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【 CASE REPORT 】

Inflammatory Hepatocellular Adenoma with Elevated Serum Protein Induced by Vitamin K Absence/Antagonist-II in Adult Males

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Abstract:
Two men (24 and 34 years of age) with a single hypervascular liver tumor were admitted to our hospital. The tumors were diagnosed as hepatocellular adenoma (HCA) by an ultrasound-guided biopsy and classified as inflammatory type by immunohistochemical staining. Considering the risk of malignant transformation, they underwent surgical resection. Although the serum levels of protein induced by vitamin K absence/antagonist-II (PIVKA-II) were slightly elevated, they normalized after the resection. The diagnosis of HCA including malignant transformation is often difficult by image findings alone. Careful immunohistochemical examinations are very useful for the diagnosis and classification of subgroups, including malignant transformation. In addition, we proved that HCA without malignant transformation expresses PIVKA-II.

Key words: inflammatory hepatocellular adenoma, beta-catenin activation, malignant transformation, protein induced by vitamin K absence/antagonist-II

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Introduction

Hepatocellular adenoma (HCA) is rare benign epithelial liver tumor. It is often observed in young women taking oral contraceptives and is rare in men. The incidence of HCA is lower in Asian countries including Japan (1, 2). HCA is classified into four groups according to the correlations of their genotype and phenotypes (3). The treatment options must be decided depending on the subgroup and other risk factors of malignant transformation (3). Although the classification of HCA is now widely accepted (3), there have been few reports about HCA in Japan. We herein report two cases of inflammatory HCA with slightly elevated serum levels of protein induced by vitamin K absence/antagonist-II (PIVKA-II) who were diagnosed by a percutaneous needle aspiration biopsy and immunohistochemical examinations.

Case Reports

Case 1

A liver tumor was detected in a 34-year-old man by ultrasonography (US) at a health examination, and he was admitted to our hospital. He had no remarkable medical history, medication, blood transfusion or alcohol consumption. He also had no family history of note. His body mass index (BMI) was 26.8 kg/m^2. There were no apparent abnormalities on a physical examination. Blood tests showed a normal blood cell count and liver function test results (Table). Viral markers were negative. Serum alpha fetoprotein (AFP) and PIVKA-II were 2.4 ng/mL and 76.0 mAU/mL, respectively.

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Table. Laboratory Findings on Admission.

Hematology	case 1	case 2		Serology	case 1	case 2	
WBC	5,400	5,500	/μL	CRP	0.24	1.8	mg/dL
RBC	463×10⁴	605×10⁴	/μL				
Hb	14.2	16.6	g/dL	Coagulation			
Ht	41.4	51.2	%	PT%	98.5	87.5	%
Plt	28.9×10⁴	15.1×10⁴	/μL	PT-INR	0.97	1.07	
				APTT	36.1	33.9	sec
Biochemistry							
TP	7.4	7.6	g/dL	Virus markers			
Alb	4.2	4.6	g/dL	HBsAg	(-)	(-)	
T-bil	0.74	0.31	mg/dL	HBcAb	(-)	(-)	
AST	22	38	IU/L	HCVAb	(-)	(-)	
ALT	22	34	IU/L				
LDH	171	173	IU/L	Tumor markers			
ALP	225	325	IU/L	AFP	2.4	2.4	ng/mL
GGT	26	80	IU/L	PIVKA-II	76	75.4	mAU/mL
BUN	7.5	9.3	mg/dL				
Cre	0.86	0.81	mg/dL				
Na	139	139	mEq/L				
K	4.07	4.91	mEq/L				
FPG	92	94	mg/dL				

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, Plt: platelet count, TP: total protein, Alb: albumin, T-bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, GGT: gamma glutamyl transpeptidase, BUN: blood urea nitrogen, Cre: creatinine, FPG: fasting plasma glucose, CRP: C-reactive protein, PT: prothrombin time, APTT: activated partial thromboplastin time, HBsAg: hepatitis B surface antigen, HBcAb: hepatitis B core antibody, HCVAb: hepatitis C antibody, AFP: alpha fetoprotein, PIVKA-II: protein induced by vitamin K absence/antagonist-II

