Malignant Transformation of Hepatocellular Adenoma

Wing Yee Kwok^a Satoru Hagiwara^a Naoshi Nishida^a Tomohiro Watanabe^a
Toshiharu Sakurai^a Hiroshi Ida^a Yasunori Minami^a Masahiro Takita^a Tomohiro Minami^a
Mina Iwanishi^a Hirokazu Chishina^a Masashi Kono^a Kazuomi Ueshima^a Yoriaki Komeda^a
Tadaaki Arizumi^a Eisuke Enoki^b Takuya Nakai^c Tsutomu Kumabe^d Osamu Nakashima^e
Fukuo Kondo^f Masatoshi Kudo^a

Departments of ^aGastroenterology and Hepatology, ^bPathology, and ^cSurgery, Kindai University Faculty of Medicine, Osaka-Sayama, ^dKumabe Clinic, Kikuchi, ^eDepartment of Clinical Laboratory Medicine, Kurume University Hospital, Kurume, and ^fDepartment of Pathology, Teikyo University Hospital, Tokyo, Japan

Key Words

Hepatocellular adenoma · Malignant transformation · Gadoteric acid-enhanced magnetic resonance imaging

Abstract

The patient was a 20-year-old male in whom a hepatic hypervascular mass accompanied by intratumoral hemorrhage was detected on examination for epigastric pain. Based on the enlargement of the mass and diagnostic imaging, hepatocellular adenoma (HCA) was suspected and hepatectomy was performed. The lesion was diagnosed as malignant transformation of β -catenin-activated HCA. There are only few reports of cases with malignant transformation of HCA in Japan; it is necessary to accumulate cases to investigate it.

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Introduction

Reportedly, the incidence of hepatocellular adenoma (HCA) in Western countries is 3–4 in 100,000 people, and there are many reports in the literature regarding HCA [1–3]. In contrast, HCA is a very rare disease in Asia, par-

ticularly in Japan. The risks of hemorrhage and malignant transformation have been well reported from Western countries, but cases of malignant transformation of HCA have not been reported in Japan so far [4, 5]. HCA presents as a hypervascular nodule and is thus sometimes difficult to differentiate from hepatocellular carcinoma (HCC) [6]. Herein we report the case of HCA with malignant transformation in a young male whose pathological study gives us a deep insight into this disease.

Case Presentation

The 20-year-old male patient was referred to our hospital for the purpose of examination and treatment of a hepatic mass. The patient and family members did not show any medical history of disease. He did not report habitual alcohol drinking or cigarette smoking.

Epigastric pain suddenly developed on May 26, 2012. The patient visited a clinic where a hepatic tumor was detected in segment 8 (S8). Percutaneous biopsy of the mass was performed and revealed no malignant finding. However, an increased level of serum des-gamma-carboxy prothrombin (DCP) (103 mAU/ml) was observed; the patient visited the Gastroenterological Surgery Department of our hospital on August 9, 2012. A benign mass was suspected based on gadoteric acid-enhanced magnetic resonance im-

Fig. 1. a A mass containing various components was present in S8. **b** The upper lesion of the mass was intensely stained in the early phase on Gd-EOB-MRI and slightly washed out in the delayed phase, and regions with reduced and increased EOB uptakes were

mixed in the hepatobiliary phase. **c** An avascular area assumed to be a hematoma was present in the center of the mass in the lower lesion.

(For Figure 1b and c see next page.)

aging (Gd-EOB-MRI), and regular follow-up of its course was started. Since the mass enlarged, the patient was referred to the Department of Gastroenterology on August 28, 2014. His height was 180 cm, body weight 113.7 kg, and BMI 35.1, with no abdominal finding or hepatosplenomegaly.

Blood Chemical Tests

The results of initial blood chemical tests on arrival to the Department of Surgery are shown in table 1; slight increases in WBC and CRP were noted. All HBV and HCV virus markers were negative. Elevation of the serum DCP level to 123 mAU/ml was observed.

Gd-EOB-MRI Findings

On arrival to the Department of Surgery in August 2012, a mass containing various components was present in S8 (fig. 1a). The upper lesion of the mass was intensely stained in the early phase on

Table 1. Blood test findings on arrival to the Department of Surgery

Hematology		Biochemistry	
WBC	10,400 μ l	CRP	0.315 mg/dl
RBC	$5.42 \times 10^4/\mu$ l	BUN	10 ng/dl
Hb	15.8 g/dl	Cr	0.74 mg/dl
Ht	46.6%	FBS	81 mg/dl
PLT	$41.5 \times 10^4/\mu$ l	HbA1c	5.8%
Coagulation		ALB	4.4 g/dl
PT	108.1%	T-bil	0.4 mg/dl
INR	0.97 index	ALT	31 IU/l
APTT	25.2 s	ALP	247 IU/l
Virus marker		TC	176 mg/dl
HBsAg	(-)	Trig	491 mg/dl
HBcAb	(-)	Tumor marker	
HBsAb	(-)	AFP	2 ng/ml
HCVAb	(-)	DCP	123 mAU/ml

AFP = Alpha-fetoprotein; PLT = platelets; PT = prothrombin time; RBC = red blood cells; WBC = white blood cells.

