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

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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.

### 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

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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 gadoxetate 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).

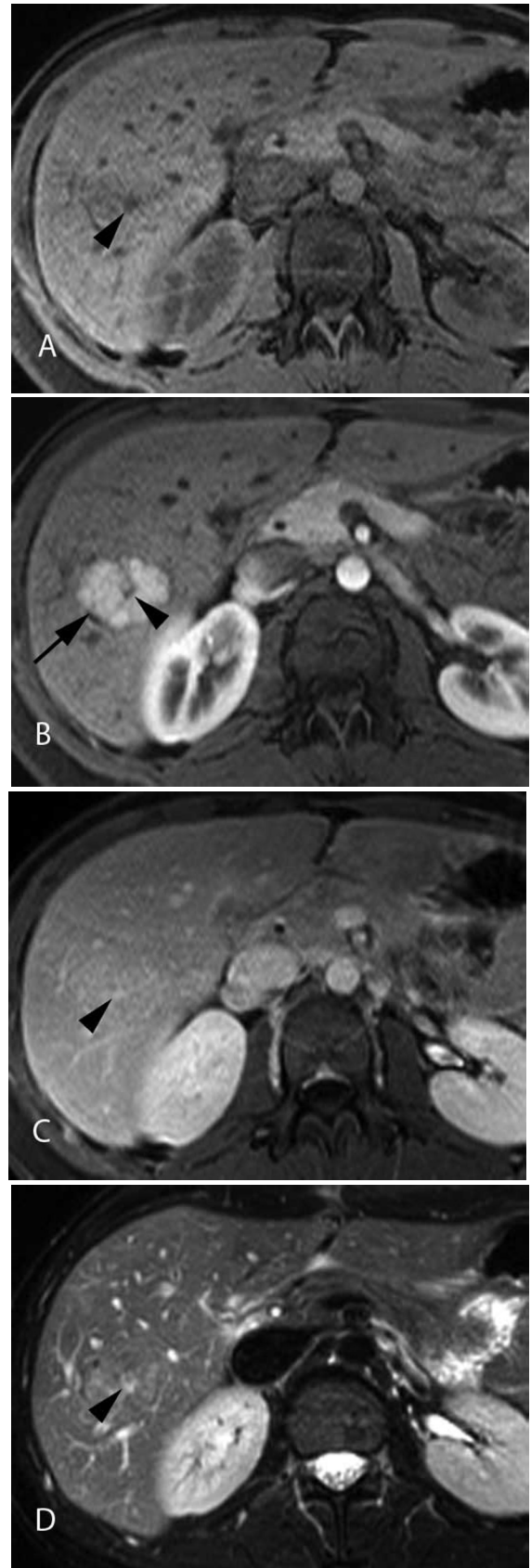
FNH has no malignant potential, and surgical excision is not indicated unless the patient is symptomatic (1). Since the 1970s, there has been controversy over the effect of oral contraceptive pills (OCP) on the natural history of FNH. Histologically, FNH in patients who use contraceptives tends to have 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).



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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

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).

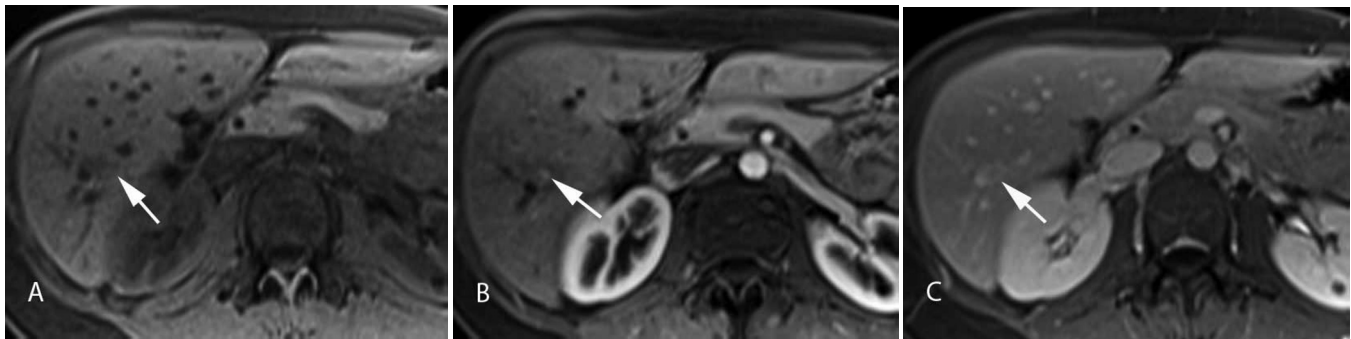


Figure 2. Near-complete regression of FNH in a 31-year-old female with a history of oral contraceptive use; images taken 48 months after Fig. 1. (A) Precontrast T1WI shows that the segment 5 mass has significantly decreased in size (arrow). (B) Following intravenous administration of gadobenate dimeglumine, a late-arterial-phase T1WI shows no significant enhancement in the expected location of the mass. (C) Three-minute-delayed postcontrast T1WI shows a small focus of enhancement (arrow), residuum of the previously seen FNH.

