Contrast-enhanced ultrasonographic findings of serum amyloid A-positive hepatocellular neoplasm: Does hepatocellular adenoma arise in cirrhotic liver?

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Abstract

Hepatocellular adenoma (HCA) was recently classified into four pathological subtypes. There have been few studies describing the findings of contrast-enhanced ultrasonography (CEUS) of each type. Our case concerns a 78-year-old man who had undergone routine medical check-ups for hepatitis C for 11 years. Abdominal ultrasound showed a 28 mm, hypo-echoic mass in the segment 4 of the liver. His integrating amount of drinking was 670 kg convert into ethanol. CEUS with Sonazoid demonstrated mild uniform hypo-enhancement with inflow of microbubbles from the periphery of the tumor in the arterial phase, and heterogeneously hypo-enhancement in the post vascular phase. Because the mass increased in size within 3 mo, a well differentiated hepatocellular carcinoma was suspected, and hepatic resection was performed. Microscopic findings showed homogeneous cell proliferation with low grade atypia, infiltration of inflammatory cells, ductular reactions, fatty deposit in part, and sinusoidal dilation. Immunohistochemistry revealed geographic positive for serum amyloid A (SAA), focal positive for glutamine.
synthetase, diffuse and strong positive for C-reactive protein, and positive for liver-type fatty acid binding protein. These pathological features corresponded to that of an inflammatory HCA. However, we could not make a clear diagnosis, because HCAs were defined as not to arise in cirrhotic liver. Finally, this tumor was diagnosed as a SAA positive hepatocellular neoplasm.

Key words: Hepatocellular adenoma; Contrast-enhanced ultrasonography; Serum amyloid A; Serum amyloid A-positive hepatocellular neoplasm; Alcoholic cirrhosis

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Core tip: Hepatocellular adenoma (HCA) was classified into four pathological subtypes. And HCA usually arises in the absence of significant fibrosis. Recently, some reports about serum amyloid A (SAA) positive hepatocellular neoplasm were published. All tumors shared features with inflammatory HCA arising in alcoholic cirrhosis. We describe the contrast-enhanced ultrasonographic findings of SAA positive HCA.

INTRODUCTION

Hepatocellular adenoma (HCA) was recently classified into four pathological subtypes; hepatocyte nuclear factor 1 alpha inactivated HCA, beta catenin activated HCA, inflammatory HCA, and unclassified HCA. Although contrast-enhanced ultrasonographic features of HCA have been reported in several literatures till now, there have been little studies that described those of each type of HCA. HCAs usually arise in the liver without steatosis, because a nodule arising in fibrotic/cirrhotic liver was not to be a HCA according to World Health Organization classification 2010. Recently, some reports about serum amyloid A (SAA) positive hepatocellular neoplasm were published. All nodules shared features with inflammatory HCA arising in alcoholic cirrhosis. In this report, we describe contrast-enhanced ultrasonographic findings of SAA positive hepatocellular neoplasm which had features similar to inflammatory HCAs.

CASE REPORT

A 78-year-old man had undergone routine medical check-ups for hepatitis C over 21 years. He received interferon therapy 21 years ago, but could not achieve complete remission. In these years, he had compensatory hepatic cirrhosis and was gave medication of glycyrrhizin formulation. Abdominal ultrasonography showed 20 mm, hypo-echoic in the segment 4 of the liver 3 mo ago. Because the tumor increased in diameter to 28 mm, he was admitted to our hospital for further examinations. He had no history of other disease. He drank two glasses of whisky and one glass of beer from 20 till 66-year-old. His integrating amount of drinking was 670 kg convert into ethanol. He had no symptoms. Physical examination showed untoward features. Blood examination demonstrated thrombocytopenia, mild hyper-bilirubinemia, elevated liver enzymes (aspartate aminotransferase, 36 IU/L; alanine aminotransferase, 35 IU/L), positive for HCV-antibody, and 6.4 log IU/mL for HCV-RNA (Table 1).

