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Novel Therapeutic Strategy Using Interventional Radiology (IVR) for Hepatitis C Virus (HCV)-Related Decompensated Liver Cirrhosis: A Case Report

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 72
Final Diagnosis: Decompensated liver cirrhosis
Symptoms: Disturbance of consciousness
Medication: —
Clinical Procedure: PSE • BRTO • HCV treatment
Specialty: Radiology

Objective: Unusual clinical course

Background: The appearance of direct acting antivirals (DAAs) has produced a major paradigm shift in hepatitis C virus (HCV) infection treatment, and virus elimination has become possible in most patients. Improvement of the model for end-stage liver disease (MELD) score by elimination of HCV has been reported, but for decompensated liver cirrhosis, it is also important to overcome various complications before antiviral treatment.

Case Report: A 72-year-old male, who had been treated for HCV-related liver cirrhosis was referred to our hospital for treatment of refractory hepatic encephalopathy. At that time, his Child-Pugh score was 10 and class was C. On contrast-enhanced computed tomography (CT), a splenorenal shunt, splenomegaly, and splenic artery aneurysm were noted. The disease was also complicated by cytopenia associated with hypersplenism, and embolization of the splenic artery aneurysm and partial splenic embolization (PSE) were concomitantly performed. One month after the PSE, balloon occluded retrograde transvenous obliteration (BRTO) for refractory hepatic encephalopathy was performed. Hepatic functional reserve improved compared with that at the first examination, and SOF/LDV therapy was initiated. Fortunately, no adverse effect occurred during treatment, and sustained virologic response (SVR) was achieved. Hepatic functional reserve further improved thereafter. At the time of this report, a Child-Pugh A status was being maintained without administration of a branched chain amino acid preparation, drugs for hyperammonemia, or diuretics.

Conclusions: We encountered a patient with decompensated liver cirrhosis accompanied by complications of hypersplenism, hepatic encephalopathy, and splenic artery aneurysm. These complications were overcome by treatment with PSE and BRTO, which led to DAAs treatment and a marked improvement of hepatic function.

MeSH Keywords: Hepatitis C Antibodies • Liver Cirrhosis • Splenomegaly

Abbreviations: **LC** – liver cirrhosis; **CT** – computed tomography; **IFN** – interferon; **DAAs** – direct acting agents; **SOF** – sofosbuvir; **LDV** – ledipasvir; **GLE** – glecaprevir; **PIB** – pibrentasvir; **PSE** – partial splenic embolization; **BRTO** – balloon-occluded retrograde transvenous obliteration; **IVR** – interventional radiology; **VEL** – velpatasvir; **ADL** – activities of daily living; **QOL** – quality of life; **HVPG** – hepatic venous pressure gradient; **MPR** – multi-planar reconstruction; **EOI** – ethanolamine oleate with iopamidol

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Background

The treatment outcome of chronic liver disease type C has markedly improved compared with that in the era of interferon (IFN)-based treatment. After telaprevir was launched in 2011, direct acting agents (DAAs) that directly inhibit virus multiplication in combination with pegylated interferon and ribavirin have greatly improved therapeutic effects [1–3]. Furthermore, a NS5A inhibitor and second-generation protease inhibitor appeared in 2014, and IFN-free therapy for genotype 1 with oral drugs alone without IFN has become possible [4]. A nucleic acid-type NS5B polymerase inhibitor, sofosbuvir (SOF), for genotype 2 then appeared in 2015 [5], and a ledipasvir (LDV)/SOF combination tablet for genotype 1 was subsequently introduced [6]. In 2017, the introduction of a pan-genotype oral drug, glecaprevir (GLE)/pibrentasvir (PIB) has allowed control of chronic liver disease type C, including compensated liver cirrhosis [7]. SOF/velpatasvir (VEL) became available for treatment of decompensated liver cirrhosis in Japan in January 2019 [8]. Decompensated liver cirrhosis may be included in the treatment target in the future and the risk of complications can be reduced by elimination of hepatitis C virus (HCV) [9–11]. However, improvement of activities of daily living (ADL) and quality of life (QOL) and prolongation of survival cannot be expected with this treatment alone, and greater importance is attached to control of various complications, such as portal hypertension. We encountered a patient with decompensated liver cirrhosis type C and several complications, including cytopenia associated with hypersplenism, hepatic encephalopathy accompanied by hyperammonemia, and splenic artery aneurysm with a risk of rupture. Treatment with partial splenic embolization (PSE) and balloon-occluded retrograde transvenous obliteration (BRTO) were performed for improvement of hepatic functional reserve and control of complications, and HCV was successfully eliminated by SOF/LDV.

