Hepatic Hemodynamics and Elevation of Liver Stiffness as Possible Predictive Markers of Late-onset Hepatic Failure

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Running title: Serial changes in hepatic hemodynamics and liver stiffness during LOHF

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Table -1

Abbreviations: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), acoustic radiation force impulse (ARFI), drug-induced liver injury (DILI), gamma-glutamyltransferase (γ-GTP), model for end-stage liver disease (MELD), shear wave velocity (SWV), total bilirubin (T-BIL), white blood cell (WBC)

CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent form is available for review from the Editor of this journal.

Abstract

A 52-year-old Japanese woman admitted to our hospital for the treatment of liver dysfunction due to an undetermined cause developed disorientation on the 58th hospital day and was diagnosed with late-onset liver failure. Abdominal ultrasound examinations were performed several times from the admission. Before the disorientation appeared, the results of the examinations revealed that the portal flow decreased, after which the hepatic arterial flow increased and the degree of liver stiffness became elevated. Although the pathophysiology of these changes remains unclear, hemodynamic changes and elevation of liver stiffness might be predictive markers of severe liver tissue damage.

Introduction

Late-onset hepatic failure (LOHF) has a relatively long precoma period (8 – 24 weeks), in which liver dysfunction, such as that due to cholestasis, coagulopathy and liver atrophy, progresses consistently, and in most cases, irreversibly (1, 2). Because these symptoms are based on the onset of severe and progressive hepatic necrosis and impaired liver regeneration, new methods to detect severe liver tissue damage may be useful for predicting and preventing the development of a coma.

We herein report the serial changes in the hepatic hemodynamics and liver stiffness in a case of LOHF treated with liver transplantation, and compared these values to the histological findings in the native liver. Based on the findings in the present case, we speculate that unique hemodynamic changes, such as a decrease in the portal flow and an increase in the hepatic arterial flow, as well as an elevation of liver stiffness on ultrasonography, precisely reflect the liver tissue damage during the development of severe encephalopathy in patients with LOHF.

Case presentation:

A 52-year-old Japanese woman visited a general physician complaining of general fatigue and icterus, and the laboratory data revealed elevation of transaminases and total bilirubin. The patient was referred for further examination and diagnosis at our department. There was no past history of surgery or blood transfusions, and no cause of acute liver injury was identified, such as viral infection, medications, familial disease, alcohol abuse or autoantibodies (Table). Moreover, abdominal computed tomography revealed no evidence of obstructive jaundice. Therefore, the patient was diagnosed to have an undetermined cause of acute liver injury with jaundice. As the laboratory data indicated an improvement in the patient after admission, the patient was placed under close observation, without any specific treatment for the acute liver injury (Figure 1). Although the serum transaminase level gradually decreased, the total bilirubin level increased and the prothrombin time declined around the 15th hospital day. Steroid pulse therapy was started on the 16th hospital day. After the administration of steroid pulse therapy, the prothrombin time increased to 60% on approximately the 45th hospital day.

Disorientation, which was subsequently diagnosed as being due to a hepatic coma, appeared on the 58th hospital day, and bilirubin absorption therapy and treatment for the hepatic coma were started. Because of the disorientation, liver atrophy and an insufficient recovery of the prothrombin time, we diagnosed the patient to have LOHF of an undetermined cause and prepared the patient for liver transplantation. The first candidate liver donor had severe fatty liver and was excluded from eligibility. The patient's prothrombin time dropped to 30% on the 70th hospital day, and a hepatic coma reappeared on the 75th hospital day. CT volumetry performed on the 84th hospital day revealed progressive liver atrophy compared with that observed on admission (Figure 2a). These data indicated that the patient's liver showed both impaired regeneration and progressive liver atrophy. The second candidate was eligible as a liver donor, and the patient underwent living donor liver transplantation on the 92nd hospital day.

The degree of liver stiffness and the hepatic hemodynamics were occasionally evaluated using abdominal ultrasound during hospitalization. The extent of liver stiffness was evaluated using the ACUSON S2000 device (Siemens Medical Solutions) with acoustic radiation force impulse (ARFI)

elastography. The method used to perform the SWV measurements has been described previously (3). Briefly, the region of interest was set at an area 2 cm from the surface of liver segment 5 via the intercostal space. The SWV value was measured 10 times using a 4.5-MHz convex type probe.

