Journal of Clinical and Translational Hepatology **2024** vol. 12(2) | 182–190
DOI: 10.14218/JCTH.2023.00265

Review Article

Focal Nodular Hyperplasia: A Comprehensive Review with a Particular Focus on Pathogenesis and Complications

Jaimy Villavicencio Kim* and George Y. Wu

Division of Gastroenterology-Hepatology, University of Connecticut Health Center, Farmington, CT, USA

Received: 9 June 2023 | **Revised:** 27 September 2023 | **Accepted:** 9 November 2023 | **Published online:** 21 December 2023

Abstract

Focal nodular hyperplasia is a benign tumor of the liver that is often found incidentally with imaging. The purpose of this review is to discuss the pathophysiology, rare complications that can occur due to these lesions, and management options. A literature review was performed on clinical trials and case reports involving focal nodular hyperplasia complications and management of these, as well as the proposed pathogenesis underlying these tumors. Although exposure to oral contraceptive pills and endogenous hormones have been thought to play a role in the development of these lesions, this has not been proven. Most recently, they are thought to arise as a consequence of a vascular anomaly causing alterations in the expression of angiopoietin genes. Complications are rare, but previous cases have reported associated pain, rupture and compression of nearby structures (hepatic vein, stomach, biliary system). Resection of focal nodular hyperplasia is not usually recommended. However, if there is associated pain with no other identifiable cause or presence of a large or growing lesion with risk of causing a complication, then surgical resection, radiofrequency ablation or arterial embolization should be considered.

Citation of this article: Villavicencio Kim J, Wu GY. Focal Nodular Hyperplasia: A Comprehensive Review with a Particular Focus on Pathogenesis and Complications. J Clin Transl Hepatol 2024;12(2):182–190. doi: 10.14218/JCTH.2023.00265.

Introduction

Focal nodular hyperplasia (FNH) is a benign tumor of the liver most commonly found in women of reproductive age.[1] It is a well-circumscribed lesion comprised of proliferating hepatocytes with a characteristic stellate central fibrous scar.[2] Although not always present, it can be identified in around 70% of lesions measuring greater than 3 cm.[1] It is also frequently characterized by a large artery in the central fibrous scar without portal vein. Occasionally, typical radiological features are not present, which can make it challenging to differentiate these lesions from hepatocellular carcinoma (HCC) or adenomas.[3]

Epidemiology

FNH accounts for 8% of all primary liver lesions and around 25% of benign lesions of the liver. It is the second most frequent benign liver lesion after hepatic hemangioma. Prevalence is estimated around 0.9–3%, but appears to be increasing.[1] Incidence is higher in females, with a ratio of 8:1, especially from ages between 20 to 50 years.[1,4] They are solitary in most cases, but are reportedly multiple in 20–30% of cases. FNH has been associated with hemangiomas in 23% of cases and less commonly associated with adenomas (3.6%).

Pathogenesis

Oral contraceptive pills (OCPs)

The pathogenesis of FNH is not fully understood. It was previously thought that FHN occurred as a consequence of use of exogenous hormones given that prevalence was higher in women who were taking OCPs. Estrogens are known to play a role in physiologic and pathologic angiogenesis. Specifically, estradiol has a proangiogenic effect through estradiol-alpha activation. It prevents endothelial dysfunction, vascular inflammation and atherosclerosis while promoting collateral vessel formation in cases of ischemia. However, it is also involved in pathologic endothelial proliferation in the setting of cancer. Estrogen stimulates vascular endothelial growth factor (VEGF) production in uterine and vascular tissues, and is thought to promote re-endothelization after vascular injury due to local VEGF from vascular smooth muscle.[5,6]

There have been many cases reporting association with use of OCPs and FNH as well as regression of FNH after discontinuation of these medications.[7] Sarma *et al*.[7] documented two cases of FNH diagnosed based on imaging in women who had regression in size over a 4-year and 7-year course after stopping OCPs. Of note, one of the cases had Cowden syndrome, which is known to be associated with increased risk of many tumors. Similarly, other cases have been reported with an increase in size during pregnancy accompanied by regression after delivery, suggesting an association with endogenous hormonal exposure. Kim *et al*.[8] described a case of a woman with FNH diagnosed based on magnetic

Keywords: Focal nodular hyperplasia; Oral contraceptives; Liver lesion.
Abbreviations: ANGPT, angiopoietin; CT, computed tomography; EGD, esophagogastroduodenoscopy; FNH, focal nodular hyperplasia; HCC, hepatocellular carcinoma; IPH, idiopathic portal hypertension; MRI, magnetic resonance imaging; NASH, non-alcoholic steatohepatitis; OCP, oral contraceptive pill; RUQ, right upper quadrant; US, ultrasound; VEGF, vascular endothelial growth factor.
***Correspondence to:** Jaimy Villavicencio Kim, Division of Gastroenterology-Hepatology, University of Connecticut Health Center, 263 Farmington Ave, Farmington, CT 06032, USA. ORCID: https://orcid.org/0000-0001-7220-5118. Tel: +1-860-899-8739, Fax: +1-860-679-3159, E-mail: villavicencio@uchc.edu

resonance imaging (MRI) and no prior use of OCPs. The lesion was monitored during pregnancy due to increasing size and was found to regress at 5 months post-partum. However, after her 1-year follow up there was a slight increase in size. It would have been helpful to know whether the patient was taking any new hormonal supplementation or OCPs at the time of progression to support an association. Furthermore, there were only small variations in size on ultrasound (US) which raises the possibility of operator-bias.

In contrast, cases with stable FNH followed throughout pregnancy and post-partum period have also been reported.[9] Weimann *et al*.[9] described 82 women with diagnosis of FNH based on two different imaging modalities (US, computed tomography [CT] or cholescintigraphy), out of which 10 were monitored with US during pregnancy and post-partum period (median of 70 months). There were no increases in tumor sizes observed during pregnancy, and only two cases had regression in size during the postpartum period. The authors mentioned that the rest of the women were taking OCPs. However, there was no information on whether this group had their lesions monitored for growth or regression. Based on the opposing previous case reports, it would be difficult to draw conclusions on whether there is a direct association between endogenous or exogenous hormonal exposure and FNH development and/or growth. It is likely that there are other underlying factors or mechanisms unaccounted for which are influencing whether the lesions grow or regress in size.

Scalori *et al*.[10] performed a case-control study of 23 women with histologically proven-FNH compared to 94 matched controls, and found that long-term use of OCPs >3 years had a higher odds ratio (specifically, 4.5) of developing FNH. It was noted that there was no increased risk in patients with children as compared to nulliparous women. Although statistically these results are convincing, limitations included a small number of cases and possible selection bias since the control group were all women who were diagnosed with FNH after getting an abdominal US due to pain. Mathieu *et al*.[11] conducted a 9-year study with 216 women with at least one FNH diagnosed either with imaging or histology and followed up with MRI imaging to monitor growth. These women were divided into five groups depending on type of OCPs used (combined or progestins only) and dose (high or low). There were no differences in number of lesions or size across the five groups nor correlation between length of OCPs use and number/size of lesions. Only four women had a change in size during the follow-up period. Out of the women who stopped OCPs, two had regression and one had progression. One patient with two lesions continued low-dose OCP while one regressed and the other remained stable on subsequent imaging. Twelve women became pregnant, and all of them had no detected change in size during imaging performed after delivery. Overall, this study was well executed with the same MRI protocol performed for each patient for a period of around 2 years and read by two different radiologists. Based on the results, neither pregnancy nor OCP use seem to have a direct association with FNH growth. The authors did point out that age seemed to correlate with size and number of lesions.

