Multiple HNF-1α Inactivated Type Hepatocellular Adenoma due to Intrahepatic Portosystemic Venous Shunt

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Abstract

We describe multiple hepatocyte nuclear factor-1 alpha (HNF-1α) inactivated type Hepatocellular Adenoma (HCA) case of 54-year-old female due to intrahepatic portosystemic venous shunt. She denied alcohol use, blood transfusion, Oral Contraceptives (OC), and drug abuse. Ultrasound (US) and angiography showed shunt formation between right portal vein and right hepatic vein. Five hyperechoic nodules were detected by US. All nodules located in segment 3, 5, 6 showed no hypervascularity by Contrast Enhanced US (CEUS), Contrast Enhanced Computed Tomography (CECT), Contrast Enhanced Magnetic Resonance Imaging (CEMRI) and CT angiogram. CEMRI in the hepatobiliary phase showed hypointense nodules in segment 3, segment 5, and segment 6 nodule respectively. The size of the nodules ranged from 10 to 25mm. US guided biopsy of the nodules in segment 3, segment 5, and segment 6 showed slight hypercellularity with fatty change without high nuclear/cell ratio and irregular thin trabecular pattern histologically. Immunohistochemical staining showed loss of Liver Fatty Acid Binding Protein (L-FABP) and negative for Serum Amyloid A (SAA), C Reactive Protein (CRP), Glutamine Synthetase (GS), Organic Anion-Transporting Polypeptide (OATP), and β-catenin. To the best of our knowledge, this is the first case of multiple HNF-1α inactivated type HCA due to intrahepatic portosystemic venous shunt as an etiology on the basis of recently established immunohistochemistry and imaging studies.

Keywords: β-catenin; Hepatocyte nuclear factor-1 alpha inactivated type adenoma; Intrahepatic portosystemic venous shunt; Liver fatty acid binding protein; Magnetic resonance imaging; Multiple hepatocellular adenoma.

Introduction

The detection of hepatic nodular lesions has become more frequent because of recent advances in imaging diagnosis techniques. Benign hepatocellular lesions such as focal nodular hyperplasia (FNH) [1], Nodular Regenerative Hyperplasia (NRH), Hepatocellular Adenoma (HCA) [2], pseudolymphoma and bile duct adenoma [3,4], as well as small hepatocellular carcinoma, are detected more frequently today. Among numerous varieties of communication between portal and systemic venous circulations, congenital extrahepatic portosystemic shunts (CEPS) are rare venous malformations whereby mesenteric venous blood drains directly into systemic circulation [5]. Hepatocellular nodules attributed to CEPS resulting in abnormal portal blood flow are mostly cases of benign FNH [6-8] that can be multifocal or massive. Although it is considered that hepatic nodules do not turn malignant, HCA [9-15], Hepatoblastoma (HB) [16-19], and...
Hepatocellular Carcinoma (HCC) [20-26] have been described in CEPS patients [27]. On the other hand, a total of 14 cases of intrahepatic portosystemic venous shunt have been described since the initial report on congenital intrahepatic shunts in 1956 [28]. Several studies on HCA due to intrahepatic portosystemic venous shunts as an etiology have been described [29,30], wherein, however, no precise imaging studies, were conducted, and no immunohistochemical analysis on the subtype of HCA was carried out. Here, to the best of our knowledge, we describe the first case of multiple HNF-1α inactivated type HCA due to an intrahepatic portosystemic venous shunt.

Case Report

A 54-year-old woman was admitted to Kobe Asahi Hospital for further examination of multiple liver nodules. She denied alcohol use, blood transfusion, oral contraceptives (OC), and drug abuse. On admission, a physical examination showed no remarkable abnormalities; she weighed 61kg, stood 163.3cm tall, with a BMI of 22.9. Hepatitis C screening was negative for antibodies and RNA. Hepatitis B including surface antigen, surface and core antibodies, and Deoxyribonucleic Acid (DNA) were negative. Laboratory data on admission were shown in table 1.

