Hyperplastic Nodular Hepatic Lesions Following End-to-side Portacaval Shunting in Childhood

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Abstract

We describe a 48-year-old man with nodular intrahepatic lesions accompanied by communication between the inferior vena cava and portal systems as well as absence of intrahepatic portal veins. After infection with malaria in childhood, end-to-side portacaval shunting had been performed to treat upper gastrointestinal bleeding at the age of 15 years. A biopsy specimen obtained under ultrasonographic guidance showed hyperplastic nodules suggestive of focal nodular hyperplasia. The estradiol concentration in the blood was elevated (55 pg/ml). This case suggests that portacaval shunting may be associated with hyperplastic liver nodules through hyperestrogenemia and abnormal hepatic hemodynamics.

Key words: portacaval anastomosis, focal nodular hyperplasia, hyperestrogenemia

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Introduction

End-to-side portacaval anastomosis, termed an Eck fistula (1, 2), is an operation performed to treat life-threatening portal hypertension by creating a major shunt between the inferior vena cava (IVC) and the portal trunk. The structural relationship between portal and systemic veins after portacaval shunting is similar to that seen in congenital absence of the portal vein (CAPV), which often is associated with hyperplastic liver lesions. Development of such lesions following a portacaval shunt procedure has been reported only in patients with type I glycogen storage disease (GSD-I). The present case appears to be the first occurrence of benign hyperplastic liver lesions to follow portosystemic shunting in a patient with no other condition predisposing to hepatic neoplasia.

Case Report

A 48-year-old Japanese man was referred to our institu-

tion because of nodular intrahepatic lesions recently detected ultrasonographically at another hospital. He was infected with malaria (from his uncle) in childhood and received medication. No further details regarding his medication were available. Splenectomy was performed when the patient was 5 years old. At 15 years old hematemesis occurred, most likely a result of portal hypertension. A shunt operation was performed, and a blood transfusion was given. Earlier abdominal ultrasonography, performed 13 months before referral to our hospital, had shown no nodular lesion in the liver.

On admission to our hospital, his performance status was excellent. No symptoms of malaria were evident. The liver was not palpable. A healed midline abdominal scar was noted. The patient's history disclosed only minimal alcohol intake. Serologic and molecular tests for hepatitis B and C viruses (HBV and HCV) indicated past infection by both viruses [HB surface antigen negative, HB core antibody positive, HCV antibody positive, HCV-RNA negative]. Serum chemistry data showed mild elevations of aspartate aminotransferase (AST, 42 U/L; normal, 13 to 33), gamma-glutamyl transpeptidase (γ -GTP, 81 U/L; normal, 10 to 47),

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lactate dehydrogenase (LDH, 331 U/L; normal, 119 to 229) and hyaluronic acid (59 ng/ml; normal, ≤ 50). Albumin was slightly low (3.49 g/dl; normal, 4.0 to 5.0). Indocyanine green retention (ICG R_{15}) was 55.3% (normal, ≤ 10), while ammonia (NH_3) was 135 $\mu\text{g/dl}$ (normal, 12 to 66).

Abdominal ultrasonography showed evidence of chronic liver damage and steatosis, as well as iso- to hypoechoic nodule in segment VI (20×21 mm in diameter) (Fig. 1). Three smaller nodules were present (7×8 mm in segment VI, 6×8 mm in segment VI, and 10×10 mm in segment VII). Color Doppler ultrasonography revealed an artery branching from an artery at the margin of the largest nodule, then approaching the center of the nodule. No “spoke-wheel” pattern was seen (Fig. 2). Dynamic computed tomography (CT) detected only the largest nodule, which was isodense prior to contrast agent administration and in the delayed phase, showing mild enhancement at the early phase (Fig. 3A, B). Portal flow within the liver or in the portal tract approaching the hepatic hilum was not detected (Fig. 3C). The IVC communicated with the superior mesenteric vein (SMV) and the narrow splenic vein (SV). A normal IVC was not seen inferior to its connection with the SMV and SV; instead, two prominent veins likely to be the left IVC and the testicular vein drained into the left renal vein from below. The complexity of portal and systemic venous anatomy were shown clearly by three-dimensional

(3D) CT (Fig. 4). Magnetic resonance imaging (MRI) showed the largest hepatic nodule to be hyperintense on both T1-weighted and T2-weighted images. Superparamagnetic iron oxide (SPIO)-enhanced MRI using Resovist as a

Figure 1. Ultrasonogram showed an iso- to hypoechoic nodule in segment VI. This largest nodule measured 20×21 mm. The echo pattern in surrounding liver parenchyma demonstrated fatty liver and associated chronic damage.

