Focal nodular hyperplasia misdiagnosed as hepatocellular carcinoma: a case report and literature review

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Abstract: Focal nodular hyperplasia (FNH) is a rare benign disease. Imaging and liver biopsy have only limited ability to distinguish it from malignant liver tumor. And preoperative diagnosis is difficult, and sometimes impossible, especially for atypical or multiple lesions. Here, we report the first case who underwent surgery for benign FNH that mimicked hepatocellular carcinoma preoperatively by both imaging and needle biopsy. A 48-year-old woman was admitted to our Department of Gastroenterology for a malignant hepatic tumor in the left lobe of the liver, 13 cm in diameter, diagnosed by computed tomography (CT) and pathological examination of a biopsy specimen. One week after diagnosis, the patient was readmitted to our Department of Hepatobiliary Surgery. The left lobe of the liver was resected. Histopathological examination using hematoxylin-eosin staining and immunohistochemical examination showed that the hepatic tumor was benign FNH. Although imaging modalities have important advantages in the diagnosis of benign and malignant tumors of the liver, and liver biopsy is the gold standard for diagnosis of liver diseases, a definitive diagnostic method for hepatic tumors remains to be established, especially when the tumor is large. Although appropriate management is controversial, a lesion strongly suspected of being a malignant tumor may experience rupture and hemorrhage and require surgical resection.

Keywords: Focal nodular hyperplasia (FNH); hepatocellular carcinoma (HCC); liver resection; histopathological examination; misdiagnosed; case report

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Introduction

Focal nodular hyperplasia (FNH) is a rare benign disease of the liver and the second most common benign lesion in healthy, young and middle-aged women (1-4). The pathogenesis of this disease is unclear (5,6). Most researchers think that it is a reactive process of the liver to vascular damage or deformity. The typical feature is that a large artery in the central fibrous scar is present, but the portal vein structure is absent (7). As FNH is rare and has atypical presentation, it is easily misdiagnosed as HCC or hepatic adenoma on imaging or in clinical practice and pathology because both types of lesions show arterial-phase enhancement. Although imaging modalities have important advantages in the diagnosis of benign and malignant tumors of the liver, and liver biopsy is the gold standard for diagnosis of liver diseases, a definitive diagnostic method for hepatic tumors remains to be established, especially when the tumor is large or with multiple lesions (8). Complications such as rupture and bleeding are extremely rare. It has been previously reported that atypical FNH presenting as acute abdomen and misdiagnosed as HCC...
caused by tumor spontaneous rupture and hemorrhage (9). Here, we report a patient with FNH that was misdiagnosed as HCC and hepatic peliosis, respectively, by imaging modalities and liver biopsy. We present the following article in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/dmr-20-157).

**Case presentation**

**Chief complaints**

A 48-year-old woman was admitted to our Department of Gastroenterology because of intermittent upper abdominal discomfort for >1 year on July 25, 2016. The patient presented with a feeling of distension, no obvious abdominal pain, nausea and vomiting, accompanied by yellowing of the skin and sclera. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

**History of present illness**

Her medical history included intermittent use of oral contraceptives for the past 20 years (dose was unknown). She denied a history of hypertension, diabetes, coronary heart disease, hepatitis or tuberculosis, residence of pastoral area, surgery or trauma. She also denied a family history of cancer. Her hemodynamic status on admission was stable. There was no relevant interventions treatment in the past.

**Physical examination**

No obvious abnormality was found in the heart and lungs; the upper abdomen was full; no gastrointestinal peristalsis waves were found; the abdomen was soft, without tenderness and rebound pain; Visible mass is palpable in the upper abdomen; the boundary at 5 cm below the liver costal margin and 7 cm below the xiphoid process was not clear; no percussion pain in the liver and kidney regions; negative shifting dullness; bowel sounds 4 times/min.