A study by Nime *et al*.[12] showed FNH cases with OCP use had a greater degree of vascular alteration and fibrosis. Pathology slides of primary liver tumors in OCP users were compared to those from non-users. These slides were evaluated by a pathologist who was unaware of the diagnosis or OCP usage. The diagnosis remained the same in 58% of cases overall, but from the FNH group the diagnosis was deemed accurate in 93% of cases. There was no statistical difference between OCP users and non-users with regard to fibrosis, hemorrhage, vascular change or thrombosis. There was, however, more peliosis hepatis and a greater degree in intimal fibrous proliferation and medial smooth muscle changes in vessels in the user group. Although the results of the study appear convincing in that use of OCPs was associated with vascular changes in FNH, the authors did disclose that the small sample size did not allow for obtainment of statistically significant calculations. In addition, they did not mention whether the lesions were studied in their entirety, as a sample of an area may not be representative of the lesion as a whole. They did mention that cases in which tissue samples were not sufficient were excluded from the study, but the specific criteria were not made clear. Based on this study it is difficult to determine whether the use of OCPs was associated with development of the lesions or simply caused further vascular changes that may or may not cause further growth. Some of these same vascular changes were found in the adenoma samples examined and in other neoplasms with stronger links to OCP use.

In summary, neither OCPs nor pregnancy have been clearly shown to play a role in development or progression of the disease.[13] Based on these previous studies and case reports, a causal association between FNH and OCP cannot be proven. FNH is commonly confused with adenomas whose development has been clearly linked to OCPs. It is possible some of these cases may have had a misdiagnosed liver lesion. Furthermore, hormonal association would be difficult to explain in cases of men or children affected. Although estrogen does play a role in endometrial neovascularization and is known to regulate liver metabolism, there is no current evidence to suggest it plays a role in neovascularization, particularly in FNH.[14]

Vascular anomalies

Most recently, FNH formation has been proposed to occur as a result of a hyperplastic reaction to a vascular anomaly (e.g., dystrophic artery, arteriovenous shunt, congenital vascular malformation, etc.). More specifically, hypoperfusion or hyperperfusion in local arteries cause altered oxygenation and oxidative stress, triggering compensatory hepatocyte hypertrophy and stellate cells to produce a central scar.[1] Scar formation has been associated with activation of the transforming growth factor-beta pathway and glutamine synthetase overexpression.[15] However, a central scar is not always present in FNH and these lesions rarely have activated stellate cells.[16] Any comorbid condition that causes predisposition to vascular malformations, such as Osler-Weber-Rendu syndrome, Budd Chiari syndrome or hemangiomas, could theoretically increase the risk of developing FNH.[1,17] It has also been reported in the pediatric population with biliary atresia both before and after a successful Kasai procedure.[18–20]

Genetic mutations

FNH in identical twins has been reported in at least one case report,[21] but there has been no evidence of genetic predisposition. Genetic analyses of FNH showed alterations in expression levels of angiopoietin (ANGPT) genes (*ANGPT1* and *ANGPT2*) involved in vessel maturation in mRNA, with an increased ANGPT1/ANGPT2 ratio[22] where ANGPT1 promotes vessel formation and ANGPT2 is an antagonist of ANGPT1.[15,23] VEGF is also thought to play a role in promoting proliferation of stellate cells and angiogenesis.[16] ANGPTs act synergistically with VEGF, and it is thought that dysregulation of these play a role in the formation of the dystrophic vessels seen in FNH.[23] However, it is unknown whether this role is

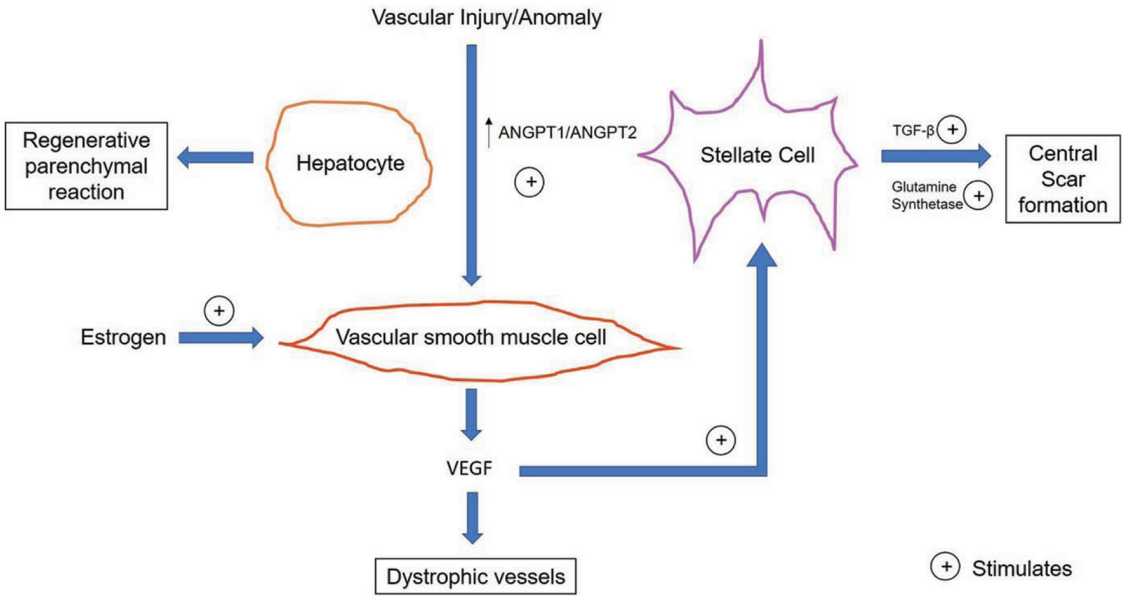

Fig. 1. Proposed mechanisms of pathogenesis of FNH. ANGPT, angiopoietin; FNH, focal nodular hyperplasia; TGF-β, transforming growth factor-beta; VEGF, vascular endothelial growth factor.

causal or reactive in nature.

In summary, it is thought that an initial vascular insult or anomaly causes an increased ANGPT1/ANGPT2 ratio which in turn stimulates the following: 1) vascular smooth muscles to create dystrophic vessels through VEGF; 2) stellate cells to form a central scar; and 3) a regenerative hyperplastic response by the hepatocytes. These are all histologic features of an FNH lesion (Fig. 1).

Clinical presentation

FNHs are usually asymptomatic and found incidentally with imaging, elective surgery or on autopsy. They can cause vague abdominal pain, early satiety and dyspepsia, especially when large in size or when causing external compression to adjacent structures. Rarely, it can present as a palpable abdominal mass.

Diagnosis

Liver enzyme tests and alpha-fetoprotein levels are generally not helpful for diagnosis as they are usually normal. Diagnosis is usually made by imaging or biopsy.

Imaging

On US, FNH appears as an isoechoic or hypoechoic mass with a hyperechoic central scar, but this may not be visible due to low sensitivity. Hyperechogenicity can occur but is much less common.[1] Use of contrast enhancement can be useful especially in conjunction with early arterial phase imaging which can reveal arterial morphology and direction of filling, and lack of venous washout.[4] A spoke-wheel filling pattern during arterial phase followed by persistent enhancement during the portal and venous phases is usually characteristic, and makes differentiation from malignant tumors easier.[1,24] Levovist,[1] sulfur hexafluoride or SonoVue,[24] and Definity (perflutren lipid microspheres)[25] contrast agents were utilized in prior studies to evaluate for this pattern.

