Imaging features of β-catenin-activated hepatocellular adenoma with weak β-catenin activation: A rare case report

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Abstract
We report valuable imaging findings in a case of β-catenin-activated hepatocellular adenoma (β-HCA) with weak β-catenin activation. A 40 year-old female presented with a liver tumor in S8 that was incidentally detected on ultrasonography. The tumor showed marked enhancement and early venous drainage into the middle hepatic vein in the arterial phase of contrast-enhanced computed tomography (CT). The tumor revealed slight hypointensity in the hepatobiliary phase of gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (EOB-MRI). Six months after detection, the tumor had increased in size and a biopsy indicated hepatocellular carcinoma. The tumor was resected and pathologically diagnosed as β-HCA with weak β-catenin activation such as exon 3 545 mutation and exon 7/8 mutation. Marked enhancement in the arterial phase of CT and MRI is a characteristic finding of β-HCA with weak β-catenin activation. Furthermore, the degree of β-catenin activation might determine the signal intensity of β-HCA in the hepatobiliary phase of EOB-MRI.

Keywords
Hepatocellular adenoma, β-catenin, magnetic resonance imaging, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid

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Introduction
Hepatocellular adenoma (HCA) is a rare benign liver tumor composed of hepatocyte-like tumor cell proliferation with poor atypia. Its prevalence is estimated as 3–4 per 100,000 population in Europe and the United States, but it is much less common in Asia, including Japan.1,2 Some subtypes of HCA are associated with intratumoral hemorrhage and malignant transformation.

In recent years, the classification of HCA subtypes has progressed by genetic analysis, and HCA is divided into six phenotype groups accordingly: HNF1α inactivated HCA, inflammatory HCA (I-HCA), β-catenin activated HCA (β-HCA), β-catenin activated inflammatory HCA, sonic hedgehog HCA, and unclassified HCA.3 Among these, β-HCA is highly associated with malignant transformation into hepatocellular carcinoma (HCC),...
and it is thus important to differentiate \( \beta \)-HCA from the other subtypes of HCA. Recent advances in genetic analysis have enabled further division of \( \beta \)-HCA into two subgroups based on the degree of \( \beta \)-catenin activation: (1) strong \( \beta \)-catenin activation, that is exon 3 non-S45 mutation; and (2) weak \( \beta \)-catenin activation, that is exon 3 S45 mutation or exon 7/8 mutation. Of these \( \beta \)-HCA subgroups, \( \beta \)-HCA with exon 3 S45 or exon 7/8 mutation is associated with a low risk of malignant transformation. Therefore, it is necessary to differentiate between the weak and strong \( \beta \)-catenin-activation subtypes of \( \beta \)-HCA.

Magnetic resonance imaging (MRI) is a useful imaging modality for evaluating HCA according to the histopathological and molecular characteristics. Several studies have reported the gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (EOB-MRI) findings of HCA. However, no imaging findings have been reported for \( \beta \)-HCA with weak \( \beta \)-catenin activation.

Here, we report the rare case of \( \beta \)-HCA with weak \( \beta \)-catenin activation and describe the characteristic imaging findings on EOB-MRI.

**Case history**

A 40-year-old woman was admitted to our hospital for further examination of a liver mass detected incidentally on routine abdominal ultrasonography (US). She was seronegative for hepatitis B surface antigen (HBsAg), antibody against HBsAg, and hepatitis C virus antibody. Laboratory data were unremarkable. Tumor marker levels of AFP and PIVKA-II were within normal limits. She had no history of oral contraceptive use.

Abdominal US showed a well-defined, hypoechoic mass measuring approximately 6 cm in segment 8. Color Doppler US showed centripetal blood flow surrounding the mass, with early venous drainage into the middle hepatic vein (Figure 1). On contrast-enhanced US (CEUS), the mass showed centripetal, rapid, and intense filling in the arterial phase and persistent enhancement in the Kupffer phase. CE-computed tomography (CT) depicted strong enhancement of the mass in the arterial phase and an early drainage vein. In the portal and delayed phases, the tumor was homogeneous and iso-attenuating to liver parenchyma (Figure 2). On MRI, the mass showed low signal intensity on T1-weighted images and slightly high signal intensity on fat-suppressed T2-weighted images. There was no intratumoral fat. EOB-MRI showed hyperenhancement in the arterial phase, iso intensity in the portal venous and equilibrium phases, and slight hypointensity in the hepatobiliary phase (Figure 3). These imaging findings suggested focal nodular hyperplasia (FNH) or HCA as the differential diagnosis, and the patient was scheduled for follow-up in 6 months. EOB-MRI performed at that follow-up showed that the mass had increased in size. Partial hepatic resection was performed after biopsy that indicated HCC. The tumor was a 7-cm well-defined nodular lesion with no apparent central scar. Histopathologically, there was sinusoidal dilation within the tumor and tumor cells had atypical nuclei. In immunohistochemical analysis, tumor cells were negative for nuclear \( \beta \)-catenin, amyloid A, and C-reactive protein (CRP); patchy positive for glutamine synthetase (GS); and positive for LFABP. Immunohistochemical staining of organic anion transporting polypeptide (OATP) 8 showed patchy expression on the membrane of tumor cells (Figure 4). Based on these findings, the final diagnosis was \( \beta \)-HCA in which the degree of \( \beta \)-catenin activation was weak. The postoperative course was uneventful with no recurrence at 3.5 years after surgery.