Sonographic examination showed a homogenous, hypo-echoic, round mass in the segment 4b of the liver (Figure 1A). Color Doppler sonography revealed no signals in the lesion (Figure 1B). Contrast-enhanced ultrasonography (CEUS) with 0.5 mL of Sonazoid (Daichi Sankyo, Tokyo, Japan) demonstrated mild global hyper-enhancement with inflow of microbubbles from the periphery of the tumor in the arterial phase (Figure 1C and D), persist enhancement in the portal venous phase (Figure 1E), and heterogeneous hypo-enhancement in the post vascular phase (Figure 1F). Plain computed tomography (CT) showed a hypodense tumor (Figure 2A). Contrast-enhanced CT showed iso-enhancement in the arterial phase (Figure 2B) and slight hypo-enhancement in the portal phase (Figure 2C). Magnetic resonance imaging (MRI) demonstrated slightly high intensity in the T1 weighted image (Figure 3A), and slightly low intensity in the T2 weighted image (Figure 3B). Contrast-enhanced MRI using Gadolinium ethoxybenzyl diethylene triamine pentaacetic acid revealed slightly high intensity in the hepatobiliary phase (Figure 3C).

Because the mass increased in size, it was suspected as being a well differentiated hepatocellular carcinoma. Considering the risk of hemorrhage and dissemination, partial segment 4 resection was performed without biopsy. Because the mass was adjacent to horizontal portion of the left portal vein and pathological diagnosis was needed, percutaneous ablation was not chosen. Microscopic findings showed homogeneous cell proliferation with low grade atypia, infiltration of inflammatory cells, ductular reactions, fatty deposit in part, and sinusoidal dilation (Figure 4). Immunohistochemistry revealed geographic positive for SAA, focal positive for glutamine synthetase, diffuse and strong positive for C-reactive protein, and positive for liver-type fatty acid binding protein (Figure 5). These pathological features corresponded to that of an inflammatory HCA.

DISCUSSION

Classification of HCA is based on molecular, pathologic, and immunohistochemical features. Inflammatory HCA accounts for 45%-60% of all HCAs, and has...
mutations of the \textit{IL6ST} gene\cite{12-14}. Alcohol intake and obesity are association with inflammatory HCA\cite{9,15-17}.

The rate of malignant transformation is unknown.

CEUS findings of HCA were described in previous

\begin{table}
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\begin{tabular}{|l|c|c|}
\hline
Patients laboratory results (the normal ranges) & & \\
\hline WBC (3.3-8.6) & 6200/μL & Total protein (6.6-8.1) & 8.0 g/dL \\
Hgb (13.7-16.8) & 15.0 g/dL & Albumin (4.1-5.1) & 4.7 g/dL \\
Platelet (148-348) & 108 × 10^3 /μL & HBs antibody & (-) \\
PT% (> 80) & 99% & HBc antigen & (-) \\
INR & 0.92 & HCV antibody & (+) \\
Total bilirubin (0.4-1.5) & 1.41 mg/dL & HCV-RNA & 6.4 logIU/mL \\
Direct bilirubin (0.05-0.4) & 0.37 mg/dL & Alpha-fetoprotein (< 20) & 6.4 ng/mL \\
Aspartate transaminase (13-30) & 36 IU/L & PIVKA-II (< 40) & 91 mAU/mL \\
Alanine transaminase (10-42) & 35 IU/L & ICG (15 s) (< 15.0) & 14.0% \\
\hline
\end{tabular}
\end{table}

WBC: White blood cell; INR: International normalized ratio; HCV: Hepatitis C virus; PIVKA-II: Prothrombin induced by vitamin K absence-II; ICG: Indocyanine green.