Color-Doppler Ultrasound (US) and Volume Rendering imaging from Computed Tomography (CT) during Arterial Portography (CTAP) showed shunt formation between the right portal vein and the right hepatic vein (Figure 1A, B). US showed five hyperechoic nodules ‘a-e’ in the right and left lobes (Table 1). The nodules ranged between 10 and 25 mm. US showed 25 mm hyperechoic nodule in segment 3 (Figure 1C). CT angiography, including CT during hepatic arteriography (CTHA), CTAP and Contrast Enhanced Magnetic Resonance Imaging (CEMRI) in the hepatobiliary phase, showed several other nodules that were not detected by US and that could not be subjected to US guided biopsy. Imaging findings with CEUS, CECT and CEMRI suggested absence of hypervascularity on all nodules (Figure 1D).

CEMRI showed no enhancement, slight hypointense nodules, and clear hypointense nodules in the early phase, the late phase, and the hepatobiliary phase, respectively (Figure 1E). CT and MRI findings of the nodules in segment 5 (hyperechoic 13 mm, ‘d’) and segment 6 (hyperechoic 10 mm, ‘e’) were almost the same as those of the nodule in segment 3 (Table 2) (Figure 1F). Positron Emission Tomography (PET)-CT showed no accumulation of 18F-FDG of PET in the 5 nodules. The absence of hypervascularity and the negative finding of PET-CT suggested more a benign lesion involving a hyperplastic nodule than a malignant lesion involving HCC. Histological aspects of US guided biopsy of the nodules located in segments 3, 5 and 6 showed slight hypercellularity with fatty change, but without a high N/C ratio, and an irregular thin trabecular pattern (Figure 2A, 2B). Immunohistochemical staining of the same nodules showed loss of liver fatty acid binding protein (L-FABP) (Figure 2C), and negative expression of Serum Amyloid A (SAA), C Reactive Protein (CRP), Glutamine Synthetase (GS), Organic Anion-Transporting Polypeptide (OATP) and β-catenin (Figure 2D). From the above findings, and through histopathological analysis the lesion was diagnosed as multiple HNF-1α inactivated type HCA.

**Table 1**: Laboratory data on admission.

<table>
<thead>
<tr>
<th></th>
<th>PLT (13.4-34.9)</th>
<th>AST (10-40)</th>
<th>ALT (5-40)</th>
<th>ALP (115-359)</th>
<th>γ-globulin (10.5-20.3)</th>
<th>ICG R15 (0-10)</th>
<th>AFP (&lt;10.0)</th>
<th>PIVKAII (&lt;40)</th>
<th>CEA (&lt;5.0)</th>
<th>CA19-9 (&lt;37.0)</th>
<th>14%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLT</td>
<td>23.3×10^3/μl</td>
<td>21 U/L</td>
<td>5 U/L</td>
<td>352 U/L</td>
<td>23%</td>
<td>14%</td>
<td>5.0 ng/mL</td>
<td>36 mAU/mL</td>
<td>1.3 ng/ml</td>
<td>34.3 U/ml</td>
<td></td>
</tr>
</tbody>
</table>

*PLT, platelets; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AFP, alpha-fetoprotein; ICG R15, indocyanine green retention15; PIVKAII, protein-induced vitamin K absence; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9. *inside ( ), normal data.

**Table 2**: US, CEMRI in the hepatobiliary phase and CT angiogram Findings.

<table>
<thead>
<tr>
<th>Location and size</th>
<th>US</th>
<th>CEMRI HBP</th>
<th>CTAP</th>
<th>CTHA early</th>
<th>CTHA late</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>S2 11 mm</td>
<td>Hyperechoic</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>b</td>
<td>S3 25 mm</td>
<td>Hyperechoic</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>c</td>
<td>S4 14 mm</td>
<td>Hyperechoic</td>
<td>Low</td>
<td>iso</td>
<td>Low + periphery iso</td>
</tr>
<tr>
<td>d</td>
<td>S5 10 mm</td>
<td>Hyperechoic</td>
<td>Low</td>
<td>Low</td>
<td>slight low</td>
</tr>
<tr>
<td>e</td>
<td>S6 12 mm</td>
<td>Hyperechoic</td>
<td>Low</td>
<td>slight low</td>
<td>slight low</td>
</tr>
</tbody>
</table>

*1 CEMRI, contrast enhanced magnetic resonance imaging
*2 HBP, hepatobiliary phase
*3 CTAP, computed tomography during arterial portography
*4 CTHA, computed tomography during hepatic arteriography
Discussion