On CT, with and without contrast, the lesions appear iso/hypodense with central scar in around 33% of cases. During arterial phase, FNH appears hyperdense. Similarly, on MRI, FNH appears isointense or hypointense on T1-weighted images and isointense/hyperintense on T2. The lesion enhances on arterial phase and becomes isointense with venous and delayed phases.[1,4] The central scar is usually relatively hypointense during arterial phase but can become hyperintense in late phase due to persistence of contrast in the scar tissue. This pattern can also appear on CT. Use of gadoxetic acid will demonstrate an iso- or hyperintense lesion in the hepatobiliary phase given its uptake in normal hepatocytes, which makes it useful in differentiating the lesion from HCC.[26] The latter usually has decreased or absent uptake unless they have overexpression of organic anion-transporting polypeptide 1B3 which transports gadoxetic acid into hepatocytes.[26] During the portal venous phase, the lesions appear isodense without washout. The combination with hepatobiliary Tc^{99m} sulfur colloid scintigraphy increases sensitivity and specificity to 99% and 100% respectively. Although uptake can be variable, FNHs usually have increased uptake as they contain Kupffer cells which are usually absent in HCC and adenomas.[4,27]

Hepatic angiography reveals a large tumor vessel entering the center of the lesion followed by radiation to the periphery in a spoke-wheel pattern.[28] There is usually initial increased vascularity within the tumor followed by delayed homogeneous staining of the lesion.[29] If present, vascularity appears decreased within the central scar and margins appear irregular.[30]

Positron emission tomography with ^{18}F-fluorodeoxyglucose usually shows normal or decreased accumulation, in contrast to malignant lesions which would normally have significantly increased uptake.[31,32] However, positron emission tomography with ^{11}C-acetate shows intense uptake, which could make differentiation from HCC difficult.[33,34]

Histology

Biopsy may be necessary in the uncommon event when diagnosis is uncertain or there is concern for underlying ma-

lignancy. On macroscopic exam, a gray-white scar commonly located in the center of the lesion with fibrous septa radiating to the periphery is pathognomonic for FNH. However, it is present only 50% of the time. The lesion commonly has a yellowish hue, well-defined borders and generally lacks a capsule. Calcification may be present, but is rare. Another common finding is the presence of multiple pseudo-lobules with fibrovascular and ductular areas that radiate from the perilobular septa, producing a stellate appearance.[1] Histologically, the central scar consists of collagen surrounded by aberrant arteries, draining veins and fibrous septae forming a pseudocapsule. This is a feature that distinguishes from HCC, fibrolamellar HCC and adenomas.[4] Immunohistochemistry can be helpful as FNHs have increased expression of glutamine synthetase in the periphery of the nodules in a geographic-like pattern.[4] Even though there can be increased expression of glutamine synthetase in a small subset of adenomas, the pattern is different. A study by Joseph *et al*.[35] compared immunohistochemistry between inflammatory adenomas, FNH and indeterminate lesions and identified five different patterns. In resected FNH lesions the pattern was map-like as mentioned above. However, in biopsy samples, pseudo-map like patterns and focal patterns have been described. In contrast, in inflammatory adenoma samples, 74% had patchy staining, 8% were diffuse and 15% were pseudo-map-like. Based on this study, a geographic or map-like pattern points towards an FNH diagnosis. However, absence of this pattern does not exclude this lesion and use of other immunohistochemical staining can likely help in identifying this lesion.[35]

Differential diagnosis

FNH can be commonly confused with adenoma, HCC and fibrolamellar-HCC. Adenomas are usually more heterogeneous and hypervascular on CT than FNH, and have contrast washout in portal and delayed phases. They usually have associated fat, calcification, intratumoral necrosis or hemorrhage.[36] With angiography, large peripheral vessels with centrifugal flow is typical, and a central avascular scar may be present due to intratumoral hemorrhage.[37] They do not retain gadoxetate on the delayed phase of MRI and have decreased uptake on Tc^{99m} sulfur colloid scintigraphy (as do fibrolamellar-HCC).[27,36] Herman *et al*.[36] attempted to differentiate adenomas and FNHs based on radiologic findings, and achieved an accurate diagnosis in 82.6% of cases after confirmation with histology. Another similar study by Kim *et al*.[38] had a 92% diagnostic accuracy using imaging in patients with liver lesions and confirmed later by pathology.

HCC is usually hypointense on gadoxetic acid-enhanced MRI due to decreased or absent uptake. Occasionally, they can be iso- or hyperintense due to overexpression of organic anion-transporting polypeptide 1B3. However, the typical pattern of arterial enhancement and venous washout of HCC (present around 88–96% of the time)[26] leads to the diagnosis.

Use of spectral CT can also distinguish HCC from FNH.[39] Indeed, one study compared morphologic and enhancement patterns using spectral CT to differentiate HCC from hemangiomas and FNHs.[40] The enhancement patterns were as described earlier for FNH while HCC showed rapid enhancement in the arterial phase and quick washout in the portal phase. However, the authors also described use of CT attenuation values and other quantifiable measurements (i.e. iodine density, water density, spectral curve) and their determination of a statistically significant difference in CT values amongst HCC and FNH (with FNH having the highest mean values in both arterial and portal phases). Specific cutoff measurements were not made clear but spectral CT might be useful in equivocal cases, particularly to increase diagnostic accuracy.

Fibrolamellar-HCC can have a central scar that makes differentiation from FNH difficult. Some features that favor fibrolamellar-HCC include calcification, large size, and signs of invasion to vascular structures or lymph nodes (50–65% of cases).[41] They have non-specific sonographic features with variable echogenicity. CT studies will most likely reveal a heterogeneous lesion, which is well-defined, hypodense, with calcification and a central stellate scar. With addition of contrast, they have hyperattenuation on arterial phase with variable enhancement patterns on venous and delayed phases. With MRI, fibrolamellar-HCC is hypointense on T1-weighted images and hyperintense on T2-weighted images.[41] The central scar is typically hypointense, which helps distinguish this lesion from FNH itself which has a hyperintense central scar on T2.[41] Tc^{99m} sulfur colloid scintigraphy can also help differentiate between the two.

Complications

Severe pain

FNHs are vascular tumors, and variations in blood flow within them are thought to cause pain due to the consequent capsular distention. Hsee *et al*.[42] studied FNH in eight patients, among which seven had right upper abdominal pain requiring work-up for pain. One patient had reported pain specifically with physical activity, while another was included in the study due to rapidly enlarging lesion seen on imaging. The work-up routines for pain included US, CT, MRI, esophagogastroduodenoscopy (EGD), colonoscopy and hepatobiliary iminodiacetic acid scan. These patients were followed for 1–7 years and all eventually had resections of the hepatic lesion due to persistent pain requiring analgesics. They were followed up for a median time of 2 years, and all seven patients with the right upper abdominal pain achieved resolution of pain without further need for pain medications. The single patient who experienced pain with exercise also achieved resolution of symptoms. Her lesion was closely related to the right and middle hepatic veins and it was thought that her lesion had caused pain due to hepatic venous outflow obstruction. Although all eight of the patients appeared to have resolution of symptoms after surgery, the sizes of the lesions and segment location were variable, making it difficult to establish an association between certain characteristics and the cause of pain.

Another study by Bonney *et al*.[43] followed 52 patients with FNH managed either surgically or conservatively. In the surgery group (n=15), the most common indication for surgery was pain (13 patients), while the other indication was having a suspicious lesion on imaging. Gastritis and cholelithiasis were excluded as potential causes of pain. Overall, patients managed surgically had greater tumor size and/or greater number of lesions compared to the conservative group. The results support a positive association between size and pain. Only one patient managed with surgery experienced recurrence of pain, although there was recurrence of FNH. In the conservatively treated group, five patients had persistent pain and were being considered for surgical management. There were no details with regard to whether these patients had increased size of FNH, which would have supported the association between size and pain.

