

# Multiple focal nodular hyperplasia and steatosis: Atypical imaging characteristics

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**RP Myers, D Downey, S Chakrabarti, PJ Marotta.** Multiple focal nodular hyperplasia and steatosis: Atypical imaging characteristics. *Can J Gastroenterol* 2001;15(2):137-142. Focal nodular hyperplasia is a rare, benign condition of the liver. A 28-year-old woman with malignant melanoma, mild liver enzyme abnormalities, steatohepatitis and newly documented hepatic lesions is described. Ultrasound, computed tomography and magnetic resonance imaging suggested only areas of focal fatty sparing but could not eliminate the concern for metastases. A <sup>99m</sup>technetium-labelled sulphur colloid scan, however, revealed areas of increased uptake consistent with multiple focal nodular hyperplasia. This diagnosis was ultimately confirmed with a liver biopsy. The investigation of a patient with a malignancy and expanding hepatic lesions is challenging. This case illustrates the usefulness of the <sup>99m</sup>technetium-labelled sulphur colloid scan in the evaluation of patients with hepatic lesions.

**Key Words:** Case report; Fatty liver; Focal nodular hyperplasia; Hepatic neoplasms

## Hyperplasie nodulaire multi-focale et stéatose : caractéristiques de l'imagerie de cas atypiques

**RÉSUMÉ :** L'hyperplasie nodulaire focale est une affection bénigne et rare du foie. Voici le cas d'une femme de 28 ans présentant un mélanome malin, de légères anomalies des enzymes hépatiques, une stéatohépatite et des lésions hépatiques avérées d'apparition récente. L'échographie, la tomodensitométrie et l'imagerie par résonance magnétique ont mis en évidence des foyers de stéatose, sans toutefois éliminer la présence de métastases. Une scintigraphie au sulfocolloïde marqué au technétium 99m a cependant révélé des zones d'hyperfixation, compatibles avec une hyperplasie nodulaire multi-focale. Une biopsie hépatique a confirmé le diagnostic. L'évaluation d'un patient qui présente une tumeur maligne et des lésions hépatiques en croissance pose problème. Le présent cas montre l'utilité de la scintigraphie au sulfocolloïde marqué au technétium 99m pour évaluer les patients atteints de lésions hépatiques.

Focal nodular hyperplasia (FNH) is a benign condition of the liver affecting 0.3% of the population (1). These lesions are typically well circumscribed, nonencapsulated and consist of normal hepatocytes without portal triads surrounding a stellate fibrous body. The fibrous body contains

prominent arteries and bile ductular proliferation (1,2). The etiology of FNH lesions is unknown. Some authors suggest that FNH is a hyperplastic response of normal hepatocytes to a pre-existing vascular malformation, because many lesions have a prominent vascular supply (3,4).

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**Figure 1)** Axial computed tomography scan with oral contrast demonstrating the hypodense fatty liver with three hyperdense focal nodular hyperplasia lesions (arrowheads)

The majority of patients with FNH (90%) are asymptomatic and have solitary lesions; approximately 20% of patients harbour multiple lesions. Typically, the lesions are discovered incidentally during imaging studies, at autopsy or during abdominal surgery for unrelated conditions (5-9). The main clinical importance of FNH lesions relates to its differentiation from other neoplasms such as hepatic adenoma and metastases. FNH lesions are rarely progressive (10) and have no reported malignant potential (1). Surgical resection of FNH is required only when the lesions are found to be enlarging, symptoms are refractory or a definitive pathological diagnosis is required (8-10).

A 28-year-old female with multiple FNH lesions, nonalcoholic steatohepatitis and a history of malignant melanoma is described. The characteristic radiographic appearance of FNH lesions is reviewed, and the difficulties of diagnosing FNH in the setting of a fatty liver are discussed. The use of the  $^{99m}$ technetium ( $^{99m}$ Tc)-labelled sulphur colloid scan in the differentiation of FNH from other hepatic lesions is emphasized. Finally, it is suggested that patients with hepatic lesions undergo evaluation by a multidisciplinary team consisting of clinicians, radiologists and nuclear medicine specialists, in an attempt to reduce the number of liver biopsies performed, and avoid the morbidity and potential mortality of this invasive procedure.

