Drastic Improvement in Hepatitis B/C Virus-induced Decompensated Liver Cirrhosis Treated by Total Management Consisting of Interventional Radiology, Endoscopy, and Pharmacotherapy

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Abstract:
Recent advances in antiviral therapy have enabled control of the hepatitis virus; however, these do not completely eliminate the pathological condition of liver disease, and portal hypertension remains a clinical problem. We herein report a case of hepatitis B virus/hepatitis C virus (HBV/HCV)-induced decompensated liver cirrhosis for which total management consisting of interventional radiology and endoscopy, based on the evidence of our clinical studies, followed by antiviral therapy for co-infection with HBV and HCV was successful. This case clearly indicates the effective timing of total management, suggesting that it prolongs the vital prognosis in addition to improving the hepatic function.

Key words: balloon-occluded retrograde transvenous obliteration, decompensated liver cirrhosis, direct-acting antiviral, endoscopic injection sclerotherapy with ligation, nucleic acid analog, partial splenic embolization

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Introduction
Although recent dramatic advances in antiviral therapy have enabled control of hepatitis B virus (HBV) and elimination of hepatitis C virus (HCV), these do not completely eliminate the pathological condition of liver disease, and portal hypertension and carcinogenesis remain clinical problems.

We herein report our experience with a case of HBV/HCV-induced decompensated liver cirrhosis wherein total management based on the clinical study findings at our medical department was successful. Considering the clinical priority due to the pathological condition in this case, our therapeutic intervention was performed as follows: partial splenic embolization (PSE) was first performed, followed by endoscopic injection sclerotherapy with ligation (EISL) and then balloon-occluded retrograde transvenous obliteration (BRTO); thereafter, direct-acting antivirals (DAAs) were administered followed by nucleic acid analogs (NAs).

Case Report
The patient was a woman in her 80s with no history of treatment for liver disease. Although she had tested positive for HBV over 30 years earlier, she discontinued interferon treatment due to thrombocytopenia and had no subsequent history of regular examinations at medical facilities. She had subjective symptoms of edema of the lower extremities for the past four months. This was gradually accompanied by general malaise, poor appetite, and a low-grade fever. Consequently, she was examined by a local physician. Blood tests and abdominal ultrasonography indicated liver cirrhosis with both HBV and HCV infections as well as splenomegaly and hypersplenism. In addition, esophagogastroduodenoscopy (EGD) revealed esophagogastric varices. Thus, she was referred to our department for multidisciplinary treatment and was admitted to the hospital.
Table. Chronological Changes in the Child-Pugh and MELD-Na Scores, and Blood Chemical Examination Results.

|                     | pre-PSE/EISL/BRTO | post-PSE/EISL/BRTO (pre-SOF/VEL) | EOT of SOF/VEL | SVR12 |
|---------------------|-------------------|----------------------------------|----------------|-------|
| Child-Pugh          | 10                | 8                                | 7              | 6     |
| MELD-Na             | 12                | 9                                | 8              | 10    |
| T-Bil (mg/dL)       | 2.3               | 1.6                              | 1.4            | 1.4   |
| Alb (g/dL)          | 2.6               | 2.8                              | 2.9            | 3.1   |
| AST (U/L)           | 36                | 29                               | 25             | 28    |
| ALT (U/L)           | 27                | 15                               | 13             | 16    |
| BUN (mg/dL)         | 15                | 19                               | 19             | 20    |
| Cre (mg/dL)         | 0.74              | 0.89                             | 0.92           | 1.03  |
| Na (mmol/L)         | 142               | 143                              | 143            | 140   |
| K (mmol/L)          | 3.4               | 4.2                              | 4.2            | 4.0   |
| WBC (10⁹/μL)        | 2.810             | 3.420                            | 4.000          | 4.300 |
| Hb (g/dL)           | 11.6              | 11.5                             | 12.1           | 12.1  |
| Plt (×10⁴/μL)       | 4.4               | 10.7                             | 9.3            | 9.7   |
| PT (%)              | 52.3              | 62.9                             | 71.0           | 72.6  |
| PT-INR              | 1.45              | 1.30                             | 1.21           | 1.21  |

