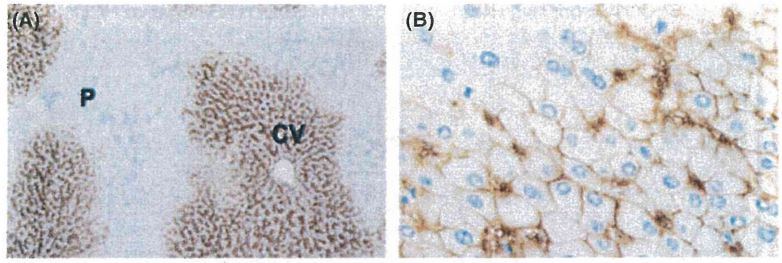

Fig. 3. SLCO1B3 expression in normal liver tissue. Normal liver tissue shows pericentral SLCO1B3 expression (A). A magnified view showing membranous expression of SLCO1B3 in normal hepatocytes (B). CV, central vein; P, portal tract.

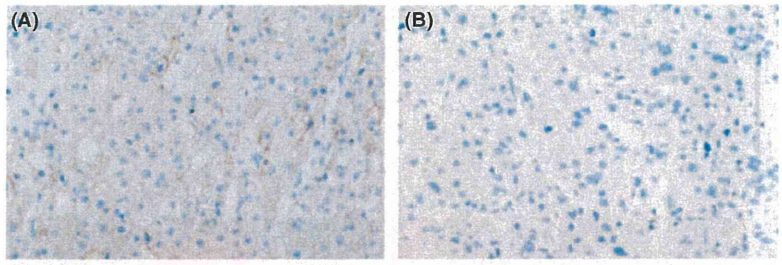

Fig. 4. MRP4 expression in hepatocellular carcinomas (HCC). Most tumor cells show membranous expression of MRP4 with some heterogeneity in this tumor (A), whereas the majority of HCC did not express immunohistochemically detectable levels of MRP4 (B).

