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Case Report

Focal Nodular Hyperplasia in a Young Male as an Incidental Finding Associated With Acute Lithiasic Chronic Cholecystitis. Case Report and Literature Review.

José J. Gómez-Ramos[a], *María G. Ascencio-Rodríguez*[b], *Alejandro Marín-Medina*[c], *Moises Alejandro Alatorre Jimenez*[d], *Vickramjeet Johal*[d], *Eduardo Esteban-Zubero*[e].

[a]*Department of Emergency Medicine, Hospital General de Zona No. 89 IMSS, Guadalajara, Jalisco, México*
[b]*Department of Pathology, Hospital General de Zona No. 89 IMSS, Guadalajara, Jalisco, México*
[c]*Department of Molecular Biology and Genomics, Centro Universitario de Ciencias de la Salud (CUCS), Universidad de Guadalajara, Guadalajara, Jalisco, México*
[d]*Department of Pediatrics, SUNY Downstate Medical Center, Brooklyn, NY, USA*
[e]*Departament of Emergency Medicine, Hospital San Pedro, Logroño, Spain*

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ABSTRACT

Focal nodular hyperplasia (FNH) is considered the second most frequent benign liver tumor with a low prevalence, with a broad predominance in the female population. Most cases are asymptomatic and are often discovered incidentally. Diagnostic imaging through MRI, CT, and ultrasound can be achieved in up to 80% of cases. In some cases, a histopathological study may be necessary, especially in view of the diagnostic uncertainty and suspicion of malignancy. To date, the management of these lesions remains controversial, conservative management is recommended for asymptomatic or small lesions, relegating surgical treatment only in cases of symptomatic lesions or uncertain behavior.

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1. INTRODUCTION

Focal nodular hyperplasia (FNH) is a benign, reactive, non-neoplastic growth of the liver [1], described and characterized in its classic form by a central stellate scar and presence of hyperplastic nodules [2].
A variety of synonyms have been used in its nomenclature, including focal cirrhosis, pedunculated adenoma, solitary hyperplastic nodule, mixed adenoma, hamartoma and hamartomatous cholangiohepatoma [1].
We present the case of a young man with chronic lithiasic cholecystitis exacerbated with FNH as an incidental finding and review the literature regarding surgical, pathological and radiological findings, as well as the management of patients with this condition.

* *Corresponding author.*
E-mail address: josejuan79@yahoo.com
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2. CASE REPORT

The patient is a 36-year-old man, with no relevant history, who presents to the emergency department with abdominal pain, associated with nausea and vomiting; being treated multiple times without success. It is hospitalized for study protocol.

Upon arrival to the emergency room, the patient was with abdominal pain, several days of evolution, located in the epigastrium and with irradiation to the right hypochondrium; reports being associated with nausea and vomiting on multiple occasions. It does not refer fever. The vital signs upon admission were: blood pressure of 157/102 mmHg, heart rate of 87 bpm, respiratory rate of 20 bpm, and temperature of 37°C. The physical examination revealed abdominal pain located in the epigastrium, with a positive Murphy sign. The requested laboratory tests showed erythrocytes 5.3 million/dL, hemoglobin 15.6 gr/dL, hematocrit 45.8%, platelets 230 mil/dL, leukocytes 14.4 mil/dL, neutrophils 75.5%, glucose 106 mg/dL, creatinine 0.80 mg/dL, total bilirubin 1.94, direct bilirubin 0.40 mg/dL, indirect bilirubin 1.55 mg/dL, amylase 43 U/L, alanine aminotransferase 52 U/L, aspartate aminotransferase 25 U/L, dehydrogenase lactic 357 U/L, lipase 47 U/L, INR (International Normalized Ratio) 1.181. The patient presents an echocardiographic evaluation in which the presence of acute lithiasic cholecystitis is described and fortuitously, the finding is described with three hypoechoic images in the right lobe.

As part of the study protocol, a new ultrasound of the liver and bile ducts was performed, which showed an increased liver size, regular borders, and increased echogenicity diffusely in relation to fat infiltration. The right lobe showed three hypoechoic images of ill-defined edges of dimensions 5.6 x 3.5 cm, 4.4 x 4.2 cm, and 2.2 x 2.0 cm, respectively (Figure 1); Doppler color did not show uptake of flow. Gallbladder with dimensions of 13 x 4 x 3.5 cm, with diffuse thickening of the wall (5 mm), several stones in its interior those greater than 21 mm in diameter, in addition to the presence of biliary slime.

