Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.5914-20
Intern Med 60: 1839-1845, 2021
http://internmed.jp

【 CASE REPORT 】

An Adult Case of Congenital Extrahepatic Portosystemic Shunt Successfully Treated with Balloon-occluded Retrograde Transvenous Obliteration

Hironori Tanaka[1], Yoshihito Saijo[2], Tetsu Tomonari[1], Takahiro Tanaka[1], Tatsuya Taniguchi[1], Shusuke Yagi[2], Koichi Okamoto[1], Hiroshi Miyamoto[1], Masahiro Sogabe[1], Yasushi Sato[1], Naoki Muguruma[1], Koichi Tsuneyama[3], Masataka Sata[2] and Tetsuji Takayama[1]

Abstract:
A 42-year-old woman visited our hospital due to syncope. Contrast-enhanced CT revealed portosystemic shunt, portal vein hypoplasia, and multiple liver nodules. The histological examination of a liver biopsy specimen exhibited portal vein hypoplasia and revealed that the liver tumor was positive for glutamine synthetase. The patient was therefore diagnosed with congenital extrahepatic portosystemic shunt type II, and with focal nodular hyperplasia (FNH)-like nodules. She had the complication of severe portopulmonary hypertension and underwent complete shunt closure by balloon-occluded retrograde transvenous obliteration (B-RTO). The intrahepatic portal vein was well developed at 1 year after B-RTO, and multiple liver nodules completely regressed. Her pulmonary hypertension also improved.

Key words: B-RTO, congenital extrahepatic portosystemic shunt, FNH-like nodule, portopulmonary hypertension

(Intern Med 60: 1839-1845, 2021)
(DOI: 10.2169/internalmedicine.5914-20)

Introduction

A congenital extrahepatic portosystemic shunt (CEPS) in association with a hypoplastic or absent portal vein is a malformation of the splanchnic venous system, which is also known as Abernethy malformation (1). In this rare condition, intestinal and splenic venous flow is diverted into the systemic circulation, bypassing the liver. Usually CEPS is seen in children and associated with multiple anomalies such as cardiac failure, skeletal abnormities, and hepatic tumors (2). We herein report a case of adult CEPS that was successfully treated with balloon-occluded retrograde transvenous obliteration (B-RTO), resulting in the complete regression of hepatic focal nodular hyperplasia-like lesions and the improvement of pulmonary hypertension.

Case Report

A 42-year-old woman presented to our hospital with syncope and dyspnea. She had a history of acute pancreatitis but no observed abnormalities at birth and no history of abdominal trauma. The results of a physical examination were unremarkable.

Laboratory data showed elevated levels of aspartate aminotransferase (53 U/L; normal, 13-30 U/L), alanine aminotransferase (34 U/L; normal, 7-23 U/L); alkaline phosphokinase (557 U/L; normal, 106-322 U/L); gamma-glutamyl transpeptidase (255 U/L; normal, 9-32 U/L); total-bilirubin (2.4 mg/dL; normal, 0.4-1.5 mg/dL); ammonia (145 μg/dL; normal, 12-66 μg/dL), and total bile acid (177.7 μmol/L; normal, 2.9-11.0 μmol/L), brain natriuretic peptide

[1]Department of Gastroenterology and Oncology, Tokushima University Graduate School of Biomedical Sciences, Japan, [2]Department of Cardiovascular Medicine, Tokushima University Graduate School of Biomedical Sciences, Japan and [3]Department of Pathology and Laboratory Medicine, Tokushima University Graduate School of Biomedical Sciences, Japan
Received: July 20, 2020; Accepted: November 27, 2020; Advance Publication by J-STAGE: January 15, 2021
Correspondence to Dr. Tetsuji Takayama, takayama@tokushima-u.ac.jp