Broker *et al*.[24] monitored 160 patients for interval growth of FNH after 6 or more months with repeat imaging. Of note, a second set of images were reviewed by a different radiologist and the diagnosis of FNH was evident from both images. Twenty-eight patients were found to have an increase in size, but an increase in size of at least 20% was found in nine-

teen of those patients. Compared to the group that did not have any growth, there were no differences in gender, age, body mass index, use of OCPs or symptomatology (including pain). Five patients out of one hundred and sixty had the FNH resected due to their abdominal pain, but only one patient achieved resolution of the symptoms after surgery. It was not specified whether the patients with pain were subject to any other work-up. However, results indicated that a large size or growing FNH was not necessarily associated with pain and resection did not cause resolution of symptoms.

Cases of acute abdominal pain due to torsion of pedunculated FNH lesions causing infarction of the mass and rupture with intra-abdominal hemorrhage have been reported.[44]

Rupture

Spontaneous rupture with hemorrhage is a rare complication that has been reported for a few cases. It has been proposed that bleeding could be due to intratumoral vascular malformations and pressure build-up.[45] Histological components such as presence of telangiectasia, thickness of blood vessels, dilatation of sinuses or sinus fibrosis might play a role in the risk of spontaneous bleeding. Abdominal trauma may be associated with rupture, although many cases did not mention previous trauma but rather spontaneous rupture.

Kinoshita *et al*.[46] described a case of a 32 year-old male with a known 8-cm FNH diagnosed by prior imaging and biopsy, who presented to the hospital with sudden onset upper abdominal pain. CT imaging without contrast showed evidence of ascites and high-density areas surrounding the tumor. An angiogram was performed, which showed active extravasation. Therefore, a transcatheter arterial embolization was performed. The patient ultimately had elective surgery with resection of the lesion, which was found to be composed of necrotic tissue and hematoma. Ultimately, the diagnosis of ruptured FNH was made.

FNH rupture with intraperitoneal hemorrhage is rare. Based on prior case reports, it appears the majority of ruptured FNHs had a size of 5 cm of greater, but some tumors were as small as 1 cm.[47–49] This suggests that there might be other characteristics that increase risk of rupture, including degree of vascular alteration. Location is less likely to be associated given there have been reports of ruptured FNHs in right, left and caudate lobes.

Compressive effects

Hepatic vein obstruction: Rangheard *et al*.[50] retrospectively studied 74 patients with FNH, 10 of which had evidence of hepatic vein obstruction (compressive group). Overall, the mean size of the lesion was bigger in the compressive group compared to the control group. Most of the lesions were also located centrally compared to the control group, in which they were mostly peripheral. In the compressive group, liver function test results showed greater elevation than in the control group. There was no mention as to whether the compressive group had any type of signs or symptoms similar to Budd-Chiari syndrome. It is possible that with slower growing lesions, progressive vein compression could lead to formation of collaterals, preventing clinical symptoms to arise as were seen in all patients in the compressive group through imaging with US, CT or MRI. Based on these cases it could be hypothesized that larger and centrally located FNH are more associated with hepatic vein compression or occlusion.

Similarly, Arrive *et al*.[51] reported a case of a woman who underwent surgery for an ovarian cyst and was incidentally found to have an FNH causing a complete occlusion or obstruction of the right hepatic vein. However, it was also noted that an intrahepatic venous collateral pathway existed between the right hepatic vein and middle hepatic vein in the patient. It was reported that the woman had normal liver function tests and was asymptomatic.

Portal hypertension: A case was reported of a 61 year-old woman with history of colon cancer treated with ileocecal resection and chemotherapy, and a live donor liver transplant due to presumed decompensated liver cirrhosis from non-alcoholic steatohepatitis (NASH).[52] She had a known liver mass measuring 20 mm × 14 mm in the right lobe and also had evidence of portal hypertension with esophageal varices requiring ligation. Imaging had also showed an atrophied liver and splenomegaly. On the explant, the lesion was determined to be an FNH with disappearance of peripheral portal vein and angiogenesis. Evaluation of the rest of the parenchyma showed no signs of fibrosis or NASH. She was ultimately diagnosed with idiopathic portal hypertension (IPH) secondary to obliterative portal venopathy. This case suggests that FNH formation can be a consequence of IPH, likely secondary to paraportal shunting and regeneration of arteries. Given the size and location of the lesion, it was considered unlikely that it was causing a portal vein obstruction.

Cases of FNH causing compressive portal hypertension are not found in the literature. Based on other cases with FNH found in patients with congenital or IPH, however, it seems that FNH might be a consequence of underlying vascular abnormalities rather than a cause of portal hypertension due to obstruction.

Biliary obstruction: Bente *et al*.[53] reported a case of a 29 year-old female with biliary colic who had a laparoscopic cholecystectomy and was found to have a liver lesion abutting the cystic duct. The lesion was biopsied and was determined to be most likely an FNH. Gallbladder pathology revealed chronic cholecystitis with two 3-mm stones and no sludge. The authors did not specify whether the patient's symptoms improved post-cholecystectomy. However, because the patient reported mainly positional right upper quadrant pain, experienced mostly at night when reclining, they questioned whether the liver lesion was causing compression of the cystic duct and obstructive pain. There was no mention of whether results of liver function tests showed elevation on presentation, which could have supported this theory.

Another case was reported of a 10-year-old presenting with epigastric pain and found to have acute cholecystitis and a liver lesion on US. The liver lesion was later determined to be a 6-cm to 7-cm FNH based on MRI findings and biopsy results. She was managed conservatively with antibiotics.[54] The FNH was located in the right hepatic lobe, but there was no mention of whether there was compression of the biliary tract. Based on this case alone, it is difficult to determine whether the hepatic lesion was the cause of acute cholecystitis or simply an incidental finding.

Gastric outlet obstruction: A 23-year-old female who presented with nausea, vomiting and abdominal pain, was reported to have gastric outlet obstruction during EGD. Cross-sectional imaging revealed a 7-cm exophytic lesion in the liver, compressing the stomach. MRI showed a hypointense lesion in T1 and slight hyperintensity on T2-weighted images. The patient underwent laparotomy, revealing a mass causing external compression of the stomach. This was resected completely and was determined to be a FNH upon histopathological and immunohistochemical examinations.[55] Unfortunately, there was no mention on whether this patient had any type of follow up or experienced resolution of symptoms.

FNH and concomitant HCC

FNH is not a premalignant lesion but has been reported to occur simultaneously with some malignant tumors. Saul *et al*.[56]

studied a 19 year-old woman with history of OCP use who was found to have an 11-cm, palpable liver mass. On CT scan this was hypodense with an enhancing central septate region. Arteriography showed a hypervascular mass with peripheral artery supply radially penetrating into the center, and in the parenchymal phase there was a dense capillary blush with stellate septate pattern and central lucency consistent with a scar. Based on the radiologic evaluation this was consistent with an FNH. For unclear reasons, she eventually had the lesion excised, and pathology exam revealed a fibrolamellar-HCC with a region showing characteristic features of FNH. These were two macroscopically and microscopically distinct regions. This case, along with several others,[57] showed histological similarity between FNH with fibrolamellar-HCC. However, there is no proof of transformation from one to another.

An association between FNH and HCC has also been studied in the past. Chen *et al*.[58] described a FNH arising from the periphery of a HCC in a 65-year-old female patient with hepatomegaly and elevated liver function test results. A hypervascular, hyperechoic and heterogeneous mass without evidence of cirrhosis was seen on multiple imaging modalities and eventually resected. On macroscopic exam, it was evident the tumor was composed of two different parts based on pathology consistent with FNH and HCC. Clonal analysis was conducted and it was determined both tumors were monoclonal. However, the inactivated alleles were not identical between the two, suggesting derivation from two different clonal origins.