To assess the hepatic hemodynamics, the velocity and related parameters were measured in the indicated regions. The portal flow was detected at the proximal position across the proper hepatic artery. The hepatic arterial flow was detected from the proper hepatic artery at the site where the portal vein crossed. The waveforms were obtained at each indicated position. The maximum velocity of the portal vein gradually decreased during hospitalization. In contrast, the maximum velocity and resistance index in the hepatic artery gradually increased, and the liver stiffness was elevated over time (Figure 3).

The resected native liver weighed 920 g, and the histological findings revealed submassive necrosis with marked cholestasis, compatible with late-onset hepatic failure. A liver specimen also showed edematous changes in the subendothelial region of the central vein, resulting in narrowing of the venous lumen (Figure 2b).

Discussion:

LOHF is classified as a disease related to acute liver failure (ALF) (1, 4) and is recognized to be a more critical disease than ALF according to a national survey in Japan covering the period from 2004 to 2009 (1). The survival rate of LOHF patients treated without liver transplantation (LT) is extremely poor compared with that of patients treated with LT (1, 4). Furthermore, because the liver dysfunction noted in cases of LOHF progresses gradually, the timing of, rather than the indications for, LT is important.

The portal vein provides the blood supply through a low pressure system (5, 6). Therefore, the portal flow, not the hepatic artery flow, is the first to decrease as the sinusoidal resistance increases (5, 6). In the present case, elevation of the liver stiffness, a decrease in the portal flow, an increase in the hepatic arterial flow and elevation of the resistance index (RI) were preceded by a decrease of the prothrombin activity, elevation of the MELD, liver atrophy and the onset of encephalopathy (Figure 1). The macroscopic findings of the resected native liver showed substantial atrophy. The microscopic findings demonstrated wall thickening of the vessels in the liver,

massive loss of hepatocytes and narrowing of the central vein as a result of edematous changes associated with a subendothelial lesion. As massive hepatocyte loss was noted, extended fibrosis and destruction of the lobular structure in the liver were revealed. Furthermore, the RI and hepatic arterial flow progressively increased over the clinical course. These data also suggested that the initially elevated sinusoidal pressure induced the decrease in the portal venous flow and the compensatory increase in the hepatic arterial flow. Based on these findings, we speculated that the artery-dominant flow in this patient might reflect massive hepatocyte loss due to severe inflammation, which subsequently led to liver atrophy and liver failure.

The degree of liver stiffness measured using ARFI elastography is associated with the shear wave velocity (SWV) (7-9). Elevation of the liver stiffness leads to an increased SWV value (10, 11). However, the SWV is affected by various factors. Inflammation, as well as fibrosis, in the liver increases the SWV value (11). In cases of acute liver injury, an increased SWV value is considered to be the result of inflammation in the liver. A previous study reported that increases in the SWV were associated with a

poor prognosis of the patients with ALF. The findings of the previous report were similar to the findings in the present study. However, the pathophysiology underlying the increases in the SWV have never been elucidated. Intriguingly, the microscopic findings of the resected liver specimen in this case demonstrated massive hepatocyte loss in addition to massive fibrotic changes in the liver. In addition, the SWV value in the present case progressively increased over the patient's clinical course. These findings suggest that persistent increases in the SWV values in LOHF patients may be associated with both inflammation and fibrosis. Intriguingly, the SWV decreased in surviving patients with ALF along with the improvement of their clinical course (10). We speculate that the hypothetical pathophysiology involving both inflammation and fibrosis leading to the increase in the SWV might occur in patients with ALF because these pathological findings have also been noted in ALF patients during disease progression. In the present case, several therapies were performed. Bilirubin absorption, plasma exchange and hemodialysis filtration all affected the hemodynamics. These therapies would affect the liver hemodynamics, although none of these therapies was being performed at most of the time

points when the liver hemodynamics were assessed, except for one point (Figure 1). Thus, we are not able to exclude the effects of these therapies on liver hemodynamics.

Based on the results observed in the present case, we speculate that (1) a decrease in the portal flow and an increase in the hepatic arterial flow might arise due to liver atrophy, which is associated with fibrosis and massive hepatocyte loss, and (2) a persistent increase in the SWV value may reflect both inflammation and fibrosis. In the present study, these two clinically significant findings appeared before the development of hepatic encephalopathy. Therefore, these findings may provide reliable markers of severe liver tissue injury, such as that due to coma-threatened LOHF, as in the current case. We recognize that this single case presentation is not able to provide sufficient evidence that both the liver hemodynamics and liver stiffness can serve as predictive parameters for the onset of LOHF. To prove the usefulness of the hepatic hemodynamics and increase of liver stiffness in LOHF, we plan to accumulate cases with acute liver injury, acute liver failure and LOHF to examine the predictive value of these parameters.