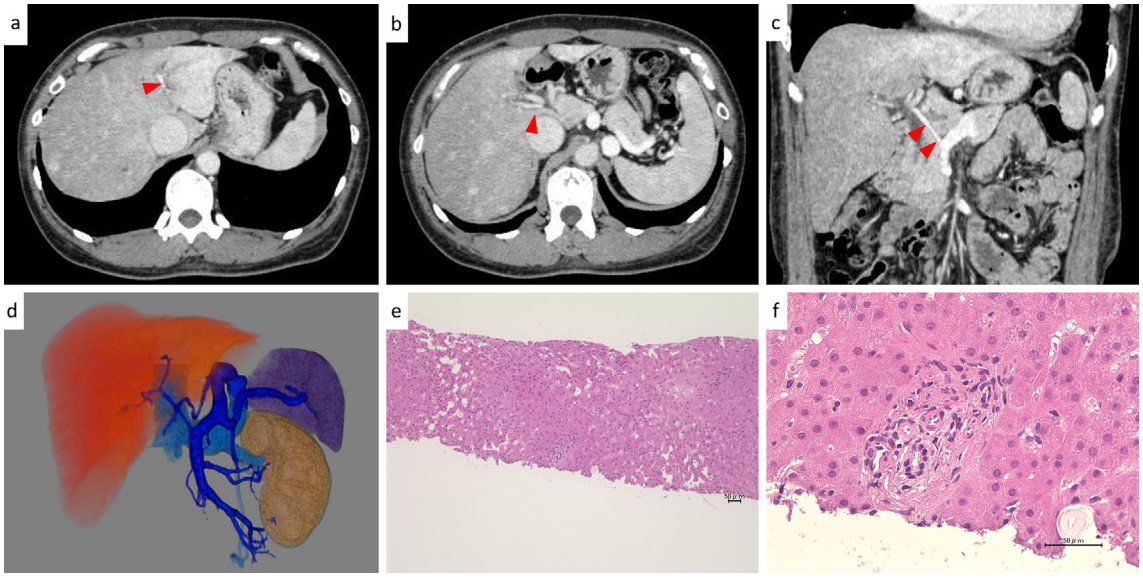

Figure 1. **Abdominal CT of portal vein hypoplasia and portosystemic shunt and histology of FNH-like lesions. (a, b) Abdominal contrast-enhanced CT showed tapering of the left and right portal vein (arrowhead). (c) Coronal CT images showed a narrowed main trunk of the portal vein. (d) Three-dimensional computed tomography showed shunt flow from the portal vein draining into the left renal vein. (e, f) A histological examination of the liver tissue revealed a decreased portal area and marked portal vein hypoplasia. No cirrhotic changes were observed. FNH: focal nodular hyperplasia**

(BNP) (314.1 pg/mL; normal, <18.4 pg/mL); and an increased prothrombin time-international normalized ratio (PT-INR) (1.48; normal, 0.85-1.15). The tumor markers α-fetoprotein and des-gamma carboxyprothrombin were within normal range (3 ng/mL and 21 mAU/mL, respectively). Tests for hepatitis viruses, autoimmune antibodies, and hyper-gammaglobulinemia were negative.

Abdominal contrast-enhanced CT showed hypoplasia of the intra- and extra-hepatic portal vein (Fig. 1a-c). CT also revealed the presence of multiple nodules of ≤2 cm in diameter in the liver. Three-dimensional (3D) vessel reconstruction revealed that the splenic and mesenteric veins joined in a regular fashion but afterward anastomosed with the left renal vein via the left and posterior gastric vein (Fig. 1d). A histological examination of liver biopsy samples from the non-nodular area exhibited portal vein hypoplasia with no evidence of cirrhosis (Fig. 1e, f). Based on these results, a diagnosis of CEPS type II was reached.

The multiple liver nodules demonstrated T1 and T2 isointensity in magnetic resonance imaging (MRI). Following the administration of the contrast agent gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA), the nodules exhibited high intensity in the arterial phase, portal-venous phase, and hepatobiliary phase (Fig. 2). Similarly, ultrasonography showed multiple low-echoic tumors in the liver. Contrast-enhanced ultrasonography showed their enhancement in the arterial phase, and sustained enhancement even in the portal and post-vascular phases (Fig. 3). The histological examination of a biopsy specimen from the nodular area revealed that the cell density was increased, although the thin cord-like structure was preserved with no attenuation of the reticulin fibers. Berlin blue staining exhibited hemosiderin deposition in the nodule tissue. Immunohistochemistry revealed that the cells in the nodule were positive for serum amyloid A (SAA), and weakly positive for glutamine synthetase (GS), but negative for heat shock protein 70 (HSP 70) and glypican 3 (Fig. 4). Based on the MRI and histological findings, the liver tumors were diagnosed as focal nodular hyperplasia (FNH)-like nodules.