US showed a well-defined tumor with heterogeneous echogenicity located in the posterior segment of the liver (Fig. 1a). The liver was normal in size and echogenicity with no suggestions of chronic liver disease. Color Doppler US revealed abundant blood flow around the tumor and arterial blood flow toward the inside of the tumor (Fig. 1b). Contrast-enhanced computed tomography (CT) showed a tumor that was 70×100 mm in diameter. It was enhanced heterogeneously during the arterial phase and obscured during the delayed phase (Fig. 1c and d). On magnetic resonance imaging (MRI), it was isointense compared with the normal liver on T1- and T2-weighted imaging (Fig. 2a and c), and the signal was not suppressed on fat-suppressed T1-weighted imaging (Fig. 2b). A funicular scar-like area was also observed in the tumor, which was hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging. After gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) administration, the tumor was enhanced heterogeneously during the arterial phase and obscured during the transitional phase (Fig. 2d and e). The lesion was almost isointense compared with the normal liver at the hepatobiliary phase (Fig. 2f). As it was difficult to make an accurate diagnosis based on these image findings alone, we performed a US-guided aspiration biopsy using a 21-gauge needle. Hematoxylin and Eosin (HE) staining of the pathological specimen showed a collection of swollen hepatocytes without cellular or structural atypia and the infiltration of inflammatory cells in the fibrous stroma with lipofuscin-like pigment deposition (Fig. 3a and b). Immunohistochemical examinations revealed the focal expression of C-reactive protein (CRP), diffuse expression of serum amyloid A (SAA) and glutamine synthetase (GS), and the nuclear expression of beta-catenin (Fig. 3c-f). The liver fatty acid binding protein (LFABP) expression was positive (Fig. 3g). We diagnosed him with inflammatory HCA overlapping with beta-catenin-activated HCA and performed posterior segmentectomy of the liver. The surgical specimen was almost totally occupied by a dark-green tumor with fibrotic changes inside surrounded by a muscular artery (Fig. 4). A histologic analysis revealed features similar to those observed in the preoperative biopsy. The glypican-3 expression was negative, although the PIVKA-II expression was positive in tumor cells of the surgical specimen (Fig. 3h and i). The patient was obese, but the background liver was normal without fibrosis or fatty changes. Serum PIVKA-II was normalized to 20.2 mAU/mL after resection.

Case 2

A 24-year-old man presented to our hospital with liver function abnormalities. He had hypothyroidism and was taking levothyroxine. He had no history of blood transfusion or alcohol consumption. His BMI was within the normal range. A physical examination showed no symptoms suggesting severe liver damage, such as jaundice or hepatosplenomegaly.

