Two cases of near-complete regression of focal nodular hyperplasia of the liver: Case reports and review of the literature

Asha Sarma, University of Utah
Akram M. Shaaban, University of Utah
Marta Heilbrun, Emory University
Maryam Rezvani, University of Utah

Journal Title: Radiology Case Reports
Volume: Volume 7, Number 3
Publisher: Elsevier | 2012-01-01, Pages 681-681
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.2484/rcr.v7i3.681
Permanent URL: https://pid.emory.edu/ark:/25593/vmdx2

Final published version: http://dx.doi.org/10.2484/rcr.v7i3.681

Copyright information:
© 2012 The Authors.

This is an Open Access work distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (https://creativecommons.org/licenses/by-nc-nd/4.0/).

Accessed July 6, 2024 8:39 AM EDT
Introduction

Focal nodular hyperplasia (FNH) is the second most common benign hepatic tumor after hemangioma (1). Considered to be a local hyperplastic response to a congenital vascular anomaly (2), FNH is most commonly found in women in their 3rd and 4th decades of life (1). These lesions are typically found incidentally at autopsy, laparotomy, or radiologic investigation performed for another indication (3). FNH is composed of normal hepatocytes that are abnormally arranged within a fibrous meshwork, usually with a prominent central fibrous scar or scars (1).

The typical appearance of FNH on imaging is a solid mass, less than 5 cm in size, with a central scar. FNH is well vascularized by thick-walled arteries; therefore, hemorrhage, necrosis, calcification, and infarction are rare. FNH appears as an iso-attenuating or slightly hypo-attenuating lesion on noncontrast-enhanced CT. Following intravenous contrast material administration, the mass enhances avidly in the late arterial phase and is isodense to surrounding normal hepatic parenchyma in the portal venous and equilibrium phases. In approximately one-third of cases, the central scar may appear hypo-attenuating on unenhanced CT, but visualization may be difficult. Overall, due to the variable vascularity and tissue composition of the central scar, its appearance in various phases of contrast and among different lesions is not predictable (1).

Typically, FNH is iso- or slightly hypo-intense relative to normal hepatic parenchyma on unenhanced, T1-weighted MRI, with a hypointense central scar. On T2-weighted images, FNH tends to be iso- to subtly hyperintense, and the central scar is typically hyperintense. With intravenous administration of gadolinium contrast material, there is avid, homogeneous enhancement of the mass in the late arterial phase, with the exception of the central scar. During the portal venous and equilibrium phases, the mass appears isointense, with the central scar enhancing in the late equilibrium phase.

Two cases of near-complete regression of focal nodular hyperplasia of the liver: Case reports and review of the literature

Asha Sarma, MD; Akram M. Shaaban, MD; Marta E. Heilbrun, MD, MS; and Maryam Rezvani, MD

While regression of focal nodular hyperplasia of the liver is not uncommon, reports of near-complete involution or regression of these lesions are rare. We report two cases of focal nodular hyperplasia that underwent near-complete regression—one in a 27-year-old female that regressed over a period of 4 years, and one in a 46-year-old female that regressed over a 7-year period. Both patients discontinued use of exogenous estrogens between the diagnosis of focal nodular hyperplasia and its subsequent regression. Although contemporary cross-sectional imaging has improved the ability to detect and follow these lesions, few studies examining the natural history of focal nodular hyperplasia have been conducted. We discuss pertinent imaging findings on magnetic resonance imaging and computed tomography, and review the literature on regression of focal nodular hyperplasia and the effects of endogenous hormones and exogenous hormone therapy.
delayed phases (1). Hepatocyte-specific contrast agents may be used to differentiate FNH from other hypervascular hepatic masses. These agents perform similarly to traditional extracellular gadolinium contrast on dynamic postcontrast imaging. Hepatocyte-specific contrast agents are variably taken up by hepatocytes and excreted into the biliary tree. More recently developed hepatocyte-specific agents, such as gadobenate disodium, demonstrate up to 50% biliary excretion, assuming normal hepatocyte function and the absence of biliary obstruction. These agents allow imaging in the “hepatocyte phase,” approximately 20 minutes after contrast administration, and can help differentiate masses that are composed of normal hepatocytes from those that are not. Lesions of hepatocellular origin, including FNH and well-differentiated hepatocellular carcinoma, take up and retain hepatocyte-specific agents. Nonhepatocellular tumors, such as metastases and cavernous hemangiomas, are hypointense relative to enhancing surrounding normal parenchyma in the hepatocyte phase. FNH is composed of normal, densely packed hepatocytes and blind-ending ductules with delayed biliary excretion; it therefore tends to retain contrast, with the lesion appearing isointense or hyperintense in the hepatocyte phase, with “popcorn-like” enhancement (4). Of note, the central scar does not enhance in the hepatocyte phase (5).