Coopersmith *et al*.[59] described a case of a 43 year-old woman who had presented with right upper quadrant abdominal pain radiating to her right shoulder. She was found to have two liver lesions on CT imaging. The lesions were biopsied and showed a right lobe mass consistent with HCC and a left lobe mass determined to be FNH. Eventually, she had a right hepatectomy and on macroscopic exam was found to have multiple liver nodules in the liver that were consistent with FNHs. At her 3-month follow up, a new 6-cm mass was discovered in the medial segment of the left lobe of the liver which was ultimately diagnosed by CT-guided biopsy to be recurrent HCC. This case once again showed HCC in a liver with concomitant FNH.

FNH and fatty liver

Hirohushi *et al*.[60] studied patients with FNH diagnosed on MRI with gadolinium-diethylenetriamine-pentaacetic acid to determine the usefulness of using in-phase and opposed-phase gradient echo in diagnosis of this lesion. They compared in-phase and opposed-phase intensities and classified patients into non-fatty liver group, mild fatty liver group and severe fatty liver group. In 29 patients, opposed-phase imaging was able to detect more lesions compared to dynamic MRI in patients with fatty liver, and these were <1 cm. Opposed-phase imaging was also able to detect fatty changes within FNH in three patients, one of which had no steatosis in the rest of the liver. One patient with fatty liver had follow up at 6 months, and the steatosis within FNH was found to have disappeared along with improvement of the fatty changes in the rest of the liver. That study's findings highlight the possible utility of opposed-phase imaging in detection of steatosis within FNH and also suggest that steatosis is reversible within the lesion as well. However, no causal association was proven between these two conditions.

Fatty infiltration is an atypical finding in FNH. Stanley *et al*.[61] described a case of a 28 year-old woman with fatty liver seen on CT imaging as well as a large liver lesion in the right hepatic lobe and multiple smaller liver lesions ranging from 1–2 cm in size in both lobes. Due to her presentation with abdominal pain and interval growth of the lesion from 4 cm to 11 cm, she had the largest lesion excised and its pathology was consistent with FNH with intratumoral fatty change. The authors emphasized that presence of steatosis may cause atypical radiologic findings (such as heterogeneity and hyperdensity), resulting in higher likelihood of misdiagnosis. The presence of steatosis within FNH might be a consequence of coexisting fatty liver disease.

Management

FNH is usually an incidental finding and patients are usually asymptomatic. Per the European Association for the Study of the Liver guidelines, follow-up imaging is not needed when diagnosis is established with imaging.[13] However, close follow up with serial imaging every 6–12 months can be considered, especially in women who continue to take OCPs or patients who are symptomatic.

Surgical resection is considered for progressive growth or large lesions >10 cm in size with symptoms of compression, increased risk of hemorrhage due to trauma (subcapsular location) or occurrence of a complication.[1] Embolization of bleeding hepatic lesion can be successful in up to 99% of patients in the acute setting, followed by second-stage mass resection.[30,45,46] Techniques including arterial embolization and radiofrequency ablation could also be considered as alternatives to surgical resection.

Conclusions

FNHs are benign liver lesions that are thought to occur as a reaction to a vascular abnormality, whether related to either hyperperfusion or hypoperfusion. They have a distinct central scar that can be useful for radiologic diagnosis, but this is not always present. Diagnosis can be made best with US or cross-sectional imaging. However, when typical radiologic findings are absent there may be diagnostic uncertainty and addition of hepatobiliary contrast agent and/or biopsy for histologic confirmation might be necessary. It is important to make the distinction from malignant lesions as well as adenomas due to complications associated with these.

These lesions rarely cause symptoms and, therefore, are usually found incidentally on imaging. Nevertheless, larger lesions can be associated with symptoms and other rare complications. Size of the lesion might be related with greater risk of rupture and compressive effects upon adjacent structures (Table 1).[24,42-47,49–51,53–55,62–76] Management with surgical resection, transarterial embolization or radiofrequency ablation should be considered in patients experiencing severe pain with no other identifiable cause or large or rapidly growing lesions with risk of causing complications.

Acknowledgments

The support of the Herman Lopata Chair in Hepatitis is gratefully acknowledged.

Funding

None to declare.

Conflict of interest

GYW has been an editor-in-chief of *Journal of Clinical and Translational Hepatology* since 2013, JVK has no conflict of interests related to this publication.

Table 1. Complications of FNH

Study	Patient	Complication	Size of lesion cm	Management
Hsee *et al*.[42]	1	RUQ pain	7×6	Resection
	2	RUQ pain	5.5×4×5	Resection
	3	RUQ pain	1.4×0.5×1	Resection
	4	RUQ pain	8×8	Resection
	5	RUQ + flank pain	4×4	Resection
	6	RUQ pain	1×2	Resection
	7	RUQ pain	7.5×6.5×5.5	Resection
Gómez García *et al*.[62]	1	Pain	4.8×4.1	Arterial embolization
	2	Pain	5.8×3.6	Arterial embolization
Pain *et al*.[63]	1	Pain	9	Resection
	2	Pain	9	Resection
	3	Pain	8	Resection
	4	Pain	7	Resection
	5	Pain	11	Resection
	6	Pain	8	Resection
	7	Pain	8	Resection
	8	Pain	4	Resection
	9	Pain	5	Resection
	10	Pain	8	Resection
Osinowo *et al*.[64]	1	Pain	13.9×8.3	Resection
Birn *et al*.[65]	*n*=12	Pain	DNA	Arterial embolization
Lee *et al*.[44]	1	Pain	4.8×3×3.6	Resection
	2	Pain	3.1×4.1×5.5	Resection
Hau *et al*.[66]	*n*=46	Pain	Mean 5.9	Resection
Bonney *et al*.[43]	*n*=13	Pain	Mean 6.1	Resection
Broker *et al*.[24]	*n*=7	Pain	DNA	Resection (*n*=5) and embolization (*n*=2)
Yan *et al*.[67]	*n*=17	Pain	Mean 10.5	Arterial embolization
Zhang *et al*.[68]	*n*=23	Pain	Mean 5	Arterial embolization
Alaoui *et al*.[69]	1	Pain	7.2×6×6	Arterial embolization + resection
	2	Pain	7.5×6.5×6.5	
Hardwigsen *et al*.[70]	1	Rupture/hemorrhage	5	Arterial embolization + right hepatectomy
Kinoshita *et al*.[46]	1	Rupture	8	Arterial embolization + resection
Mays *et al*.[71]	1	Rupture/hemorrhage	10	Resection
Becker *et al*.[72]	1	Rupture/hemorrhage	4.5	Resection
Bathe *et al*.[73]	1	Rupture/hemorrhage	6	Resection
Rahili *et al*.[74]	1	Rupture/hemorrhage	9.8	Resection
Chang *et al*.[75]	1	Rupture/hemorrhage	10	Resection
Demarco *et al*.[49]	1	Rupture/hemorrhage	5.2	Resection
Li *et al*.[76]	1	Rupture/hemorrhage	15	Resection
Yajima *et al*.[47]	1	Rupture/hemorrhage	1	N/A (revealed at autopsy)

(continued)

Table 1. *(continued)*

Study	Patient	Complication	Size of lesion cm	Management
Si *et al*.[45]	1	Rupture/hemorrhage	8×8	Arterial embolization and right hepatectomy
Rangheard *et al*.[50]	*n*=10	Hepatic vein compression	DNA	DNA
Arrive *et al*.[51]	1	Hepatic vein compression	DNA	DNA
Bente *et al*.[53]	1	Cystic duct compression	DNA	None
Shehri *et al*.[54]	1	Acute cholecystitis and cystic duct compression	6.5×7.5	None
Eris *et al*.[55]	1	Pain/gastric outlet obstruction	7.8×5.5×5.6	Resection

DNA, data not available; N/A, not applicable; RUQ, right upper quadrant; FNH, focal nodular hyperplasia.