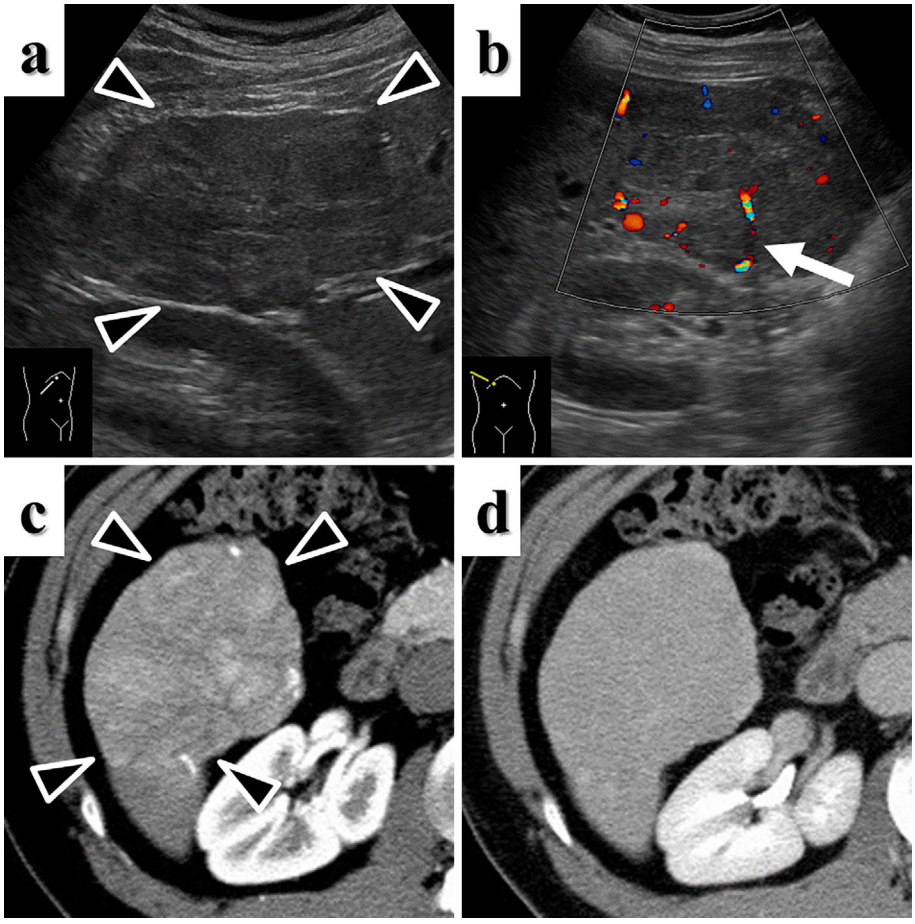

Figure 1. **Case 1. Abdominal ultrasonography showed a well-defined tumor with heterogeneous echogenicity located in the posterior segment of the liver (a) (arrowheads). An abundant blood flow around the tumor and arterial blood flow toward inside the tumor were observed on color Doppler ultrasonography (b) (arrow). Contrast-enhanced computed tomography showed a tumor that was 70×100 mm in diameter. It was enhanced heterogeneously at the arterial phase (c) (arrowheads) and obscured at the delayed phase (d).**

Blood tests showed a normal blood cell count and mild elevation of liver enzymes (Table). Viral markers were negative. Serum AFP and PIVKA-II levels were 2.4 ng/mL and 75.4 mAU/mL, respectively. Abdominal US showed a well-defined tumor with homogenous hyperechogenicity located in the lateral segment of the liver (Fig. 5a). The liver was normal in size and echogenicity with no suggestion of chronic liver disease. Color Doppler US revealed blood flow around the tumor (Fig. 5b). Contrast-enhanced CT scan showed a tumor that was 70×55 mm in diameter. It was enhanced heterogeneously during the arterial phase and clearly washed out during the delayed phase (Fig. 5c and d). On MRI, it was hyperintense compared with normal liver on T 1- and T2-weighted imaging (Fig. 6a and c), while the signal was suppressed on fat-suppressed T1-weighted imaging (Fig. 6b). After Gd-EOB-DTPA administration, the lesion was heterogeneously enhanced during the arterial phase and clearly washed out during the transitional phase (Fig. 6d and e). It was also revealed as a clear hypointense lesion at the hepatobiliary phase (Fig. 6f). We performed a US-guided aspiration biopsy using a 21-gauge needle. HE staining of the pathological specimen showed macrovesicular fatty degeneration of hepatocytes without cellular or structural atypia. The portal area disappeared, and abnormal muscular vessels were recognized (Fig. 7a and b). Immunohistochemical studies revealed diffuse but strong expression of CRP and SAA (Fig. 7c and d). The GS expression was positive (Fig. 7e). Beta-catenin was expressed in the cell membrane (Fig. 7f). The LFABP expression was positive (Fig. 7g). We diagnosed him with inflammatory HCA according to the findings of a histologic analysis and performed laparoscopic left lateral segmentectomy of the liver. The surgical specimen was almost totally occupied by a xanthochromatic tumor (Fig. 8). A histologic analysis revealed features similar to those observed in the preoperative biopsy except for regarding GS. The GS expression was focally positive but was almost negative in the surgical specimen. The glypican-3 expression was negative, although the PIVKA-II expression was weakly positive in the tumor cells of the surgical specimen (Fig. 7h and i). The background liver was normal without fibrosis or fatty changes. Serum PIVKA-II was normalized to 34.2 mAU/mL after resection.

