Estrogen-Driven Growth of Focal Nodular Hyperplasia: Truth or Myth?

Ashraf A. Ashhab, MD1, Ahmad Abu-Sulb, MD2, Ju Dong Yang, MD1, Mazen Noureddin, MD1, Vinay Sundaram, MD1, Alexander Kuo, MD1, and Walid S. Ayoub, MD1

1Division of Digestive and Liver Diseases, Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, CA
2Division of Pediatrics, Legacy Community Health, Houston, TX

ABSTRACT

The etiologic association between focal nodular hyperplasia (FNH) and estrogen has been a subject of doubt and controversy. We present a case of a female patient with FNH that had been monitored for several years with noted size stability and later regression, who developed tumor growth during pregnancy. This case suggests that a subset of FNH is indeed hormone sensitive, as opposed to what has been frequently suggested by many other reports that question the association, a finding that may have clinical implications, in terms of monitoring of patients with high estrogen statuses.

INTRODUCTION

Focal nodular hyperplasia (FNH) is the second most common benign liver tumor.1 Although FNH is mostly asymptomatic and is classically detected incidentally on imaging, some patients present with abdominal pain, constitutional symptoms, or a palpable liver lesion.2 In addition, hepatomegaly and abnormal serum liver tests can provoke evaluation.3,4 Management of FNH is usually conservative, although resection, embolization, and ablation can be performed in symptomatic patients.5 In addition, although rare, complications including intralesional bleeding, spontaneous rupture, and intraperitoneal hemorrhage, as well as Kasabach-Merritt syndrome, have been reported, warranting urgent surgical interventions.6,7 We report a case of FNH that increased in size during pregnancy.

CASE REPORT

A 29-year-old woman who has been on oral contraceptive pills (OCPs) for 12 years was referred to our clinic for evaluation of a liver mass. This was incidentally noted on abdominal computed tomography that was obtained in the setting of left-sided abdominal pain that was attributed to a muscle spam. The mass was believed to represent a hepatic adenoma or FNH. Because of the concern for adenoma, OCPs were held.

On presentation to the hepatology clinic 2 months later, she was asymptomatic. Her medical, surgical, and family history were nonsignificant, and she was not taking any medications. She was not a smoker and used alcohol occasionally. Her liver enzymes and international normalized ratio were normal, and she tested negative for viral hepatitides.

A repeat magnetic resonance imaging (MRI) was obtained, showing the mass to be within segment 4 in the left hepatic lobe, measuring $3.4 \times 3.7$ cm in diameter. The mass had a central stellate scar, with T2 hyperintensity, and was believed to represent FNH (Figure 1). A decision was made to obtain sequential MRIs for monitoring, which were performed at 6-month intervals, and showed stability in the size of the mass for 3 years, with reduction in the size to $2.6 \times 2.1$ cm 4 years from the presentation (Figure 2).
One year later, the patient became pregnant and was seen 2 months after delivery after an uneventful pregnancy. Her MRI showed the FNH lesion to have increased in size to 4.5 cm (Figure 3). The patient remained asymptomatic, repeat liver tests were within normal limit, as was serum \( \alpha \)-fetoprotein.

**DISCUSSION**

A role of hormones in FNH remains controversial.\(^7\) Cases with increased tumor size with OCP use, as well as regression after discontinuation of OCPs or high estrogen therapy, have been reported.\(^8-10\) Scott et al described regression of FNH after discontinuation of OCPs, with later increase in its size during pregnancy, suggesting its growth was at least partly hormone dependent.\(^11\) Size progression during pregnancy and regression after delivery has also been reported.\(^12\) Scalori et al compared 23 women with FNH with 94 controls. They found that patients with OCP use had a higher odds ratio of developing FNH, concluding that hormone use is associated with the disease.\(^7\) Weimann et al followed 82 patients with FNH, 10 of which became pregnant during the time of the study, 3 of them twice. No increase in the size of tumor was noted in any of those patients. Interestingly, however, all patients in that study had a history of OCP use.\(^13\) Mathieu et al assessed 216 patients with FNH. When comparing patients depending on their OCP use, the dose, and presence of estrogen, no difference in the size or number of the lesions in any of their groups was found. On follow-up of 89 women who stopped OCPs, no consistent trend in the mass behavior was found. Twelve patients also became pregnant during the course of the study, none of which had a change in their tumor size after delivery. Notably, 87% of patients in this study had a history of OCP use.\(^14\)

In another study where 44 patients with FNH were followed for a median of 45 months, no clear correlation between pregnancy or OCP use with the clinical course was found because size stability, progression, and regression were all reported in patients who became pregnant or stopped OCPs during the course of the study.\(^15\) Notably, tumor stability and regression were proportionately higher in women who stopped using OCPs (18/21, 86%) than in the remaining women (14/23, 61%) \((P = .09)\).\(^16\) The reason for the discrepancy in the findings among different studies is not clear, but this could be related to the heterogeneity of the expression of estrogen receptors compared with normal parenchyma between different patients.\(^16\) OCPs also seem to have an etiologic contribution in FNH because studies continue to consistently show that most patients with FNH have a history of OCP use.\(^7\) In a review of 53 FNH cases, Naganuma et al found that all their male patients had a history of metabolic disease, possibly indicating that those patients were obese and had higher levels of estrogen through an adipose conversion.\(^17\) The etiologic association could be a consequence of estrogen’s promotion of angiogenesis.\(^13,18\) It has been histologically demonstrated that FNH patients with OCP use have a greater degree of vascular alteration, more fibrosis, and increased tumor size.\(^19\) There currently exists no consensus on recommendations to hold or continue OCPs in patients with FNH.\(^6\) Although tumor growth has been reported with ongoing OCP use, no reports of

---

**Figure 1.** Abdominal magnetic resonance imaging at T2 phase, showing a 3.4 \( \times \) 3.7-cm mass in segment 4, in the left hepatic lobe (yellow arrow), with a central scar (red arrow) that is characteristic of focal nodular hyperplasia.