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FIGURE LEGENDS

Figure 1. The patient's clinical course. The upper panel demonstrates the serial changes in the liver volume and the shear wave velocity (SWV). The second panel from the top demonstrates the serial changes in the hemodynamic parameters of the liver. The third panel from the top demonstrates the serial changes in the laboratory data, total bilirubin (T.Bil) or alanine transaminase (ALT). The bottom panel shows the serial changes of the prothrombin time (PT) and model for end-stage liver disease (MELD) score. HA, the maximum velocity of the hepatic artery; RI, resistance index; PV, maximum velocity of the portal vein; PSL, prednisolone; M-PSL, methyl prednisolone; NH3, ammonia; BA, bilirubin absorption; PE, plasma exchange; HDF, hemodialysis filtration; CHDF, continuous hemodiafiltration.

Figure 2. The histopathological findings of the resected liver and the changes in the computed tomography findings of the liver. (a) The liver volume measured by CT was 1,185 ml on the day of admission. A progression of liver atrophy was seen on the 28^{th}, 69^{th} and 84^{th} hospital days, with volumes of

1,010, 985 and 898 ml, respectively. (b) Hematoxylin and eosin staining (×40). The histological findings revealed submassive necrosis. The central vein (V) showed edematous changes in a subendothelial lesion in the central vein, which resulted in a narrowing of the venous lumen.

Figure 1

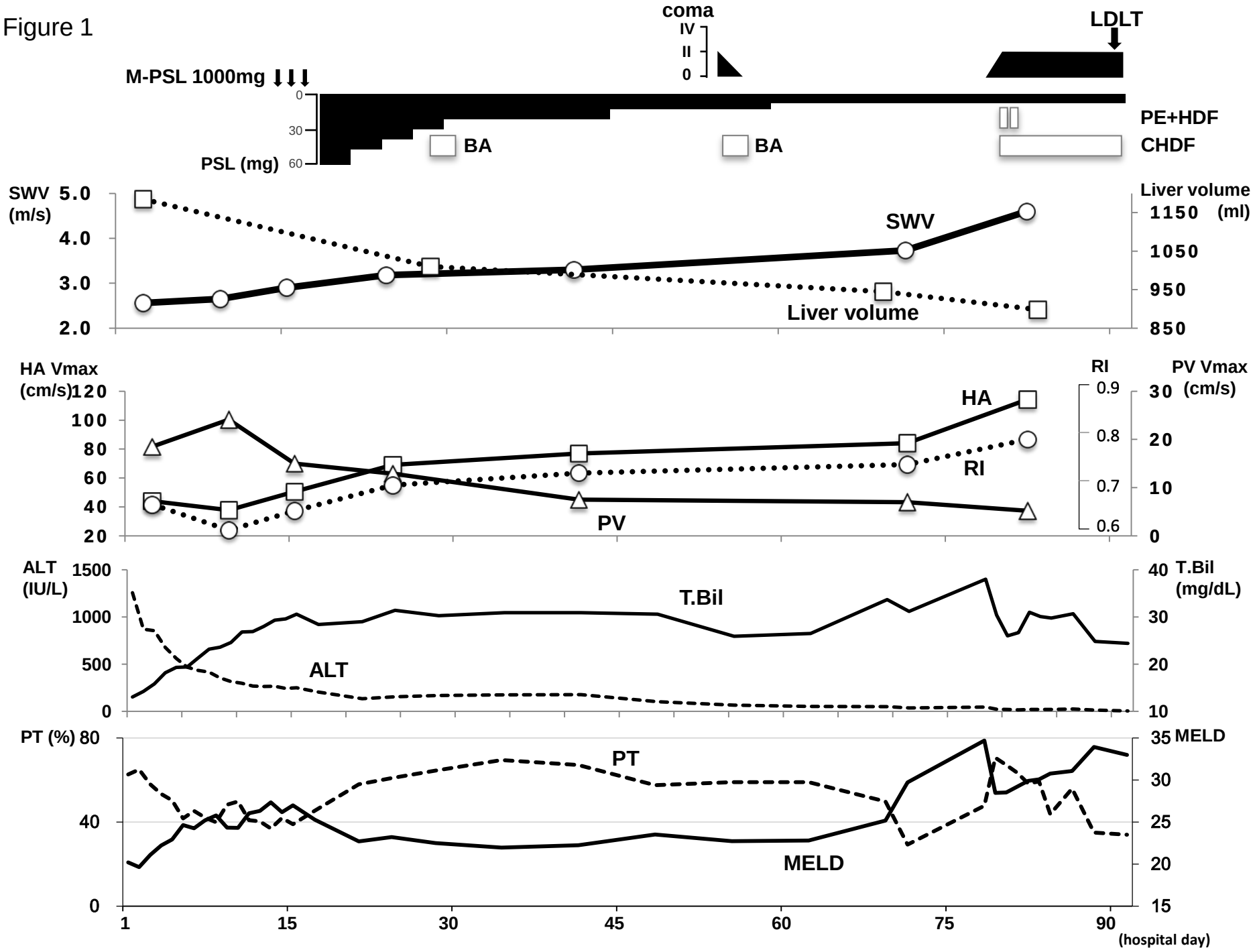
coma
IV
II
0
LDLT
M-PSL 1000mg
0
30
60
PSL (mg)
BA
BA
PE+HDF
CHDF
SWV (m/s)
5.0
4.0
3.0
2.0
SWV
Liver volume
Liver volume (ml)
1150
1050
950
850
HA Vmax (cm/s)
120
100
80
60
40
20
HA
RI
PV
RI
0.9
0.8
0.7
0.6
PV Vmax (cm/s)
30
20
10
0
ALT (IU/L)
1500
1000
500
0
T.Bil
ALT
T.Bil (mg/dL)
40
30
20
10
PT (%)
80
40
0
PT
MELD
MELD
35
30
25
20
15
1
15
30
45
60
75
90
(hospital day)