Author contributions

Wrote manuscript and prepared figures (JVK), and proposed idea for the review and revised the manuscript with critical revisions (GYW).

References

[1] Venturi A, Piscaglia F, Vidili G, Flori S, Righini R, Golfieri R, *et al*. Diagnosis and management of hepatic focal nodular hyperplasia. J Ultrasound 2007;10(3):116–127. doi:10.1016/j.jus.2007.06.001, PMID:23396642.

[2] Choi JY, Lee HC, Yim JH, Shim JH, Lim YS, Shin YM, *et al*. Focal nodular hyperplasia or focal nodular hyperplasia-like lesions of the liver: a special emphasis on diagnosis. J Gastroenterol Hepatol 2011;26(6):1004–1009. doi:10.1111/J.1440-1746.2011.06659.X, PMID:21251063.

[3] Yang ZY, Bao GQ. Focal nodular hyperplasia misdiagnosed as hepatocellular carcinoma: a case report and literature review. Dig Med Res 2021;4:17. doi:10.21037/DMR-20-157.

[4] Pinotti E, Ratti F, Cipriani F, Paganelli M, Catena M, Finazzi R, *et al*. Focal Nodular Hyperplasia. Benign Tumors of the Liver. Cham: Springer International Publishing; 2015:159–168. doi:10.1007/978-3-319-12985-3_12.

[5] Trenti A, Tedesco S, Boscaro C, Trevisi L, Bolego C, Cignarella A. Estrogen, Angiogenesis, Immunity and Cell Metabolism: Solving the Puzzle. Int J Mol Sci 2018;19(3):859. doi:10.3390/IJMS19030859, PMID:29543707.

[6] Losordo DW, Isner JM. Estrogen and angiogenesis: A review. Arterioscler Thromb Vasc Biol 2001;21(1):6–12. doi:10.1161/01.atv.21.1.6, PMID:11145928.

[7] Sarma A, Shaaban AM, Heilbrun ME, Rezvani M. Two cases of near-complete regression of focal nodular hyperplasia of the liver: Case reports and review of the literature. Radiol Case Rep 2012;7(3):681. doi:10.2484/RCR.V7I3.681, PMID:27326295.

[8] 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):392–397. doi:10.3350/cmh.2014.20.4.392, PMID:25548746.

[9] Weimann A, Mössinger M, Fronhoff K, Nadalin S, Raab R. Pregnancy in women with observed focal nodular hyperplasia of the liver. Lancet 1998;351(9111):1251–1252. doi:10.1016/S0140-6736(05)79318-1, PMID:9643751.

[10] 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):195–197. doi:10.1067/MOB.2002.120277, PMID:11854634.

[11] Mathieu D, Kobeiter H, Maison P, Rahmouni A, Cherqui D, Zafrani ES, *et al*. Oral contraceptive use and focal nodular hyperplasia of the liver. Gastroenterology 2000;118(3):560–564. doi:10.1016/s0016-5085(00)70262-9, PMID:10702207.

[12] Nime F, Pickren JW, Vana J, Aronoff BL, Baker HW, Murphy GP. The histology of liver tumors in oral contraceptive users observed during a national survey by the American College of Surgeons Commission on Cancer. Cancer 1979;44(4):1481–1489. doi:10.1002/1097-0142(197910)44:4<1481::AID-CNCR2820440443>3.0.CO;2-1, PMID:227566.

[13] European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines on the management of benign liver tumours. J Hepatol 2016;65(2):386–398. doi:10.1016/J.JHEP.2016.04.001, PMID:27085809.

[14] Carruba G. Estrogens in Hepatocellular Carcinoma: Friends or Foes? Cancers (Basel) 2021;13(9):2085. doi:10.3390/CANCERS13092085, PMID:33925807.

[15] Geller SA, de Campos FPF. Focal nodular hyperplasia of the liver. Autops Case Rep 2014;4(4):5–8. doi:10.4322/ACR.2014.033, PMID:28573123.

[16] Sato Y, Harada K, Ikeda H, Fijii T, Sasaki M, Zen Y, *et al*. Hepatic stellate cells are activated around central scars of focal nodular hyperplasia of the liver—a potential mechanism of central scar formation. Hum Pathol 2009;40(2):181–188. doi:10.1016/j.humpath.2008.04.024, PMID:18799187.

[17] Buscarini E, Danesino C, Plauchu H, de Fazio C, Olivieri C, Brambilla G, *et al*. High prevalence of hepatic focal nodular hyperplasia in subjects with hereditary hemorrhagic telangiectasia. Ultrasound Med Biol 2004;30(9):1089–1097. doi:10.1016/J.ULTRASMEDBIO.2004.08.004, PMID:15550313.

[18] Okugawa Y, Uchida K, Inoue M, Kawamoto A, Ohtake K, Sakurai H, *et al*. Focal nodular hyperplasia in biliary atresia patient after Kasai hepatic portoenterostomy. Pediatr Surg Int 2008;24(5):609–612. doi:10.1007/S00383-007-2090-8, PMID:18084770.

[19] Yoon HJ, Jeon TY, Yoo SY, Kim JH, Eo H, Lee SK, *et al*. Hepatic tumours in children with biliary atresia: single-centre experience in 13 cases and review of the literature. Clin Radiol 2014;69(3):e113–e119. doi:10.1016/j.crad.2013.10.017, PMID:24332171.

[20] Cha DI, Yoo SY, Kim JH, Jeon TY, Eo H. Clinical and imaging features of focal nodular hyperplasia in children. AJR Am J Roentgenol 2014;202(5):960–965. doi:10.2214/AJR.13.11856, PMID:24758647.

[21] Mindikoglu AL, Regev A, Levi JU, Casillas J, Schiff ER. Focal nodular hyperplasia in identical twins. Am J Gastroenterol 2005;100(7):1616–1619. doi:10.1111/J.1572-0241.2005.41898.X, PMID:15984990.

[22] Rebouissou S, Bioulac-Sage P, Zucman-Rossi J. Molecular pathogenesis of focal nodular hyperplasia and hepatocellular adenoma. J Hepatol 2008;48(1):163–170. doi:10.1016/J.JHEP.2007.10.003, PMID:17997499.

[23] Paradis V, Bièche I, Dargère D, Laurendeau I, Nectoux J, Degott C, *et al*. A quantitative gene expression study suggests a role for angiopoietins in focal nodular hyperplasia. Gastroenterology 2003;124(3):651–659. doi:10.1053/GAST.2003.50104, PMID:12612904.

[24] Bröker MEE, Klompenhouwer AJ, Gaspersz MP, Alleleyn AME, Dwarkasing RS, Pieters IC, *et al*. Growth of Focal Nodular Hyperplasia is Not a Reason for Surgical Intervention, but Patients Should be Referred to a Tertiary Referral Centre. World J Surg 2018;42(5):1506–1513. doi:10.1007/s00268-017-4335-6, PMID:29167952.

[25] Kim TK, Jang HJ, Burns PN, Murphy-Lavallee J, Wilson SR. Focal nodular hyperplasia and hepatic adenoma: differentiation with low-mechanical-index contrast-enhanced sonography. AJR Am J Roentgenol 2008;190(1):58–66. doi:10.2214/AJR.07.2493, PMID:18094294.

[26] Kitao A, Matsui O, Yoneda N, Kita R, Kozaka K, Kobayashi S, *et al*. Differentiation Between Hepatocellular Carcinoma Showing Hyperintensity on the Hepatobiliary Phase of Gadoxetic Acid-Enhanced MRI and Focal Nodular Hyperplasia by CT and MRI. AJR Am J Roentgenol 2018;211(2):347–357. doi:10.2214/AJR.17.19341, PMID:29708786.