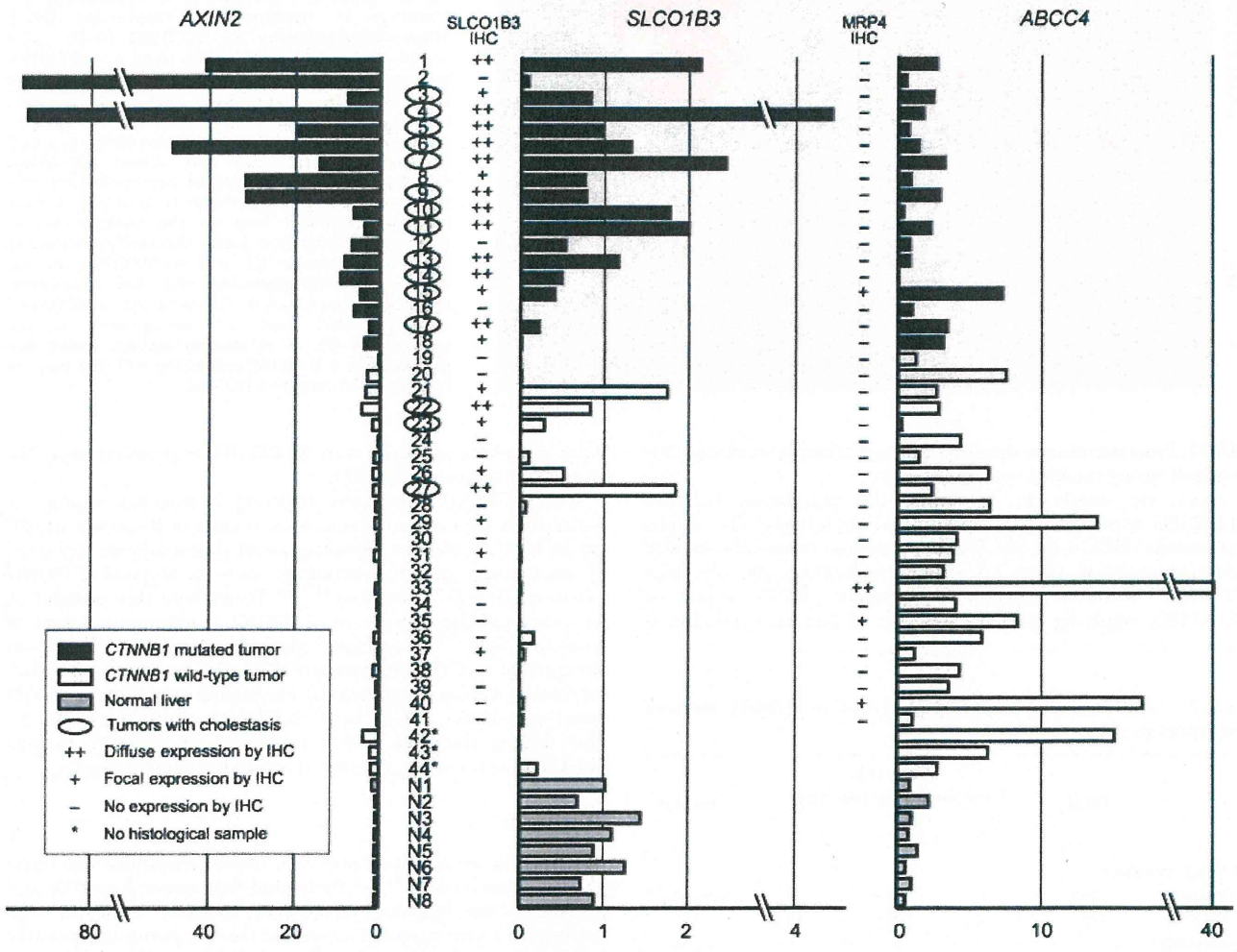

Fig. 5. Expressions of *SLCO1B3*, *ABCC4* and *AXIN2* mRNA, SLCO1B3 and MRP4 protein, *CTNNB1* mutation status and intratumoral cholestasis in each tumor sample. The expressions of *SLCO1B3*, *ABCC4* and *AXIN2* were determined using quantitative RT-PCR. SLCO1B3 and MRP4 expressions were determined using immunohistochemistry (IHC). The results of the *CTNNB1* mutation analysis and for intratumoral cholestasis were obtained in our previous study.[8] The case numbers are identical to those in our previous study.

CTNNB1 mutations and more closely with intratumoral cholestasis. SLCO1B3 is physiologically involved in the uptake of bile acids;[22–26] however, *CTNNB1*-mutated HCC did not exhibit elevated *NR0B2* levels, a hallmark of active bile acid signaling.[15,16] These findings suggest that the cholestatic appearance of HCC is not linked to an increase in bile acid synthesis or uptake.

The exact mechanism by which mutated β-catenin induces *SLCO1B3* remains elusive. While we performed *in vitro* studies using several HCC cell lines, the activation of β-catenin signaling did not induce *SLCO1B3* expression in any of the cell lines (data not shown). Furthermore, some of the HCC expressed high levels of *SLCO1B3* in the absence of *CTNNB1* mutations. These observations imply the presence of β-catenin-independent regulation of SLCO1B3 in some HCC.

MRP4 is a basolateral transporter involved in the efflux of bile acids, steroids and a range of xenobiotic substances.[27] *ABCC4*, encoding MRP4, was significantly upregulated in HCC with wild-type *CTNNB1*. However, the MRP4 protein was expressed at low levels in most of the HCC compared with prostatic tissue, where MRP4 is physiologically expressed. While a significant correlation was observed between *ABCC4* expression and *CTNNB1* mutation in HCC, the functional significance remains to be elucidated.

Bilirubin, the main bile pigment, is another important substrate of SLCO1B3. Previous *in vitro* experiments have shown that the introduction of SLCO1B3 into human cells or xenopus oocytes induced bilirubin uptake.[24,25] Furthermore, two genome-wide association studies identified genetic variations within *SLCO1B3* as being associated with serum bilirubin levels,[28,29] suggesting a physiological role in bilirubin clearance *in vivo*. As the green color of bile is caused by its bilirubin content, it is reasonable to assume that the cholestatic appearance of HCC mainly reflects their ability to uptake bilirubin. While some previous studies reported conflicting results on the correlation between intratumoral cholestasis and SLCO1B3 expression,[30–32] our data suggest that expression of SLCO1B3 is the major determinant of intratumoral cholestasis in HCC.

Eight cases of SLCO1B3-positive HCC without cholestasis were observed. In fact, SLCO1B3 is a bidirectional carrier, and the efflux of bilirubin is reduced by binding to glutathione S-transferase.[33] Furthermore, some transporters, such as MRP3, can export bilirubin. Thus, SLCO1B3 expression is a critical, but not the sole, determinant of bilirubin accumulation in cells. It is expected that some molecules involved in bilirubin transport, other than SLCO1B3, are expressed differently in SLCO1B3-positive HCC without cholestasis.