**Laboratory examination**

Liver function, routine blood tests, blood coagulation index and tumor markers were nearly normal. Liver function: aspartate transaminase 23 U/L, alanine aminotransferase 20 U/L, alkaline phosphatase 123 U/L, albumin 43.4 g/L, total bilirubin 11.4 μmol/L, direct bilirubin 3.7 μmol/L, cholinesterase 5,405 U/L, γ-glutamyl transferase 136 U/L, prothrombin time 10.3 s, activated partial thromboplastin time 22.9 s, fibrinogen degradation products 5.8 μg/mL, D-dimer 2.444 μg/mL. Routine blood tests: white blood cells 6.39×10⁹/L, blood platelets 229×10⁹/L, red blood cells 3.9×10¹²/L, hemoglobin 125 g/L. Tumors markers: carcinoembryonic antigen: 1.16 ng/mL, α-fetoprotein 1.52 ng/mL, carbohydrate antigen 19-9 32.84 U/mL, carbohydrate antigen 125 21.13 U/mL. Hepatitis virus antibodies were all negative.

**Imaging examination**

Dynamic abdominal computed tomography (CT) revealed a 13.8 cm × 13.3 cm × 9.8 cm mass of irregular patchy low density with fuzzy boundaries that originated from the lateral segment of the liver left lobe. Other multiple spots of calcareous density were seen in the mass. The tumor exhibited inhomogeneous enhancement; contrast agent in the portal venous phase and delayed phase did not obviously subside; and adjacent stomach, pancreas, and hepatic arteries were compressed by the tumor. The tumor contained a low-density area that was considered to be hepatic cystadenoma and cholangiocarcinoma, which should to be excluded by needle biopsy (Figure 1A,B,C).

**Further diagnostic work-up**

The patient underwent a percutaneous liver biopsy on July 28, 2016. Pathological examination of biopsied liver tissue showed necrosis of liver cells and the cytoplasm was loose and turbid, and some of the liver cells had dysplasia. The local histological features could not rule out the possibility of canceration of a few liver cells (well-differentiated HCC) (Figure 1D,E).

**Final diagnosis**

The patient was diagnosed with HCC and transferred to our Department of General Surgery.

**Treatment and outcome**

The patient underwent resection of the left lobe of the liver under general anesthesia on August 9, 2016. Normal
liver size and moderate proportions were found during the operation. The texture was fragile and soft, showing fatty-liver-like changes. Cystic lesions of about 14 cm × 13 cm were seen in the left lobe of the liver, including convex growth, compression of the lesser curvature of the stomach, no invasion and adhesion between the mass and the stomach, irregular septation-like changes on the surface of the mass, the texture was still soft, and the connection with normal liver tissue was more obvious (Figure 1F,G). According to the results of preoperative pathological examination, the anterior approach was selected to perform partial hepatectomy of the left lobe. The operation was successful, and the patient recovered well after the operation.

**Postoperative pathological findings**

The left lobe of the liver tissue was 15 cm × 9.5 cm × 5.5 cm. There was a palpable, slightly hard, grey-white area, 8 cm × 4.5 cm × 2.5 cm, FNH of the liver with local hepatic steatosis and local hemorrhagic polarization, fibrous nodal tissue hyperplasia, hyaline degeneration and focal calcification, massive blood cavity formation in the liver parenchyma, and histological features suggesting hepatic purpura (Figure 1H,I). The pathological manifestations were complex, and the tumor had many pathological features of benign liver tumors. Therefore, we conducted a second pathological consultation in Xijing Hospital of our college. Adenomatous hyperplasia of the liver was observed that conformed to the diagnostic criteria for liver adenoma (Figure 2A,B,C). Immunochemistry showed staining of CD34 molecules (Figure 2D) that revealed vascularization of hepatic sinusoidal endothelial cells and reticular tissue (Figure 2E) with incomplete microstructure; therefore, its local pathological features also had the characteristics of hepatic purpura (Figure 2F). The histopathological features of most lesions were consistent with the appearance of FNH, and cytokeratin 7 staining demonstrated histological features of...
intrahepatic bile duct transition (Figure 2G,H,I) and a large number of areas of tissue necrosis (Figure 2G), crystalline components (Figure 2J,K) and calcification (Figure 2L). After discussion with a multidisciplinary team (MDT), the hepatic tumor was diagnosed as benign FNH. The patient was stable and has survived without symptoms and recurrence for 4 years.