[27] Meenakshi LA, Ravichandran B, Rajaraman V, Pandit N. Tc-99m Sulfur Colloid Scintigraphy in Differentiating Fat Sparing from Lymphomatous Involvement of Liver-Old Wine in New Bottle. Indian J Nucl Med 2022;37(4):400–401. doi:10.4103/ijnm.ijnm_107_22, PMID:36817209.

[28] Takayasu K, Muramatsu Y, Moriyama N, Yamazaki S, Takayama T, Hirohashi S, *et al*. Focal nodular hyperplasia of the liver: arterial angio-CT and microangiography. J Comput Assist Tomogr 1992;16(2):212–215. doi:10.1097/00004728-199203000-00007, PMID:1545015.

[29] Cheon JE, Kim WS, Kim IO, Jang JJ, Seo JK, Yeon KM. Radiological features of focal nodular hyperplasia of the liver in children. Pediatr Radiol 1998;28(11):878–883. doi:10.1007/S002470050487/METRICS, PMID:9799323.

[30] Ohno K, Moriyama N, Takayasu K, Muramatsu Y, Terui K, Matsue H, *et al*. [Radiologic features of focal nodular hyperplasia. Comparison with hepatocellular carcinoma by angiography and CT scan]. Nihon Igaku Hoshasen Gakkai Zasshi 1991;51(5):479–486. PMID:1651469.

[31] Kurtaran A, Becherer A, Pfeffel F, Müller C, Traub T, Schmaljohann J, *et al*. 18F-fluorodeoxyglucose (FDG)-PET features of focal nodular hyperplasia (FNH) of the liver. Liver 2000;20(6):487–490. doi:10.1034/j.1600-0676.2000.020006487.x, PMID:11169064.

[32] Aznar DL, Ojeda R, Garcia EU, Aparici F, Sánchez PA, Flores D, *et al*. Focal nodular hyperplasia (FNH): a potential cause of false-positive positron emission tomography. Clin Nucl Med 2005;30(9):636–637. doi:10.1097/01.RLU.0000174209.49753.A5, PMID:16100492.

[33] Magini G, Farsad M, Frigerio M, Serra C, Colecchia A, Jovine E, *et al*. C-11 acetate does not enhance usefulness of F-18 FDG PET/CT in differentiating between focal nodular hyperplasia and hepatic adenoma. Clin Nucl Med 2009;34(10):659–665. doi:10.1097/RLU.0b013e3181b53488, PMID:19893396.