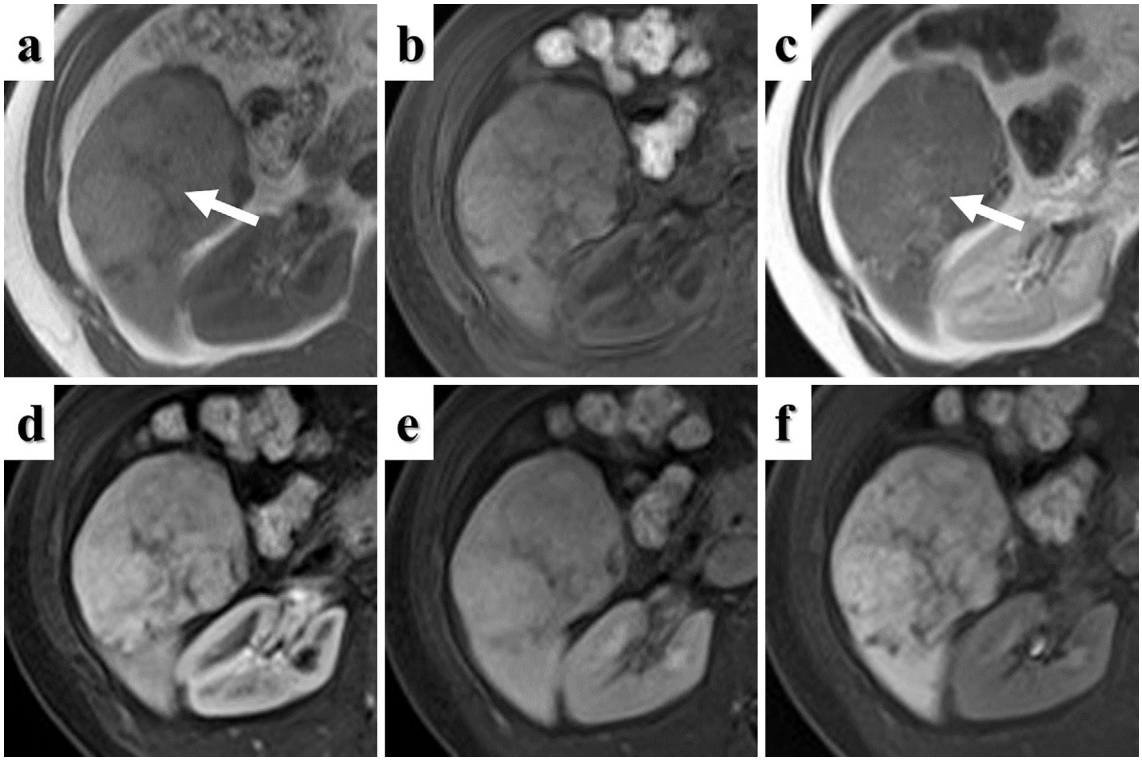

Figure 2. **Case 1. On magnetic resonance imaging, the tumor was isointense compared with the normal liver on T1- (a) and T2- (c) weighted imaging, and the signal was not suppressed in fat-suppressed T1-weighted imaging (b). A funicular scar-like area was also observed in the tumor, which was hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging (a, c) (arrow). After gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid administration, the tumor was enhanced heterogeneously during the arterial phase (d) and obscured during the transitional phase (e), the lesion was almost isointense compared with the normal liver at the hepatobiliary phase (f).**

Discussion

HCA is a rare benign liver tumor that usually develops in non-cirrhotic liver and is common in young women in association with taking oral contraceptives. Although the incidence of HCA is estimated to be 3-4 per 100,000 population in Europe and North America (4), it is lower in Asian countries, including Japan, probably due to fewer users of oral contraceptives (2, 5). The administration of anabolic steroids, glycogen storage disease, familial polyposis coli, obesity and metabolic syndrome have been identified as risk factors of HCA (6-9). Major complications of HCA that can be fatal include hemorrhaging and malignant transformation. Hemorrhaging due to spontaneous rupture has been reported in up to 30% of cases (10). Malignant transformation of HCA over a decade that was not initially immunohistochemically diagnosed as HCA has been reported (11). The correct diagnosis is therefore essential to avoid these fatal complications in patients with HCA. Bioulac-Sage et al. described four subgroups of HCA according to the genetic, pathological, and clinical features: hepatocyte-nuclear-factor-1 alpha mutated (H-HCA), beta-catenin-mutated type with upregulation of GS (b-HCA), inflammatory type (I-HCA) with SAA and CRP overexpression, and unclassified type (3). Recently, these four subgroups were further subdivided into eight subgroups in order to evaluate the above-mentioned complications of HCA (12). HCA must be appropriately treated depending on the classification and considering the risk of malignant transformation. However, it is often difficult to make a diagnosis of HCA only by image findings. HCA is usually a hypervascular tumor with various forms, such as intratumoral hemorrhaging, necrosis, steatosis and fibrosis. Owing to this variety of imaging findings, it is difficult to distinguish HCA from other hypervascular lesions, such as fibrolamellar hepatocellular carcinoma (HCC), focal nodular hyperplasia, angiomyolipoma and metastases. Thus, a pathological diagnosis is necessary for the diagnosis of HCA.

Contrast-enhanced MRI plays an important role in the diagnosis and subtype characterization of HCA (13). Case 1 showed near isointensity compared with the adjacent liver parenchyma at the hepatobiliary phase, which is sometimes observed in b-HCA patients in correlation with beta-catenin signaling and OATP1B3 expression (14). Fukusato et al. reported that the OATP1B3 expression tended to be preserved or enhanced in b-HCA patients, in contrast to the decrease noted in most other HCA patients (15). An intratumoral scar-like lesion on T2-weighted imaging, which was observed in case 1, has also been reported in b-HCA pa-

