HEPATOCELLULAR CARCINOMA MIMICKING FOCAL NODULAR HYPERPLASIA: A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Focal nodular hyperplasia (FNH) is the second most common benign hepatic lesion, characterized by a central fibrous scar with radiating septa. It is typically asymptomatic and often discovered incidentally. Several reports in the literature have described misdiagnoses of FNH as fibrolamellar variant of hepatocellular carcinoma (HCC), and rare cases of HCC arising in the background of FNH have also been documented.

We report the case of a 64-year-old male patient accidentally found to have hepatitis B and a left hepatic mass measuring 88 mm which was done core biopsy showing FNH while contrast-enhanced computed tomography favored a diagnosis of HCC over FNH. A resection of hepatic segments III and IV was performed, along with cholecystectomy. Postoperative histopathological examination demonstrated moderately differentiated HCC.

Keywords: Focal nodular hyperplasia, Hepatocellular carcinoma.

I. INTRODUCTION

Focal nodular hyperplasia (FNH) accounts for approximately 8% of all primary liver tumors and is the second most common benign hepatic lesion after hemangioma. It is more frequently observed in women (80–95% of cases), typically between 30 and 40 years of age. FNH is considered a hyperplastic response to increased local blood flow rather than a true neoplastic process. Various vascular abnormalities, including capillary telangiectasia, arteriovenous malformations, and anomalous venous drainage, are thought to be associated with its development.[1]

Histopathologically, FNH is characterized by hyperplasia of hepatocytes with normal morphology. A central fibrous scar with radiating fibrous septa is typically present, containing large, anomalous feeding arteries and their branches. Ductular proliferation is a characteristic feature along the fibrous septa.[2] The central fibrous area consists of dense connective tissue with numerous thick-walled abnormal arteries. Ductular proliferation is accompanied by inflammatory cell infiltrates within and at the periphery of the fibrous septa. Kupffer cells are also present within FNH lesions.[1]

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Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver. Although FNH is generally considered a benign lesion with no malignant potential, rare cases of HCC arising in association with FNH have been reported in the literature. Differentiating between FNH and HCC (particularly in atypical cases or when HCC develops within FNH) with risks of sampling error in needle biopsies can pose a significant diagnostic challenge. This discrepancy underscores the critical importance of accurately distinguishing between benign and malignant hepatic lesions in order to develop an optimal treatment strategy for the patient. Authors report a case of HCC mimicking FNH and provide a brief review of the literature, highlighting the clinical and pathological characteristics of this entity.

2. CASE PRESENTATION

A 64-year-old male with a history of hypertension under medical management was found to have a liver mass 2 months before admission. A liver biopsy performed at a provincial hospital revealed histopathological findings consistent with FNH, characterized by trabecular structures composed of 1–2 layers of hepatocytes interspersed with thin-walled sinusoidal spaces. Tumor cells exhibited small, uniform nuclei with mild hyperchromasia, inconspicuous or absent nucleoli, and clear to eosinophilic cytoplasm, with focal fatty change.

The patient was admitted with right upper quadrant abdominal pain, without fever, jaundice, or weight loss. On physical examination, the patient had a moderate general condition (BMI: 19.84 kg/m^2), heart rate of 80 beats per minute, and blood pressure of 120/70 mmHg. No peripheral lymphadenopathy was detected. The abdomen was soft and non-distended, with no palpable masses; the liver and spleen were not enlarged.

Contrast-enhanced computed tomography (CT) of the abdomen revealed a hypodense lesion involving segments III and IV of the liver, measuring 65 × 88 mm, with pathognomic features. Internal fibrous bands were noted. The lesion demonstrated intense arterial enhancement followed by washout, favoring a diagnosis of hepatocellular carcinoma over FNH.

Serum tumor marker alpha-fetoprotein (AFP) was within the normal range (2.84 ng/mL). The patient tested positive for HBsAg. Other laboratory investigations, including complete blood count, coagulation profile, biochemistry, microbiology, and immunological tests, were within normal limits.