[34] Grassi I, Nanni C, Allegri V, Morigi JJ, Montini GC, Castellucci P, *et al*. The clinical use of PET with (11)C-acetate. Am J Nucl Med Mol Imaging 2012;2(1):33–47. PMID:23133801.
[35] Joseph NM, Ferrell LD, Jain D, Torbenson MS, Wu TT, Yeh MM, *et al*. Diagnostic utility and limitations of glutamine synthetase and serum amyloid-associated protein immunohistochemistry in the distinction of focal nodular hyperplasia and inflammatory hepatocellular adenoma. Mod Pathol 2014;27(1):62–72. doi:10.1038/modpathol.2013.114, PMID:23807780.
[36] Herman P, Pugliese V, Machado MA, Montagnini AL, Salem MZ, Bacchella T, *et al*. Hepatic adenoma and focal nodular hyperplasia: differential diagnosis and treatment. World J Surg 2000;24(3):372–376. doi:10.1007/S002689910059/METRICS, PMID:10658075.
[37] Lizardi-Cervera J, Cuéllar-Gamboa L, Motola-Kuba D. Focal nodular hyperplasia and hepatic adenoma: a review. Ann Hepatol 2006;5(3):206–211. PMID:17060885.
[38] Kim J, Ahmad SA, Lowy AM, Buell JF, Pennington LJ, Moulton JS, *et al*. An algorithm for the accurate identification of benign liver lesions. Am J Surg 2004;187(2):274–279. doi:10.1016/J.AMJSURG.2003.11.018, PMID:14769319.
[39] Fei X, Han P, Jiang B, Zhu L, Tian W, Sang M, *et al*. High Frame Rate Contrast-enhanced Ultrasound Helps Differentiate Malignant and Benign Focal Liver Lesions. J Clin Transl Hepatol 2022;10(1):26–33. doi:10.14218/JCTH.2020.00172, PMID:35233370.
[40] Li W, Li R, Zhao X, Lin X, Yu Y, Zhang J, *et al*. Differentiation of Hepatocellular Carcinoma from Hepatic Hemangioma and Focal Nodular Hyperplasia using Computed Tomographic Spectral Imaging. J Clin Transl Hepatol 2021;9(3):315–323. doi:10.14218/JCTH.2020.00173, PMID:34221917.
[41] Ganeshan D, Szklaruk J, Kundra V, Kaseb A, Rashid A, Elsayes KM. Imaging features of fibrolamellar hepatocellular carcinoma. AJR Am J Roentgenol 2014;202(3):544–552. doi:10.2214/AJR.13.11117, PMID:24555590.
[42] Hsee LC, McCall JL, Koea JB. Focal nodular hyperplasia: what are the indications for resection? HPB (Oxford) 2005;7(4):298–302. doi:10.1080/13651820500273624, PMID:18333211.
[43] Bonney GK, Gomez D, Al-Mukhtar A, Toogood GJ, Lodge JP, Prasad R. Indication for treatment and long-term outcome of focal nodular hyperplasia. HPB (Oxford) 2007;9(5):368–372. doi:10.1080/13651820701504173, PMID:18345321.
[44] Lee J, Molitor M, Alashari M, Winters W, Skarda DE. Exophytic focal nodular hyperplasia torsion: A rare cause of sudden-onset epigastric pediatric abdominal pain. J Pediatr Surg Case Reports 2014;2(9):407–409. doi:10.1016/J.EPSC.2014.08.010.
[45] Si Y, Sun B, Zhao T, Xiao K, Zhao DX, Huang YM. Case Report: Rare Acute Abdomen: Focal Nodular Hyperplasia With Spontaneous Rupture. Front Oncol 2022;12:873338. doi:10.3389/FONC.2022.873338, PMID:35912213.
[46] Kinoshita M, Takemura S, Tanaka S, Hamano G, Ito T, Aota T, *et al*. Ruptured focal nodular hyperplasia observed during follow-up: a case report. Surg Case Rep 2017;3(1):44. doi:10.1186/s40792-017-0320-4, PMID:28315131.
[47] Yajima D, Kondo F, Nakatani Y, Saitoh H, Hayakawa M, Sato Y, *et al*. A fatal case of subcapsular liver hemorrhage in late pregnancy: a review of hemorrhages caused by hepatocellular hyperplastic nodules. J Forensic Sci 2013;58(Suppl 1):S253–S257. doi:10.1111/j.1556-4029.2012.02246.x, PMID:22900716.
[48] Behrend M, Flemming P, Halbfass HJ. [Spontaneous bleeding of focal nodular hyperplasia as a rare cause of acute abdomen]. Chirurg 2001;72(10):1201–1204. doi:10.1007/s001040170061, PMID:11715625.
[49] Demarco MP, Shen P, Bradley RF, Levine EA. Intraperitoneal hemorrhage in a patient with hepatic focal nodular hyperplasia. Am Surg 2006;72(6):555–559. doi:10.1177/000313480607200620, PMID:16808214.
[50] Rangheard AS, Vilgrain V, Audet P, O'Toole D, Vullierme MP, Valla D, *et al*. Focal nodular hyperplasia inducing hepatic vein obstruction. AJR Am J Roentgenol 2002;179(3):759–762. doi:10.2214/AJR.179.3.1790759, PMID:12185058.
[51] Arrivé L, Dahan H, Tubiana JM. Hepatic vein obstruction in a case of focal nodular hyperplasia. AJR Am J Roentgenol 1999;173(3):857. doi:10.2214/AJR.173.3.10470963, PMID:10470963.
[52] Tanji Y, Furukawa K, Igarashi Y, Yanagaki M, Haruki K, Shirai Y, *et al*. Living donor liver transplantation for idiopathic portal hypertension with focal nodular hyperplasia. Surg Case Rep 2022;8(1):73. doi:10.1186/s40792-022-01428-3, PMID:35445894.
[53] Bente A, Ouedraogo M, Kasbawala KN, Glasgow KM. Compression of cystic duct caused by focal nodular hyperplasia. J Surg Case Rep 2019;2019(10):rjz254. doi:10.1093/jscr/rjz254, PMID:31616554.
[54] Al Shehri F. Focal Nodular Hyperplasia in children presenting as acute Cholecystitis. Int J Health Sci (Qassim) 2010;4(2):194–197. PMID:21475557.
[55] Eris C, Yildiz MK, Odabasi M, Akbulut S, Abuoglu H, Ozkan E. Gastric outlet obstruction caused by focal nodular hyperplasia of the liver: A case report and literature review. Int J Surg Case Rep 2013;4(8):681–683. doi:10.1016/J.IJSCR.2013.05.004, PMID:23792480.
[56] Saul SH, Titelbaum DS, Gansler TS, Varello M, Burke DR, Atkinson BF, *et al*. The fibrolamellar variant of hepatocellular carcinoma. Its association with focal nodular hyperplasia. Cancer 1987;60(12):3049–3055. doi:10.1002/1097-0142, PMID:2824023.
[57] Saxena R, Humphreys S, Williams R, Portmann B. Nodular hyperplasia surrounding fibrolamellar carcinoma: a zone of arterialized liver parenchyma. Histopathology 1994;25(3):275–278. doi:10.1111/J.1365-2559.1994.TB01328.X, PMID:7821896.
[58] Chen TC, Chou TB, Ng KF, Hsieh LL, Chou YH. Hepatocellular carcinoma associated with focal nodular hyperplasia. Report of a case with clonal analysis. Virchows Arch 2001;438(4):408–411. doi:10.1007/S004280000348, PMID:11355178.
[59] Coopersmith CM, Lowell JA, Hassan A, Howard TK. Hepatocellular carcinoma in a patient with focal nodular hyperplasia. HPB (Oxford) 2002;4(3):135–138. doi:10.1080/136518202760388046, PMID:18332941.
[60] Hirohushi S, Kituno S, Tuupitz M, Humm B. Hepatic focal nodular hyperplasia in fatty liver in comparison to non-fatty liver: evaluation with plain in-phase and opposed-phase gradient echo and contrast enhanced dynamic MR imaging. Proc Intl SOC Mag Reson Med 2002;10:2002.
[61] Stanley G, Jeffrey RB Jr, Feliz B. CT findings and mistopathology of intratumoral steatosis in focal nodular hyperplasia: case report and review of the literature. J Comput Assist Tomogr 2002;26(5):815–817. doi:10.1097/00004728-200209000-00025, PMID:12439320.
[62] Gómez García MP, Cruz González I, Peña Baranda B, Atín del Campo VM, Méndez Martín JJ. [Treatment of symptomatic focal nodular hyperplasia by arterial embolization]. Cir Esp 2014;92(2):135–137. doi:10.1016/J.CIRENG.2013.03.005, PMID:24216287.
[63] Pain JA, Gimson AE, Williams R, Howard ER. Focal nodular hyperplasia of the liver: results of treatment and options in management. Gut 1991;32(5):524–527. doi:10.1136/gut.32.5.524, PMID:2040476.
[64] Osinowo AO, Balogun OS, Olajide TO, Badmos KB. Focal Nodular Hyperplasia of the Liver Presenting as Right Upper Quadrant Mass. J Case Reports 2018;8(3):198–201. doi:10.17659/01.2018.0053.
[65] Birn J, Williams TR, Croteau D, Schwartz S, Sturza S, Getzen T. Transarterial embolization of symptomatic focal nodular hyperplasia. J Vasc Interv Radiol 2013;24(11):1647–1655. doi:10.1016/j.jvir.2013.07.012, PMID:24001972.
[66] Hau HM, Atanasov G, Tautenhahn HM, Ascherl R, Wiltberger G, Schoenberg MB, *et al*. The value of liver resection for focal nodular hyperplasia: resection yes or no? Eur J Med Res 2015;20:86. doi:10.1186/S40001-015-0181-X/TABLES/8, PMID:26494164.
[67] Yan JY, Duan F, Fu JX, Wang Y, Zhang JL, Guan Y, *et al*. Outcomes of transarterial embolization for large symptomatic focal nodular hyperplasia in 17 pediatric patients. Dig Liver Dis 2023;55(7):899–906. doi:10.1016/j.dld.2022.12.025, PMID:36669995.
[68] Zhang G, Wang M, Duan F, Yuan K, Li K, Yan J, *et al*. Transarterial embolization with bleomycin for symptomatic hepatic focal nodular hyperplasia. Diagn Interv Radiol 2017;23(1):66–70. doi:10.5152/DIR.2016.16061, PMID:27910813.
[69] Alaoui O, Mahmoudi A, Khattala K, Bouabdallah Y. Resection of symptomatic focal nodular hyperplasia of the liver with pre-operative angioembolization. J Pediatr Surg Case Reports 2022;84:102383. doi:10.1016/J.EPSC.2022.102383.
[70] Hardwigsen J, Pons J, Veit V, Garcia S, Le Treut YP. A life-threatening complication of focal nodular hyperplasia. J Hepatol 2001;35(2):310–312. doi:10.1016/S0168-8278(01)00096-4, PMID:11580160.
[71] Mays ET, Christopherson WM, Barrows GH. Focal nodular hyperplasia of the liver. Possible relationship to oral contraceptives. Am J Clin Pathol 1974;61(6):735–746. doi:10.1093/AJCP/61.6.735, PMID:4364925.
[72] Becker YT, Raiford DS, Webb L, Wright JK, Chapman WC, Pinson CW. Rupture and hemorrhage of hepatic focal nodular hyperplasia. Am Surg 1995;61(3):210–214. PMID:7887531.
[73] Bathe OF, Mies C, Franceschi D, Casillas J, Livingstone AS. Massive hemorrhage and infarction complicating focal nodular hyperplasia of the liver. HPB (Oxford) 2003;5(2):123–126. doi:10.1080/13651820310000, PMID:18332970.
[74] Rahili A, Cai J, Trastour C, Juwid A, Benchimol D, Zheng M, *et al*. Spontaneous rupture and hemorrhage of hepatic focal nodular hyperplasia in lobus caudatus. J Hepatobiliary Pancreat Surg 2005;12(2):138–142. doi:10.1007/S00534-004-0936-1/METRICS, PMID:15868078.
[75] Chang SK, Chung YF, Thng CH, Loo HW. Focal nodular hyperplasia presenting as acute abdomen. Singapore Med J 2005;46(2):90–92. PMID:15678292.
[76] Li T, Qin LX, Ji Y, Sun HC, Ye QH, Wang L, *et al*. Atypical hepatic focal nodular hyperplasia presenting as acute abdomen and misdiagnosed as hepatocellular carcinoma. Hepatol Res 2007;37(12):1100–1105. doi:10.1111/J.1872-034X.2007.00164.X, PMID:17608671.