Case Report

The patient was a male in his 70s. He had been diagnosed with chronic hepatitis C at about 40 years old and the disease course was followed with therapy for liver support. Decreases in platelets and choline esterase were noted from 2006 and the patient was diagnosed with hepatic cirrhosis. Treatment continued thereafter, but he became aware of disturbance of consciousness while driving a car in 2014, and Aminoleban administration was initiated for a diagnosis of hepatic encephalopathy. Control of the disease by dietary and drug therapies became difficult in June 2015, and the patient was referred to our hospital for close examination and treatment of refractory hepatic encephalopathy.

Blood test data in the first examination are shown in Table 1. Pancytopenia and increases in enzymes of the hepatobiliary system and serum ammonia were detected. The Child-Pugh score was 9. On contrast-enhanced computed tomography (CT),

Table 1. Blood test data from the first examination.

WBC	2170/μL	TP	6.9 g/dL	BUN	13 mg/dL
Neutro	35.1%	Alb	2.6 g/dL	Cre	0.65 mg/dL
Eosino	6.0%	T. bil	1.6 mg/dL	Na	138 mEq/L
Basophils	0.9%	D. bil	0.6 mg/dL	K	4.1 mEq/L
Lymphocytes	43.3%	ALT	51 U/L	Cl	109 mEq/L
Monocytes	14.7%	AST	75 U/L	NH3	40 μmol/L
RBC	299×10^4/μ	ALP	328 U/L	PT (%)	52.6%
Hemoglobin	7.5 g/dL	γ-GTP	15 U/L	PT-INR	1.42
Platelet	8.7×10^4/L	LDH	218 U/L	Fib	247 mg/dL
		CK	71 U/L	ATIII	57.2%
		HCV-RNA	5.0 logIU/mL	D-dimer	2.9 mg/L
		HCV genotype	1b	AFP	5.6 ng/mL
				AFP-L3	5.6%
				PIVKA-II	16.2 mAU/mL

WBC – white blood cell count; RBC – red blood cells; TP – total protein; Alb – albumin; T. bil – total bilirubin; D. bil – direct bilirubin; ALT – alanine transaminase; AST – aspartate aminotransferase; ALP – alkaline phosphatase; γ-GTP – γ-glutamyl transpeptidase; LDH – lactate dehydrogenase; CK – creatine kinase; BUN – blood urea nitrogen; Cre – creatinine; Na – sodium; K – potassium; Cl – chloride; NH3 – ammonia; PT% – prothrombin time; PT-INR – prothrombin time-international normalized ratio; Fib – fibrinogen; ATIII – antithrombin III activity; AFP – α-fetoprotein; PIVKA-II – protein induced by vitamin K absence or antagonists-II.