A chest X-ray revealed remarkable hilar pulmonary artery dilatation and a cardiothoracic ratio (CTR) of 62% (Fig. 5a). Thoracic CT showed cardiomegaly and pulmonary artery dilation. Electrocardiography (ECG) showed regular sinus rhythm and right ventricular hypertrophy (Fig. 5b). Echocardiography revealed dilation of the right atrium and right ventricle, and severe tricuspid regurgitation. The peak velocity of tricuspid regurgitation was 4.6 m/s, and the tricuspid regurgitation pressure gradient (TRPG) was 85 mmHg (Fig. 5c-e). A cardiac catheter examination at rest showed a mean pulmonary arterial pressure (PAP) of 67 mmHg, pulmonary vascular resistance (PVR) of 16.6 Wood units, left ventricular end-diastolic pressure of 10 mmHg, and cardiac index of 2.7 L/min/m^2, with a normal left ventricular ejection fraction and no coronary artery lesions. The 6-min walk distance (6MWD) was 270 m. Therefore, a diagnosis of severe portopulmonary hypertension (PoPH) was reached, based on the diagnostic criteria for PoPH (3). Esophagogastroduodenoscopy did not show any evidence of esophageal varices.

Since angiography revealed that the intrahepatic portal vein was preserved to some degree, we decided to perform interventional closure of the portosystemic shunt. Under lo-

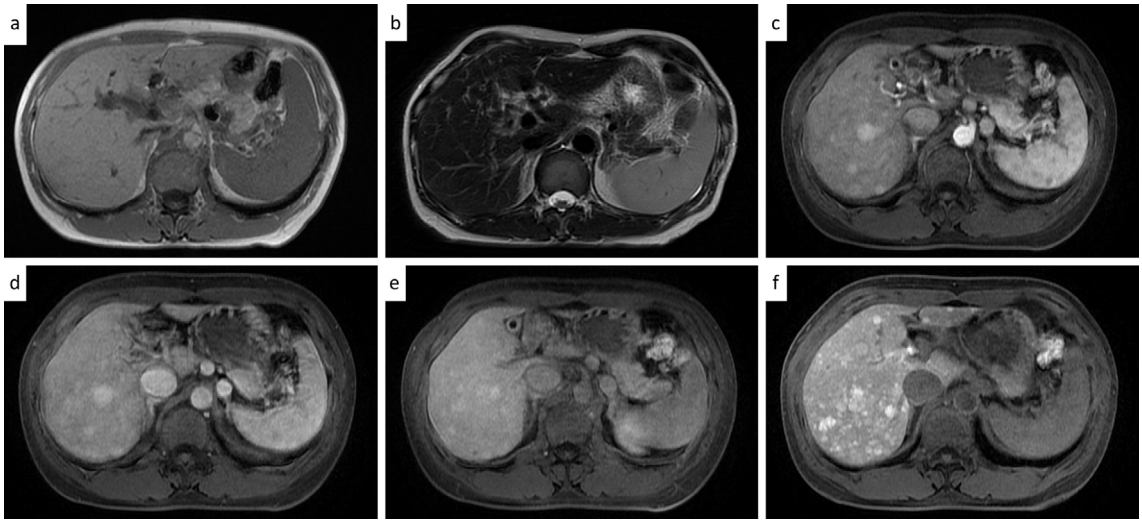

Figure 2. **Gadoxetic acid (Gd-EOB-DTPA) enhanced magnetic resonance imaging. (a, b) T1 and T2-weighted MRI images. (c-f) Following the administration of the contrast agent Gd-EOB-DTPA, enhancement of the nodule was observed at the arterial phase (c), the enhancement persisted through the portal phase (d), and delayed phase (e), and Gd-EOB-DTPA was taken up into the cells in the hepatocellular phase (f).**