MELD: Model for End-Stage Liver Disease, T-Bil: total bilirubin, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, BUN: blood urine nitrogen, Cre: creatinine, Na: sodium, K: potassium, WBC: white blood cell, Hb: hemoglobin concentration, Plt: platelet count, PT: prothrombin time, PSE: partial splenic embolization, EISL: endoscopic injection sclerotherapy with ligation, BRTO: balloon-occluded retrograde obliteration, SOF/VEL: sofosbuvir and velpatasvir, EOT: end of treatment, SVR12: sustained virological response at 12 weeks post-treatment

Table shows the blood biochemical examination results on admission. Her condition was critical, with a Child-Pugh score of 10, Model for End-Stage Liver Disease-sodium (MELD-Na) score of 12, and platelet count of 4.4×10⁴/μL. She tested positive for hepatitis B surface antigen; in contrast, she tested negative for hepatitis B envelope antigen and hepatitis B envelope antibody. The HBV-DNA level was less than 1.3 log IU/mL (genotype C); however, the HCV-RNA level was 4.9 log IU/mL (genotype 1B). EGD showed beady esophageal varices with red color signs in the middle esophagus and nodular gastric varices without red color signs in the cardia and fundus (Fig. 1A, B), according to the General Rules for Study of Portal Hypertension developed by the Japan Society for Portal Hypertension (1). Contrast-enhanced computed tomography (CT) revealed significant splenomegaly (517 cm³) and a small amount of ascites, along with the development of multiple portosystemic shunts (Fig. 1C, D). The feeding veins for the esophageal and gastric varices were the left and posterior gastric veins, respectively. In addition, her liver stiffness (LS) measured by transient elastography was 27.2 kPa.

Since advanced splenomegaly, thrombocytopenia, and esophageal varices with an extremely high risk of hemorrhaging were observed, we prioritized the treatment of these diseases. After delivering a sufficient explanation of the therapeutic procedures that included potential postprocedural complications, consent was obtained from the patient and her family, and PSE was first performed to reduce the portal pressure and increase the platelet count. We embolized the lower and middle branches of the splenic artery using the Takatsuka method (2), which entails the use of a platinum coil and gelatin sponge (Fig. 2A-C). Next, EISL was performed for esophageal varices. Under fluoroscopic guidance, we administered 4.5 mL of 5% ethanolamine oleate with iopamidol (EOI) intravenously, and band ligation was subsequently performed at the injection sites (Fig. 2D-F). Consequently, the LS decreased to 20.9 kPa following PSE and EISL. Subsequently, BRTO was performed for gastric varices. Because of the extremely advanced development of collateral vessels, a double-balloon catheter system was adopted for downgrading from Grade 4 to Grade 2 Hirota’s classification (3). Afterward, we injected 10.5 mL of 5% EOI and conducted a series of procedures using the 2-day method (Fig. 2G-I).

Contrast-enhanced CT findings before and after each treatment are shown in Fig. 3. The splenic infarction rate by PSE was 79.0%; the blood flow to the esophageal varices disappeared due to the EISL, and satisfactory embolization of the gastric varices and gastrorenal shunt was achieved by BRTO (Fig. 3A-C). EGD after EISL followed by BRTO, before anti-HCV therapy initiation, showed that the beady esophageal varices had disappeared, and the nodular gastric varices had noticeably shrunk in size (Fig. 3D, E). Treatments for various complications related to decompensated cirrhosis were successfully completed. In addition, blood biochemistry test findings (Table) revealed hepatic functional amelioration with an improvement from Child-Pugh class C (score 10) to class B (score 8) and an increase in the platelet counts.

Thereafter, the administration of sofosbuvir and velpatasvir...
Figure 1. EGD and contrast-enhanced CT findings before interventional radiology and endoscopic treatment. (A, B) Esophagogastroduodenoscopy (EGD) shows beady esophageal varices with red color signs in the middle esophagus and nodular gastric varices without red color signs in the cardia and fundus. (C, D) Contrast-enhanced computed tomography (CT) reveals significant splenomegaly (517 cm³) and the development of multiple portosystemic shunts.