**Discussion**

\( \beta \)-HCA is found in 10%–15% of HCA and is caused by mutations in the CTNNB1 gene encoding \( \beta \)-catenin. \( \beta \)-HCA

![Figure 1. Abdominal ultrasonography (US). (a) A well-demarcated tumor in S8 is hypoechoic on B-mode US. (b) Color Doppler US shows centripetal blood flow surrounding the tumor, with early venous drainage into the middle hepatic vein.](image-url)
Figure 2. Computed tomography (CT). (a) Plain CT shows a hypodense tumor in S8. (b) On contrast-enhanced CT, the tumor shows markedly homogeneous enhancement in the arterial phase with early venous drainage into the hepatic vein. (c, d) In the portal and delayed phases, the tumor shows the same degree of enhancement as the background liver.

Figure 3. Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging. (a) The tumor shows slightly high signal intensity in fat-suppressed T2-weighted image. (b, c) The tumor shows low signal intensity in T1-weighted image and shows no loss of signal between T1 in-phase and opposed-phase sequences. (d) On diffusion-weighted image, the tumor shows slightly high signal intensity compared to the background liver. (e) The tumor shows hypointensity on precontrast T1-weighted image. (f) There is markedly homogeneous enhancement of the tumor in the arterial phase, with early venous drainage into the hepatic vein. (g) In the portal phase, the tumor has similar intensity to the background liver. (h) The tumor is slightly hypointense in the hepatobiliary phase.
is marked histopathologically by cellular atypia of tumor cells and is often associated with pseudoglandular structures, which sometimes makes it difficult to differentiate from HCC. Recent molecular classification of HCA has divided β-HCA into several types according to the mutation point in the CTNNB1 gene. Immunohistochemistry for β-catenin and GS is known to be useful for subclassification of β-HCA. In our case, β-catenin was nucleus-negative and GS was mottled-positive, suggesting β-HCA with weak β-catenin activation. Furthermore, with regard to the pattern of GS expression, our case could be classified as exon 7/8 mutated type of β-HCA with weak β-catenin activation.

Several studies have reported the EOB-MRI imaging findings of β-HCA. Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) is taken up by hepatocytes through OATP, a transporter located in the cellular membrane of hepatocytes. A significant correlation has been found between OATP8 and β-catenin expression in HCC cells, which suggests that β-catenin may be an important molecule in the regulation of OATP8 expression. It has been reported that OATP8 expression is preserved or enhanced in β-HCA and that the characteristic imaging finding of β-HCA is iso-to-high signal intensity in the hepatobiliary phase of EOB-MRI due to Gd-EOB-DTPA uptake. However, as β-HCA can now be subdivided according to the genetic characteristics, it is necessary to determine the imaging findings of each subclassification. A recent study has reported an association of exon 3 non-S45 mutated β-HCA with Gd-EOB-DTPA uptake in the hepatobiliary phase. No imaging findings have been reported for β-HCA with weak β-catenin activation, such as exon 3 S45 or exon 7/8 mutated β-HCA; however, Zulfiqar et al. expected β-HCA with weak β-catenin activation to show little or no uptake of Gd-EOB-DTPA in the hepatobiliary phase. In the present case, the tumor was slightly hypointense compared with background liver in the hepatobiliary phase of EOB-MRI, and OATP was weakly expressed in the membrane of tumor cells, whereas β-catenin was negative immunohistochemically. Therefore, the imaging findings of β-HCA in the hepatobiliary phase of EOB-MRI may vary with the degree of β-catenin activation.

In previous reports, β-HCA has shown various degrees of enhancement, ranging from mild to strong. In our case, the tumor showed marked enhancement in the arterial phase, which has been reported as a characteristic finding of I-HCA. However, it has been recently reported that the distribution and expression of CD34 differ among β-HCA subtypes. CD34 is a marker of microvessel density, which is known to be significantly correlated with arterial enhancement of hypervascular tumors in dynamic CT. HCA with exon 3 S45 mutation and exon 7/8 mutation shows diffuse CD34 expression that leads to marked enhancement in the arterial phase of dynamic CT and MRI, as was observed in our case.

The present tumor also showed early venous drainage into the middle hepatic vein in the arterial phase, which has not been previously reported in β-HCA. Early venous drainage into the hepatic vein is considered a characteristic finding of hepatic angiolipoma and FNH. Previous reports suggest that early venous drainage can be caused by tumor hypervascularity or shunt formation. It has also been reported that the drainage vessel can change from the hepatic vein to finally the portal vein in the progression from dysplastic nodule to HCC. It is unclear why early venous drainage is observed in β-HCA.
drainage was seen in the present case; however, we assumed that as described in previous reports, the present tumor was benign and hypervascular with venous preservation.

Differentiating HCA from FNH is important because HCA carries the risk of intratumoral hemorrhage and malignant transformation. FNH shows hyperenhancement in the arterial phase and high signal intensity in the HBP of EOB-MRI, presenting imaging findings similar to those of some subtypes of HCA. In a previous report, color Doppler US and CEUS showed centripetal blood flow in HCA, whereas centrifugal blood flow was observed in FNH. In addition, Auer et al. reported that a lobulated appearance and a central scar are useful in differentiating FNH from HCA. It might have been possible to suggest a higher possibility of HCA preoperatively in this case, as the tumor was a round and internally homogeneous mass without a scar, in addition to having centripetal blood flow on US.

In conclusion, the present imaging findings indicate that the signal intensity of β-HCA in the hepatobiliary phase of EOB-MRI may depend on the degree of β-catenin activation. It is also important to know that β-HCA with weak β-catenin activation shows marked hypervascularity and that early venous drainage to the hepatic vein might be seen occasionally.

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Informed consent
Written informed consent was obtained from the patient for publication of this case report.

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