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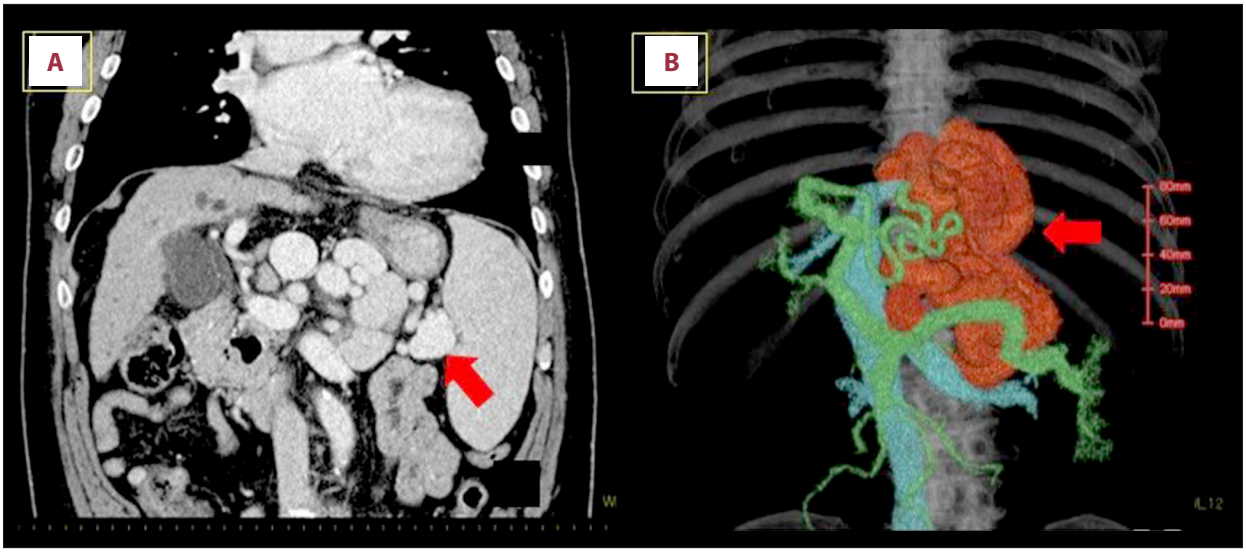

Figure 1. (**A**) Multi-planar reconstruction (MPR) image of contrast-enhanced computed tomography (CT). Cysts were occasionally noted in the liver, but hepatocellular carcinoma (HCC) could not be clearly identified. The intrahepatic portal vein was narrowed, but no thrombus was clearly observed. Splenomegaly was noted and an aneurysm of the splenic artery was present. Red arrow indicates aneurysm of the splenic artery. (**B**) 3-dimensional computed tomography image. The splenorenal shunt and paraumbilical vein were dilated. A red arrow indicates splenorenal shunt.