Figure 2

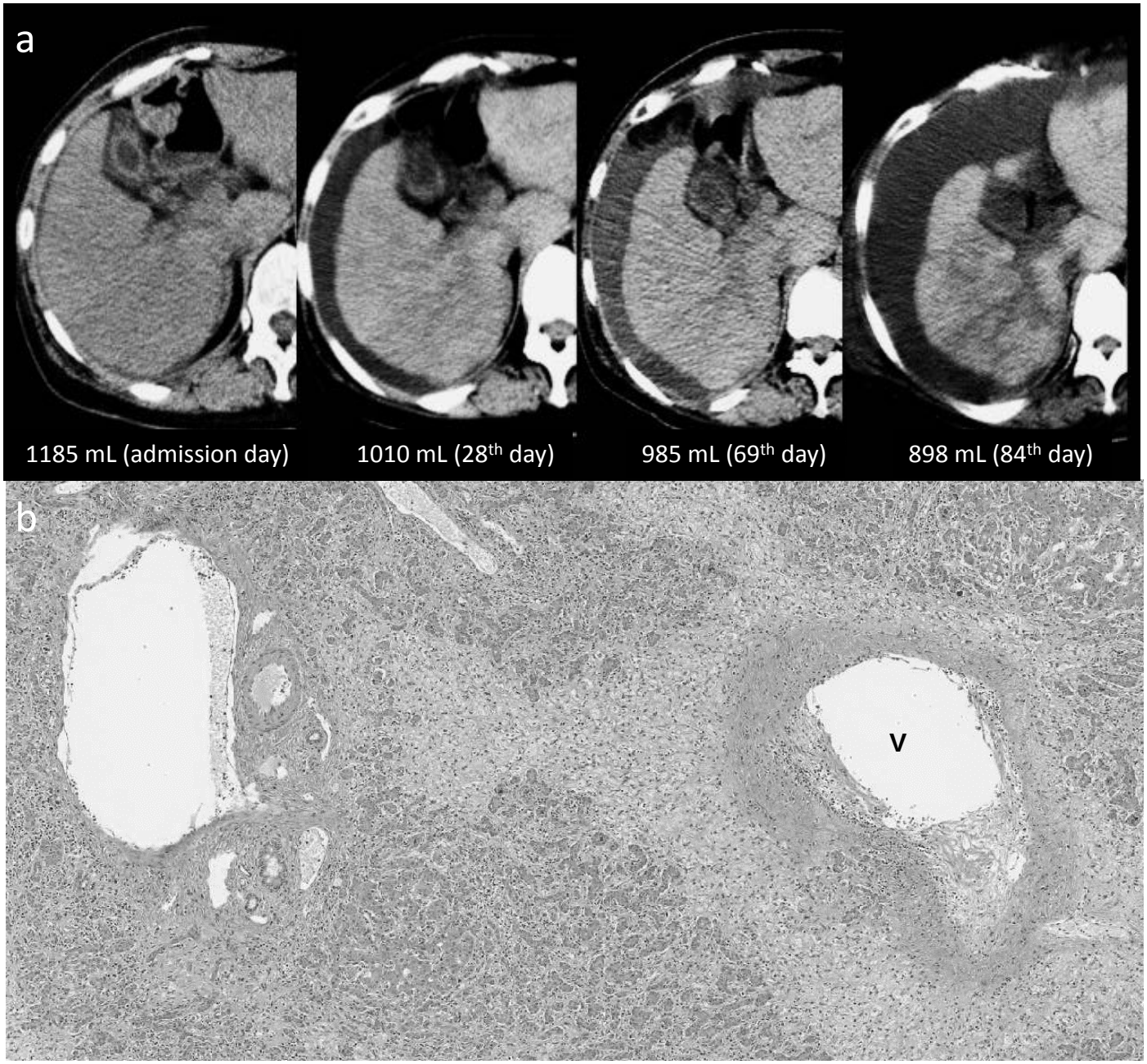
a
1185 mL (admission day)
1010 mL (28th day)
985 mL (69th day)
898 mL (84th day)
b
v