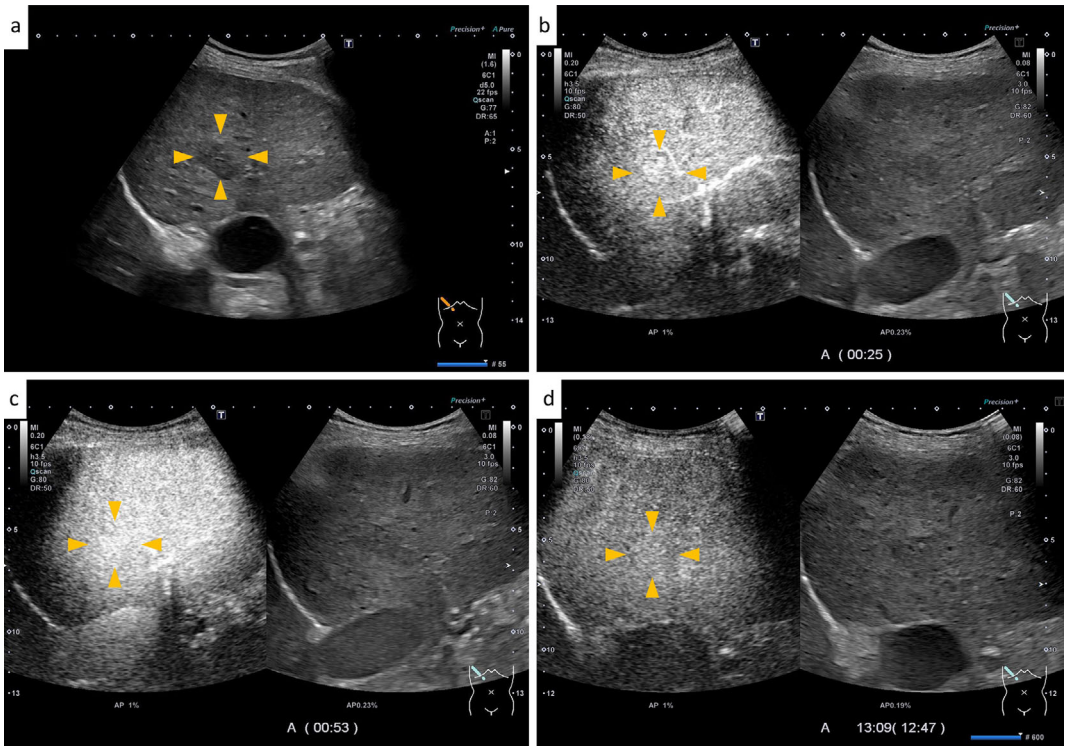

Figure 3. **Abdominal ultrasonography imaging. (a) B-mode imaging showed multiple low echoic masses. (b-d) Contrast-enhanced ultrasonography showed enhancement in the arterial phase and sustained enhancement in the portal and post-vascular phases.**

cal anesthesia, a balloon catheter (Serecon MP catheter II; Terumo Clinical, Tokyo, Japan) was inserted into the porto-systemic shunt through the right femoral vein. Balloon-occluded retrograde transvenous venography (B-RTV) revealed severe hypoplasia of the portal vein (Fig. 6a). The direct portal venous pressure before occlusion was slightly elevated (20 mmH_2O) but was not increased after balloon occlusion. Because we confirmed that shunt occlusion did not elevate the portal pressure, we carried out shunt closure by B-RTO. The first embolization was deploying a micro-coil (Target XL; Stryker, Kalamazoo, USA) in the posterior gastric vein (PGV), a thicker shunt vessel, through a balloon catheter under temporary balloon occlusion. Four months after the first embolization, B-RTV revealed dilation of the