HCA is a rare benign liver tumor, the major risk factor of which is exposure to estrogenic or androgenic steroids. Among young women with HCA, 80% have of OC, and the risk increases with duration of use [2,31]. The prevalence of HCA appears to be declining as low-estrogen preparations become more widespread. The lesions usually shrink after abstaining from OC or discontinuing it after menopause. Patients taking androgens for Fanconi anaemia or for acquired aplastic anaemia are also at risk. Nonhormonal risk factors include glycogenosis type 1 (von Gierke disease) or 3 (Forbes disease), galactosaemia [32], tyrosinaemia, familial polyposis coli, and hepatic iron overload with β-thalassaemia. Obesity has recently been shown to be a risk factor for a particular HCA subtype [33]. In the present case, no such factors were in evidence.

Clinical presentation may include abdominal pain, abdominal mass, intraperitoneal hemorrhage, abnormal liver tests, or a liver mass found incidentally during imaging studies. In our study, liver nodules were found incidentally during imaging studies, in the absence of characteristic symptoms. Clinically significant hemorrhage is observed in 20-25% of HCA cases [1]; the risk being highest when the tumours are > 5 cm. Malignant transformation to HCC is rare but well-documented, occurring in up to 7% of cases reported from referral centers. The risk of transformation varies with HCA subtype and with clinical association, being higher in patients with glycogenosis or androgenic-anabolic steroid use [33].

Recently, a comprehensive analysis of genetic, pathological, and clinical features in a series of 96 HCA cases has identified 4 subtypes [33-36]. The authors tested for the expression of candidate genes at the Ribonucleic Acid (RNA) level, using Quantitative Reverse Transcriptase Polymerase Chain Reaction (QRT-PCR), and at the protein level, using immunohistochemistry [34]. Biallelic HNF-1α mutations defined the first group of HCA, phenotypically characterized by marked steatosis, lack of cytological abnormalities, and inflammatory infiltrates. Immunohistochemistry validation confirmed that the absence of L-FABP expression rightly indicated HNF-1α mutation (100% sensitivity and specificity). Presence of β-catenin-activating mutation defined the second group of HCA, representing 15% of the cases generally characterized by a higher risk of malignant transformation in HCC. The combination of glutamine synthetase overexpression and nuclear β-catenin staining were excellent predictors of β-catenin-activating mutation (85% sensitivity, 100% specificity). The third group of HCA was defined by the presence of inflammatory infiltrates and showed more or less obvious additional features such as sinusoidal dilatation, dystrophic vessels, and ductular reaction. SAA hepatocytic staining was ideal for classifying inflammatory HCA (91% sensitivity and specificity). Using this classification, the lesions initially termed telangiectatic FNH and recently proposed as an HCA subtype resembled inflammatory HCA. Finally, the fourth group of HCA included nonmutated HNF-1α lesions or β-catenin, but not inflammatory infiltrates [34].

Immunohistochemical diagnostic modalities can be used to identify patients with HCA who are at risk of developing HCC, and may, therefore, also provide important information for clinical decision-making in terms of treatment and follow-up of patients. To make differential diagnoses among HCA, FNH and well-differentiated HCC, and to classify HCA subtypes, US guided liver biopsy was carried out in our case. The nodules in S3, S5 and S6 showed slight hypercellularity with fatty change, without a high N/C ratio; histological aspects showed an irregular thin trabecular pattern. Immunohistochemical staining showed loss of L-FABP and negativity for SAA, CRP, GS, OATP and β-catenin. The above histopathological findings led to our diagnosis of multiple HCA (HNF-1α inactivated type) attributed to an intrahepatic portosystemic venous shunt. Radiological diagnosis can be challenging because of the various and nonspecific features of HCA.