**Discussion**

FNH is a nontumorous benign nodular disease of the liver and the second most common benign tumor in the liver (7,9-11). Although the disease is not limited by age and sex, it is more common in women aged 20–30 years. Most FNH patients have no clinical symptoms and are diagnosed by imaging and physical examination. Only a small number of patients have atypical clinical symptoms such as right upper abdominal pain, discomfort, nausea, vomiting and other gastrointestinal symptoms. The pathogenesis of this disease is unclear. Most researchers think it is a reactive process of the liver to vascular damage or deformity. The typical features are a large artery in the central fibrous scar and absence of portal vein structure (7).

We report this patient who was misdiagnosed due to preoperative needle biopsy pathology and imaging for the first time. Although imaging modalities have important advantages in the diagnosis of benign and malignant tumors of the liver, and liver biopsy is the gold standard for diagnosis of liver diseases, a definitive diagnostic method for hepatic tumors remains to be established, especially when the tumor is large or with multiple lesions. At the same time, we also emphasize the importance of MDT of difficult pathology. Therefore, I would like to thank the Department of Pathology of Xijing Hospital for its strong support to the pathological diagnosis of this patient. However, this report has many limitations. Firstly, due to full belief in pathological biopsy, no specific magnetic resonance imaging (MRI) was performed before surgery to further clarify the diagnosis. Secondly, we failed to take multiple points during the preoperative liver biopsy, leading
to misdiagnosis of pathology, especially for this larger and multiple lesions patient. Finally, for this patient, we did not have the awareness of the differential diagnosis of liver dysplasia nodules during the preoperative diagnosis.

Most liver tumors are malignant (12), especially in China, within the context of hepatitis and cirrhosis. The incidence rate of FNH is low and the clinical diagnosis is difficult, resulting in many clinicians lacking awareness of the disease and being prone to misdiagnosis or mistreatment. As in this patient, preoperative imaging and pathological biopsy suggested that the tumor was HCC, but the final pathological diagnosis was FNH.

Imaging is the most important diagnostic modality, such as color Doppler ultrasound, CT and MRI. Ultrasonography shows no specificity for FNH, and most lesions are hypoechoic. The contrast-enhanced ultrasonography findings of FNHs show a centrifugal spoke-wheel filling pattern in the arterial phase, followed by sustained homogeneous enhancement during the portal venous and late phases. A cinematic loop is recommended to check frame by frame for assessment of the filling pattern (13). Therefore, it is difficult to distinguish FNH from other liver diseases by ultrasonography.

CT of FNH shows localized lesion with low or equal density. Rapid enhancement in arterial lesions can be observed, while the portal delay phase often shows equal density. FNH tumors often show a typical central stellate scar or low density in the arterial phase. The typical central stellate scar shows low density in the dual phase and can strengthen in the delayed phase (14).

It is reported that the sensitivity of MRI for FNH diagnosis is 75% and the specificity is 98% (15,16). The typical performance of MRI is low signal on T1-weighted images, and equal signal or slightly higher signal on T2-weighted images. Contrast enhancement with specific particles, such as gadolinium and super-paramagnetic iron oxide, is helpful to improve the sensitivity and specificity of MRI in the diagnosis of FNH. In recent years, a number of hepatospecific MR contrast agents have become available, such as Gd-BOPTA, Gd-EOB-DTPA, and/or superparamagnetic iron oxide (SPIO)-enhanced MRI. MRI shows low signal intensity, atypical features for the hepatobiliary phase (17-21). Thus, MRI using a hepatospecific contrast agent may result in better depiction of FNH, but atypical features may complicate specific diagnosis (19,22).

Radionuclide scanning diagnosis of FNH depends on the uptake of radiolabeled sulfur colloids by Kupffer cells of the liver lesions. Normal or increased uptake of radiolabeled \(^{99m}\text{Tc}\)-sulfur colloids by the lesion contributes to the specific diagnosis of FNH. However, about 50% of the FNH lesions do not take up sulfur colloid, manifested as “cold area” (non-radioactive), so it is difficult to distinguish FNH from other liver parenchymal tumors by radionuclide surface scanning. Therefore, the correct diagnosis of FNH by radionuclide scanning must be combined with medical history and other imaging examinations (23).