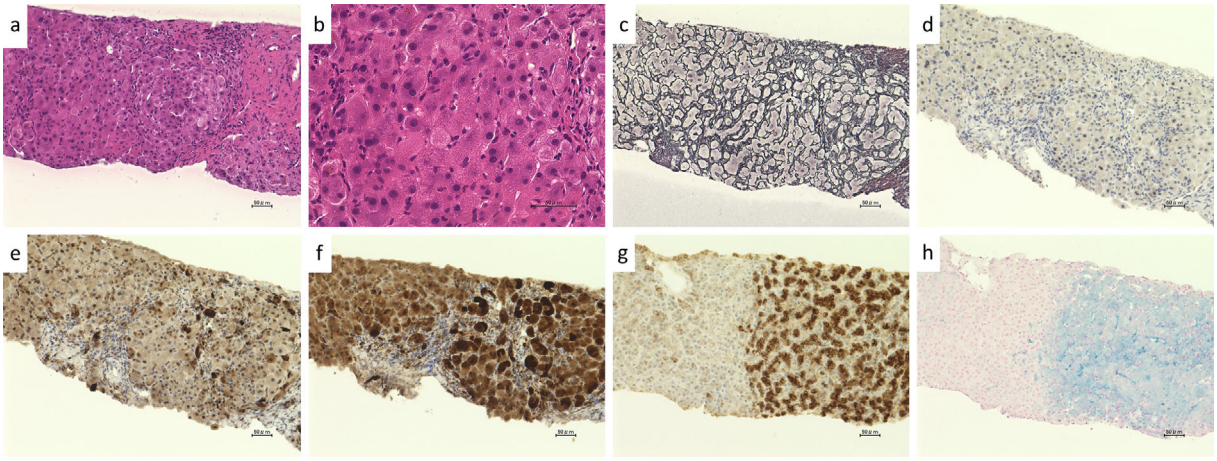

Figure 4. **Histological findings of a biopsy sample from an FNH-like nodule in the liver. (a, b) Low and high magnification of Hematoxylin and Eosin staining sections. The liver cell density was slightly increased. (c) Reticulin staining showed reticulin fibrosis along the liver sinusoids. (d, e) Cells in the nodule were negative for glypican 3 (d) and HSP 70 (e). (f, g) Cells in the nodule were positive for glutamine synthetase (f) and serum amyloid A (g). (h) Berlin blue staining showed hemosiderin deposition.**