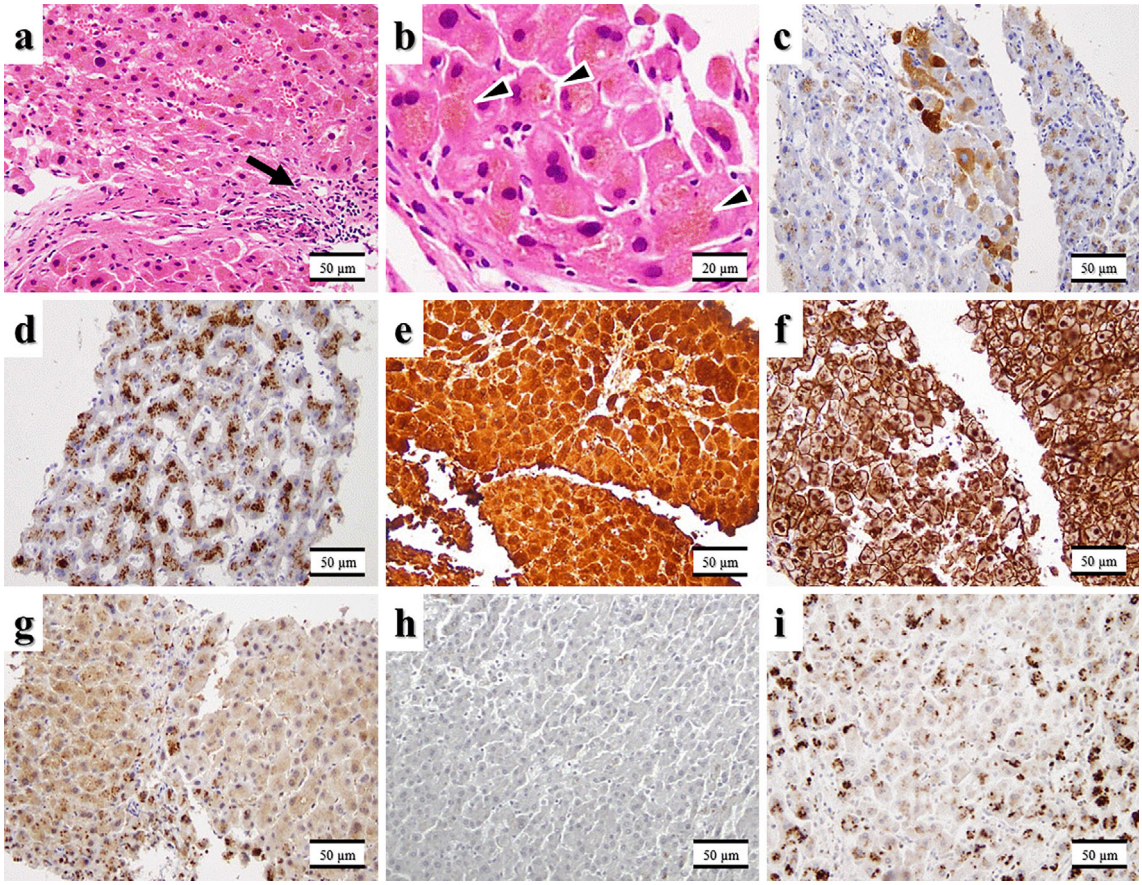

Figure 3. **Case 1. Hematoxylin and Eosin staining of the pathological specimen showed a collection of swollen hepatocytes without atypia, with the infiltration of inflammatory cells (a) (arrow) in fibrous stroma and the deposition of lipofuscin like pigments (b) (arrowheads). Immunohistochemical studies revealed the focal expression of C-reactive protein (c), diffuse expression of serum amyloid A (d) and glutamine synthetase (e), and the nuclear expression of beta-catenin (f). The liver fatty acid binding protein expression was positive (g). The glypican-3 expression was negative (h), although the PIVKA-II expression was positive in the tumor cells of the surgical specimen (i) (anti-PIVKA-II monoclonal antibody: SEKISUI MEDICAL, Tokyo, Japan)**

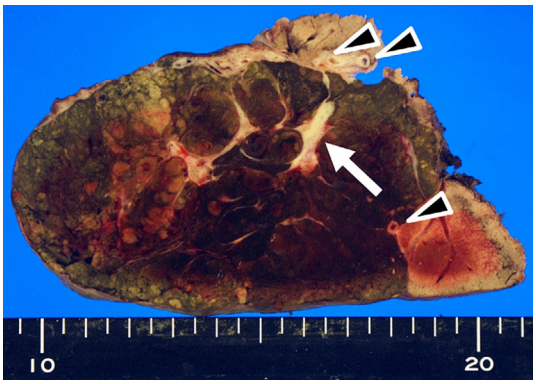

Figure 4. **Case 1. The surgical specimen was almost totally occupied by a dark-green tumor with fibrotic changes inside (arrow) surrounded by a muscular artery (arrowheads).**

tients (16). Immunohistochemical examinations showed diffuse positivity for GS and nuclear staining for beta-catenin as well as the increased expression of SAA and CRP. In approximately 10-20% of I-HCA lesions, beta-catenin activation is found, as in case 1 (17). Case 1 was diagnosed with I-HCA overlapping with b-HCA.