Figure 2. Color Doppler examination. A: Color Doppler image showed an artery running along the margin of nodule, with a branch turning toward the center of the nodule. B: Fast Fourier transformation indistinctly demonstrated an arterial pulsatile wave in this branched artery.

Figure 3. Abdominal computed tomography. A: The largest nodule showed contrast enhancement in the early phase (arrow). B: The largest nodule appeared isodense in the delayed phase (arrow). C: No portal flow is shown in the liver (delayed phase).

Figure 4. Three-dimensional computed tomography of the venous system. The inferior vena cava (IVC) communicated with the superior mesenteric vein (SMV) and the splenic vein (SV). The IVC disappeared below the level of its connection with the SMV and SV. Two veins, apparently a left IVC and the testicular vein, flowed into the left renal vein. A: Anterior view. B: Right lateral view. IVC: the inferior vena cava, SMV: the superior mesenteric vein, SV: the splenic vein.

contrast agent showed the largest nodule to be hyperintense relative to surrounding liver, indicating less accumulation of Resovist in the nodule (Fig. 5).

A biopsy specimen from the largest nodule consisted of tissue from the nodular lesion and also from surrounding liver (Fig. 6A). Histopathologically, the nodule showed mildly increased cellularity with distinct trabecular architecture, and occasionally a pseudoglandular pattern. Surrounding liver tissue showed mild fatty change. A specimen from a smaller nodule was similar to the trabecular areas of the larger nodule. Both nodules contained areas of fibrous scarring, with a few anomalous arterial vessels and biliary pseudoductules (Fig. 6B). Immunohistochemically, nodule tissue

was strongly reactive to anti-CD34 along sinusoids, while surrounding liver tissue was not (Fig. 6C). Cells reactive to anti-CD68 along a nodule sinusoid were fewer than in surrounding liver (Fig. 6D). The nodules were diagnosed as showing the morphology of focal nodular hyperplasia (FNH). We decided to maintain outpatient clinical follow-up as opposed to treatment for tumors such as resection.

Discussion

We could not obtain any detailed early-life medical records concerning the patient's infection with malaria, splenectomy or shunt operation. Based upon radiologic findings

and any past history that the patient and his mother could remember, we concluded that somehow he was infected with malaria from his uncle, then underwent splenectomy as a treatment related to malaria. End-to-side portacaval shunting was carried out as treatment for portal hypertension conse-

Figure 5. Magnetic resonance imaging using superparamagnetic iron oxide (Resovist). This enhanced imaging showed the largest nodule to be hyperintense relative to surrounding liver (arrow).

quent to malaria or to portal thrombosis after splenectomy. Antibodies characteristic of malarial infection were negative, and no organisms could be found in blood smears when the patient was admitted, most likely because the infection was remote.

Paucity of intrahepatic portal blood flow resulted from the shunt operation at age 15. Images from 3D-CT suggested the absence of the IVC below its junction with the left renal vein was congenital. Lack of intrahepatic portal blood flow and radiologic configurations of the portal and systemic veins in the present patient resembled those of congenital absence of the portal vein (CAPV) type Ib (liver not perfuse with portal blood, while the SMV and SV form a confluence) (3, 4). Although our patient was not examined by angiography, 3D-CT clearly depicted the complexities of the abnormal abdominal vascular anatomy.

Biopsy specimens from nodular hepatic lesions in the present case showed marked hepatocytic hyperplasia with an area of fibrosis scarring containing anomalous vessels and showing marked sinusoidal capillarization as seen in FNH. Hirohashi et al demonstrated that FNH included capillarized sinusoids (5), while Tanaka et al showed that 15% of FNH cases showed fewer Kupffer cells in nodules than in surrounding liver tissue (6). Imaging findings in the largest nodule closely depicted the pathologic findings. Hypervascu-

Figure 6. Pathologic findings in biopsy specimens. A: A specimen from the largest nodule (20×21 mm, in segment IV) consisted of tissue from the nodule (left) and surrounding liver (right). Tissue from the nodule showed mildly increased cellularity, a distinct trabecular pattern, and occasional pseudoglands. The surrounding liver showed mild fatty change (hematoxylin and eosin stain, ×200). B: A specimen from a smaller nodule (7×8 mm, in segment IV) contained a fibrous scar with anomalous arterial blood vessels (Azan stain, ×100). C: Immunostaining with anti-CD34 showed a strongly positive reaction in sinusoidal endothelial cells (capillarization) in tissue from the largest nodule (left), exceeding the reactivity in the surrounding tissue (right)(×200). D: Immunostaining with anti-CD68 demonstrated fewer positive cells in the largest nodule (left) than in the surrounding liver (right)(×200).

larity seen by dynamic CT corresponded to anomalous arterial vessels in a fibrous scar, as well as marked sinusoidal capillarization. Findings by SPIO-enhanced MRI are explained by a decrement of CD-68-positive cells, possibly Kupffer cells, along the sinusoids. Accordingly, the nodules were highly suggestive of multiple FNH lesions.