### CASE PRESENTATION

A 28-year-old woman presented for further evaluation of multiple hepatic lesions. Fifteen months before the authors' assessment, a superficial, spreading, malignant melanoma (Clark stage 3) on the right thigh was treated with local excision and skin grafting. No adjuvant therapy was given. At that time, elevated hepatic enzyme levels were detected (alkaline phosphatase 142 U/L [normal 50 to 136 U/L], gamma-guanosine triphosphate 163 U/L [normal 5 to 55 U/L]), and an abdominal ultrasound revealed a diffuse increase in hepatic echogenicity consistent with fatty infiltration. In addition, five solid, hypoechoic lesions were

noted – the largest was in the right lobe measuring 6.4 cm in diameter and the others were 2.1, 2.2, 2.4 and 3.1 cm in maximum dimension. A computed tomography (CT) scan with both oral and intravenous contrast confirmed the presence of multiple, high attenuation lesions in both lobes of the liver corresponding to the lesions observed by ultrasound. There were no pelvic, abdominal or pulmonary abnormalities. An ultrasound-guided fine needle aspirate of the largest lesion was nondiagnostic, revealing only scattered inflammatory cells and a few clusters of benign-appearing hepatocytes.

The patient underwent repeated ultrasound examinations over a 10-month period. Five months before the authors' evaluation, the large lesion in the right lobe had increased from 6.4 cm to 8.9 cm in maximum dimension. In addition, a new, irregular, hypoechoic, solid nodule was discovered along the inferior aspect of the right lobe, measuring 1.7 cm in diameter. The remaining lesions were unchanged. Due to the progression of these lesions, the patient was referred to the authors' institution for further evaluation.

The patient denied abdominal pain, anorexia, nausea, vomiting and constitutional symptoms. In addition to the resected melanoma, her past medical history was significant for mild asthma, depression and two uneventful pregnancies. Her medications included salbutamol, fluoxetine and the oral contraceptive pill (OCP), which she was taking for the three years up to the day of the authors' evaluation. She had no risk factors for chronic liver disease. In particular, she denied a history of blood transfusions, intravenous drug abuse, sexual promiscuity or tattoos. She was a nonsmoker, alcohol intake was minimal, and she denied a family history of liver disease.

Her body mass index was 43.5. The abdomen was obese with multiple striae; the liver and spleen were not palpable. By percussion, the liver measured 16 cm in the right mid-clavicular line. There were no hepatic bruits, rubs or stigmata of chronic liver disease. The remainder of the physical examination was unremarkable. Laboratory investigations revealed normal hemoglobin, leukocyte and platelet counts. Her aminotransferase, bilirubin, international normalized ratio and albumin levels were normal. Her alkaline phosphatase level was mildly elevated at 105 U/L (normal 20 to 94 U/L). The serum alpha-fetoprotein concentration was 1.8 U/mL (normal 0 to 8 U/mL).

An abdominal ultrasound at the authors' institution revealed increased hepatic echogenicity consistent with diffuse fatty infiltration. Eight hypoechoic lesions were now identified, the smallest measuring  $0.9 \times 0.8 \times 0.8$  cm and the largest  $8.6 \times 6.3 \times 6.2$  cm in the right lobe. The lesions were sharply demarcated with geographic borders. A dual-phase, contrast-enhanced CT scan illustrated six of these lesions – two in the right lobe and four in the left lobe. On the unenhanced images, these lesions were homogeneous and of relatively normal density. They were hyperdense compared with the remaining fatty liver (Figure 1). During the arterial phase (AP) and portal venous phase (PVP), the lesions remained hyperdense



**Figure 2)** Axial computed scan with intravenous contrast (at a slightly lower level than Figure 1) showing enhancement of the focal nodular hyperplasia lesions following contrast administration (arrowheads)

(Figure 2). No feeding vessels or central scars were identified. The lesions were thought to represent focal fatty sparing by both ultrasound and CT imaging.