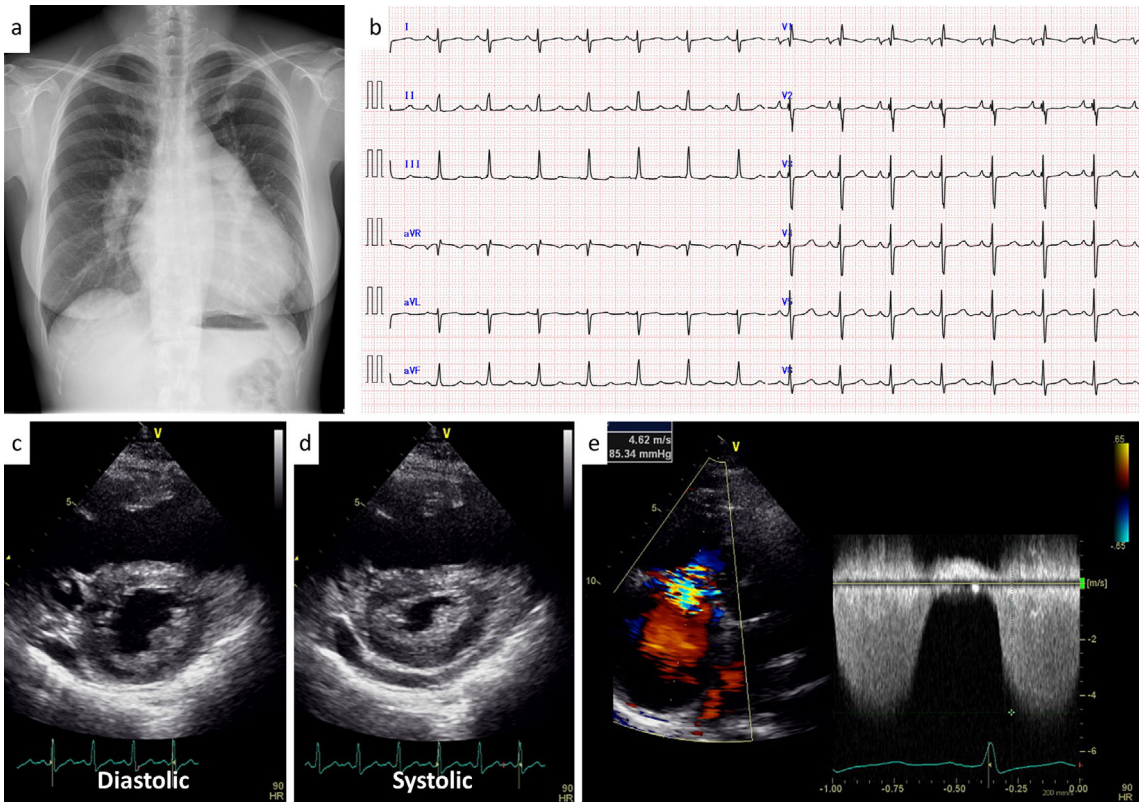

Figure 5. **Chest X-ray, electrocardiography (ECG) and ultrasound imaging of the heart. (a) A chest X-ray showed remarkable hilar pulmonary artery dilatation; the cardiothoracic ratio was 62%. (b) ECG showed regular sinus rhythm and right ventricular hypertrophy. (c, d) The parasternal short-axis view showed an enlarged right ventricle and flattened ventricular septum. (e) A Color Doppler examination showed severe tricuspid regurgitation. The tricuspid regurgitation pressure gradient was calculated to be 85 mmHg.**

portal vein, suggesting increased blood flow in the portal vein (Fig. 6b). We then performed a second embolization by deploying a micro coil in the left gastric vein (LGV), a thinner shunt vessel, using the same method. At nine months after the first embolization, we performed a final embolization by injecting monoethanolamine oleate (Oldamin®, Fuji

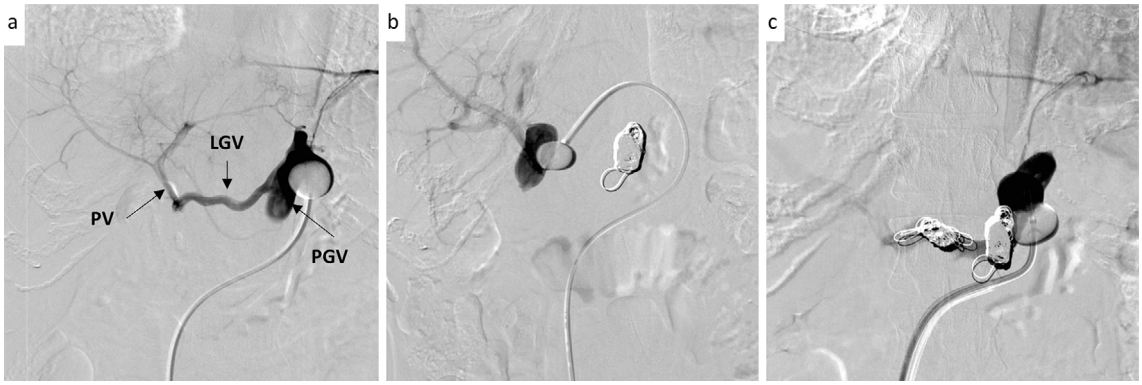

Figure 6. **Balloon-occluded retrograde transvenous venography (B-RTV). (a) B-RTV revealed severe hypoplasia of the portal vein and dilated left gastric vein (LGV) and post gastric vein (PGV) before treatment. (b) Four months after the first embolization of PGV, B-RTV resulted in improvement of PGV dilatation and increased the blood flow of the portal vein, while LGV dilatation remained. (c) At 9 months after the first embolization (5 months after the embolization of LGV), B-RTV showed residual blood flow in the LGV with improvement of LGV dilatation.**