Table Laboratory data of the present patient on the admission day.

Complete blood counts		Biochemistry				Virus markers	
WBC	4,040 /uL	T.Bil	14 mg/dL	NH3	60 ug/dL	HBs Ag	0.1 IU/mL
Neu	37.0 %	AST	643 IU/L	BS	114 mg/dL	HBs Ab	0.1 mIU/mL
Lym	41.0 %	ALT	871 IU/L	IgG	2010 mg/dL	IgM-HBc Ab	(-)
Mo	13.0 %	γ-GTP	266 IU/L	IgA	477 mg/dL	HCVAb	0.1 S/CO
Eo	6.0 %	ChE	211 IU/L	IgM	112 mg/dL	HCV RNA	(-)
Ba	1.0 %	ALP	513 IU/L			HEV IgM	(-)
RBC	405 ×104 /uL	TP	6.4 g/dL	Autoantibodies		HEV IgG	(-)
Hb	11.7 g/dL	Alb	2.8 g/dl	ANA	(-)	CMV IgM	<×10
Plt	14.4 ×104 /uL	BUN	7.3 mg/dL	AMA	(-)	EBV VCA IgM	<×10
Coagulation tests		Cre	0.68 mg/dl			CMV IgG	<×10
APTT	35.3 sec	Na	139 mEq/L	Others		EBV VCA IgG	(+)
HPT	31.7 %	K	3.8 mEq/L	AFP	111.6 ng/mL	EBV EBNA	(+)
PT	65.2 %	Cl	106 mEq/L	HGF	0.71 ng/mL	HSV IgM	<×10
- INR	1.33	AMY	87 IU/L	Hyaruronate	116 ng/dL	HHV6 IgM	<×10
Fib	170 mg/dL	CRP	0.5 mg/dL			ParvoB19 IgM	(-)

WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; Plt, pletelets; APTT, Activated partial thromboplastin time; HPT, hepaplastin test; PT, prothrombin time; Fib, fibrinogen; T.Bil., total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; ChE, choline esterase; ALP, alkaline phosphatase; TP, total protein; Alb, albumin; BUN, blood urea nitrogen; Cre, creatinine; AMY, amylase; CRP, C-reactive protein; BS, blood sugar; Ig, immunoglobulin; ANA, anti-nuclear antibody; AMA, anti-mitochondrial antibody; AFP, α-fetoprotein; HGF, hepatocyte growth factor; Ab, antibody; Ag, antigen; HB, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; CMV, cytomegalovirus; EB, Epstein–Barr virus; VCA, Viral capsid antigen; EBNA, EBV nuclear antigen; HSV, herpes simplex virus; HHV, human herpes virus; ParvoB19, parvovirus B19