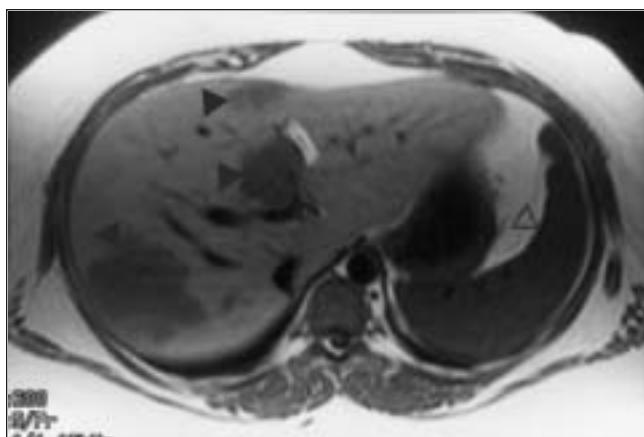
A gadolinium-enhanced magnetic resonance image (MRI) of the liver demonstrated five homogeneous lesions in the liver. These lesions were hypointense on the T1-weighted sequences (Figure 3) and slightly hyperintense on the T2-weighted sequences, being virtually isointense to the fatty liver. They demonstrated uniform enhancement after intravenous injection of gadolinium (Figure 4) but remained hypointense to the liver on the postgadolinium T1 sequences. There was no evidence of central scarring. Based on these findings, focal fatty sparing was the preferred diagnosis.

A  $^{99m}$ Tc-labelled sulphur colloid scan revealed increased uptake in several lesions consistent with those seen on previous images. There were no cold defects. In contrast with the previous imaging studies, these findings were reported as being diagnostic of multiple FNH.

For confirmation, an ultrasound-guided core biopsy of the larger lesion and the unaffected hepatic parenchyma was performed. The biopsy of the lesion displayed normal-appearing hepatocytes, as well as a well defined area of scarring with focal bile ductular proliferation and occasional blood vessels, all features of FNH (Figures 5A and B). The latter biopsies revealed severe, diffuse, macrovesicular steatosis (Figure 5C).

## DISCUSSION

The discovery of multiple hepatic lesions progressing in size is worrisome, particularly in an individual with a history of malignancy. When the lesions described in this case were first discovered, metastatic melanoma was considered to be the most likely diagnosis. However, the stability of the patient's hepatic masses over a period of 22 months and the negative fine needle aspirate suggested a benign process such as multiple hepatic adenoma, focal fatty sparing or



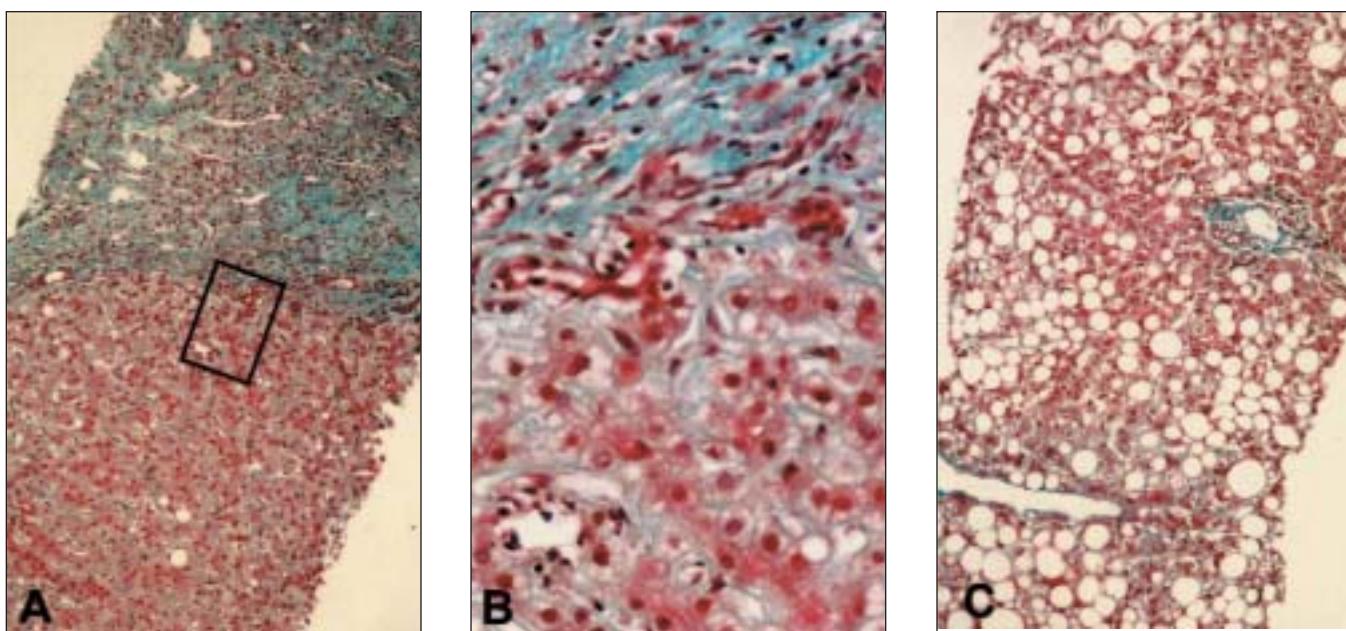
**Figure 3)** T1-weighted spin-echo magnetic resonance image demonstrating the fatty liver with increased signal intensity compared with the spleen (open arrowhead). Three hypoechoic focal nodular hyperplasia lesions are illustrated as in Figure 1 (arrowheads)