Fig. 2. a Compared with the EOB-MRI findings from August 2012, the mass had apparently enlarged. **b** The upper lesion of the mass was intensely stained in the early phase on Gd-EOB-MRI and slightly washed out in the delayed phase, and regions with reduced and increased EOB uptakes were mixed in the hepatobiliary phase.

c On the other hand, in the lower lesion, the margin of the mass was intensely stained in the early phase and slightly washed out in the delayed phase. The hematoma in the center of the mass pointed out on the previous MRI had been absorbed and replaced by a mass with an increased EOB uptake in the hepatobiliary phase.

(For Figure 2b and c see next page.)

Gd-EOB-MRI and slightly washed out in the delayed phase. The image in the hepatobiliary phase revealed mixed regions in terms of reduced and increased EOB uptakes (fig. 1b). In contrast, in the lower lesion, an avascular area assumed to be a hematoma was present in the center of the mass (fig. 1c).

In August 2013, about 1 year after the previous Gd-EOB-MRI, the mass had apparently enlarged (fig. 2a) compared with August 2012. The upper lesion of the mass was intensely stained in the early phase on Gd-EOB-MRI and slightly washed out in the delayed phase. Heterogeneous regions for uptake of EOB were confirmed in the hepatobiliary phase (fig. 2b). In the lower lesion, the margin of the mass was intensely stained in the early phase and slightly washed out in the delayed phase. The hematoma previously observed in the center of the mass had been absorbed and replaced by a mass with an increased EOB uptake in the hepatobiliary phase (fig. 2c).

Abdominal Contrast Computed Tomography

When the patient was referred to the Department of Gastroenterology in August 2014, heterogeneous regions for vascularity, showing abundant and scarce blood flows, was observed in both the upper and lower lesions of the mass (fig. 3a). The portal vein was also observed to penetrate the mass (fig. 3b).

Abdominal Contrast-Enhanced Ultrasound

When the patient was referred to the Department of Gastroenterology in August 2014, the mass was entirely stained in the early vascular phase, and a heterogeneously attenuated image of the entire mass was observed in the postvascular phase. In addition, the hepatic vein was the route of blood discharge from the mass (figure not shown).

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(For legend see next page.)

Treatment Course

Since the tumor was enlarged, the serum DCP level was high, and primary HCC or malignant transformation of HCA was strongly suspected on diagnostic imaging, two segments in the central liver were resected at the Department of Surgery.

Resected Specimen and Schematic Diagram

On macroscopic observation and H&E staining of the resected specimen, HCC regions were scattered in the HCA tissue. In addition, hemorrhage and necrosis were noted within the tumor (fig. 4a). These are presented in the schematic diagram (fig. 4b). This nodular lesion consisted of three kinds of neoplastic lesions as follows: (1) HCA region (GS-positive, SAA-negative), blue region; (2) HCA region (GS-positive, SAA-positive), orange-colored region; and (3) HCC (GS-positive, SAA-positive), red regions.

Histological and Immunohistochemical Findings of the Boundary between the HCA Region and the Normal Liver

In the boundary between the HCA region and the normal liver (fig. 5a), the artery in the portal tract was abnormally thick compared with the portal vein and bile duct (fig. 5b) (the d region of normal liver is shown in yellow in fig. 4b). In the HCA region, which corresponds to the e region in figure 4b (shown in blue), similar to those shown in figure 5b, the artery in the portal tract was abnormally thick compared with the portal vein and the bile duct (fig. 5c). In the HCA region, which corresponded to the f region in figure 4b (shown in blue), the artery was not abnormally thick, but the portal vein and the bile duct were retained (fig. 5d). These pathological findings were different from those of conventional HCA.

In the HCA region, which corresponded to the c region in figure 4b (shown in blue), mild cellular and structural atypia was observed; no invasive growth was noted in the portal region (fig. 6a, b). GS immunostaining was diffusely positive (fig. 6c) without any nuclear accumulation of β -catenin (fig. 6d), and SAA immunostaining was also negative (fig. 6e). In the b region of HCA, shown in orange in figure 4b, mild cellular and structural atypia was observed, and no invasive growth was noted in the portal tract (fig. 7a, b). GS immunostaining was diffusely positive (fig. 7c), nuclear accumulation of β -catenin was noted on immunostaining (fig. 7d), and SAA immunostaining was positive (fig. 7e). Because of definite nuclear accumulation of β -catenin, this tumor was diagnosed as β -catenin-activated HCA.