**Figure 2.** Abdominal magnetic resonance imaging showing a reduction in the size of the mass to 2.6 \( \times \) 2.1 cm (red arrow).

**Figure 3.** Abdominal magnetic resonance imaging at T2 phase, showing the same mass 3.4 \( \times \) 3.7-cm mass (red arrow) in segment 4 of the liver with a central scar (yellow arrow) to have increased in size to 4.5 \( \times \) 4 cm.
complications or need for surgery for previously asymptomatic small masses developed with ongoing use. Our case further validates the controversial observation that a subset of FNH is hormone sensitive and may grow in response to high estrogen statuses. In our patient, given her lack of symptoms, a conservative approach was recommended and future pregnancies were not discouraged, although her mass seemed to be hormone sensitive. Larger studies or meta-analyses could shed more light on the topic.

DISCLOSURES

Author contributions: AA Ashhab and A. Abu-Sulb wrote the manuscript. JD Yang, M. Noureddin, V. Sundaram, A. Kuo, and WS Ayoub revised the manuscript for intellectual content. AA Ashhab is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received April 19, 2020; Accepted September 4, 2020

REFERENCES

1. Maillette de Buy Wenniger L, Terpstra V, Beuers U. Focal nodular hyperplasia and hepatic adenoma: Epidemiology and pathology. Dig Surg. 2010; 27(1):24–31.
2. Nagorney DM. Benign hepatic tumors: Focal nodular hyperplasia and hepatocellular adenoma. World J Surg. 1995;19:13–8.
3. Weimann A, Ringe B, Klemppnauer J, et al. Benign liver tumors: Differential diagnosis and indications for surgery. World J Surg. 1997;21:983–90.
4. Charny CK, Jarnagin WR, Schwartz LH, et al. Management of 155 patients with benign liver tumours. Br J Surg. 2001;88:808–13.
5. Perrakis A, Demir R, Müller V, et al. Management of the focal nodular hyperplasia of the liver: Evaluation of the surgical treatment comparing with observation only. Am J Surg. 2012;204(5):689–96.
6. Rahili A, Cai J, Trastour C, et al. Spontaneous rupture and hemorrhage of hepatic focal nodular hyperplasia in lobus caudatus. J Hepatobiliary Pancreat Surg. 2005;12(2):138–42.
7. Scalori A, Tavani A, Gallus S, La Vecchia C, Colombo M. Oral contraceptives and the risk of focal nodular hyperplasia of the liver: A case-control study. Am J Obstet Gynecol. 2002;186(2):195–7.
8. Nakamuta M, Ohashi M, Fukutomi T, et al. Oral contraceptive-dependent growth of focal nodular hyperplasia. J Gastroenterol Hepatol. 1994;9:5213.
9. Ross D, Pina J, Mirza M, Galvan A, Ponce L. Letter: Regression of focal nodular hyperplasia after discontinuation of oral contraceptives. Ann Intern Med. 1976;85:203–4.
10. Aldinger K, Ben-Menachem Y, Whalen G. Focal nodular hyperplasia of the liver associated with high-dosage estrogens. Arch Intern Med. 1977;137:357–9.
11. Scott LD, Katz AR, Duke JH, Cowan DF, Maklad NF. Oral contraceptives, pregnancy, and focal nodular hyperplasia of the liver. JAMA. 1984;251(11):1461–3.
12. Kim MJ, Han SY, Baek YH, Lee SW, Kwon HJ. A case of focal nodular hyperplasia with growth progression during pregnancy. Clin Mol Hepatol. 2014;20(4):392–7.
13. Weimann A, Mössinger M, Fromhoff K, Nadalin S, Raab R. Pregnancy in women with observed focal nodular hyperplasia of the liver. Lancet. 1998;351:1251–2.
14. Mathieu D, Kobeiter H, Maison P. Oral contraceptive use and focal nodular hyperplasia of the liver. Gastroenterology. 2000;118:560–4.
15. D’Halluin V, Vilgrain V, Pelletier G. Natural history of focal nodular hyperplasia: A retrospective study of 44 cases. Gastroenterol Clin Biol. 2001;25:1008–1010. [French.]
16. Chandrasegaram M, Shah A, Chen J, et al. Oestrogen hormone receptors in focal nodular hyperplasia. HPB (Oxford). 2015;17:502–7.
17. Naganuma H, Ishida H, Ogawa M, et al. Focal nodular hyperplasia: Our experience of 53 Japanese cases. J Med Ultrason (2001). 2017;44:79–88.
18. Irey NS, Norris HJ. Intimal vascular lesions associated with female reproductive steroids. Arch Pathol. 1973;96:227–34.
19. Pain JA, Gimson AES, Williams R, Howard ER. Focal nodular hyperplasia of the liver: Results of treatment and options in management. Gut. 1991;32:524–7.

Copyright: © 2021 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of The American College of Gastroenterology. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.