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-oophorectomy) 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

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  $\geq 3$  years is associated with it (OR = 4.5, 95% CI =

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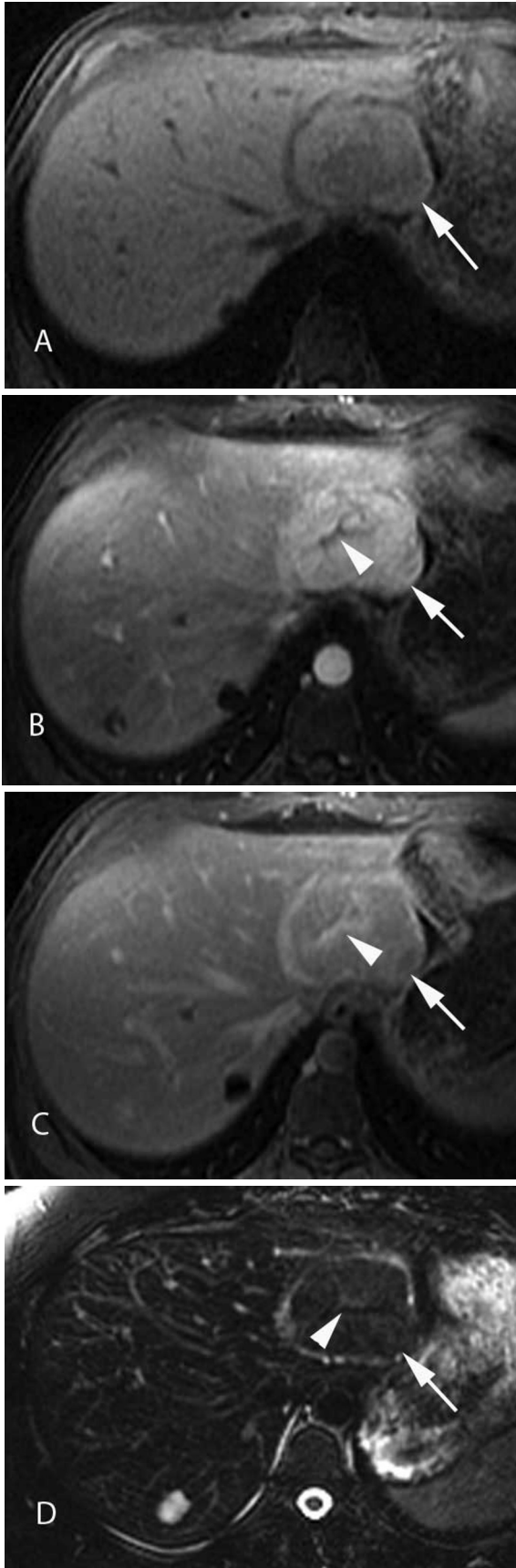


Figure 3. FNH in a 46-year-old female with Cowden syndrome and a history of hormone replacement therapy. (A) Precontrast T1WI shows a 6.5-x-4.4cm mass that is isointense to the liver parenchyma in segment 2 of the liver (arrow). (B) Following intravenous administration of gadodiamide, the mass avidly enhances in the late arterial phase T1WI. The fibrous central scar is nonenhancing (arrowhead). (C) On a five-minute-delayed T1WI, the central scar enhances. Note that the left hepatic vein is displaced by the mass, mimicking rim enhancement. (D) On T2WI, the central scar within this FNH lesion lacks typical hyperintensity.

1.2-16.9). 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–

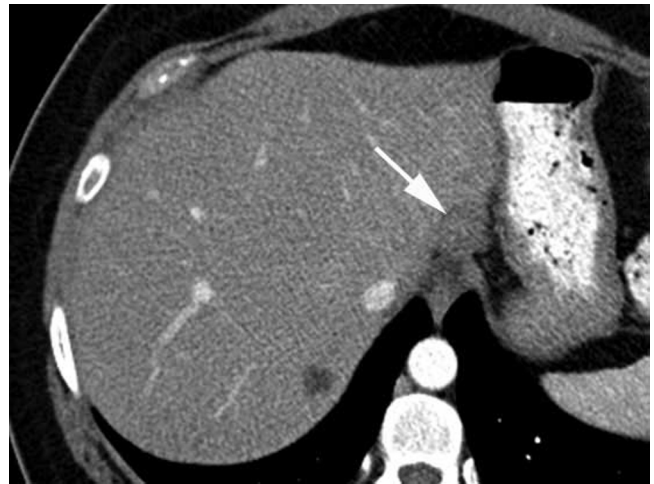


Figure 4. A 53-year-old female with Cowden's syndrome whose FNH lesion (arrow) has regressed. An enhanced CT image taken 90 months after Figure 3 shows marked involution of the mass in segment 2 of the liver. The mass measures 2.1 x 1.9 cm.

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

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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.

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