A number of chemotherapeutic and diagnostic agents, in addition to bile acids and bilirubin, are also known as substrates of SLCO1B3[26,34–36] For example, gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA), an increasingly used magnetic resonance imaging contrast agent, is also a substrate of SLCO1B3.[35] The majority of HCC are depicted as hypointense areas during the hepatobiliary phase of Gd-EOB-DTPA-enhanced magnetic resonance imaging as HCC generally have a decreased capacity to take up this contrast agent. However, a subset of HCC that express high levels of SLCO1B3 can be detected as iso- or hyperintense masses.[30–32] Considering these previous and current observations, a significant proportion of Gd-EOB-DTPA-accumulating HCC might harbor *CTNNB1* mutations. The present observations suggest that SLCO1B3 expression and the status of *CTNNB1* mutation might need to be considered in drug delivery to HCC.

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Disclosure Statement

The authors have no conflict of interest.

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CASE REPORT

Ring-like enhancement of focal nodular hyperplasia with hepatobiliary-phase Gd-EOB-DTPA-enhanced magnetic resonance imaging: radiological-pathological correlation

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Abstract
We report a case of focal nodular hyperplasia in a patient for whom gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI) and histological analysis results were available. Dynamic contrast-enhanced computed tomography showed a well-defined hypervascular lesion 14 mm in diameter with no visible central scars. Gd-EOB-DTPA-enhanced MRI demonstrated strong peripheral enhancement of the lesion during the hepatobiliary phase, resulting in ring-like enhancement. The pathology examination revealed that the lesion was focal nodular hyperplasia (FNH). Immunohistochemistry showed positive expression of OATP8 in the hepatocytes in the peripheral areas of the lesion, whereas expression of OATP8 was lacking in hepatocytes surrounding the central radiating scar. Ring-like enhancement during the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI may be an important clue for the diagnosis of small FNH.

Key words Focal nodular hyperplasia · MRI · Gd-EOB-DTPA · Organic anion transporter

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Introduction

Focal nodular hypoplasia (FNH) is a common benign lesion of the liver. Because FNH has no malignant potential, surgical intervention is not required when a diagnosis is made clinically. Radiographic imaging plays a central role in the diagnosis of FNH, and the characteristic radiological findings of FNH on computed tomography (CT) and magnetic resonance imaging (MRI) have been well documented.[1,2] However, the distinction of FNH from other hypervascular hepatic lesions is sometimes difficult, particularly in cases with atypical radiological findings or small lesions. Herein, we present a case with FNH that exhibited a peculiar radiographic finding during a Gd-EOB-DTPA-enhanced MRI examination, especially focusing on the spatial correlation between the areas of Gd-EOB-DTPA enhancement and the distribution of the expression of a hepatic uptake transporter, OATP8, in FNH.

Case report

A 36-year-old man with no remarkable past medical history was referred to our institution for further evaluation of a 14-mm focal nodular lesion in the liver. The