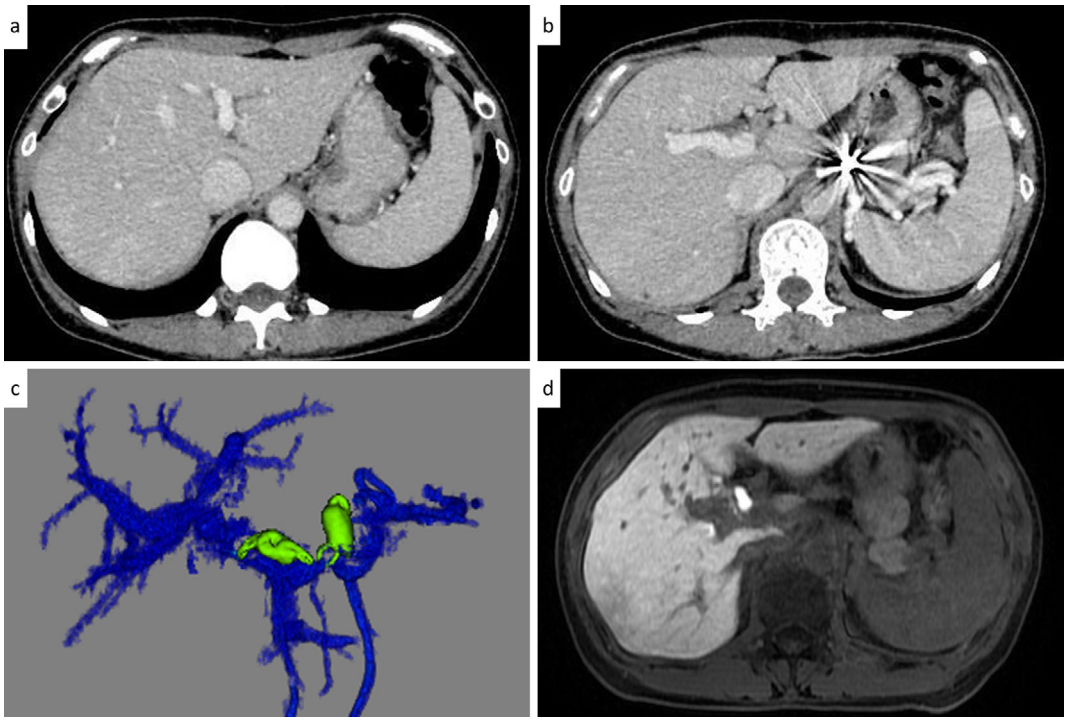

Figure 7. **Abdominal CT and MRI findings after balloon-occluded retrograde transvenous obliteration (B-RTO). (a, b) Axial CT images after B-RTO showed development of intra- and extrahepatic portal veins. (c) Three-dimensional computed tomography imaging showed intra- and extrahepatic portal vein development. The coils were placed on the left and post gastric veins, shown in the image, and the shunt vessel disappeared completely at 6 months after B-RTO. (d) Gd-EOB-DTPA enhanced MRI at 6 months after B-RTO showed complete regression of multiple FNA-like lesions in the hepatobiliary phase.**

Chemical Industry, Toyama, Japan) to obtain complete portosystemic shunt closure (Fig. 6c). No apparent complications occurred either during or after this procedure.

At six months after complete occlusion, the hepatic function improved and the ammonia level significantly decreased. The intrahepatic portal vein was developed considerably better on contrast-enhanced CT at 1 year after the first occlusion in comparison to before treatment. Gd-EOB-DTPA enhanced MRI showed marked regression of multiple liver nodules (Fig. 7). Following treatment with antipulmonary hypertension agents (tadalafil, macitentan and selexipag in combination), the patient's 6MWD improved (535 m) and her BNP was normalized (Table). The TRPG assessed by echocardiography decreased to 62 mmHg. A

Table. Parameters Associated with Pulmonary Arterial Hypertension Measured before and after B-RTO.

Parameter	Before B-RTO	After B-RTO
Brain natriuretic peptide (BNP) (pg/mL)	314.1	7.7
Tricuspid regurgitation pressure gradient (TPRG) (mmHg)	85	62
Systolic/diastolic (mean) pulmonary arterial pressure (PAP) (mmHg)	103/48 (67)	55/27(39)
Pulmonary vascular resistance (PVR) (Wood Units)	16.6	7.7
6-minute walk distance (6MWD) (m)	270	535

B-RTO: balloon-occluded retrograde transvenous obliteration

cardiac catheter examination also showed a decreased mean PAP (39 mmHg) and PVR (7.7 Wood units). The hepatocellular uptake index (HUI) of Gd-EOB-DTPA on MRI, which is correlated with the liver function, increased to 1.91 from 0.69 before treatment, suggesting an improvement of the liver function.