**Figure 4)** Three-dimensional spoiled gradient-echo magnetic resonance image 8 min after injection of intravenous gadolinium showing persistent enhancement of the lesions (arrowheads). No central scars are visible in any of the focal nodular hyperplasia lesions

multiple FNH. The investigation of this patient was complicated by multiple factors, particularly the patient's history of malignant melanoma, underlying fatty liver, and progressive enlargement and atypical appearance of the hepatic lesions.

Most cases of FNH occur in young females. In the largest series of adults with FNH lesions from the Mayo clinic, 36 of 41 patients (88%) were female; the average age was 41 years (6). The majority of patients are asymptomatic, and FNH lesions are generally discovered incidentally during routine evaluation or when abdominal imaging is performed for other reasons (6,8,9). In the Mayo clinic series, only 9.8% of patients were symptomatic with chronic or intermittent



**Figure 5** **A** Photomicrograph from a liver nodule showing fibrous strands and proliferation of bile ductules (trichrome stain). **B** Magnification of the boxed area in **A**. **C** The surrounding liver shows a marked fatty change and absence of fibrosis (trichrome stain)

abdominal pain. In contrast, 52% of patients with hepatic adenoma in the same series complained of abdominal pain. The onset of abdominal pain was acute in 75% of these patients, who presented with hemoperitoneum or hemorrhage within the tumour (6). Such catastrophic presentations are rarely described in patients with FNH lesions (11).

The patient described in this case was using the OCP. While an association exists between OCP use and hepatic adenoma (12-14), a causal relationship with FNH has not been elucidated. Although there is no evidence that oral contraceptives promote the development of FNH de novo, multiple studies suggest that estrogens exert a trophic effect on FNH lesions (15,16). Numerous cases have documented the regression of tumours following cessation of OCP use, and recurrence or progression of tumours in patients who continued to use OCPs (17-19). Others have documented the growth of FNH lesions during pregnancy (17).

The multiplicity of the FNH lesions in this patient is intriguing; eight lesions were visualized on an abdominal ultrasound. Although up to 20% of patients have multiple FNH, most have fewer than three lesions (6,7). Sporadic forms of multiple FNH are most common; however, Wanless et al (3) described a syndrome of multiple FNH in association with a variety of vascular anomalies or brain neoplasms, including hepatic hemangiomas, berry aneurysms, astrocytomas and meningiomas. Multiple FNH lesions have also been described in association with the Klippel-Trenaunay-Weber syndrome, an idiopathic congenital condition characterized by vascular malformations and hemihypertrophy (4). Wanless et al (3) and others (2,4) suggest that these syndromes support the hypothesis that FNH lesions are a hyperplastic response of normal hepatocytes to an irregular vascular supply. To the best of our

knowledge, the patient described in this case does not have any of these associated conditions.

The radiographic images of this patient illustrate some of the difficulties of diagnosing FNH in the setting of a fatty liver. Abdominal ultrasonography revealed multiple hypoechoic lesions, dispersed throughout an echogenic (fatty) liver. These findings are consistent with an ultrasonographic series of FNH lesions in which approximately 80% of the masses were hypoechoic or isoechoic to the normal hepatic parenchyma. In the same series, 80% of the FNH lesions were homogeneous (20). Interestingly, the ultrasound at our institution showed that these lesions were well circumscribed with angulated, geographic borders suggestive of focal fatty sparing (21). To our knowledge, this feature has not been previously reported in histologically proven FNH.