In contrast, the signal of the tumor was hypointense at the hepatobiliary phase with markedly diffuse intratumoral steatosis in case 2. We considered angiomyolipoma and H-HCA as the differential diagnoses because of the rich steatosis, but the tumor was diagnosed as I-HCA according to immunostaining findings that showed diffuse positivity of SAA and CRP. Beta-catenin activation was negative, because its expression was not observed in the nucleus, only in the cell membrane. The focal expression of GS is sometimes observed in several types of HCA. We herein report the first case of I-HCA with diffuse intratumoral fat deposition after proposition of subtype classification of HCA, although it is noted that intratumoral steatosis is not sufficient for diagnosing HCA subtypes, as other subtypes besides H-HCA may also exhibit intratumoral steatosis (17). In both cases, a percutaneous biopsy was essential for the accurate diagnosis.

The frequency of malignant transformation of HCA is reported to be 4% in women and 47% in men, a 10-fold dif-

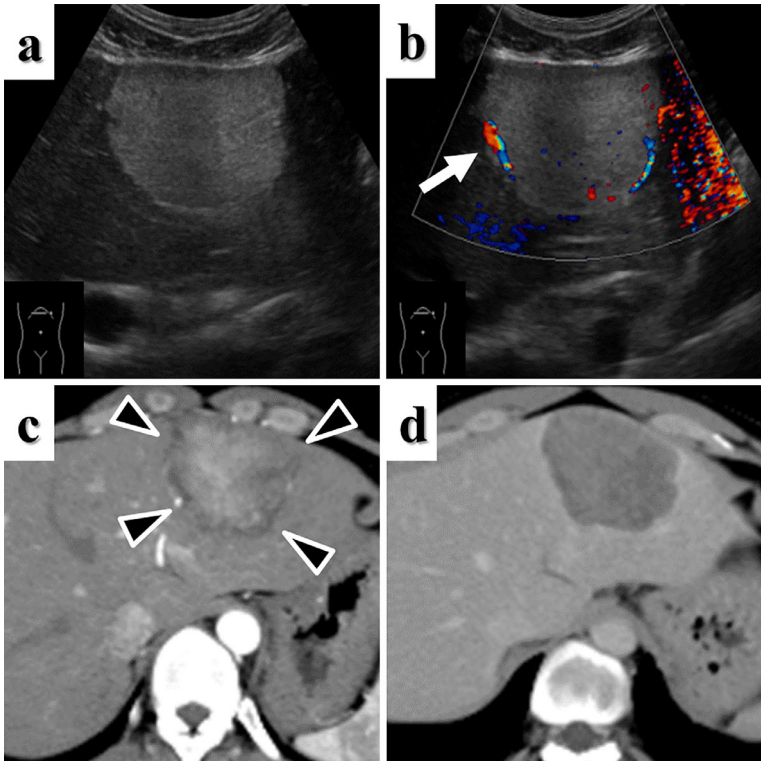

Figure 5. **Case 2. Abdominal ultrasonography showed a well-defined homogenous hyperechoic tumor located in the lateral segment of the liver (a). Blood flow around the tumor was observed on color Doppler ultrasonography (b) (arrow). Contrast-enhanced computed tomography showed a tumor that was 70×55 mm in diameter. It was enhanced heterogeneously at the arterial phase (c) (arrow heads) and clearly washed out at the delayed phase (d).**