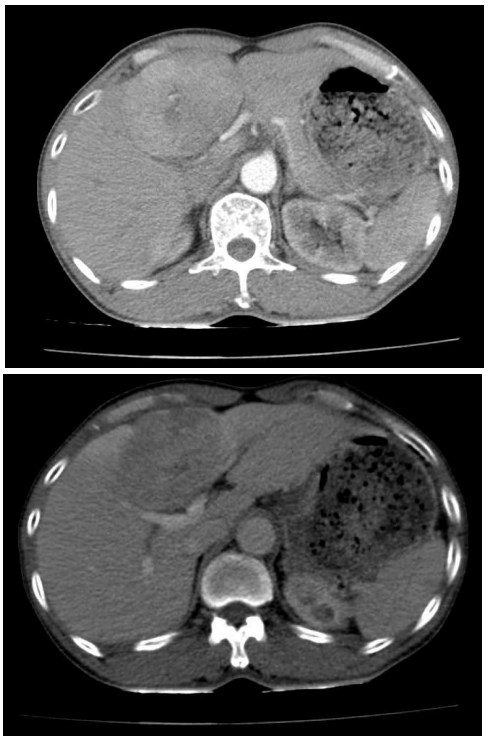

Figure 1. CT scan: Subsegmental mass III and IV measuring 65 × 88 mm, showing arterial phase enhancement and venous washout, with well-defined margins and a distinct capsule, indicative of HCC lesion.

The patient was initially diagnosed with focal nodular hyperplasia (FNH) involving hepatic segments III and IV and underwent surgery on February 7, 2025. Intraoperative exploration revealed a dry abdominal cavity, smooth peritoneal surfaces, and a non-cirrhotic liver. A multilobulated mass measuring approximately 8 cm in diameter was identified in segment IV and partially in segment III, protruding from the liver parenchyma.

A resection of hepatic segments III and IV was performed, along with cholecystectomy. Postoperative histopathological examination demonstrated a tumor composed of maligant hepatocytes with increased nuclear-to-cytoplasmic ratio, pleomorphic nuclei, prominent nucleoli, and occasional mitotic figures. The tumor cells were arranged in trabecular, nested, and pseudoglandular patterns. The tumor was divided into small lobules separated by thick fibrous septa. No vascular invasion was identified. The final diagnosis was moderately differentiated hepatocellular carcinoma (HCC).

The postoperative course was uneventful, and the patient was discharged after 10 days with a final diagnosis of HCC involving segments III and IV. At the 1-month postoperative follow-up, no abnormalities were detected.

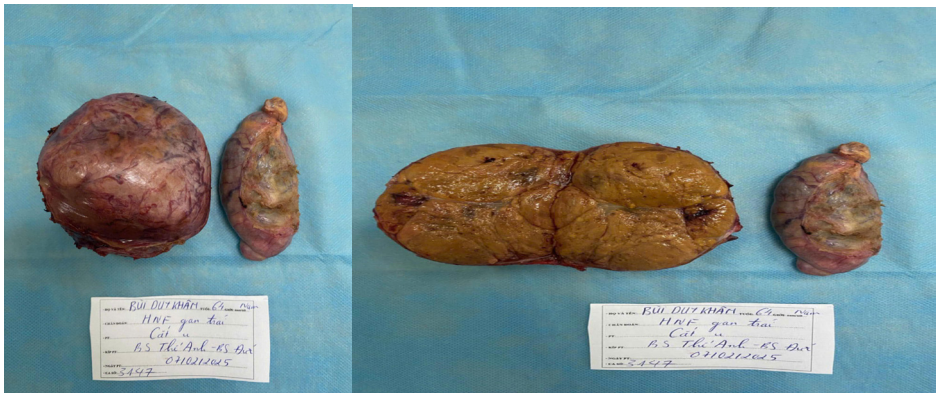

Figure 2a, b. Gross (macroscopic) appearance of the resected lesion.

