Case Series

Novel Strategy for Diagnosis of Focal Nodular Hyperplasia Using Gadolinium Ethoxybenzyl Diethylenetriaminepentaacetic Acid-Enhanced Magnetic Resonance Imaging and Magnetic Resonance Elastography

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Keywords

Gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid-enhanced magnetic resonance imaging · Magnetic resonance elastography · Focal nodular hyperplasia

Abstract

Focal nodular hyperplasia (FNH) is the second most frequent benign liver tumor, and it is a fiber-rich stiff lesion. Typically, FNH can be diagnosed by imaging without biopsy. However, liver biopsy and diagnostic resection may be required to differentiate atypical FNH from other liver tumors, such as hepatocellular adenoma (HCA). Therefore, improved noninvasive diagnostic methods are needed. We experienced 2 cases where combination of magnetic resonance elastography (MRE) and gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI) helped diagnose FNH. A 36-year-old woman and 17-year-old boy with liver tumors measuring 40 mm in diameter each showed hypointense nodule centers, indicating a central scar, surrounded by hyperintense signals during the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI. To rule out HCA, we performed MRE and liver biopsy. On MRE, the mean stiffness of the mass was 11.6 kPa (mean stiffness of the background liver was 1.7 kPa) and 11.1 kPa (mean stiffness of the background liver was 2.4 kPa) in the first and second patients, respectively. Histological examination of both specimens showed CK7-positive bile-ductular proliferations, abundant fibrous tissue, and few Ki-67-positive cells. Based on these results, we diagnosed these tumors as FNH. Combination of Gd-EOB-DTPA-enhanced MRI and MRE can evaluate the character and stiffness of lesion and help in the diagnosis of FNH.

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Introduction

Focal nodular hyperplasia (FNH) is a hyperplastic lesion seen in patients without chronic liver disease, and it accounts for approximately 8% of all liver neoplasms. It is the second most frequent benign liver tumor after hemangioma [1]. FNH is considered as a hyperplastic response of the hepatic parenchyma to abnormal blood flow [2]; however, it is not yet clear. FNH is macroscopically seen as a fiber-rich stiff lesion with a fibrous septum in the central lesion, called the central scar, and appearance of CK7-positive ductular cells. On computed tomography (CT), the lesion is seen as shows a hypervascular mass in the arterial phase, which is iso- or hypointense in the portal phase without wash out. On magnetic resonance imaging (MRI), FNH is iso- or hypointense on T1-weighted images and hyper- or isointense on T2-weighted images. Gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA)-enhanced MRI shows FNH as a hypervascular lesion in the arterial phase and hyperintense area in the hepatobiliary phase where some hypointense suspected scar area is detected [1, 3, 4].

Based on above features, typical FNH is diagnosed by imaging without biopsy, and the patient undergoes regular follow-up without treatment. In contrast, differentiation of atypical FNH from well-differentiated hepatocellular carcinoma (HCC) or hepatocellular adenoma (HCA) is difficult and may require liver biopsy or diagnostic resection; hence, improved noninvasive diagnosis methods are needed.

In this report, we present 2 cases where FNH was suspected based on contrast ultrasonography (US), contrast CT, and Gd-EOB-DTPA-enhanced MRI; it was recognized as a stiff mass on magnetic resonance elastography (MRE) and diagnosed as FNH following liver biopsy.

There are few reports in the literature which present the value of elastic parameters of FNH along with MRE and liver biopsy. We report these cases to discuss the potential diagnostic modalities to avoid unnecessary biopsies and resections.

Case Presentation

Case 1

A 36-year-old woman was referred to our hospital because of a liver tumor detected coincidentally on abdominal echography during her medical examination. No symptoms were evident. She was a social drinker and had no history of disease. Laboratory examinations showed no abnormal findings (including hepatitis B and C) or increased tumor markers.