FNH has no malignant potential, and surgical excision is not indicated unless the patient is symptomatic (1). Since the 1970s, there has been controversy over the effect of oral contraceptive pills (OCP) on the natural history of FNH. Histologically, FNH in patients who use contraceptives tends to have greater vascular alterations, fibrosis, peliosis, and size (6). Spontaneous regression of FNH is not uncommon, but cases of near-complete regression or complete involution are rare.

These two cases of FNH underwent near-complete regression. Between the initial diagnosis and subsequent regression, both patients discontinued exogenous estrogen therapy.

Case report

Case 1: A 27-year-old female with a history of oral contraceptive use presented with right-upper-quadrant abdominal pain, nausea, and vomiting.

Figure 1. FNH in a 27-year-old female with a history of oral contraceptive pill use. (A) Precontrast T1WI shows an isointense mass with a hypointense central scar (arrowhead) in segment 5 of the liver. (B) Following intravenous administration of gadobenate dimeglumine, a late arterial phase T1WI shows an avidly enhancing lobular mass (arrow) with a nonenhancing central scar (arrowhead). Note the hypovascular fibrous septa radiating from the scar. (C) Five-minute-delayed T1WI shows that the mass is isointense, with the liver parenchyma and the central scar enhancing. (D) A T2WI view with fat saturation shows the isointense mass and hyperintense central scar (arrowhead).
A transabdominal ultrasound examination demonstrated cholelithiasis and a 2.7-cm, hyperechoic, solid mass in the right lobe of the liver.

Dynamic contrast-enhanced magnetic resonance imaging (MRI) to further evaluate the hepatic mass confirmed the presence of a hypervascular mass with a central scar in hepatic segment 5, measuring 2.9 x 3.6 cm. The mass was hypo-intense on T1-weighted imaging, iso-intense to mildly hyperintense on T2-weighted imaging, and iso-intense on delayed postcontrast sequences. The central scar was hyperintense on T2-weighted imaging and demonstrated delayed enhancement (Fig. 1).

Forty-eight months later, at which time OCP use was no longer documented in the patient's chart, she underwent MRI of the abdomen with and without contrast. On this followup study, the FNH lesion in the inferior right lobe of the liver had significantly regressed, measuring 0.6 x 0.8 cm in its largest dimensions (Fig. 2).

Case 2: A 46-year-old female with a four-year history of estrogen therapy (following salpingo-oopherectomy) and Cowden syndrome presented with right-lower-quadrant pain and underwent contrast-enhanced CT. A 6 x 5-cm enhancing mass with a central scar was observed in segment 2 of the liver.

Further evaluation with contrast-enhanced liver MRI confirmed a hypervascular mass with a central scar in segment 2, measuring 6.5 x 4.4 cm. In the late arterial phase, the mass enhanced avidly and homogeneously, with the exception of the central scar. The mass was iso-intense on T1 and T2-weighted images, as well as on delayed postcontrast sequences. The central scar enhanced on delayed postcontrast images; however, it did not exhibit typical T2 hyperintensity. Hemangiomas and cysts were also observed in the liver (Fig. 3).

Shortly after the initial diagnosis of FNH was made, the patient discontinued estrogen replacement therapy.

Ninety months after the initial diagnosis of FNH, contrast-enhanced CT was performed to re-examine the patient’s liver lesions and evaluate a colonic lipoma. The previously observed FNH within the left lobe of the liver had regressed to 2.1 x 1.9 cm (Fig. 4).

Discussion

FNH is the second most common tumor arising from the hepatic parenchyma. Because FNH typically occurs in women of reproductive age, and a large proportion (50-75%) of patients with FNH are OCP users, many have speculated that hormones play a role in the pathogenesis of these tumors (1). Endogenous and exogenous estrogens play a clear role in the pathogenesis of hepatic adenoma (7); their relationship with liver hemangioma and focal nodular hyperplasia has been the subject of controversy (8-16).