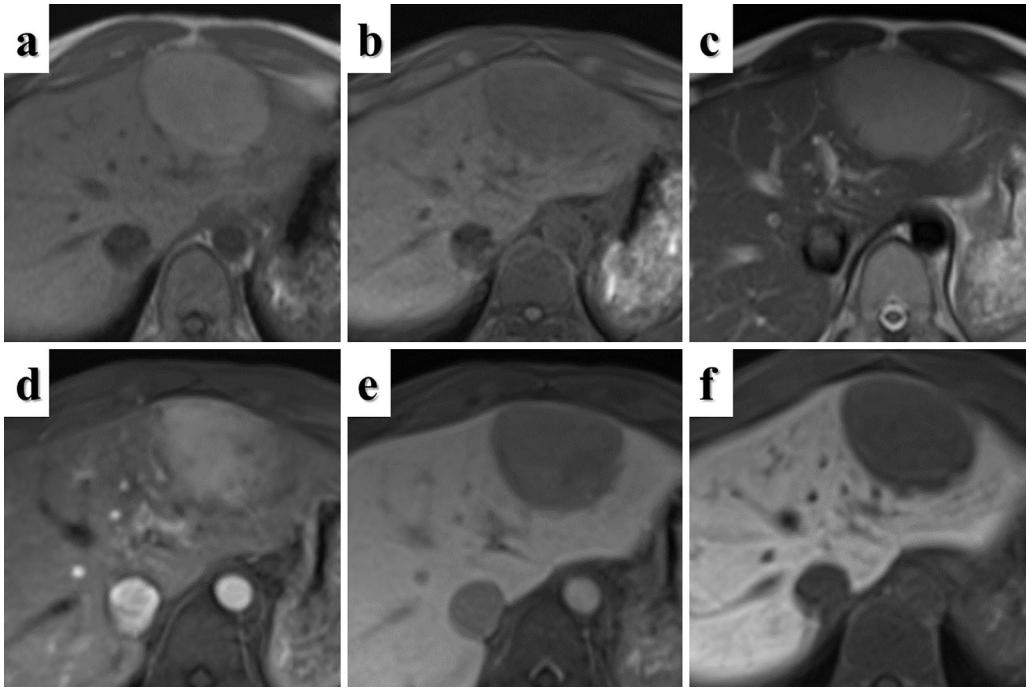

Figure 6. **Case 2. On magnetic resonance imaging, the tumor was hyperintense compared with the normal liver on T1- (a) and T2- (c) weighted imaging and the signal was suppressed in fat-suppressed T1-weighted imaging (b). After gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid administration, the lesion was heterogeneously enhanced during the arterial phase (d) and clearly washed out during the transitional phase (e). It also showed a hypointense lesion at the hepatobiliary phase (f).**