On the other hand, MRI facilitates the differentiation between FNH and HCA [27]. Recent studies have provided evidence that OATP1B3 contributes to the uptake by hepatocytes of CEMRI, a recently developed hepatocyte-specific contrast agent for MRI, which has provided more useful information for improving the detection and diagnosis of many hepatocellular nodules, including HCC and FNH [7]. The authors have shown that a close association between preserved or enhanced OATP1B3 expression and β-catenin activated type HCA provides an important modality for clinical decisions in the treatment and follow-up of patients with HCA [37]. In our case, immunohistochemical analysis showed no OATP1B3 expression; MRI imaging, on the other hand, showed hypointense nodules in the hepatobiliary phase in the nodules in segments 3, 5 and 6. Some cases of HNF-1α inactivated adenoma have demonstrated high uptake of 18F-FDG of PET, although the precise mechanism of the uptake remains to be elucidated [3]. In our case, uptake of 18F- FDG was not observed.

Well-known typical lesions (FNH, NRH and Idiopathic Portal Hypertension (IPH)) are explained by a single etiological mechanism of “Anomaly of the portal tract” and are collectively called “Anomalous portal tract syndrome” [38]. CEPS are rare venous malformations wherein mesenteric venous blood drains directly into the systemic circulation. Hepatocellular nodules attributed to CEPS and resulting in abnormal portal blood flow have been reported in over 40% of CEPS patients, and to be mostly cases of benign FNH, sometimes HCA, HB and HCC that can be multifocal or massive.

On the other hand, since the initial report of congenital intrahepatic shunt in 1956 [28], the 14 intrahepatic portohepatic
venous shunts described can be arbitrarily categorized into four different morphologic types [39]: The first and most common type is a single large tube of constant diameter that connects the right portal vein to the inferior vena cava. The second is a localized peripheral shunt with single or multiple communications between the peripheral branches of portal and hepatic veins in one hepatic vein segment. The third is aneurysmal: peripheral portal and hepatic veins are connected through an aneurysm. The fourth has multiple communications between peripheral portal and hepatic veins, diffusely in both lobes. The tubular shunt in our case was of the first type. In most reports the patients were over 50 years old (the oldest was 75 years old), and the chief complaints were personality changes or abnormal mental status due to portosystemic encephalopathy.

Most patients with this type of intrahepatic portosystemic shunt demonstrated clinical evidence of liver cirrhosis and portal hypertension. One researcher considered this unusual communication of portal vein to the vena cava was a patent ductus arteriosus. Nonetheless, Park et al. [39] considered the typical course of this type of intrahepatic portosystemic shunt is different from that of the patent ductus arteriosus. First, the shunt connects the right portal vein instead of the left to the vena cava [39]. Second, the relation of the intrahepatic course of the shunt to the caudate lobe and the fissure for the ductus venosus was different from that of the patent ductus arteriosus. The cause of intrahepatic portosystemic venous shunts is unknown. Another researcher considered the abnormality to be acquired because microscopic examination showed both the muscular layer and the elastic lamellae had disappeared abruptly from the wall of the shunt and because cerebral manifestation was not apparent until an older age [40].

Nevertheless, a congenital origin of this abnormality has also been postulated. One embryologic explanation for shunts in the right lobe is the persistence of high-flow communication between the omphalomesenteric venous system and the right horn of the sinus venosus. Decreasing tolerance to toxic metabolites with increasing age may explain the late clinical manifestation [39]. In our case, no clinical evidence was found of liver cirrhosis, portal hypertension, particular personal change or abnormal status. The imbalance of portal and hepatic arterial flow [27] is thought to be involved in hepatocellular nodules resulting from CEPS; however, whether that is attributable to an intrahepatic portosystemic venous shunt is unclear. In our case, careful follow-up study was needed for the early detection of HCC irrespective of the HNF-1α inactivated subtype with low risk of malignant transformation. However, she did not come to our hospital again irrespective of repeated our recommendation. To the best of our knowledge, this is the first case of multiple HNF-1α inactivated type HCA due to an intrahepatic portosystemic venous shunt. Further studies may provide insights into diagnostic strategies and the mechanism of the histogenesis of HCA.

**Author Contributions**

Kim SK conceived the case and wrote the manuscript; Kim SR and Imoto S observed the clinical course of the patient and made the figures; Fujii Y, Fujii T, Yuasa K, Ohtani A and Hayakumo T observed the clinical course of the patient; Kobayashi H conducted the radiological examinations; Hayashi Y, Koma Y and Nakashima O examined histology of the specimen; Kumabe T and Kudo M interpreted the imaging findings.

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**References**