In the HCC region that corresponded to the regions shown in red in figure 4b, well-differentiated HCC with a slightly disturbed trabecular structure was detected on H&E staining (fig. 8a). On Masson trichrome staining, the tumor tissue invaded the vascular wall and reached right below the vascular endothelium or was exposed to the vascular lumen (fig. 8b). The tumor tissue was diffusely positive on GS immunostaining (fig. 8c), and nuclear accumulation was not found on immunostaining (fig. 8d). SAA immunostaining was also positive (fig. 8e).

Based on the above findings, the final pathological diagnosis was HCA (β -catenin-activated type) with a component of malignant transformation.

Fig. 3. Images from referral to the Department of Gastroenterology in August 2014. **a** Regions with abundant and scarce blood flow were mixed in both the upper and lower lesions of the mass. **b** The portal vein was observed to penetrate the mass.

Discussion

Generally, HCA is a benign tumor developing in the liver without chronic hepatitis or hepatic cirrhosis. It has recently been clarified that HCA develops due to gene aberration [7, 8]. According to the WHO classification, HCA is roughly classified into four types through the genotype- and phenotype-based subtype classification. Previous reports from Western countries have shown that the inactive hepatocyte nuclear factor (HNF) 1 α type of

Fig. 4. **a** Macroscopic findings of the resected specimen. The tumor consisted of various components. **b** Schematic diagram of the resected specimen. Red: HCC regions (GS-positive, SAA-positive). Blue: HCA region (GS-positive, SAA-negative). Orange: HCA region (GS-positive, SAA-positive). Green: Necrosis and hemorrhage. Yellow: Normal liver.

HCA develops based on the *HNF1A* gene mutation, and that its phenotype is negative for the expression of liver fatty acid-binding protein. It reportedly develops mainly in women and is associated with oral contraceptives. HCC scarcely takes place in this subtype [7–9]. On the other hand, inflammatory HCA is caused by mutations of the *gp130* and *STAT3* genes, and SAA and CRP are positive as its phenotype [10–13]. It occurs in both genders, and obesity and alcohol drinking are reported as risk fac-

tors. Reportedly, the frequency of HCC emergence from β -catenin-activated HCA is considerably high [7, 8]. Gene mutation and histological characteristics are unclear in the unclassifiable types.

Beta-catenin-activated HCA should be attributed to the *CTNNB1* mutation; immunohistochemical analyses revealed positivity for GS and nuclear β -catenin [7, 8, 14]. The frequency of its malignant transformation is higher than those of the other subtypes in Western countries, but

Fig. 5. Boundary between the HCA region and normal liver. **a** GS immunostaining. Boundary between the HCA region and normal liver (d region shown in yellow in fig. 4b). Bar: 2 mm. **b** Masson trichrome staining of the same region. The artery (a) in the portal tract was abnormally thick compared with the portal vein (p) and the bile duct (b). Bar: 2 mm. **c** The e region in the HCA nodule re-

gion shown in figure 4b. Similar to **b**, the artery (a) in the portal tract was abnormally thick compared with the portal vein (p) and the bile duct (b). Bar: 200 μ m. **d** The f region in the deep region of the HCA nodule shown in figure 4b. The artery was not abnormally thick, but the portal vein (p) and bile duct (b) were retained. Bar: 200 μ m.

Fig. 6. HCA region (c region shown in blue in fig. 4b). **a** Mild cellular and structural atypia was observed, and no infiltration was noted in the portal region. Bar: 500 μ m. **b** Masson trichrome staining. No invasive growth was noted in the portal tract. Bar: 500 μ m.

c GS immunostaining was diffusely positive. Bar: 500 μ m. **d** Beta-catenin immunostaining. No nuclear accumulation was noted. Bar: 100 μ m. **e** SAA immunostaining was negative. Bar: 100 μ m.

there have been only few reports in the literature regarding malignant transformation of HCA in Japan [4]. Thus the present case, in which the surgical specimen was pathologically examined, is valuable for understanding the difference of HCC pathogenesis based the HCA subtype.

