH: CEA in tumors of other than colorectal origin. *Semin Surg Oncol* 1991; 7:162–166. [PubMed: 2068450]
54. Fleming S, Symes CE: The distribution of cytokeratin antigens in the kidney and in renal tumours. *Histopathology* 1987; 11:157–170. [PubMed: 2437002]
55. Tu SH, Hsieh YC, Huang LC, Lin CY, Hsu KW, Hsieh WS, Chi WM, Lee CH: A rapid and quantitative method to detect human circulating tumor cells in a preclinical animal model. *BMC cancer* 2017; 17:440. [PubMed: 28645267]
56. Toyoda H, Kumada T, Osaki Y, Oka H, Kudo M: Role of tumor markers in assessment of tumor progression and prediction of outcomes in patients with hepatocellular carcinoma. *Hepatology research : the official journal of the Japan Society of Hepatology* 2007; 37 Suppl 2:S166–171. [PubMed: 17877479]
57. Topic A, Ljubic M, Radojkovic D: Alpha-1-antitrypsin in pathogenesis of hepatocellular carcinoma. *Hepat Mon* 2012; 12:e7042. [PubMed: 23162602]
58. Kin M, Torimura T, Ueno T, Inuzuka S, Tanikawa K: Sinusoidal capillarization in small hepatocellular carcinoma. *Pathol Int* 1994; 44:771–778. [PubMed: 7530563]
59. Higgins PB, Bastarrachea RA, Lopez-Alvarenga JC, Garcia-Forey M, Proffitt JM, Voruganti VS, Tejero ME, Mattern V, Haack K, Shade RE, Cole SA, Comuzzie AG: Eight week exposure to a high sugar high fat diet results in adiposity gain and alterations in metabolic biomarkers in baboons (*Papio hamadryas* sp.). *Cardiovascular diabetology* 2010; 9:71. [PubMed: 21034486]
60. Higgins PB, Rodriguez PJ, Voruganti VS, Mattern V, Bastarrachea RA, Rice K, Raabe T, Comuzzie AG: Body composition and cardiometabolic disease risk factors in captive baboons (*Papio hamadryas* sp.): sexual dimorphism. *American journal of physical anthropology* 2014; 153:9–14. [PubMed: 24318937]
61. Mahaney MC, Karere GM, Rainwater DL, Voruganti VS, Dick EJ, Jr., Owston MA, Rice KS, Cox LA, Comuzzie AG, VandeBerg JL: Diet-induced early-stage atherosclerosis in baboons: Lipoproteins, atherogenesis, and arterial compliance. *Journal of medical primatology* 2018; 47:3–17. [PubMed: 28620920]
62. Kamath S, Chavez AO, Gastaldelli A, Casiraghi F, Half GA, Abrahamian GA, Davalli AM, Bastarrachea RA, Comuzzie AG, Guardado-Mendoza R, Jimenez-Ceja LM, Mattern V, Paez AM, Ricotti A, Tejero ME, Higgins PB, Rodriguez-Sanchez IP, Tripathy D, DeFronzo RA, Dick EJ, Jr., Cline GW, Folli F: Coordinated defects in hepatic long chain fatty acid metabolism and triglyceride accumulation contribute to insulin resistance in non-human primates. *PloS one* 2011; 6:e27617. [PubMed: 22125617]
63. Aloisio F, Dick EJ, Jr., Hubbard GB: Primary hepatic neuroendocrine carcinoma in a baboon (*Papio* sp.). *Journal of medical primatology* 2009; 38:23–26. [PubMed: 18715267]