Discussion

We experienced a case of drastic improvement in HBV/HCV-induced decompensated liver cirrhosis successfully treated by total management consisting of interventional radiology (IVR), endoscopy, and pharmacotherapy based on evidence of our clinical studies. Antiviral therapy with DAAs for HCV-induced chronic hepatitis and compensated liver cirrhosis began in 2014, and high degrees of SVR have recently been obtained through their use. In addition, in Japan, SOF/VEL was approved in 2019 for insurance coverage for the treatment of decompensated liver cirrhosis, which was not covered by insurance previously, and it has been reported to be clinically effective (4). Nevertheless, phase III trials and post-marketing surveillance have reported some cases of death caused by variceal hemorrhaging and advancement to liver failure (5). Therefore, further studies of its safety and preventative measures against potentially fatal complications are warranted.

At the initial examination, the present case had a Child-Pugh class of C (score 10), indicating a markedly poor hepatic reserve, and thrombocytopenia associated with hypersplenism and esophagogastric varices at high risk of hemorrhaging were observed. Thus, our therapeutic strategy was to treat all of the complications of decompensated liver cirrhosis prior to starting SOF/VEL.

Not only does PSE increase blood cells (6, 7), it has also been proven effective in decreasing portal pressure (8, 9) and improving the liver function (10-12). In our medical department, a “history of PSE” has been identified as an inde-
Figure 2. Interventional radiology and endoscopic treatment. PSE: (A) Digital subtraction angiography (DSA) before PSE, (B) DSA after PSE, and (C) contrast-enhanced computed tomography one week after PSE. We performed embolization of the lower and middle branches of the splenic artery using a platinum coil and gelatin sponge (splenic infarction rate: 79.0%). EISL: (D) sclerotherapy (endoscopy), (E) sclerotherapy (X-ray), and (F) band ligation. We administered 4.5 mL of 5% ethanolamine oleate with iopamidol (EOI) intravenously, and band ligation was subsequently performed at the injection sites. BRTO: (G) balloon-occluded retrograde variceography (BRTV) -1, (H) BRTV-2 after downgrading, and (I) X-ray after 5% EOI injection under balloon occlusion. We used a double-balloon catheter system for downgrading from Grade 4 to Grade 2 Hirota’s classification and injected 10.5 mL of 5% EOI PSE: partial splenic embolization, EISL: endoscopic injection sclerotherapy with ligation, BRTO: balloon-occluded retrograde obliteration, EOI: ethanolamine oleate with iopamidol

Our therapeutic strategy required the use of BRTO to prevent the rupture of gastric varices. BRTO is effective for encephalopathy and gastric varices (3, 15, 16) and is well known to contribute to the improvement in the hepatic function (17-19). However, in our medical department, “LS as identified by FibroScan” is an independent factor for a post-BRTO decrease in the MELD-Na score (i.e. an extension of the vital prognosis), and the overall survival rate is significantly higher in cases of LS <21.6 kPa than in cases of LS ≥21.6 kPa (20). Since the post-PSE/EISL LS decreased from 27.2 to 20.9 kPa in the present case, we expect BRTO to be effective for not only controlling the gastric varices but also improving the MELD-Na score; as evidence showed, the MELD-Na score decreased from 9 to 8 at one month following BRTO. Anti-HCV treatment was initiated upon successful treatment of complications, such as hypersplenism.
and esophageal varices, by combining IVR and endoscopic treatment.