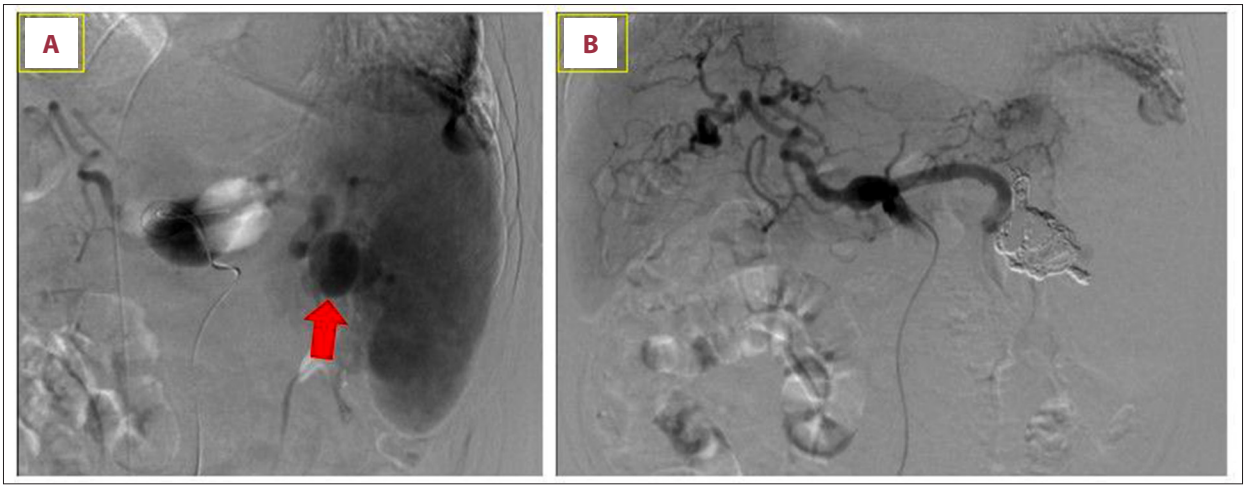

Figure 2. (**A**) Angiography from splenic artery. The trunk of the splenic artery was occluded with a balloon on the proximal side of the aneurysm and then celiac angiography was performed. Blood flow from the root of the splenic artery to the pancreatic tail region was observed, confirming anastomosis between this blood vessel and the superior polar branch of the splenic artery. Using a platinum coil and gelatin sponge, the inferior polar branch of the splenic artery was successfully selectively embolized, but deep insertion of a microcatheter into the middle polar branch was difficult. Thus, splenic artery embolization was applied, including the aneurysm. A red arrow indicates a splenic aneurysm. (**B**) Celiac artery angiography after partial splenic embolization (PSE) and splenic aneurysm embolization. Conservation of blood flow in the upper pole of the spleen from the root of the splenic artery was confirmed by angiography and the operation was completed. The blood flow of the middle and lower spleen and splenic artery aneurysm disappeared after PSE.

a splenorenal shunt and the paraumbilical vein were markedly dilated, and splenomegaly (610 cm^3) and splenic artery aneurysm (diameter 3 cm) were noted (Figure 1).

Since the splenic artery aneurysm was located close to the tail of the pancreas, combined surgical resection of the spleen and tail of the pancreas was desirable, but the risk was considered to be high based on the hepatic functional reserve, and interventional radiology (IVR) was selected. The disease was also complicated by cytopenia associated with hypersplenism, and embolization of the splenic artery aneurysm and PSE were concomitantly performed (Figure 2). Since the platelet count

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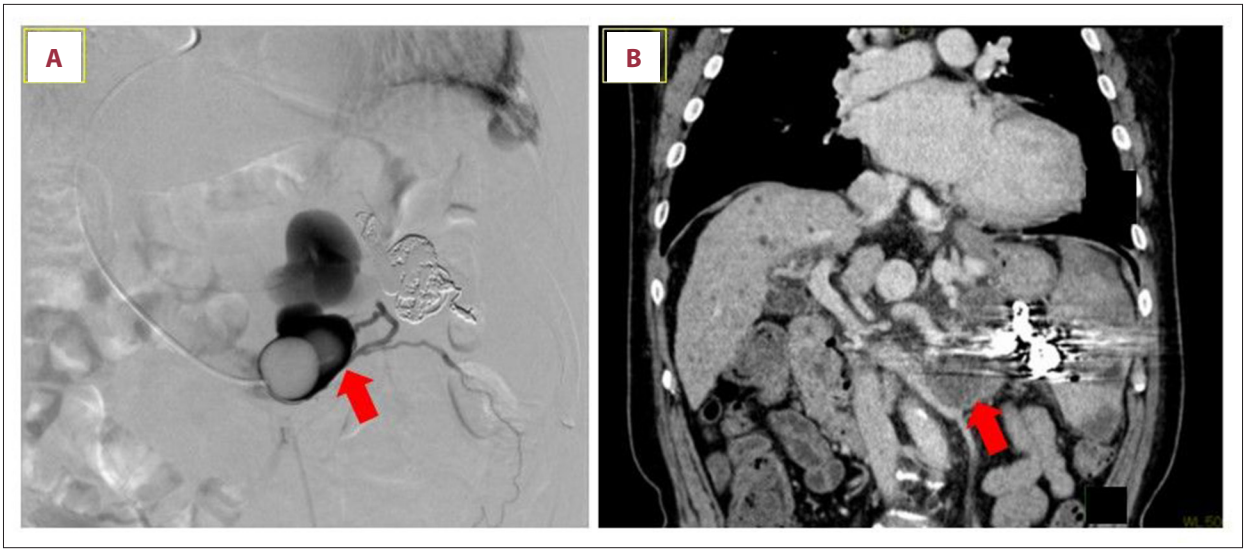