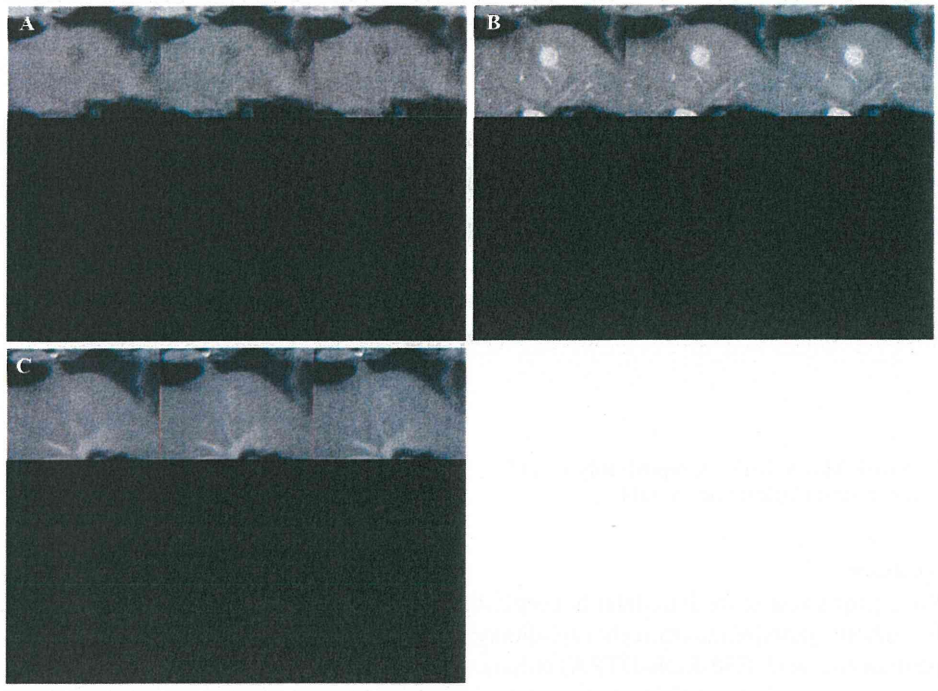

Fig. 1. Dynamic contrast-enhanced computed tomography (CT). **A** Unenhanced CT shows a slightly hypoattenuating hepatic nodule. **B** Lesion is strongly enhanced during the arterial phase of dynamic contrast-enhanced CT. **C** In the equilibrium phase, the lesion is almost isoattenuating relative to the surrounding liver without corona enhancement

lesion was incidentally found in segment 4 during an abdominal ultrasonography examination performed as part of a health checkup. His liver function was normal, and serological tests for hepatitis B and C were negative. Physicians at the previous hospital had considered the possibility of hepatocellular carcinoma (HCC) based on CT scans and MRI findings and had performed a needle biopsy. The pathological diagnosis of the biopsy specimen was suggestive of a well-differentiated HCC.

An unenhanced CT image showed a slightly hypoattenuating lesion relative to the surrounding liver (Fig. 1A). An arterial phase contrast-enhanced CT image demonstrated strong heterogeneous enhancement (Fig. 1B). An equilibrium phase contrast-enhanced CT examination showed that the lesion was almost isoattenuated relative to the surrounding liver (Fig. 1C). A central scar was not clearly seen in any phase of the CT scans.

The abdominal MRI scan was performed using a 1.5-T unit (Intera Achieva; Philips Medical Systems, Best, The Netherlands). The lesion was hypointense on T1-weighted images and inhomogeneously hyperintense on T2-weighted images (Fig. 2A,B). After the administration of Gd-EOB-DTPA (Primovist; Bayer HealthCare, Osaka, Japan), the lesion showed marked heterogeneous enhancement during the arterial phase, similar to the results obtained using dynamic contrast-enhanced CT (Fig. 2C). During the hepatobiliary phase, the lesion showed ring-like enhancement, with peripheral uptake of Gd-EOB-DTPA (Fig. 2D). Because the possibility of malignancy could not be excluded based on these radiological findings, the lesion was removed during a partial segmentectomy.

The pathological diagnosis of the surgically resected specimen was FNH. The lesion was well demarcated and had a central radial scar (Fig. 3A). The central scar was not well developed and consisted of thin, fibrous septa containing vessels and bile ducts. Immunohistochemistry for hepatocyte-specific antigen indicated that most areas of the FNH, except the thin, radial, fibrous septa, consisted of hepatocytes (Fig. 3B). The hepatocytes in the peripheral areas of the lesion exhibited strong OATP8 expression, whereas the hepatocytes in the central areas, surrounding the thin radial scars, were negative for it (Fig. 3C,D). In the liver tissue surrounding the lesion, OATP8 was expressed in the pericentral hepatocytes.

Discussion

The typical MRI findings for FNH are homogeneous isointensity or slight hypointensity on T1-weighted images and isointensity or slight hyperintensity on T2-weighted images.[1,2] The central scar appears as a hyperintense area on T2-weighted images.[1,2] Because the lesion in our case showed inhomogeneous hyperintensity without a central scar on T2-weighted images, these findings obtained using unenhanced MRI did not allow a