US revealed a nodule measuring 40 mm in diameter with clear borders and slightly hyperechoic signals in segment 6 on B-mode imaging. The use of Sonazoid contrast agent revealed hypervascular nodules in the arterial phase; however, we could not recognize the defect in the Kupffer phase in most parts where the minor parts are detected as defect.

We performed Gd-EOB-DTPA-enhanced MRI, and on T1-weighted images, the nodule was hypointense, while on T2-weighted images, it showed a hyperintense center (Fig. 1a, b). A dynamic study with T1-weighted imaging showed a hypervascular lesion. In the hepatobiliary phase, the nodule center was hypointense indicating a central scar surrounded by hyperintense signals (Fig. 1c–e).

We performed MRE and liver biopsy to rule out HCA. The mean stiffness of the mass was 12.2 ± 0.5 kPa (mean stiffness of the background liver was 1.8 ± 0.3 kPa) on MRE (Fig. 1f). Histological examination of the specimens (Fig. 2a–f) showed that the background liver was normal (Fig. 2a–c); however, the tumor lesions included cytokeratin7 (CK7)-positive bile-ductular proliferation (Fig. 2e). Azan staining of the lesion showed the presence of abundant fibrous tissue (Fig. 2f). Moreover, the lesion contained a few Ki-67-positive cells which were

Fig. 1. Findings of the Gd-EOB-DTPA-enhanced MRI and MRE. **a–f** MRI findings of the tumor. T1-weighted image (**a**), T2-weighted image (**b**), arterial phase (**c**), late phase (**d**), hepatobiliary phase (**e**) of MRE shown (**f**). White arrowheads indicate the tumor. MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; Gd-EOB-DTPA, gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid.

similar to the background cells in the nontumor area. Based on these results, we diagnosed this tumor as FNH.

Case 2

A 17-year-old boy was referred to our hospital with a liver tumor that was detected coincidentally on US obtained for investigations for complaints of frequent urination. He had no history of disease. Laboratory examinations showed no abnormal findings (including hepatitis B and C) or increased tumor markers. US revealed a nodule measuring 55 mm in diameter with clear borders and hyperechoic signals in segment 6 on B-mode imaging. The use of Sonazoid contrast agent revealed hypervascular nodules in the arterial phase, and we could recognize the defect partially in the Kupffer phase. Dynamic CT revealed a hypervascular tumor without defect in the late phase with some areas suggestive of nonvascular central scar.

On Gd-EOB-DTPA-enhanced MRI, the nodule was hypointense on T1-weighted images with a hyperintense center on T2-weighted images (Fig. 3a, b). Dynamic study with T1-weighted imaging showed a hypervascular lesion. In the hepatobiliary phase, the nodule center was hypointense, indicating a central scar, surrounded by hyperintense signals (Fig. 3c–e). The mean stiffness of the mass was 11.1 ± 0.5 kPa (mean stiffness of the background liver was 2.4 ± 0.3 kPa) on MRE.

Histological examination of the specimens (Fig. 4a–f) showed that the background liver was normal (Fig. 4a–c). However, the tumor lesions included CK7-positive bile-ductular proliferation (Fig. 4e). Azan staining of the lesion showed the presence of abundant fibrous tissue (Fig. 4f). The lesion contained a few Ki-67-positive cells with similar background as the nontumor area. Based on these results, we diagnosed this tumor as FNH.

Fig. 2. Histological and immunohistochemical findings. **a–c** Hematoxylin and eosin staining, cytokeratin 7 (CK7) immunohistochemistry, Azan staining of the background of the liver. Hematoxylin and eosin staining, CK7 immunohistochemistry, Azan staining of the tumor (**d–f**); CK7 immunohistochemistry shows diffuse positivity in the lesion representing ductular proliferation (red flame shows the magnified view) (**e**); Azan staining demonstrates the presence of fibrous tissue throughout the lesion (red flame shows the magnified view) (**f**). Scale bar = 500 μ m (**a, d**), and 200 μ m (**b, c, e, f**).