Figure 3. (**A**) Balloon-occluded splenorenal shunt angiography. Balloon-occluded retrograde transvenous obliteration (BRTO): a balloon catheter was inserted through the right internal jugular vein into the blood vessel. After confirming the distribution of the shunt blood vessels, including auxiliary outflow vessels, by angiography, 5 mL of 50% glucose solution and 19 mL of 5% solution of ethanolamine oleate with iopamidol (EOI) were injected and the operation was completed. A red arrow indicates the splenorenal shunt imaged under balloon occlusion. (**B**) Multi-planar reconstruction (MPR) image of contrast-enhanced computed tomography (CT) 1 week after balloon-occluded retrograde transvenous obliteration (BRTO). An additional injection of 7 mL of 5% EOI was given on day 2 to complete the procedure. One week after BRTO, thrombosis of the splenorenal shunt was confirmed by contrast-enhanced CT. A red arrow indicates the thrombosis of the splenorenal shunt after BRTO.

Table 2. Changes in hepatic functional reserve.

	Before PSE	Before BRTO	One month after BRTO	6 months after BRTO	Before DAAs	12 weeks after DAAs	24 weeks after DAAs
Albumin	2.6	2.8	2.6	2.8	3.2	3.8	4
Total bilirubin	1.6	1.6	1.1	1.0	0.9	1.2	1
PT%	52.6	55.2	51.5	59.4	73.1	73.9	76.9
Ascites	2	2	2	2	2	1	1
Hepatic coma	2	2	1	1	1	1	1
Child-Pugh score	10	9	9	8	7	5	5
MELD score	12	12	11	10	8	9	8

PT% – prothrombin time; PSE – partial splenic embolization; BRTO – balloon-occluded retrograde transvenous obliteration; DAAs – direct acting antivirals.

increased to about 100 000/L thereafter and the effect of aneurysm embolization was favorable, the patient was discharged. Elective BRTO for refractory hepatic encephalopathy after discharge was scheduled, but hepatic encephalopathy recurred, and the patient was urgently readmitted. BRTO was performed (Figure 3A) after the condition was stabilized by treatment with drip infusion, and complete obstruction of the shunt vessels was confirmed by postoperative CT (Figure 3B). No complication developed and the patient was discharged with rapid remission.

Outpatient treatment was continued thereafter, and more than 1 year passed without recurrence of hepatic encephalopathy or development of hepatocellular carcinoma (HCC). Hepatic functional reserve improved compared with that at the first examination (Table 2), and treatment of HCV was initiated in response to a request from the patient. At this time, decompensated liver cirrhosis was not covered by national health insurance and there was a possibility of adverse effects. After a sufficient explanation that included these issues, consent

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was obtained from the patient and his family, and SOF/LDV therapy was initiated. Fortunately, no adverse effect occurred during treatment, and SVR was achieved. Hepatic functional reserve further improved thereafter. At present, a Child-Pugh A status is being maintained without administration of a branched chain amino acid preparation, drugs for hyperammonemia, or diuretics.

Discussion

We encountered a patient with decompensated liver cirrhosis accompanied by complications of hypersplenism, hepatic encephalopathy, and splenic artery aneurysm. These complications were overcome by treatment with PSE and BRTO, which led to DAAs treatment and a marked improvement of hepatic functional reserve. Liver transplantation for decompensated liver cirrhosis is the only life-saving treatment for end-stage liver failure, but it was difficult to perform in our patient due to his age and the absence of a donor. The appearance of DAAs has produced a major paradigm shift in HCV treatment, and virus elimination has become possible in most patients. Compensated liver cirrhosis was the original target of DAAs (SOF/LDV, etc.), but SOF/VEL became available for treatment of decompensated liver cirrhosis in Japan in January 2019. However, when this case was treated, SOF/VEL could not be used yet, so we had to use SOF/LDV, which has no indication for decompensated cirrhosis. The patient himself strongly requested HCV treatment; his hepatic functional reserve was on an improving trend until the situation close to the compensated cirrhosis. Therefore, treatment was performed after giving sufficient informed consent to the person and family. Improvement of the model for end-stage liver disease (MELD) score by elimination of HCV has been reported [12], but for decompensated liver cirrhosis, it is also important to overcome various complications before antiviral treatment.