The characteristic imaging findings of this case were: (1) the main part of the tumor exhibited hypervascularity; (2) there were also mixed lesions with hyper- and hypovascular pattern; (3) presence of intratumoral hemorrhage; (4) penetration of the portal vein into the tumor;

(5) there were slightly high-intensity regions on diffusion-weighted imaging, which were regarded as nontumorous liver based on apparent diffusion coefficient map; (6) heterogeneous high-intensity regions were observed in the hepatocellular phase on Gd-EOB-DTPA contrast-enhanced MRI; (7) the entire tumor represented a heterogeneously attenuated image on the Kupffer phase of contrast-enhanced ultrasound. Based on the unique feature of imaging, it could be speculated for differential diagnosis that there was intratumoral hemorrhage that was detected as heterogeneously high-intensity regions in

Fig. 7. HCA region (b region shown in orange in fig. 4b). **a** Mild cellular and structural atypia was observed and no infiltration was noted in the portal region Bar: 500 μ m. **b** Masson trichrome staining. No invasive growth was noted. Bar: 500 μ m. **c** GS immuno-

staining was diffusely positive. Bar: 500 μ m. **d** Nuclear accumulation was observed on β -catenin immunostaining. Bar: 100 μ m. **e** SAA immunostaining was positive. Bar: 100 μ m.

the hepatocellular phase of Gd-EOB-DTPA contrast-enhanced MRI. Several types of tumors are known to show hemorrhage in the mass, such as HCC [15], HCA [16], metastatic tumors of lung and renal cancers [17], and angiomyolipoma (AML) [18]. In the present patient, imaging studies revealed no findings of metastatic liver tumor or AML; neither metastatic liver tumor nor AML show any enhancement on Gd-EOB-DTPA in the hepatocellular phase on contrast-enhanced MRI. On the other hand, focal nodular hyperplasia is known as a hypervas-

cular tumor, but intratumoral hemorrhage should be rare, indicating the low priority for diagnosis.

HCC and HCA may present as heterogeneous high-intensity masses in the hepatocellular phase on Gd-EOB-DTPA contrast-enhanced MRI [19–21]. Generally, high intensity in the hepatocellular phase suggests a benign or less malignant tumor. However, since OATP8 is under the control of Wnt/ β -catenin signaling, β -catenin-activated HCA may well show increased intensity in the hepatocellular phase on EOB-MRI. Indeed, OATP8 is

Fig. 8. HCC region (a region shown in red in fig. 4b). **a** H&E staining. Well-differentiated HCC with a slightly disturbed trabecular structure. Bar: 500 μ m. **b** Masson trichrome staining. Tumor tissue invaded into the vascular wall and reached right below the vascular endothelium or was exposed to the vascular lumen. Bar: 500 μ m.

c GS immunostaining. Tumor tissue was diffusely positive. Bar: 500 μ m. **d** Beta-catenin immunostaining. Nuclear accumulation was not found. Bar: 100 μ m. **e** SAA immunostaining was positive. Bar: 100 μ m.

pathologically well preserved in β -catenin-activated HCA [22]. As malignant transformation is most likely in the β -catenin-activated HCA than any other types of HCA, HCA showing the high intensity in the hepatocellular phase of EOB-MRI should be observed carefully in clinical practice.

Regarding the characteristics of the pathological findings, a thickened artery wall was detected in the portal tract located at the boundary between the HCA and normal liver, suggesting the presence of abnormal blood flow

in the background liver and HCA. However, inside the HCA nodule, the components of portal tract were retained, which was different from typical HCA. Generally, no abnormal blood flow is present in the surrounding normal liver of HCA cases. Therefore, a benign nonneoplastic hepatocellular nodule may have emerged from the liver, carrying abnormal blood flow in advance of HCA formation. The reports regarding HCA development from a benign nonneoplastic hepatocellular nodule also support this hypothesis [23–25].

Based on the immunopathological findings, the mass should subsequently acquire the nuclear β -catenin accumulation-positive and GS-positive characters (c region, blue in fig. 4b) as well as SAA-positive character (b region, orange in fig. 4b), which led to the diagnosis of β -catenin-activated HCA. In this case, the nuclear β -catenin accumulation is limited to a small region. In general, not all regions of β -catenin-activated HCA exhibit diffuse nuclear accumulation. Therefore, nuclear accumulation in the b region (orange in fig. 4b) provides evidence for β -catenin-activated HCA. In the WHO classification, HCA is diagnosed mainly based on gene mutation and immunopathological findings. However, in patients showing abnormal blood flow in the background liver, it seems to be difficult to understand the development of HCA based on only immunopathological findings.

Although as described above the factors of HCA development are controversial, the diagnosis of β -catenin-activated HCA is solid in this case, where HCC with a similar immunopathological feature and structural atypia might develop from the β -catenin-activated HCA. Many cases of malignant transformation from HCA have

been reported in Western countries. However, to our best knowledge, this is the first Japanese case reported, the reason for the discrepancy of the frequency between Western countries and Japan remaining to be elucidated.

Conclusion

We encountered a young patient with malignant transformation of β -catenin-activated HCA. Beta-catenin-activated HCA may show characteristic findings, such as high intensity in the hepatocellular phase on EOB-MRI. HCA might develop based on the intrahepatic abnormal blood flow, which finally reaches malignant transformation. In Japan, malignant transformation of HCA is very rare, but further accumulation of cases and investigation are necessary.

Disclosure Statement

The authors have no conflicts of interest to declare.

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