Since the 1970s, many cases of FNH have been reported in patients taking both high- and low-dose OCPS. Some authors have suggested that OCPS are not the pathophysiologic cause of FNH (as in hepatic adenoma) (1); however, the correlation between regression of FNH lesions and the discontinuation of OCPS in several cases have suggested that exogenous estrogens may act as trophic agents (8, 16-21). Some groups have argued that FNH may regress spontaneously, regardless of patients’ OCP use or endogenous hormonal status (10, 13, 14, 22-24). Others have posited that there is a direct association between OCP use and FNH (15), and that withdrawal of OCPS may lead to its regression (12, 17-20). Several groups have reported data on the natural history of FNH, the highlights of which are summarized in Table 1.

To further investigate the posited association between OCP use and FNH from previous case-only and clinical observation studies, Scalori et al. (15) conducted a case-control study of 23 patients with FNH and 94 matched control subjects. They concluded that, while endogenous hormonal factors are not associated with FNH, OCP use for ≥3 years is associated with it (OR = 4.5, 95% CI =
A trend in risk was noted with increased duration of OCP use ($\chi^2 = 5.19$, $p = 0.023$). Lastly, patient age $< 20$ at first use of OCPs was also associated with FNH (OR = 5.71, 95% CI = 1.20-27.14). In a subanalysis to identify characteristics that predict involution of FNH, Kuo et al. reported that, though there were no differences between FNH lesions that decreased in size and those that did not, complete radiologic involution of FNH lesions was associated with patients of older age, and nodule diameter of $< 2$ cm ($p$-values $< 0.05$). Multiple logistic regression analysis showed that both older age (OR = 1.26, 95% CI = 1.02–1.56) and longer followup time (OR = 1.1, 95% CI = 1.01–1.21) were independent factors associated with complete involution of FNH lesions (OR = 1.1, 95% CI = 1.01–1.21).

Data from the case series presented by Leconte et al. (12) show that discontinuation of OCPs at the time of diagnosis of FNH was associated with a trend toward decrease in lesion size.

Effect sizes in the aforementioned studies were modest. Because FNH is a rare entity, it has been difficult to study...
Two cases of near-complete regression of focal nodular hyperplasia of the liver

its natural history in large groups of patients. Moreover, existent studies of the natural history of FNH are difficult to compare given heterogeneity in imaging modalities used, parameters for defining change in size of FNH lesion, length of followup, diagnostic criteria, and other factors.

Ample data about the frequency of regression and involution of FNH have been presented. While it is not unusual for FNH lesions to decrease in size, to our knowledge, only 9 cases of complete radiologic involution have been reported (10, 13, 14, 19, 23). Among the lesions that completely involuted, no pattern can be discerned with regard to OCP use status. Six FNH lesions disappeared in patients with no significant history of OCP use (23), two disappeared in spite of ongoing OCP use (10, 13, 14), and one disappeared 5 years after the discontinuation of OCPs (19).

We present two cases of near-complete regression of FNH: one patient’s FNH lesion decreased in size over the course of a 4-year period, and the other over the course of a 7-year period. Both patients had a history of exogenous estrogen use prior to the initial diagnosis of FNH, and both discontinued estrogen therapy between their initial presentation and near-complete involution of their FNH lesions. The long duration of followup in our cases was similar to that in the series presented by Kuo et al. (23), and may have improved our ability to detect regression of our patients’ FNH lesions. There is not sufficient data to conclude that the natural history of our patients’ lesions can be attributed to their cessation of exogenous estrogen use. Nor is there sufficient data to conclude contrarily. Indeed, there is a distinct possibility that these lesions would have involuted regardless of exogenous estrogen status.

Our cases, however, provide yet more anecdotal evidence to the body of literature that suggests that exogenous estrogens may contribute to the growth or maintenance of FNH lesions. Due to the amount of conflicting data in the FNH literature, and the fact that many conclusions on the effect of exogenous estrogens are founded on weakly significant data, further study is necessary to firmly establish the role of OCPs in the natural history of FNH. MRI is now an ideal modality for the diagnosis and followup of FNH, as it has well-defined diagnostic criteria for FNH and eliminates the carcinogenic ionizing radiation of CT and operator dependence of ultrasound. Therefore, a case-control or prospective cohort study that employs long followup using strictly defined MRI criteria could potentially provide resolution.