The patient underwent open cholecystectomy and liver tumor resection without complications. The following postoperative findings were reported: distended gallbladder with purulent inflammatory fluid in its interior, in an approximate amount of 50 ml, as well as multiple stones. A multinodular hepatic tumor of approximately 12 x 8 cm in diameter, with firm consistency, is also located in segment VII of the liver in the free border.

The patient had a postoperative course without complications. He was discharged 3 days later.

The histopathological study reported: surgical piece product of hepatic resection in 10% formaldehyde, of nodular aspect with dimensions of 6 x 4 x 3 cm; of irregular surface. When cutting, a central zone with a fibrous, whitish aspect with stellar edges was highlighted, the rest of the parenchyma was made up of several nodules of different size (Figure 2). Hematoxylin-Eosin (HE) staining was performed, and microscopic examination revealed nodular hepatic lesions with multiple fibrous tracts, forming a large central scar with a radial appearance, in which anomalous vascular structures were identified. Ductal proliferation predominantly in the periphery of the nodules was also observed. The histopathological study was complemented with Masson's trichrome stain, presence of fibrous tracts were reported, as well as ductal fibrosis, concluding Classic Focal Nodular Hyperplasia (Figure 3).

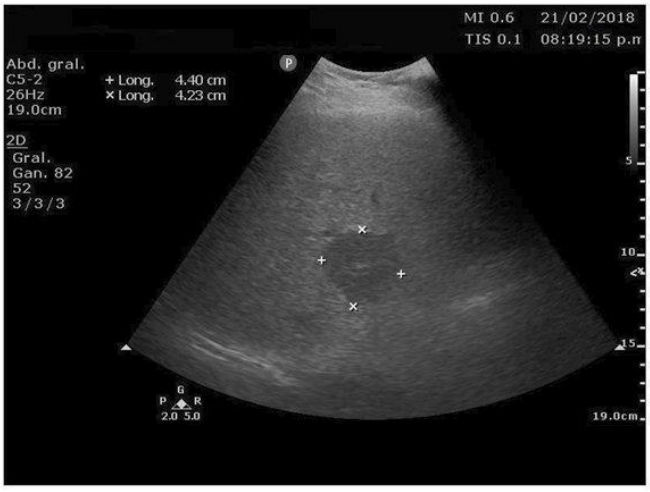

Figure 1: *FNH features on conventional B-mode ultrasound: a hypoechoic image of poorly defined borders is observed in the right hepatic lobe.*

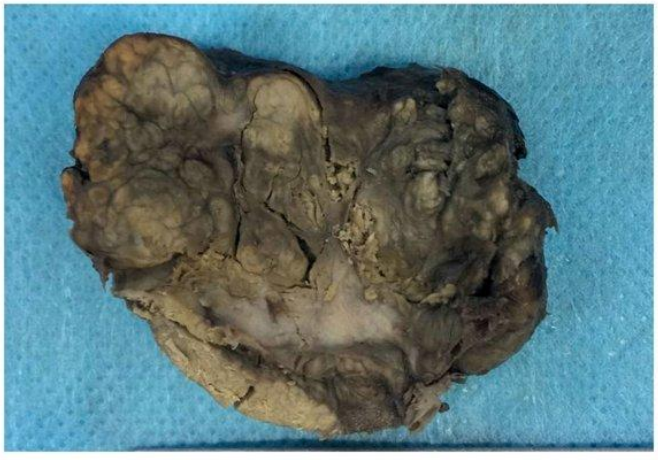

Figure 2: *A 6x4x3 cm, nodule of focal nodular hyperplasia found incidentally in a young man. It shows the gross appearance of classical FNH. Nodular appearance lesion is observed, in addition the typical central scar with radial fibrous bands.*