64. Bommineni YR, Dick EJ, Jr., Malapati AR, Owston MA, Hubbard GB: Natural pathology of the Baboon (*Papio spp.*). *Journal of medical primatology* 2011; 40:142–155. [PubMed: 21226714]
65. Day PE, Ntani G, Crozier SR, Mahon PA, Inskip HM, Cooper C, Harvey NC, Godfrey KM, Hanson MA, Lewis RM, Cleal JK: Maternal Factors Are Associated with the Expression of Placental Genes Involved in Amino Acid Metabolism and Transport. *PloS one* 2015; 10:e0143653. [PubMed: 26657885]
66. Nathanielsz PW, Ford SP, Long NM, Vega CC, Reyes-Castro LA, Zambrano E: Interventions to prevent adverse fetal programming due to maternal obesity during pregnancy. *Nutrition reviews* 2013; 71 Suppl 1:S78–87. [PubMed: 24147928]
67. Yang J, Wang C, Zhao F, Luo X, Qin M, Arunachalam E, Ge Z, Wang N, Deng X, Jin G, Cong W, Qin W: Loss of FBP1 facilitates aggressive features of hepatocellular carcinoma cells through the Warburg effect. *Carcinogenesis* 2017; 38:134–143. [PubMed: 27742690]
68. Yan BC, Gong C, Song J, Krausz T, Tretiakova M, Hyjek E, Al-Ahmadie H, Alves V, Xiao SY, Anders RA, Hart JA: Arginase-1: a new immunohistochemical marker of hepatocytes and hepatocellular neoplasms. *Am J Surg Pathol* 2010; 34:1147–1154. [PubMed: 20661013]
69. Di Tommaso L, Roncalli M: Tissue Biomarkers in Hepatocellular Tumors: Which, When, and How. *Frontiers in medicine* 2017; 4:10. [PubMed: 28280721]
70. Koehne de Gonzalez AK, Salomao MA, Lagana SM: Current concepts in the immunohistochemical evaluation of liver tumors. *World journal of hepatology* 2015; 7:1403–1411. [PubMed: 26052385]
71. Blakolmer K, Jaskiewicz K, Dunsford HA, Robson SC: Hematopoietic stem cell markers are expressed by ductal plate and bile duct cells in developing human liver. *Hepatology* 1995; 21:1510–1516. [PubMed: 7539394]
72. Graham RP, Torbenson MS: Fibrolamellar carcinoma: A histologically unique tumor with unique molecular findings. *Seminars in diagnostic pathology* 2017; 34:146–152. [PubMed: 28110996]
73. Riggle KM, Turnham R, Scott JD, Yeung RS, Riehle KJ: Fibrolamellar Hepatocellular Carcinoma: Mechanistic Distinction From Adult Hepatocellular Carcinoma. *Pediatric blood & cancer* 2016; 63:1163–1167. [PubMed: 26990031]
74. Garg R, Srinivasan R, Dey P, Singh P, Gupta N, Rajwanshi A: Utility of Cytokeratin7 Immunocytochemistry in the Cytopathological Diagnosis of Fibrolamellar Hepatocellular Carcinoma. *Journal of cytology* 2018; 35:75–78. [PubMed: 29643652]
75. Sergi CM: Hepatocellular Carcinoma, Fibrolamellar Variant: Diagnostic Pathologic Criteria and Molecular Pathology Update. *A Primer. Diagnostics (Basel, Switzerland)* 2015; 6.
76. Lim II, Farber BA, LaQuaglia MP: Advances in fibrolamellar hepatocellular carcinoma: a review. *European journal of pediatric surgery : official journal of Austrian Association of Pediatric Surgery [et al.] = Zeitschrift fur Kinderchirurgie* 2014; 24:461–466.
77. Lafaro KJ, Pawlik TM: Fibrolamellar hepatocellular carcinoma: current clinical perspectives. *Journal of hepatocellular carcinoma* 2015; 2:151–157. [PubMed: 27508204]

Figure 1.

Fetal HCC microscopy: **(A, B)** Hematoxylin and Eosin (H&E) staining, **A** Subgross image of the neoplasm, **B1**- Tumor cells resemble hepatocytes, **B2** - Focal spindle cell pattern; **(C)** Strong cytoplasmic vimentin positivity; (x40); **(D)** Focally strong cytoplasmic Ae1/Ae3 positivity; **(E)** Focally cytoplasmic and nuclear arginase positivity; **(F)** Focally cytoplasmic glutamine synthetase positivity; **(G)** Focally membranous CD10 positivity; **(H)** Nuclear INI-1 positivity. Scale bar for all images is 100 μ m with a magnification of 20X except for: **A** with a scale bar of 700 μ m, **F** with a scale bar of 50 μ m and a magnification of 40X, and **B1** and **B2** with a magnification of 40X. All inserts have a magnification of 40X.