Previous series have documented the CT characteristics of FNH lesions, but all of them compared lesions with normal liver parenchyma. Typically, FNH lesions are hypodense on unenhanced images, becoming isodense or hyperdense following contrast administration (22-24). In comparison with the surrounding fatty liver (with decreased density), the lesions in our patient were hyperdense on unenhanced and contrast-enhanced AP and PVP images. Unfortunately, hepatic adenoma, metastases and cavernous hemangiomas may also have this appearance in the setting of a fatty liver (25). In a recent series (26) documenting the use of dual-phase CT scans in the evaluation of noncystic focal hepatic masses, all FNH lesions were homogeneous on PVP images; 90% were hyperdense or isodense. A homogeneous hyperdense pattern on both PVP and AP images was specific for FNH lesions (specificities 92% and 88%, respectively). Other highly specific (100%)

but less sensitive characteristics of FNH lesions include the presence of a spoke wheel pattern and central feeding vessel on AP images. These findings correspond to the large supplying arteries often seen in FNH lesions pathologically and during angiography.

A gadolinium-enhanced MRI of the liver was also performed in this patient. Classic MRI findings in FNH lesions include isointensity on T1- and T2-weighted sequences, a central hyperintense scar on T2-weighted sequences and homogeneous signal intensity (27). Unfortunately, having all three of these characteristics is reported in only 9% to 50% of patients with documented FNH lesions (28,29). The findings in our patient were atypical of FNH, with hypointense lesions on the T1-weighted sequences, slightly hyperintense lesions on the T2-weighted sequences and no central scarring. However, the appearance of the post-gadolinium-enhanced sequences was typical, with early, uniform enhancement of all lesions. One series documented this pattern in 96% of FNH lesions compared with only 32% of hypervascular malignant masses (30).

Although the abdominal ultrasound, dual-phase CT and gadolinium-enhanced MRIs all suggested focal fatty sparing, the  $^{99m}$ Tc-labelled sulphur colloid scan in this patient was classic of FNH. Because FNH lesions consist of normal hepatic parenchyma, including Kupffer's cells, 80% of FNH lesions show uptake of  $^{99m}$ Tc-labelled sulphur colloid on scintigraphy (24). Fifty per cent of these lesions show uptake greater than or equal to that of a normal liver, and the remainder show less uptake (21,24). Hepatic adenomas, on the other hand, typically appear as cold defects on  $^{99m}$ Tc-labelled sulphur colloid scans because of the absence or relative lack of Kupffer cells in these lesions (6,20,24). This finding of the increased uptake of sulphur

colloid in the hepatic lesions of our patient was diagnostic of multiple FNH.

Considering the findings of the  $^{99m}$ Tc-labelled sulphur colloid scan and the atypical imaging features of this case, as well as the patient's history of malignant melanoma, a histological diagnosis was required. Consequently, a core biopsy of one of the patient's hepatic lesions was performed that revealed normal hepatocytes with a well defined area of fibrous scarring. Within the scar were occasional blood vessels and proliferating bile ductules – classic findings of FNH lesions. A fine needle aspirate of a lesion from this patient had been performed before our assessment that demonstrated scattered inflammatory cells and benign-appearing hepatocytes. These findings are typical of FNH lesions but are also seen in hepatic adenoma, thus demonstrating the importance of obtaining a core liver biopsy sample rather than a fine needle aspirate when attempting to differentiate between hepatic adenoma and FNH.

This patient with multiple FNH lesions demonstrates several of the classic features of this disorder. However, the multiplicity of the lesions and the imaging characteristics were quite atypical, predominantly due to the coexistence of severe fatty infiltration. Ultimately, a  $^{99m}$ Tc-labelled sulphur colloid scan was the most accurate noninvasive investigation performed. We suggest that  $^{99m}$ Tc-labelled sulphur colloid scans are quite useful in the investigation of patients with multiple hepatic lesions. It is recommended that patients with hepatic lesions be evaluated by a multidisciplinary team consisting of clinicians, radiologists and nuclear medicine specialists experienced in hepatic imaging. Such an approach may lead to fewer invasive procedures such as angiography and percutaneous liver biopsy, which are associated with morbidity and, although rarely, mortality.

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