Various hyperplastic liver lesions have been associated with portal venous abnormalities, and frequently occurring in association with CAPV (7), a rare malformation seen mostly in children. Reviewing the literature concerning CAPV, De Gaetano et al found that 15 of 31 cases had hepatic tumors (7): hepatoblastoma in 1, FNH in 9, adenoma in 1, nodular regenerative hyperplasia (NRH) in 1, hemangioma in 1, and hepatocellular carcinoma (HCC) in 2. Additionally, 2 cases of CAPV with FNH (8, 9), 1 case with HCC (10), 3 cases with NRH (11, 12), and 3 cases with hyperplastic nodular hepatic lesions (13-15) recently were reported. Hemodynamic imbalance with insufficient blood supply and nonuniform arterial perfusion to the liver would appear likely to induce hyperplasia in livers of patients with CAPV (16, 17). In addition, the portal vein carries substances in splanchnic venous blood such as insulin, glucagon, epidermal growth factor and other hepatotrophic peptides. As these substances regulate hepatocytic function and development, diversion of portal flow may induce abnormalities by causing dysregulation (18, 19).

Alteration of portal and systemic venous structure thus would appear to be a likely cause of hyperplasia of hepatocytes in the present case, as in the occurrence of hyperplastic liver lesions in patients with CAPV. Grün et al reported that portacaval anastomosis in rats resulted in hyperestrogenemia and hypoandrogenemia, while the occurrence of FNH also has been observed (20). In the present case testosterone was in the normal range (5.30 ng/ml; normal, 2.07 to 7.61), while estradiol was elevated (55 pg/ml; normal, 15 to 35). Elevated estrogen in the systemic circulation after portacaval shunting may induce formation of hyperplastic nodular lesions in the liver. The observed association of FNH with oral contraceptive use (21), as well as estrogen receptor expression in mammalian hepatocytes (22) would support this speculation.

While the occurrence of hyperplastic liver lesions includ-

ing FNH has been observed in animal model after experimental portacaval shunting (20, 23), few reports have described benign hyperplastic lesions in livers of a patient with portacaval anastomosis. FNH has been reported in nine patients with type I glycogen storage disease (GSD-I), while five of these nine patients had been treated with a portacaval shunt (24, 25). Takamura et al (24) suggested that portacaval shunts favored the development of FNH in livers of the patients with GSD-I, an inherited disorder frequently accompanied by hepatic tumors (mainly adenomas). Additionally, several studies suggested that portasystemic shunt was associated with a higher risk of developing HCC in the patients with cirrhosis (26, 27). From such previous literature portacaval anastomosis is considered to promote induction of tumor in the liver essentially inclined to develop liver tumor, for example cirrhotic liver or liver of patient with GSD-I. Webster et al (28) reported a hepatic adenoma that became greater after mesocaval shunt for portal venous obstruction, suggesting that portasystemic shunt promotes the development of hyperplastic lesion that already existed in the liver. The liver of present patient was not cirrhotic, Budd-Chiari syndrome and GSD-I were also excluded, and earlier abdominal ultrasonography had shown no nodular lesion in the liver. Thus, our case suggested that portasystemic shunt may produce a tumor in a liver with originally no tumor, and in the liver of a patient with no inclination to develop hepatic neoplasm. Previous malaria infection might have been associated with the occurrence of hyperplastic lesion in the present case. However, there is no report of hepatic tumor of a patient with malaria, only fibrosing necrotic nodule has been reported (29). One study suggested a negative correlation of malaria with HCC (30).

Our report appears to be the first to describe benign hyperplastic lesions in the human liver following portasystemic anastomosis, except for patients with GSD-I. This case suggests that iatrogenic changes in the portal and systemic venous systems can result in hyperestrogenemia and disappearance of intrahepatic portal flow to cause hyperplastic nodule formation in a previously normal liver. This case supports the theory that abnormality of intrahepatic blood flow initiates hyperplasia of hepatocytes which is often observed in the liver of patients with CAPV.

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