Table 1:

Selected references to source of antibodies/markers and their expression in the present study

Antibodies, used in the study	References	Immuno-reactivity in human HCC cases and in NHP tissues	Immuno-reactivity in the present case and antibodies' information *
CAM 5.2 (Low molecular weight cytokeratin: 7 and 8)	Marker for cells of epithelial origin [18], stains mature hepatocytes and hepatocellular nodules[19]	+ [11–13, 20]	- Becton Dickinson, #349205
Cytokeratin AE1/AE3	Marker for cells of epithelial origin [18], negative in mature hepatocytes. [19]	– [11, 13, 21]	+760–2135 **
CD10	Epithelial cells marker of angiogenesis and acute lymphoblastic leukemia[22], stains bile canaliculi in better-differentiated HCC [19]	+ [5, 23]	+ #790–4506 **
Estrogen Receptor (ER)	Estrogen receptors in tumors	+ [24, 25]	- #790–4324 **
Desmin	Earliest protein marker for muscle tissue in embryogenesis [26]	HCA combined with testicular teratoma [27, 28]	- #760–2513 **
D240	Lymphatic marker [29]	NA	- Biolegend, #916604
CD31	Vascular endothelial marker, positive in sinusoidal cells of the portal regions of normal adult liver and more diffusely in hepatocellular carcinoma.	+ [13] – [11, 30]	- #760–4378 **
S-100	Marker for melanomas, schwannomas, neurofibromas and epidermal differentiation. [31]	– [13, 28]	- #760–2523 **
Vimentin	Marker of mesenchymal cells[32]	+ [13, 28]	+++ #790–2917 **
Arginase-1	Well differentiated hepatocellular carcinoma[33]	+ [34, 35] – [36, 37]	++ #760–4801 **
Beta Catenin	Involved in cell-cell adhesion, overexpression is associated with cancers including hepatocellular carcinoma[38]	+ [39, 40]	- #760–4242 **
C-reactive protein (CRP)	Proinflammatory cytokine[41]	+ [42, 43]	- Abcam, #32412,
Fatty acid binding protein (FABP)	Normally expressed at high levels in hepatocyte cytoplasm[44]	+/-[45]	- Abcam, # 82157
Chromatin-remodeling factor Ini-1	BRG1-associated factor, for non-small cell carcinoma [46]	+ [47]	+++ BD Biosciences, #612110
Glypican-3	Expressed in fetal hepatocytes [33]	+ [48, 49]	- #790–4564 **
Glutamine synthetase	Early marker for HCC [50]	+ [51, 52]	++ #760–4898 **
Published HCC markers			
Carcinoembryonic antigen (CEA)	Indicative of metastasis, colorectal cancer, and other malignancies such as: breast, liver, stomach and pancreatic cancer[53], stain bile canaliculi in better-differentiated HCC[19]	+ [11–13]	NA
PKK1 (Low molecular weight cytokeratin)	Marker for cells of epithelial origin [54].	– [12]	NA
MAK-6 (Cytokeratins 8,14,15,16,18,19)	Adinocarcinoma, marker for cells of epithelial origin [18]	+ [12]	NA
Alpha-fetoprotein (AFP)	Expressed in fetal hepatic cells[55], Increased in conventional HCC[56]	+ [12, 13] – [11]	NA
Alpha-1-antitrypsin	Most abundant hepatic protein[57]	+ [12]	NA

Antibodies, used in the study	References	Immuno-reactivity in human HCC cases and in NHP tissues	Immuno-reactivity in the present case and antibodies' information *
Factor VIII-related antigen	Marker of marker for clotting factor produced in hepatic sinusoidal cells and general endothelial cells [58]	+ [12] – [13]	NA

* Company (if different from Roche) and catalog #.

** Roche Molecular Systems, Inc (IN, USA). HCC- hepatocellular carcinoma