Discussion

CEPS is a rare congenital malformation characterized by the partial or complete absence of the portal vein and subsequent development of an extrahepatic portosystemic shunt (1). Patients with this malformation experience various symptoms including nausea, fatigue, epigastric pain, anorexia, jaundice, encephalopathy due to hyperammonemia (4), hepatopulmonary syndrome (HPS) (5), and PoPH (6-8). The age at the diagnosis ranges from prenatal to 84 years, with 66% of patients diagnosed before 12 years of age (9). Baiges et al. reported that PoPH was diagnosed at a mean age of 20 years (10), while our case was much older. It appears that because the degree of malformation in our case was mild, PoPH developed slowly and was diagnosed when the patient was 42 years of age. PoPH has been reported to be strictly associated with the presence of portosystemic shunt. This suggests that circulating vasoactive factors from the splanchnic circulation play a role in the disease's pathogenesis (11). These shunts divert a large quantity of portal blood flow away from the liver into the systemic circulation. In this way, a number of vascular mediators, proinflammatory cytokines, proangiogenic factors, and bacterial endotoxins circulate directly from the gut into the lung, without being inactivated from the hepatic metabolism; thus, they damage the vascular pulmonary endothelium, promoting endothelial cell proliferation, smooth muscle hypertrophy, and *in situ* thrombosis, and favor the development of PoPH. Furthermore, blood clots from the portal vein can flow into the pulmonary circulation through a portosystemic shunt, contributing to the exacerbation of pulmonary hypertension (12). Finally, the presence of high cardiac output facilitates hypertrophy, proliferation, and vasoconstriction of pulmonary endothelial cells (13).

The liver nodular lesion in our patient showed arterial enhancement and sustained enhancement in the portal and post-vascular phases. The liver nodular lesion in our patient was histologically diagnosed as an FNH-like nodule; it was positive for hemosiderin, GS, and SAA. SAA is frequently positive in FNH-like nodules, as well as in inflammatory hepatocellular adenoma (14). Based on the pathological findings and the presence of portal vein hypoplasia in the patient's liver, the hepatic lesion was diagnosed as an FNH-like nodule. Liver nodular lesions are detected in 15-65% of CEPS cases (9, 10, 15-19). Most are thought to involve benign hepatocellular nodules, such as FNH-like nodules (20, 21), and benign nodules were identified at a median age of 20 years (10). Gulsen et al. hypothesized that liver nodules developed via a mechanism involving changes in liver perfusion (i.e., a large decline in portal blood flow and increased arterial flow) (22, 23). Although central scarring, a characteristic of FNH-like lesions, was not observed, this might be explained by the fact that the nodule was so small. Brancatelli et al. reported that 50% of FNH nodules showed central scarring. However, in nodules of ≤3 cm in diameter, only 3% of FNH nodules showed central scarring (24).

In pediatric cases with CEPS, one-step closure of the shunt is reportedly possible in the absence of portal hypertension (25); however, there is no evidence of the safety of one-step closure in adult cases. Thus, we attempted to close the shunts gradually in multiple steps of B-RTO. The first B-RTO embolized the PGV, a relatively thick vessel, and the second embolized the thinner LGV. However, complete occlusion was difficult with 2 B-RTOs; thus, the third attempt involved complete occlusion using ordamine. After shunt occlusion, the multiple liver nodules in our patient completely regressed. To date, regression of liver nodules and intrahepatic portal vein formation after shunt closure have only been reported in children (17, 26). Franchi-Abella et al. reported that among 22 children who underwent shunt closure, complete regression of liver nodules was observed in 7 patients, and partial regression was observed in 3 patients (25). However, few adult cases of CEPS have been reported in which the liver nodules were completely regressed (27, 28), and there have been no reports of decreased pulmonary arterial pressure. Shunt closure should ideally be performed while the patient is young because the plasticity potential of the intrahepatic portal system in young children would be better than that in adults, probably due to better regeneration (6, 29). We were able to improve the intrahepatic portal flow and liver function by shunt occlusion with B-RTO in this adult case, and as a result, the liver nodules completely

regressed. Moreover, it has been reported that the survival outcome of patients with PoPH is worse than that of patients with idiopathic/familial pulmonary arterial hypertension (i.e., the 2-year survival rate was 67% and 85%, respectively) (30). In our case, however, it was possible to reduce PAP using a combination of B-RTO and anti-pulmonary hypertension agents; the mean PAP decreased from 67 mmHg to 39 mmHg after B-RTO. It is hypothesized that the pulmonary hypertension improved because the closure of the shunt prevented vasoactive factors from flowing into the systemic circulation from the portal circulation.

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

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