Our patient was first treated for complications of splenic artery aneurysm with a risk of rupture and hypersplenism-associated thrombocytopenia. For the treatment method, PSE and splenectomy were considered, but surgical resection was judged to be high-risk based on the hepatic functional reserve. PSE has become safely applicable to the periphery of the splenic artery with advances in IVR, and its use as pretreatment for hepatitis C has been frequently reported as complications have decreased [13,14]. PSE can amend not only hematological abnormalities, including thrombocytopenia and leukopenia, but also abnormal portal hemodynamics [15,16]. The hepatic venous pressure gradient (HVPG) that reflects portal pressure and its changes may predict the development of new varices and variceal hemorrhage in patients with portal hypertension [17]. Thus, in the treatment strategy, PSE to correct pancytopenia and coil embolization of the splenic artery aneurysm with a risk of rupture were performed first. After these procedures, the platelet count increased as expected and no severe complication occurred.

The patient had repeatedly developed hepatic encephalopathy, which was considered to be caused by the presence of a well-developed splenorenal shunt. Thus, BRTO was performed 1 month after PSE. BRTO decreased the serum ammonia level, and together with an increase in portal blood flow, hepatic functional reserve gradually increased, as previously reported [18–20]. Some studies have demonstrated that blood steal from the portal-splenic venous system to the systemic circulation through large collateral pathways might contribute to worsened hepatic functional reverse, and the presence of major shunts might be one of the prognostic factors in patients with portal hypertension [21–23]. On the other hand, some reports have described not only amelioration of hepatic function, but also improvement in vital prognosis due to increased portal flow volume by occlusion of portosystemic shunts [18,20,23,24]. The patient was followed at the outpatient clinic thereafter. Hepatic functional reserve stably improved with an increase in albumin, and diuretic administration became unnecessary. Thus, subsequently, we decided to treat HCV infection. Hepatic functional reserve further improved thereafter.

Treatment with DAAs may be increasingly used for decompensated liver cirrhosis. The most important points in this approach are to complete treatment safely and improve hepatic functional reserve to extend survival, for which the maximum therapeutic intervention for decompensated liver cirrhosis may be desirable. The LDV/SOF tablet used in our patient is a combination of a nucleic acid-type NS5B polymerase inhibitor, sofosbuvir, which is a “chain terminator” that directly inhibits HCV RNA synthesis, and an NS5A inhibitor, ledipasvir. Sofosbuvir exerts its pharmacological after metabolism in the liver [25]. In cases with a very large portal-systemic shunt, as in our patient, it is unclear whether such drugs appropriately reach the liver and exert a pharmacological effect. In these cases, treatment after obstruction of the shunt may be desirable to acquire the maximum therapeutic effect on HCV infection. Antiviral therapy alone may also be insufficient to improve hepatic functional reserve in many cases of decompensated liver cirrhosis, but improvement to close to a normal level may be possible through a combined approach of correcting splenomegaly and shunt vessels.

Patients with hepatic cirrhosis of Child-Pugh grade C in Japan have a 3-year survival rate of 30.7%. Our patient has maintained a Child-Pugh grade A status as of 3 years after treatment, showing marked improvement of survival of a patient with liver failure. The combination of treatment reported here

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requires further validation in more cases of decompensated liver cirrhosis.

Conclusions

We encountered a patient with decompensated liver cirrhosis accompanied by complications of hypersplenism, hepatic encephalopathy, and splenic artery aneurysm. These complications were overcome by treatment with PSE and BRTO, which led to DAAs treatment and a marked improvement of hepatic function.

Conflict of interest

None.

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