The morphology of FNH may sometimes be a challenge for pathologists, particularly when these lesions show histological variations and overlapping features with HCC and other hepatocellular lesions, and particularly when small biopsy samples are evaluated (8,24). Percutaneous liver biopsy can be used in the diagnosis of uncertain liver lesions, when diagnosis by combined imaging examination is still difficult. If a single needle biopsy fails to make a definite diagnosis, it is feasible to perform multiple needle aspirations. However, this is controversial, and some researchers believe that needle biopsy often leads to misdiagnosis because of limited tissue sampling (25). At the same time, FNH is a hypervascularized lesion and is associated with an increased bleeding risk. If it is a malignant tumor, it may lead to metastasis along the needle tract, so it is rarely used clinically. Furthermore, tumor biopsy is associated with a low diagnostic sensitivity, with only 30–45% of all biopsies being consistent with the histology of surgical specimens (26).

FNH treatment depends on the correct diagnosis. Most of the lesions of FNH are small, slow growing, and have a low canceration rate for many years. Therefore, asymptomatic patients with imaging confirmation can be followed up every 6 months. Patients with nonsurgical treatment should be regularly followed up by B ultrasound and CT at least once a year. If the tumor continues to increase or spontaneous rupture and bleeding, it is recommended for surgical resection. If the mass is larger (>5 cm), combined with CT findings, the location of the tumor and distribution of blood flow should be considered comprehensively, and if necessary, transarterial chemoembolization (TACE) is feasible (27,28). Minimally invasive treatment with ethanol injection and radiofrequency ablation (RFA) is suitable for small tumor foci. Although appropriate management is controversial, a lesion strongly suspected of being a malignant tumor may experience rupture and hemorrhage and require surgical resection. However, if the diagnosis is clear, its application is questionable (26,29).

Many researchers believe that clinical symptoms are an
indication for surgery for FNH (30). Surgical resection is mostly recommended in patients with obvious clinical symptoms, undiagnosed nodules, and tumor diameter >5 cm. The lesions can be removed and pathological diagnosis can be made. Apart from surgical management of symptomatic FNH, percutaneous radiological modalities have to be considered and include TACE and RFA (26,31,32).

According to the pathological features, FNH can be divided into two types (33). Type 1: classical type, one of the most common, has the structure of regional central stellate fibers with abnormal arterial structure and absence of the portal vein in this area, which contains approximately normal hepatocytes and proliferating cholangial cells. Type 2, accounting for about 19.7%, encompasses cases in which the central region can be seen in the portal vein or the lack of certain structural features typical of FNH, and can be divided into three sub-types (33,34): vascular expansion, adenomatous hyperplasia and atypical large cell types. The clinicopathological features of FNH-like nodules support the hypothesis that vascular alterations in liver cirrhosis play an important role in their pathogenesis and that FNH-like nodules do not have an increased risk of malignant transformation (8). They are sometimes misdiagnosed as HCC on imaging because both types of lesions show arterial-phase atypical enhancement (8,34-36).

Conclusions

Spiral CT and MRI can diagnose FNH correctly in patients with typical features. Liver biopsy is one of the most important methods for definitive diagnosis, but because of limited material, sometimes it may result in misdiagnosis. We should make a reasonable choice in the treatment of FNH, that is, it is necessary to avoid delayed treatment because of missed diagnosis and misdiagnosis, especially for patients with malignant liver lesions or potential malignant risks, and to avoid unnecessary surgical treatment. This case report demonstrates that, despite improved diagnostic methods, there remain some hepatic lesions that cannot be reliably identified by imaging. For those uncertain diagnoses, especially in patients with suspected hepatocellular adenoma or a family history of malignant tumors, marked tumor enlargement and/or jaundice, bleeding and other complications, surgical resection should be considered. In case of symptomatic liver lesions, surgical resection should only be indicated in patients with tumor-specific symptoms (26,30,37). Liver resection is safe and effective for benign tumors if it is performed in specialized departments of hepatobiliary surgery. The benefit of surgery is significantly associated with preoperative symptoms of patients with FNH.

This case reports also demonstrates that although imaging modalities and liver biopsy have important advantages in the diagnosis of benign and malignant tumors of the liver, misdiagnosis or missed diagnosis would occur, and a definitive diagnostic method for hepatic tumors remains to be established, especially when the tumor is large or with multiple lesions. And surgical resection should only be indicated in patients with tumor-specific symptoms.

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Footnote

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/dmr-20-157). Both authors report National Natural Science Foundation of China (No. 81572916) Funding for this study.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

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