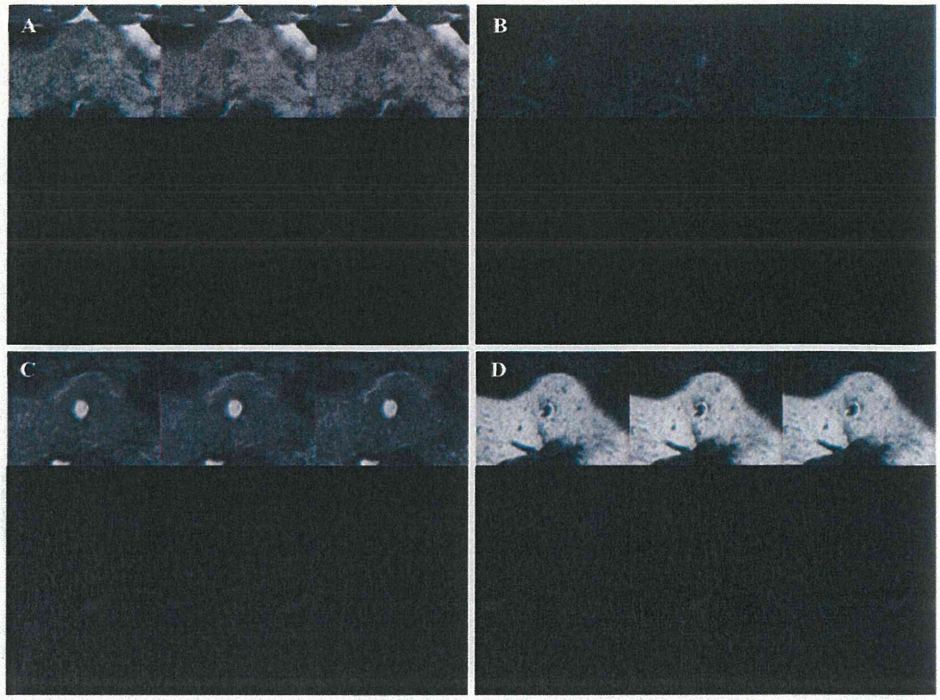

Fig. 2. Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI). **A** On unenhanced T1-weighted imaging (TR/TE 4.0/2.1), the nodular lesion appears as central hypointensity with peripheral isointensity. **B** T2-weighted MRI (TR/effective TE 2000/100) shows inhomogeneous signal intensity. **C** Arterial phase of Gd-EOB-DTPA-enhanced dynamic MRI (TR/TE 4.0/2.1) shows a well-demarcated, nearly homogeneously enhanced lesion. **D** During the hepatobiliary phase obtained 15 min after injection, the lesion exhibited ring-like enhancement, with strong enhancement of the peripheral portion that shows isointensity in **A**, the unenhanced T1-weighted image

definitive diagnosis of FNH. In some cases, particularly with small FNH (≤3 cm), the central scar may be extremely small or even undetectable on CT (61%–80%) and MRI (80%).[3]

Gd-EOB-DTPA, an increasingly used hepatobiliary-specific contrast agent for MRI, is actively taken up by hepatocytes and excreted into bile. Hepatobiliary-specific agents are particularly useful for determining whether a lesion is of hepatocellular origin.[3,4] The characterization of FNH provided by Gd-EOB-DTPA-enhanced MRI is superior to that provided by unenhanced MRI or dynamic CT.[5] FNH shows intense enhancement similar to that of other extracellular gadolinium-based contrast agents during the arterial phase after the bolus injection of Gd-EOB-DTPA.[4,5] In the hepatobiliary phase, enhancement is regularly seen (88%–90%) as hyperintense or isointense relative to the liver.[5]

Central scars appear as hypointense areas in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI.[4,6,7] On the other hand, central scars show delayed enhancement on MRI when using other extracellular fluid gadolinium-based contrast agents.[6,7] However, previous reports have not examined the precise radiological–pathological correlation; their observations were mainly based on comparisons of radiological findings using various modalities with different contrast materials. The present FNH lesion showed a central hypointense area with peripheral hyperintensity in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI. As mentioned above, however, the central scar in this case could not be detected on either CT or MRI. Indeed, the pathological features agreed with the findings of dynamic CT and unenhanced MRI; the central radial scar consisted of thin, fibrous septa and was not well developed. Taken together, the presence of the central scar does not explain the hypointense area that was observed in the center of this lesion during the hepatobiliary phase.

OATP8 is a member of the solute carrier organic anion transporter family and is specifically expressed at the basolateral membrane of hepatocytes. Expression of OATP8 is associated with uptake of Gd-EOB-DTPA in HCCs.[8,9] Interestingly, the present lesion exhibited strong expression of OATP8 in peripheral areas of the lesion, consistent with a previous report.[10]