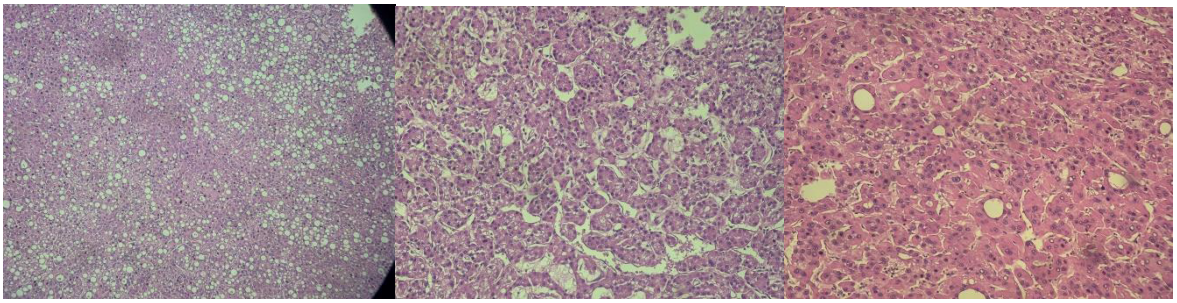

Figure 3a, b, c. Histopathological features of the resected lesion.

3. DISCUSSION

Our case study describes a 64-year-old male who was initially diagnosed with focal nodular hyperplasia (FNH) based on preoperative biopsy; however, postoperative histopathological examination revealed hepatocellular carcinoma (HCC). This discrepancy underscores the critical

importance of accurately distinguishing between benign and malignant hepatic lesions in order to develop an optimal treatment strategy for the patient.

3.1. Differentiation of lesions using imaging diagnostics

Abdominal CT scans revealed a lesion with arterial phase hyperenhancement and venous phase washout, imaging features that are more suggestive of hepatocellular carcinoma (HCC) than focal nodular hyperplasia (FNH). The radiological-pathological discordance between imaging findings and the initial biopsy result raised concerns about a sampling error regarding the limitation of initial 1-2 layers hepatocyte biospy in a huge mass, and consequently led to the indication for surgery. This case highlights the critical role of imaging in differentiating hepatic lesions with similar clinical and histological characteristics.

On non-contrast CT, FNH typically appears hypoattenuating or isoattenuating relative to the surrounding liver parenchyma; however, it may appear hyperattenuating in the setting of hepatic steatosis. A central scar, a characteristic feature, is observed in approximately 60% of lesions larger than 3 cm, although its absence may complicate the diagnosis. During the arterial phase, FNH typically demonstrates intense and homogeneous enhancement, occasionally with prominent central feeding arteries. In the portal venous phase, the lesion becomes slightly hyperattenuating or isoattenuating relative to the liver, making detection more challenging; the central scar remains hypoattenuating and may demonstrate delayed enhancement in approximately 80% of cases.

However, atypical imaging features of FNH are relatively common, occurring in 10–50% of cases, including the presence of a pseudocapsule due to compression of adjacent liver parenchyma—a feature also frequently observed in HCC.[2] A study by Kitao A et al. demonstrated that arterial phase hyperenhancement with early washout on CT, combined with a low apparent diffusion coefficient (ADC) on MRI, are important factors in differentiating HCC from FNH.[3] The degree of arterial enhancement on CT is generally higher in FNH than in HCC, reflecting differences in pathophysiology: HCC arises from neoangiogenesis driven by hypoxia, whereas FNH results from localized vascular hyperplasia and increased blood flow.[3]

Venous drainage patterns also play an important role in differentiation. FNH typically drains via small hepatic veins associated with the central scar, whereas HCC tends to compress and obliterate hepatic veins, resulting in predominant drainage through the portal venous system. The classic CT imaging feature of HCC is arterial phase hyperenhancement with washout in the delayed phase, observed in up to 96% of lesions exhibiting T1 hyperintensity on MRI. In contrast, FNH demonstrates arterial phase hyperenhancement without delayed washout in approximately 78% of cases, consistent with previous reports.[3]

On magnetic resonance imaging (MRI), FNH typically appears iso- to mildly hypointense on T1-weighted sequences and iso- to mildly hyperintense on T2-weighted sequences. The central scar is hypointense on T1-weighted images and hyperintense on T2-weighted images. Following gadolinium administration, FNH demonstrates strong arterial phase enhancement, and the central scar may exhibit delayed enhancement. When hepatocyte-specific contrast agents such as gadoxetate disodium (Eovist/ Primovist) are used, FNH typically shows uptake and retention in the hepatobiliary phase, appearing iso- or slightly hyperintense relative to the surrounding liver parenchyma, while the central scar remains hypointense in this phase.