References
1. Buetow PC, Pantongrag-Brown L, Buck JL, et al. Focal nodular hyperplasia of the liver: radiologic-pathologic correlation. Radiographics 1996; 16:369-388 [PubMed]
2. Wanless IR, Mawdsley C, Adams R. On the pathogenesis of focal nodular hyperplasia of the liver. Hepatology 1985; 5:1194-1200 [PubMed]
3. Sternberg SS. Diagnostic surgical pathology. 2nd ed. New York, N.Y.: Raven Press, 1994
4. Fidler J, Hough D. Hepatocyte-specific magnetic resonance imaging contrast agents. Hepatology 2011; 53:678-682 [PubMed]
5. Ringe KI, Husarik DB, Sirlin CB, et al. Gadodiamde-enhanced MRI of the liver: part 1, protocol optimization and lesion appearance in the noncirrhotic liver. AJR 2010; 195:13-28 [PubMed]
6. Nime F, Pickren JW, Vana J, et al. The histology of liver tumors in oral contraceptive users observed during a national survey by the American College of Surgeons Commission on Cancer. i 1979; 44:1481-1489 [PubMed]
7. Giannitrapani L, Soresi M, La Spada E, et al. Sex hormones and risk of liver tumor. i 2006; 1089:228-236 [PubMed]
8. Aldinger K, Ben-Menachem Y, Whalen G. Focal nodular hyperplasia of the liver associated with high-dosage estrogens. Archives of Internal Medicine 1977; 137:357-359 [PubMed]
9. Conter RL, Longmire WP, Jr. Recurrent hepatic hemangiomata. Possible association with estrogen therapy. Annals of Surgery 1988; 207:115-119 [PubMed]
10. Di Stasi M, Caturelli E, De Sio I, et al. Natural history of focal nodular hyperplasia of the liver: an ultrasound study. Journal of Clinical Ultrasound 1996; 24:345-350 [PubMed]
11. Geman O, Moscovici O, Ben-Horin CL, et al. Oral contraceptives and liver hemangioma: a case-control study. Acta Obstetricia et Gynecologica Scandinavica 2004; 83:1199-1201 [PubMed]
12. Leconte I, Van Beers BE, Lacrosse M, et al. Focal nodular hyperplasia: natural course observed with CT and MRI. Journal of Computer-Assisted Tomography 2000; 24:61-66 [PubMed]
13. Mathieu D, Koberite H, Cherqui D, et al. Oral contraceptive intake in women with focal nodular hyperplasia of the liver. Lancet 1998; 352:1679-1680 [PubMed]
14. Mathieu D, Koberite H, Maison P, et al. Oral contraceptive use and focal nodular hyperplasia of the liver. Gastroenterology 2000; 118:560-564 [PubMed]
15. Scalori A, Tavani A, Gallus S, et al. Oral contraceptives and the risk of focal nodular hyperplasia of the liver: a case-control study. American Journal of Obstetrics and Gynecology 2002; 186:195-197 [PubMed]
16. Scott LD, Katz AR, Duke, JH, et al. Oral contraceptives, pregnancy, and focal nodular hyperplasia of the liver. JAMA 1984; 251:1461-1463 [PubMed]
17. Auffert S, Gallix BP, Perney P, et al. [Spontaneous regression of a focal nodular hyperplasia]. Journal de Radiologie 9103; 84:705-708 [PubMed]
18. Cote C. Regression of focal nodular hyperplasia of the liver after oral contraceptive discontinuation. Clinical Nuclear Medicine 1997; 22:587-590 [PubMed]
19. Meunier F, Boyer L, Abergel A, et al. [Regression of a focal nodular hyperplasia after stopping oral contraceptives]. Journal de Radiologie 1998; 79:341-343 [PubMed]
20. Ohmoto K, Honda T, Hirokawa M, et al. Spontaneous regression of focal nodular hyperplasia of the liver. Journal of Gastroenterology 2002; 37:849-853 [PubMed]
Two cases of near-complete regression of focal nodular hyperplasia of the liver

21. Ross D, Pina J, Mirza M, et al. Letter: Regression of focal nodular hyperplasia after discontinuation of oral contraceptives. Annals of Internal Medicine 1976; 85:203-204 [PubMed]

22. D’Halluin V, Vilgrain V, Pelletier G, et al. [Natural history of focal nodular hyperplasia. A retrospective study of 44 cases]. Gastroenterologie Clinique et Biologique 2001; 25:1008-1010 [PubMed]

23. Kuo YH, Wang JH, Lu SN, et al. Natural course of hepatic focal nodular hyperplasia: a long-term follow-up study with sonography. Journal of Clinical Ultrasound 2009; 37:132-137 [PubMed]

24. Weimann A, Mossinger M, Fronhoff K, et al. Pregnancy in women with observed focal nodular hyperplasia of the liver. Lancet 1998; 351:1251-1252 [PubMed]