Four weeks after the initiation of SOF/VEL, HCV-RNA decreased to an undetectable level. As the present case had dual infection of HBV and HCV, the patient tested positive for HBV-DNA (1.9 log IU/mL) at that time, and the level was elevated to 2.1 log IU/mL another 4 weeks later (i.e., 8 weeks after the start of SOF/VEL), as we predicted at the start of treatment. Therefore, TAF was additionally administered, leading to a rapid decrease in HBV-DNA to undetectable levels. In cases of HBV/HCV infection, the viruses generally interfere with each other, and an increase in endogenous interferon caused by HCV infection controls the proliferation of HBV. Consequently, HCV usually becomes the dominant virus (21, 22). In the present case, HCV was eradicated using DAAs, which abolished its control on HBV proliferation and resulted in the reactivation of HBV. Subsequently, combination therapy of DAAs and NAs sustained the HBV-negative status, and an SVR to HCV was achieved. At 12 weeks post-treatment (SVR12), the Child-Pugh class was A (score of 6). Combined IVR, endoscopy, and pharmacotherapy at our hospital led to a dramatic improvement from Child-Pugh class C to class A nine months after the start of therapeutic intervention.

Takehara et al. reported no cases of improvement of two classes from Child-Pugh class C to class A due to SOF/VEL administration (5). However, in the present case, combination therapy consisting of IVR and endoscopic treatment led to improvement from class C to class B, and subsequent SOF/VEL treatment led to further improvement from class B to class A due to an SVR. Thus, we achieved an improvement of two classes regarding the Child-Pugh score. In terms of SOF/VEL treatment for decompensated liver cirrhosis, Child-Pugh class C cases have a lower SVR rate (80% vs. 95%) and more cases of death (12 vs. 3) than class B cases (5, 23), suggesting that it is better to introduce SOF/VEL for class B cases than for class C cases. When total management by IVR, endoscopy, and pharmacotherapy is planned, from the standpoint of both safety and efficacy, it is better to introduce DAAs after treating complications by IVR and endoscopic treatment and improvement from Child-Pugh class C to B, rather than introducing DAAs at
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Figure 4. Transition of HCV-RNA and HBV-DNA after antiviral therapy intervention. The patient tested negative for HCV-RNA 4 weeks after the administration of SOF/VEL but positive for HBV-DNA (1.9 logIU/mL), the level of which increased to 2.1 logIU/mL another 4 weeks later. Subsequently, TAF was additionally administered, and the combined antiviral therapy resulted in the achievement of an SVR for HCV and maintenance of a negative (undetectable level) status for HBV. SOF/VEL: sofosbuvir and velpatasvir, TAF: tenofovir alafenamide fumarate, HCV: hepatitis C virus, RNA: ribonucleic acid, HBV: hepatitis B virus, DNA: deoxyribonucleic acid, EOT: end of treatment, SVR: sustained virological response

class C without treating the severe complications.

SOF, a nucleic acid-type NS5B polymerase inhibitor, is a precursor with enhanced hepatocyte migration that exerts its pharmacological effects after being metabolized in the liver (24). This suggests that the administration of SOF after improving portal hemodynamics with the portal flow volume increased by BRTO can increase its uptake into liver cells, leading to the improvement of the therapeutic efficacy by increasing the metabolic efficiency. Therefore, in cases of portosystemic shunt complications, SOF/VEL administration after BRTO appears to be the ideal approach.

Antiviral therapy alone may also be insufficient to improve the hepatic functional reserve in many cases of decompensated liver cirrhosis; however, improvement to near-normal levels may be possible through a combined approach of correcting portal-splenic hemodynamics. To our knowledge, there are few reports clearly indicating the effective timing of IVR therapy, such as BRTO and PSE, endoscopic treatment, and antiviral therapy for HBV/HCV-induced decompensated liver cirrhosis. One limitation of the present study was that the data were derived from only one case, and this should be considered when interpreting the results. In future studies, we aim to clarify this mechanism during the post-treatment clinical course. Finally, in addition to the present case, much larger and longer prospective cohort studies will be necessary to validate the findings of our previous retrospective studies.

Conclusions

We herein report our experience with a case of HBV/HCV-induced decompensated liver cirrhosis wherein total management consisting of IVR, endoscopy, and pharmacotherapy was successful. The combination of treatment reported here is expected to improve not only the hepatic function but also the vital prognosis in cases of decompensated liver cirrhosis more efficiently and less invasively than traditional treatment methods.

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

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