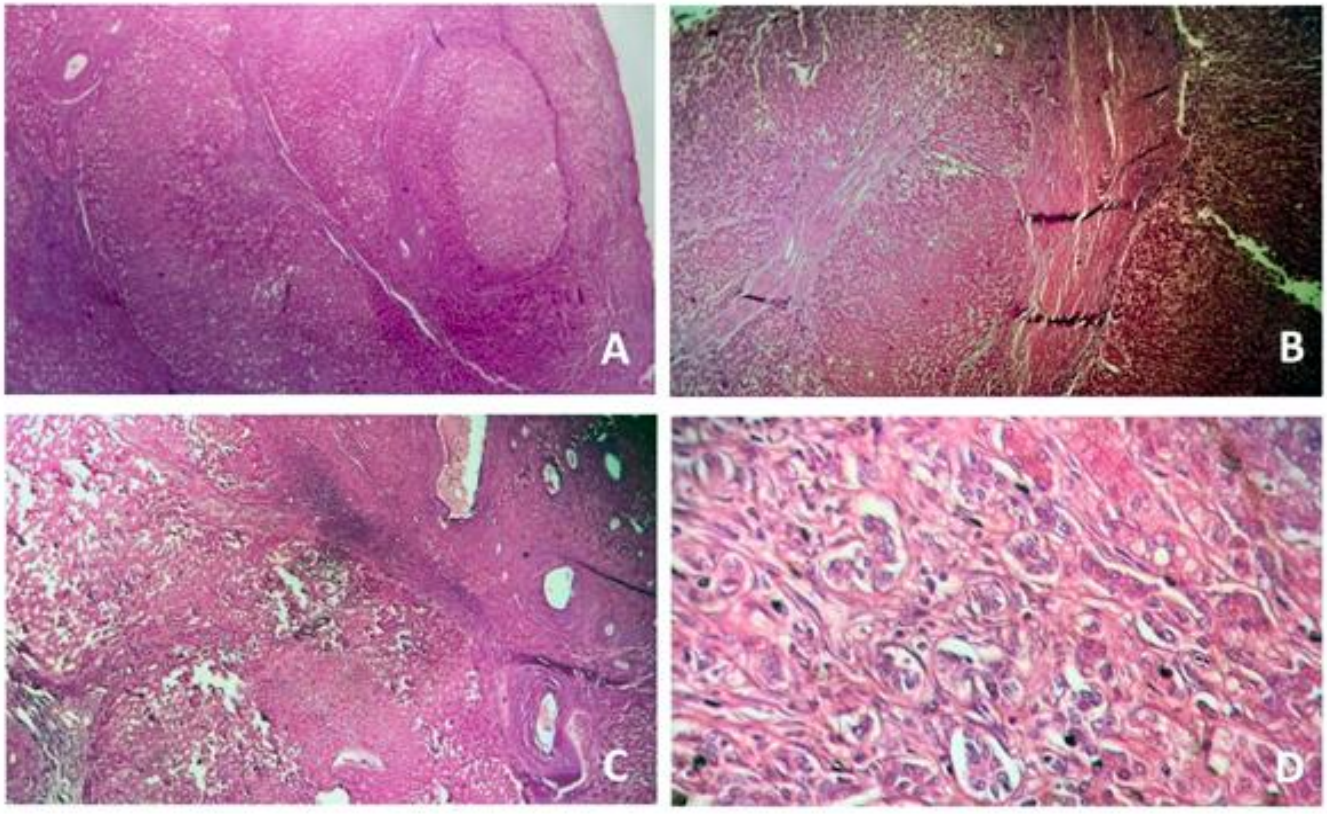

Figure 3: *Hematoxylin-eosin staining revealed (A) (5x) enlargement at low magnification with lesions in the hepatic parenchyma of nodular appearance and divided by fibrous septa; (B) (10x) fibrous septum containing medium-sized vessels; (C) (10x) fibrous septum forming part of a large stellate central scar, where numerous thick-walled arteries are identified; (D) (40x) a greater increase ductal proliferation is identified in the junction between the fibrous septa and the hepatic parenchyma.*

3. INTRODUCTION

The majority of FNH are asymptomatic and are discovered incidentally during physical examination, abdominal surgery, or autopsy, but some large FNH may be associated with significant symptoms. It is difficult to make a definitive preoperative diagnosis for FNH and to differentiate FNH from other benign and malignant tumors before operation, especially when the focus is small [2].

Although epidemiological data on FNH are scarce, it is considered the second most common benign hepatic tumor in adults; representing approximately 8% of all primary liver tumors [1,3], and is between 3 and 10 times more common than hepatic hemangioma. Its prevalence is reported between 0.4% and 3% of the general adult population and thought to increase with age. The prevalence of FNH is higher in females, but the reported rates vary enormously. The female to male ratio of FNH is approximately 13-15:1, although ratios up to 26:1 have been reported. This makes FNH typically a condition found in females [3].

The FNH is classified according to its histological presentation, being able to find classic lesions and non-classical lesions; in turn, classic lesions can be subdivided into lesions with telangiectatic form, mixed form (hyperplastic and adenomatous) and large cell atypia [4]. The non-classical forms show unusual characteristics such as steatosis, large cell changes, Mallory bodies and cholestasis. Abnormal architecture or vascular malformations may be absent in non-classical forms, but proliferation of the bile duct is always present [5].