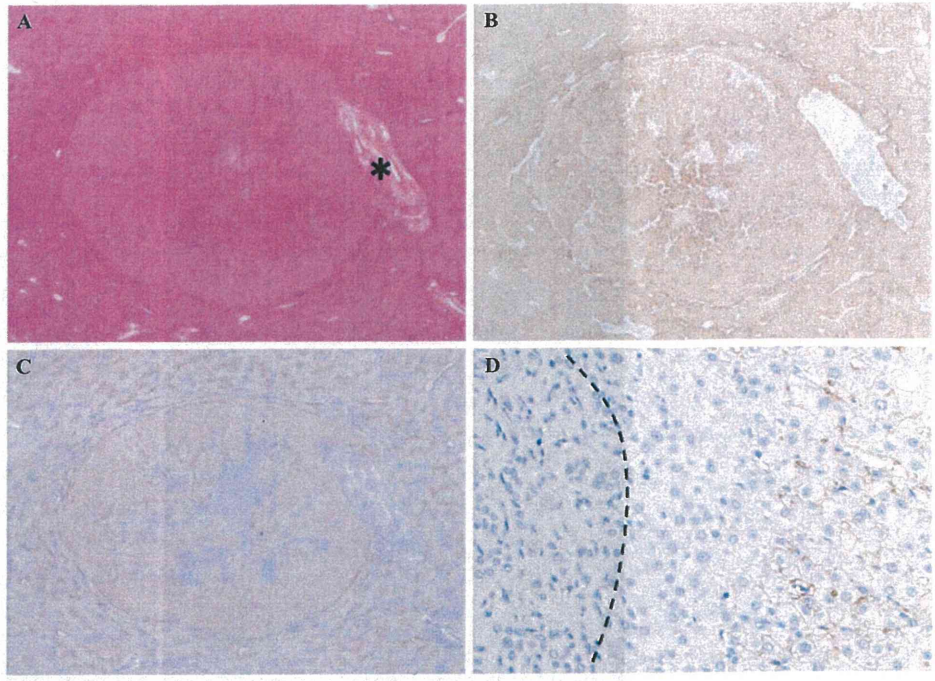

Fig. 3. Histological and immunohistochemical findings. **A** Histology of the lesion. Focal nodular hypoplasia (FNH) is well demarcated and has a central radial scar. A large portal tract (*asterisk*) is located adjacent to the lesion (H&E). **B** Immunohistochemistry (IHC) for hepatocyte-specific antigen. Most FNH areas show positive staining, indicating that the lesion is mostly composed of hepatocytes. Radial fibrous scars in the lesion and portal tracts in surrounding liver tissue are visible as nonstained areas. **C** IHC for OATP8. Peripheral portion of the lesion strongly expresses OATP8, whereas the central area is negative. Areas of OATP8-negative hepatocytes become evident when compared with the staining for hepatocyte-specific antigen (**B**). Normal liver tissue exhibits a pericentral expression pattern. **D** Magnified view of OATP8 staining in the lesion. *Dashed line* indicates the border between the fibrous scar (*left*) and hepatocytes (*right*). Hepatocytes close to the fibrous scar are negative for OATP8. Other peripheral hepatocytes exhibit membranous expression of OATP8

In the normal liver, OATP8 is expressed in pericentral hepatocytes but is absent in periportal hepatocytes.[10] Considering the fact that the central scar of FNH contains bile ducts, it is reasonable that hepatocytes surrounding the central scar do not express OATP8, similar to periportal hepatocytes. On the basis of the suggested role of OATP8 in Gd-EOB-DTPA uptake,[8,9] this distinct localization pattern of OATP8 expression (i.e., centrally negative versus peripherally positive) reasonably explains the ring-like enhancement pattern observed on Gd-EOB-DTPA-enhanced MRI. We suggest that the central hypointense area was due not only to the presence of the central scar but also to the absence of OATP8 expression in the hepatocytes surrounding the central scar. Thus, the ring-like enhancement on Gd-EOB-DTPA-enhanced MRI seems to be a diagnostic clue for small FNH, even in the presence of atypical radiological features of FNH (e.g., inhomogeneous enhancement or a missing central scar) that may cause problems in differentiating this lesion from other liver lesions. However, this finding can be observed theoretically in HCCs or hepatic adenomas with central necrosis and nodule-in-nodule-type HCC. An analysis of additional cases should help to elucidate the specificity of this finding and the differential diagnosis.

Conclusion

The presence of a ring-like enhancement during the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI may be an important radiographic feature of small FNH, regardless of the presence of central scar. The good spatial correlation between the OATP8-expressing area and the enhanced area on hepatobiliary-phase Gd-EOB-DTPA-enhanced MRI observed for the present FNH lesion further supports the role of OATP8 as a major transporter of Gd-EOB-DTPA.

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