Typical HCC appears iso- to mildly hypointense on T1-weighted imaging and moderately hyperintense on T2-weighted imaging, although these features may vary depending on histological components such as fat, necrosis, or hemorrhage. In the hepatobiliary phase, HCC typically appears hypointense relative to the surrounding liver due to reduced uptake of contrast agents.

Contrast-enhanced ultrasound (CEUS) and microvascular imaging techniques have also been applied in differentiating atypical HCC from FNH. Although FNH may demonstrate rapid arterial enhancement similar to HCC, microvascular imaging can help identify distinguishing features such as a spoke-wheel arterial pattern in FNH and disorganized vascular architecture in HCC.

Table 1: Comparison of imaging characteristics of FNH and HCC

Imaging Characteristics		FNH	HCC
Computed tomography (CT)	Central scar	Commonly present	Usually absent
	Arterial phase enhancement	Intense and homogeneous	Intense, may be heterogeneous
	Venous phase washout	Typically absent	Typically present
	Capsule	Usually absent; may have a pseudocapsule (atypical)	Usually present
Magnetic resonance imaging (MRI)	Hepatobiliary phase enhancement	Isointense or slightly hyperintense	Hypointense
	T1-weighted signal	Isointense to mildly hypointense	Variable
	T2-weighted signal	Isointense to mildly hypointense	Variable
	Capsule	Usually absent; may have a pseudocapsule (atypical)	Usually present
Contrast-enhanced ultrasound (CEUS)	Spoke-wheel vascular pattern	Commonly present	Typically absent

3.2. Role of Histopathology in Diagnosis

Although the initial biopsy suggested focal nodular hyperplasia (FNH), the imaging findings on contrast-enhanced computed tomography (CT) were not consistent with this diagnosis. This discordance highlights the inherent limitations of needle biopsy in the evaluation of focal liver lesions. Some tumors may exhibit mixed histological features, and although rare, the development of hepatocellular carcinoma (HCC) within the background of FNH has been reported in the literature.[4] In the present case, the large tumor size (8 cm) raises the possibility that the initial biopsy sampled a region with histopathological features consistent with FNH, while other areas harbored HCC.

Histologically, FNH is characterized by a nodular architecture composed of benign hepatocytes arranged in trabeculae one to two cells thick. Abnormally thick-walled arteries are typically

present within the central scar. Ductular reaction can be highlighted by immunohistochemical staining for cytokeratin 7 (CK7) and cytokeratin 19 (CK19) at the interface between fibrous septa and hepatocellular nodules. Although the central fibrous area may contain radiating fibrous septa resembling portal tracts, true portal tracts are absent. Inflammatory infiltrates, either lymphocytic or mixed, may be observed. Immunohistochemical staining for glutamine synthetase (GS) demonstrates broad, interconnected bands of hepatocytes forming a characteristic "map-like" pattern.[5]

HCC can be distinguished from FNH by the presence of cytological atypia, thickened trabeculae (>2 cells thick), and loss of the reticulin framework. Diffuse GS staining observed in HCC may occasionally be mistaken for the map-like pattern seen in FNH, particularly in needle biopsy specimens. Fibrolamellar hepatocellular carcinoma (FL-HCC) is characterized by large polygonal tumor cells with abundant eosinophilic cytoplasm, prominent nuclei, and dense lamellar fibrosis, and is associated with the DnaJ homolog subfamily B member 1 (DNAJB1) gene fusion.[5]

Table 2: Key histopathological characteristics to differentiate FNH from HCC

Histopathological characteristics	FNH	HCC
Hepatocyte arrangement	Nodular; trabeculae 1-2 cells thick	Variable; typically trabeculae >2 cells thick
Cytological atypia	Absent	Present, variable degree
Reticulin framework	Preserved	Reduced or lost
Bile ductules	Proliferation within fibrous septa	May be present or absent
Central scar	Present, containing abnormal vessels	Usually absent
Vascular invasion	Absent	May be present
Glutamine Synthetase (GS) staining patterns	"Map-like" pattern	Typically diffuse staining or negative

3.3. Role of Alpha-Fetoprotein (AFP)

The patient's alpha-fetoprotein (AFP) level was 2.84 ng/mL, which is within the normal range. AFP is a commonly used biomarker for the diagnosis and monitoring of hepatocellular carcinoma (HCC). However, this case highlights the limitations of relying on AFP to exclude HCC.