The etiology of FNH continues to be an enigma. The suggested etiologies of FNH in the literature include oral contraceptives, hamartoma and vascular abnormalities [6]. Over the years, special emphasis has been placed on the role of oral contraceptives in the etiology of FNH. As a result of clinical and epidemiological observations in FNH, with approximately 50% to 75% of women with FNH are oral contraceptives users, particularly those with symptoms or larger nodules [7], which also places the role of female hormones in the development of this pathology [8]; although the natural history of FNH has been studied only in small series of patients, with contradictory results, some studies suggest that neither the size or the number of FNH lesions are influenced by the use of oral contraceptives [9], while others suggest an association between use of exogenous hormones not only with FNH (both in the incidence and in the size of the lesions), but also with other hepatic conditions including hepatocellular adenomas, hepatocellular carcinomas and some other benign lesions

[7]. FNH is also related to well-known vascular diseases, such as hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease) or the congenital absence of portal vein [10-11].

The prevailing theory of the development of FNH is that this tumor arises from a vascular malformation, mediated possibly by the dysregulation of angiopoietin genes (ANGPT1 and ANGPT2), which leads to blood hyperperfusion triggering a secondary hyperplastic/regenerative response in the liver parenchyma. This response is mediated by the increased expression of vascular endothelial and somatic growth factors that trigger an activation of the hepatic stellate cells [10,11].

Most cases of FNH are asymptomatic, however, some authors have suggested that large subcapsular lesions may cause the Glisson capsule to stretch or the displacement of adjacent organs and that this may cause vague abdominal pain [12,13], located in the upper right quadrant and that is usually not acute [14]; some lesions can grow extremely large, up to 190 mm12, and manifest as hepatomegaly, reaching palpable mass in up to 2-4% [4,12]. Major complications, such as acute bleeding and perforation are rare [11,12,14].

Abnormalities in liver function tests are infrequent [12,13,14]. Alphafetoproein levels are also usually within normal limits, however, high levels of serum gamma-glutamyltransferase [12,13] can be found in up to half of cases [13], especially in those cases in which the lesions are large enough to cause extrinsic compression of the intrahepatic bile duct12. Abnormalities in liver function tests have been reported in up to 12-13% of patients with FNH, which entails the performance of other diagnostic tests [3].

It has been shown that magnetic resonance imaging (MRI) enhanced by contrast is the most sensitive modality to characterize this lesion, while triple-phase spiral computed tomography (CT) (with portal, arterial, venous vein) and contrasting ultrasound can be used as other diagnostic tools [11]. By combining several imaging techniques, the definitive diagnosis rate is generally 50% and sometimes more than 80% [2].

The histological features that distinguish FNH from other focal hepatic lesions are also important in the ultrasound examination: the presence of a feeding arteriole that develops centripetally and is enclosed within the central scar, and the radiation pattern of the intralesional arteries [13].

On B-mode echographic studies, the appearance of FNH is nonspecific and variable. In approximately 75-80% of cases, the lesion appears to be isoechoic or mildly hypoechoic with respect to the surrounding hepatic parenchyma. Hyperechoic nodules are less common [13,14,15]. When the nodule is isoechoic, displacement of vascular structures may be the only sign of its presence. In some cases, the lobulated profile of the nodule can be appreciated, and the margins can be quite clear or poorly defined. Some nodules also have a hypoechoic halo [13,14] that represents perilesional tissues (parenchyma or blood vessels) compressed by the nodule [13], although it is usually not observed, compatible with the absence of a true capsule [12]. The central scar may be difficult to visualize [15], some authors report a limited percentage of visualization that varies from 19% to 47% [12,13].

Color and power Doppler studies of the FNH nodules provide sufficient data to reach the diagnosis (65-70% of the studies performed), but in around one-third of all cases they do not reveal the typical distribution of the stellate or radial arteries from a centrally supplying hypertrophic artery that generally increases in caliber as the blood supply increases [12,13]. In most cases, the spectral analysis will reveal the arterial signals in and around the nodule. Flow through the central artery is pulsatile with a high peak systolic frequency (>1 kHz) and low impedance, which corresponds to a resistance index (RI) of less than 0.65. Measurement of impedance on arterial tracings during spectral analysis is important for distinguishing FNH nodules from malignant lesions, such as hepatocellular carcinoma or liver metastases. In all three types of lesions, spectral tracings may present high peak systolic frequency values, but the RI of an FNH nodule is generally lower than that of a malignant lesion, which is usually >0.70 [13].