Discussion

This report demonstrated the novel concept that stiffness on MRE improved the diagnostic ability of FNH, which is a fiber-rich stiff lesion. The benefit of Gd-EOB-DTPA-enhanced MRI in the diagnosis of HCC is widely accepted, and it is heavily used in the clinical setting. In addition, because MRE can evaluate the stiffness of the liver, which can estimate the collateral circulation and risk of cancer occurrence, the usefulness of MRI is increased.

The characteristic feature of FNH in MRI is that it is iso- or hypointense in T1WI, hyper- or isointense in T2WI, hyperintense in the arterial phase, and hyper- or isointense in the hepatobiliary phase [1, 3]. HCC (especially scirrhous type HCC), cholangiocarcinoma, and HCA are the differential diagnoses of FNH.

Scirrhous type HCC and cholangiocarcinoma are similar to FNH in terms of abundance of fibers, but different in terms of being clearly defective in the hepatobiliary phase. In contrast, HCA is similar to FNH in terms of being hypervascular but unlikely to be defective in the hepatobiliary phase, but different in terms of softness. Owing to the lack of fibers, HCA is not as stiff as FNH, and it is recognized as a soft lesion on MRE. Using this difference, we can differentiate HCA from FNH, despite it being atypical. Ultrasound elastography, which has become more popular in the recent years, also recognizes FNH as a stiffer mass than HCA, as in this case [5]. However, as mentioned above, MRE is more useful than ultrasound elastography because it can be used simultaneously for HCC screening and staging in Gd-EOB-DTPA-enhanced MRI.

Thus, the combination of Gd-EOB-DTPA-enhanced MRI, which is frequently used for screening, and MRE can be used not only to diagnose the morphology of the tumor based on

Fig. 3. Findings of the Gd-EOB-DTPA-enhanced MRI and MRE. **a–f** MRI findings of the tumor. T1-weighted image (**a**), T2-weighted image (**b**), arterial phase (**c**), late phase (**d**), hepatobiliary phase (**e**) of MRE data were shown (**f**). White arrowheads indicate the tumor. MRE, magnetic resonance elastography; Gd-EOB-DTPA, gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid; MRI, magnetic resonance imaging.

hemodynamics but also to analyze its stiffness. This report can improve the diagnostic ability and avoid unnecessary liver biopsy or short-term follow-up.

Statement of Ethics

This research was conducted in accordance with the World Medical Association Declaration of Helsinki and local guideline of Niigata University. Written informed consent was obtained from the patient (case 1) or the parent of the patient (case 2) for publication of the details of their medical case and any accompanying images. Written informed consent was obtained from the patient for publication and of this case report and any accompanying images. There is a local rule that says that if the case report contains <9 cases and study without intervention is not necessary to submit it to the ethical board.

Conflict of Interest Statement

The authors of this manuscript do not have any conflict of interest to declare.

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The authors declare that they have no current financial arrangement or affiliation with any organization that may have a direct influence on their work.

Fig. 4. Histological and immunohistochemical findings. **a–c** Hematoxylin and eosin staining, cytokeratin 7 (CK7) immunohistochemistry, Azan staining of the background of the liver. Hematoxylin and eosin staining, CK7 immunohistochemistry, Azan staining in the tumor (**d–f**); CK7 immunohistochemistry shows diffuse positivity in the lesion representing ductular proliferation (red flame shows the magnified view) (**e**); Azan staining demonstrates the presence of fibrous tissue throughout the lesion (red flame shows the magnified view) (**f**). Scale bar = 500 µm (**a, d**), and 200 µm (**b, c, e, f**).

Author Contributions

N.T., A.T., K.N., Y.I., Y.A., N.K., K.T., S.T., and K.H. collected the data and wrote the manuscript. M.T. and S.T. supervised this case report. All the authors approved the final version of the manuscript.

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