In previously reported cases of HCC arising in focal nodular hyperplasia (FNH), tumor markers, including AFP, have remained within normal limits.[4] This suggests that HCC—even in tumors of considerable size, as in our case—may present with normal AFP levels. Serum AFP remains the most widely used biomarker for HCC screening, early detection, treatment response assessment, and prognostication. Nevertheless, not all HCCs secrete AFP, and elevated AFP levels may also be observed in patients with cirrhosis or hepatitis.

A systematic review reported a sensitivity of 41–65% and a specificity of 80–94% for AFP at a diagnostic cutoff of ≥20 ng/mL for HCC. A large multicenter study demonstrated an AFP positivity rate (cutoff >11 ng/mL) of 46% across all HCC cases and 23.4% in tumors smaller than 2 cm.

Another large multicenter analysis showed that AFP levels <20 ng/mL were observed in 52% of patients with tumors smaller than 3 cm, 53.5% of patients with stage I disease (TNM classification), 48% of those with Okuda stage I, and even among patients with advanced disease (41.5% in TNM stage IV and 28% in Okuda stage III). These findings indicate that nearly half of HCC patients may have AFP-negative disease, particularly in early-stage tumors and small lesions.[6]

3.4. Association between Hepatitis B Virus Infection and HCC

Hepatitis B virus (HBV) infection is a major risk factor for the development of hepatocellular carcinoma (HCC), particularly in Southeast Asia, where HBV prevalence remains high. A 2023 meta-analysis reported an HCC prevalence of up to 45.8% among HBV-infected individuals in Southeast Asia, with a rate of 22.4% in Vietnam.[7] Several studies have demonstrated that patients with high HBV viral load remain at increased risk of developing HCC, even in the inactive phase of infection (HBeAg-negative).[8]

In the present case, in addition to the typical imaging features of HCC on contrast-enhanced computed tomography (CT), the presence of positive hepatitis B surface antigen (HBsAg) further supported our decision to proceed with surgical resection.

3.5. Literature Review

A previously reported case described HCC arising in the background of FNH in an 86-year-old woman. In that case, imaging findings on abdominal CT were typical of HCC, tumor markers were not elevated, and preoperative biopsy suggested HCC. However, the initial postoperative histopathological diagnosis was FNH. Subsequent additional sampling revealed two nodules with marked cytological atypia, thickened trabeculae, and loss of the reticulin framework, leading to a final diagnosis of HCC.[4] This case raises the possibility that HCC may arise within or adjacent to areas resembling FNH, emphasizing the importance of adequate and representative tissue sampling.

Another report described a patient with multiple hepatic nodules, in whom biopsy revealed HCC in one region of the liver and FNH in another.[9] It is also important to note that FNH may be misdiagnosed as HCC. One case described a 48-year-old woman initially diagnosed with well-differentiated HCC based on CT imaging and biopsy; however, postoperative histopathology confirmed benign FNH.[10]

The discrepancy between the initial histopathological findings and CT imaging in this case highlights the need for a multidisciplinary approach involving clinicians, radiologists, and pathologists in the diagnosis and management of hepatic tumors. International guidelines for HCC management also emphasize the importance of multidisciplinary evaluation.

4. CONCLUSION

HCC mimicking FNH is a rare clinical entity. The diagnosis of HCC may be missed due to limitations of needle biopsy, atypical imaging enhancement patterns, and non-elevated tumor markers. Therefore, a multidisciplinary approach is essential to improve diagnostic accuracy and to guide appropriate treatment strategies for patients.

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