The first reports of CT scanning in the detection of FNH showed that it has a sensitivity and specificity of 75% and 92%, respectively [12,15]. Before the administration of the contrast agent, FNH nodules are classically considered as a solitary, homogeneous, and isodense or mildly hypodense zone compared with the normal liver [12,13,15]. In approximately 20% of patients, a hypodense central scar can be seen in about one-third of all cases. In contrast-enhanced CT, during the arterial phase of hepatic enhancement, FNH shows an immediate and intense improvement (96%). CT performed during the portal venous peak shows a decrease in the enhancement of the lesion in relation to normal hepatic parenchyma enhanced, which results in a mitigating lesion of the liver (isodensity) [13,15,16]. In late CT, the central scar may appear hyperattenuated [12,13,15,16].

Typical MR features of focal nodular hiperplasia are iso- or hypointensity on T1-weighted images (94–100%) [12,16]; slight hyper- or isointensity on T2-weighted images (94-100%) [12,13,16], or homogeneity (96%). The central scar can be identified in 50 to 70% of the nodules of moderate to large size and a much lower percentage of small lesions (<3 cm) [16], appears hypointense in T12 [12,13,16], and hyperintense in the images enhanced in T2 (84%) [12,13,14,16]. After administration of gadolinium chelates, the enhancement profile is identical to that seen on contrast-enhanced CT: dramatic enhancement in the arterial phase16, followed by the isointensity of the lesion during the portal venous phase [12,13,16]. On delayed phase imaging, the central scar shows high signal intensity due to the accumulation of contrast material [16].

MRI imaging findings using strict criteria provide specificity up to 100%. The presence of these MR imaging criteria indicates a definitive diagnosis of FNH and avoids

the need for invasive procedures (Table 1) [9].

1.	Slightly hyperintense or isointense on T2-weighted images.
2.	Homogeneous signal intensity.
3.	Presence of a central stellate area hyperintense on T2-weighted images and hypointense on T1-weighted images.
4.	Marked enhancement of the lesion at the arterial phase.
5.	Accumulation of gadolinium chelates within the central área on delayed contrast-enhanced T1-weighted images.
6.	Absence of tumor capsule.

Table 1: *Combination of MR Criteria Required for Diagnosis of FNH. Data from Mathieu, et al [9].*

Although the typical appearance of FNH lesions in different imaging modalities has been described, the similarity between this and other hepatic lesions can cause diagnostic dilemmas [12]; especially when these findings are atypical, requiring more invasive diagnostic measures to confirm or exclude the diagnosis [12].

Given the greater heterogeneity of the Hepatocellular adenoma (HCA) (main and most important differential diagnosis) and in the presence of a radiologically doubtful FNH, it may be necessary to perform a liver biopsy5.

Performing needle biopsies are controversially discussed, as these tumors are prone to bleeding [3] and the risk of seeding of malignant cells if the lesión is not benign [3,12]; in addition, in many cases, the amount of obtained material is often not sufficient to reliably confirm the diagnosis, surgical excision being necessary to distinguish between FNH and other hepatic lesions [3].

From the histopathological point of view, FNH presents as a solitary nodule in up to two-third of cases, the rest of the liver tissue is usually normal. FNH is associated with hepatic hemangioma in 20% of cases and its association with HCA is not rare [17].

Macroscopically, classic FNH is shown as a firm mass, measuring from a few millimeters to more than 10 centimeters in diameter [17], often with a lighter color than the surrounding normal liver tissue [3,17]. The margin is well delimited, being a lobed mass17 not encapsulated [3,17]. The lesion is composed of nodules each measuring 2-3 mm, each separated by zones of atrophy that give the lesion a multinodular appearance. The lesion characteristically has a central or eccentric stellate fibrous scar [17], from which fibrous septa with an abnormal vasculature radiate towards the periphery of the lesion3 surrounding some nodules [17], but this can not always be visualized before resection [3].