\textbf{Figure 1 Sonography.} Sonographic examination showed a homogenous, hypo-echoic, round mass in segment 4 of the liver (A). Color Doppler sonography revealed no signals in the lesion (B). CEUS demonstrated mild global hypo-enhancement (D, arrow) with inflow of microbubbles from peripheral of the tumor (C, arrow) in the arterial phase, persist enhancement in the portal venous phase (E, arrow), and heterogeneous hypo-enhancement in the post vascular phase (F, arrow). CEUS: Contrast-enhanced ultrasonography.
In one study which investigated 18 lesions, which were iso-hypoechoic in 9, hyper-enhancing in all in the arterial phase, and iso or hypo-enhancement in all in the late phase. Ricci et al. emphasized homogeneous and centripetal enhancement during artery phase was showed in almost all. In accordance with previous studies, HCA lesions had some typical features, including early, homogeneous, centripetal, and strong enhancement in the arterial phase and the lack of a portal vein supply. According to a study, a number of HCAs demonstrated persistent enhancement. Dong et al. said “slow wash-out” (persistent enhancement during portal venous and late phase) may be a discriminant sign for HCAs in CEUS. In our case, the arterial phase findings were not so strong but homogenous and centripetal hyper-enhancement and some peripheral vessels were showed. The contrast medium that used in that study was gadolinium ethoxybenzyl diethylene triamine pentaacetic acid (Gd-EOB-DTPA).
was Sonovue (Bracco, Milan, Italy) whereas Sonazoid was administered to our patient. Sonovue and Sonazoid are phagocytosed by Kupffer cells, and visualize clearly malignant tumor as defect. CEUS using Sonazoid revealed hypo-enhancement in the post vascular phase in our patient which was interpreted as lack of Kupffer cells in the tumor.

Recently SAA-positive hepatocellular neoplasms were proposed\(^{10,11}\). Generally, HCA arises from normal liver\(^{1,23}\). Although SAA-positive hepatocellular neoplasms have similar features to inflammatory HCA, they arise from alcoholic cirrhosis. Sasaki et al\(^{10,11}\) suggested, considering that the patient exposed to alcohol in inflammatory HCA, it may be not be surprising that inflammatory HCA arise in alcoholic hepatic disease or cirrhosis. Our case had liver cirrhosis with HCV infection, moreover had a history of excessive amounts-alcohol consumption. We considered that our case is SAA-positive hepatocellular neoplasm.

In conclusion, CEUS revealed homogeneous mild hyper-enhancement in the arterial phase and heterogeneous hypo-enhancement in the post vascular phase in our case. Some of CEUS findings corresponded to features of HCA. Our patient had both HCV infection and alcohol abuse, and it was not typical for inflammatory HCA. It may be a case of so-called SAA-positive hepatocellular neoplasm.

**COMMENTS**

**Case characteristics**
A 78-year-old man with hepatitis C and hepatic cirrhosis received abdominal ultrasoundography, in which 20 mm, homogenous, hypo-echoic, round mass was shown in the segment 4b of the liver.

**Clinical diagnosis**
Because the mass increased in size and he had hepatic cirrhosis, a well differentiated hepatocellular carcinoma was suspected.

**Differential diagnosis**
Dysplastic nodule, large regenerative nodule, hepatocellular adenoma (HCA), and focal nodular hyperplasia.

**Laboratory diagnosis**
Hepatic pre-cirrhosis with early hepatocellular carcinoma.

**Imaging diagnosis**
A well differentiated hepatocellular carcinoma was suspected.

**Pathological diagnosis**
Inflammatory HCA.

**Treatment**
Segment 4 partial resection.

**Related reports**
HCA was classified into four pathological subtypes and usually arises in the absence of significant fibrosis. Serum amyloid A (SAA)-positive hepatocellular neoplasm shares features with inflammatory HCA arising in alcoholic cirrhosis.

**Term explanation**
SAA-positive hepatocellular neoplasms have similar features to inflammatory HCA, they arise from alcoholic cirrhosis.

**Experience and lessons**
Considering that the patient exposed to alcohol in inflammatory HCA, it may
This is a very interesting case, well investigated and presented with also pathological comparison images.

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