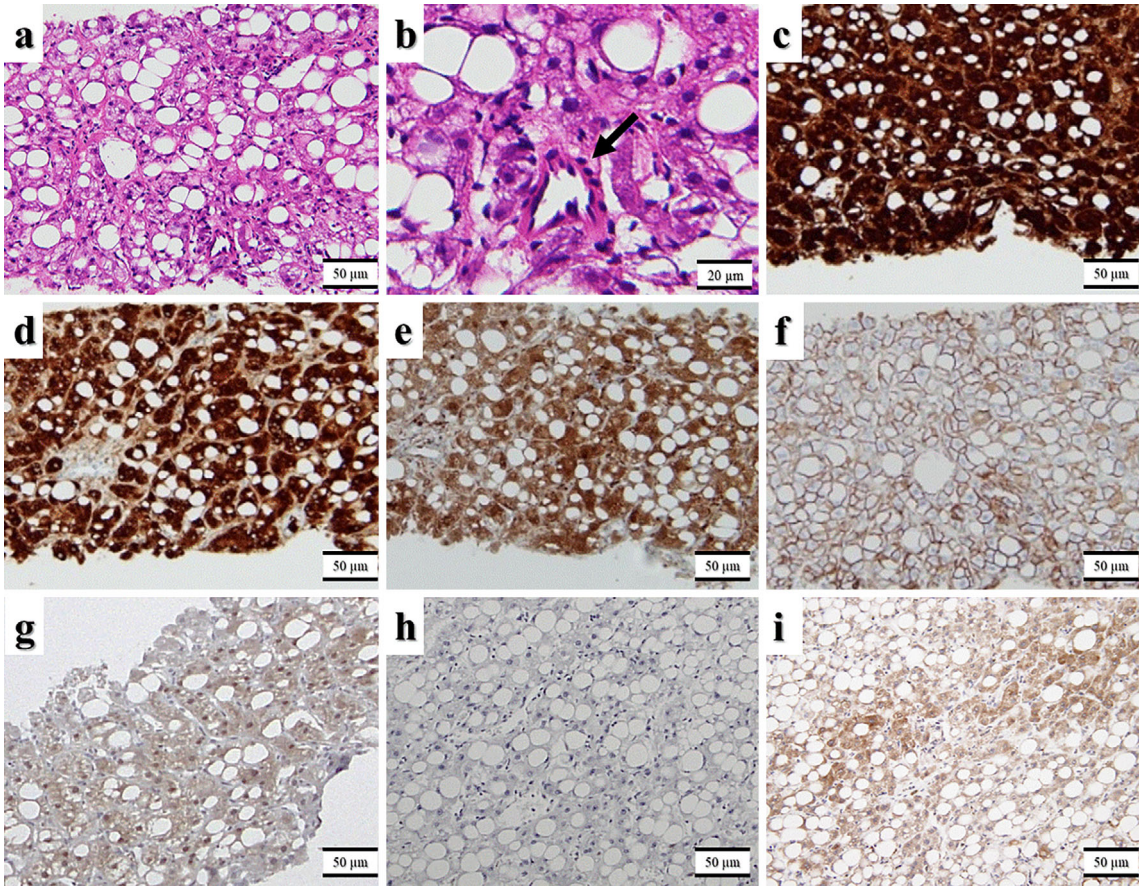

Figure 7. **Case 2. Hematoxylin and Eosin staining of specimen showed macrovesicular fatty degeneration of hepatocytes without atypia (a). The portal area disappeared, and abnormal muscular vessels were recognized (b) (arrow). Immunohistochemical studies revealed the diffuse but strong expression of C-reactive protein (c) and serum amyloid A (d), and the cell membrane expression of beta-catenin (f). The glutamine synthetase expression was positive (e). The liver fatty acid binding protein expression was positive (g). The glypican-3 expression was negative (h), although the PIVKA-II expression was weakly positive in the tumor cells of the surgical specimen (i) (anti-PIVKA-II monoclonal antibody: SEKISUI MEDICAL, Tokyo, Japan)**

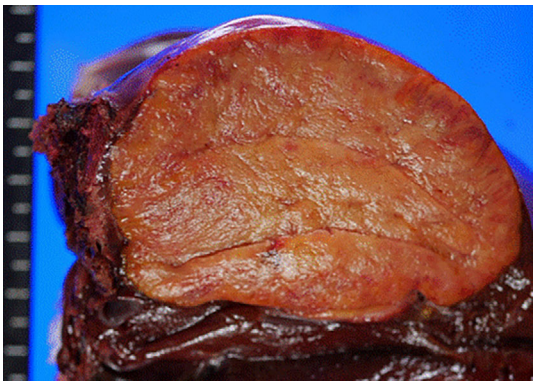

Figure 8. **Case 2. The surgical specimen was almost totally occupied by a xanthochromatic tumor.**

ference (18). In addition to male sex, the prolonged use of exogenous steroids, tumor size >5 cm, type I glycogen storage disease, obesity or metabolic syndrome, and beta-catenin activation are risk factors for malignant transformation (18-20). Mutations of the beta-catenin gene in HCA, which have identified and activated beta-catenin mutations, deregulate the beta-catenin pathway. The pathway is part of the more complex Wnt signaling pathway, which plays a major role in the proliferation of liver cells. These mutations may lead to the hyperproliferation of liver cells and result in malignant transformation (19, 21-23). Because the frequency of malignant transformation is high and tumor regression after the discontinuation of contraceptives, as in women, cannot be expected, surgical treatment is recommended as the first-line approach for men with HCA irrespective of tumor size or subtypes (24). We preoperatively suspected the partial malignant transformation of the tumors because of the aforementioned risk factors and elevated serum levels of PIVKA-II in both cases.

The PIVKA-II and AFP levels are common tumor markers of HCC. In these two cases, the AFP level was within the normal limits, but the PIVKA-II level was slightly elevated before resection and normalized after the removal of the tumor. Fujioka et al. reported that PIVKA-II tended to be expressed in well-differentiated HCCs, where AFP tended

to be expressed in moderately differentiated HCCs (25). Most HCCs accompanied by HCA are the well-differentiated type. The elevation of serum PIVKA-II levels has been reported in HCA patients with malignant transformation and is described as useful for predicting the malignant transformation of HCA (26, 27). In both of the present cases, the expression of PIVKA-II in the tumor was proven immunohistochemically. To date, there has been only one case report of HCA with elevated serum PIVKA-II levels with the tumor cells proven to generate PIVKA-II immunohistochemically (28). In both of our cases, malignant transformation was denied by the absence of cellular or structural atypia of tumor cells and the negative staining for glypican-3. Possible mechanisms for PIVKA-II production in HCC include a qualitative or quantitative abnormality of prothrombin precursors, altered activity of gamma-glutamyl carboxylase, an abnormality in the vitamin K cycle or a lack of vitamin K (28). Although PIVKA-II is a well-known tumor marker of HCC, similar mechanisms for PIVKA-II production could occur in both HCAs. PIVKA-II should be regarded as not only a tumor marker of HCC but also a marker of a dysfunctional state of hepatocytes induced by neoplastic changes.

We should consider HCA when we encounter hypervascular tumors in a non-cirrhotic liver. In addition, as it is difficult to diagnose and distinguish between different types of HCA based on imaging findings alone, a biopsy and careful pathological examination including immunohistochemistry are prerequisite for the correct diagnosis (3, 29). We should perform appropriate therapies according to the subgroup classification in order to avoid fatal complications, including malignant transformation, in patients with HCA.

The authors state that they have no Conflict of Interest (COI).

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