Classic microscopic lesions of FNH show nodules of benign-appearing hepatocytes arranged in plates no more than 2 cells in thickness [12,17], the hepatocytes maintain their normal phenotype [3]. There may be steatosis, usually focal. The central scar is often edematous or congested [17] and is composed of bile ductules, cholangiolar proliferation with surrounding inflammatory infiltrates, and malformed vessels including arteries and capillaries but without portal veins [14]. The large vessels have irregular fibrous thickening of the intima with focal thinning of the media. The central fibrous region has radiating branches composed of portal tract-like structures that contain an artery unaccompanied by portal veins or ducts [12,18] and which divides the tumor into several nodules [12,14]. A lymphocytic or mixed inflammatory infiltrate is frequent in fibrous regions. At the interface between fibrous regions and the nodules, there are often features of stasis of cholate that include feathery degeneration of hepatocytes, Mallory-Denk bodies, and a ductular reaction that may be highlighted with CK7 and CK19 immunostaining. Sinusoids adjacent to arterial sources are lined by CD34-positive endothelium [18].

According to some previously published surgical series, the presence of fibrous bands, presence of abnormal vessels, presence of reactive ducts (mild-marked) and nodularity have been considered as the main histopathological characteristics of this lesion [18].

Cases of atypical FNH are considered incomplete or early forms that may lack a central scar, incomplete multinodular organization or absence of nodules and sometimes exhibit more or less prominent regions of congestion [18].

Considering the presence of fibrous bands as one of the main diagnostic features of FNH, Masson's trichrome staining plays an important role in its diagnosis. The stain imparts a blue color to collagen against a red background of hepatocytes and other structures. It stains type 1 collagen that is normally present in the portal tracts and vessel walls, but also highlights the presence and distribution of reactive fibrosis as a result of liver injury; in addition, helps to delineate patterns of injury, such as perisinusoidal fibrosis and periductal fibrosis [19].

Although in most cases, a biopsy with standard and/or immunohistochemical stains may be sufficient to make the diagnosis of FNH [18], in the presence of non-conclusive liver histology and in the absence of accepted FNH diagnostic guidelines, it has been proposed multiple diagnostic algorithms for the study of these lesions in liver biopsies, with emphasis on the diagnosis and classification of HCA.

Molecular analysis of the FNH lesions allowed the identification upregulation of extracellular matrix genes associated with activation of the signaling pathway of the transforming growth factor beta (TGF- β) signaling pathway and overexpression of Wnt/β-catenin target genes, including GLUL, coding for glutamine synthase. Such β -catenin activation without β -catenin activating mutations results in a typical map-like pattern of glutamine synthase (GS) overexpression in the periphery of the nodules, close to the vessels. This map-like pattern of GS expression is specific to FNH; what makes GC staining a very useful resource that is frequently used to facilitate anatomopathological diagnosis in difficult cases, so it is not always mandatory to perform it [18,20].

The evidence base for the management of FNH is weak due to the absence of multicenter randomized clinical trials comparing operative with conservative management

strategies [21]. Even today, the treatment remains controversial, in fact, much of the debate focuses on the diagnosis "indeterminate lesion" that frequently describes the lesion preoperatively diagnosed [11].

In patients whom the diagnosis is uncertain, therapeutic options include resection, biopsy with histological analysis and conservative management with repeated images [11]; on the other hand, it is suggested that, in the face of diagnostic uncertainty, and especially in those patients with a history of cancer, they should be treated surgically even in the presence of small lesions (<3 cm) [21].

In general, it is accepted that small and asymptomatic FNH, without tendency to enlargement, should be managed conservatively [21]. Some studies suggest that the majority of FNH lesions managed conservatively remain stable after diagnosis and a proportion even presents a regressive character over time [11].

In patients with symptomatic FNH [11,21], or in the presence of a marked increase in tumor size (>3-4 cm, or 0.5 cm, per year) during follow-up, they are indications for surgical treatment21. Several studies have reported that surgical resection is an effective treatment that provides favorable levels of patient satisfaction and a low incidence of symptom recurrence. However, some studies have found that up to 80% of symptomatic cases get to experience resolution of symptoms with conservative treatment. Hepatic resection for benign pathology is associated with acceptably low incidence of morbidity and mortality. The levels of morbidity observed are also acceptable and compare favorably with those observed after resections for malignant disease [11].

In the era of laparoscopic liver surgery, which offers possible postoperative and operative benefits, the optimal treatment of FNH treatment could be reconsidered in favor of elective minimally invasive surgery, although these benefits should still be investigated in large prospective randomized studies [21].

4. CONCLUSION

Focal nodular hyperplasia is a benign liver lesion. At present, the evidence base for the management of HNF is weak. Some authors suggest a multicenter randomized study in symptomatic patients comparing both surgical treatment and conservative treatment that provides level I evidence for the management of these lesions. In the clinical setting of an urgent surgical approach and in the face of diagnostic uncertainty, the histopathological study is very useful in the diagnosis of FNH.

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