Hypothyroidism Enhanced Portal Hypertension in a Patient with Alcoholic Liver Cirrhosis, Resulting in the Development of Ascites

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Abbreviations: alanine aminotransferase (ALT), galactosyl sialyl albumin (GSA), hepatocellular carcinoma (HCC), hepatic vein pressure gradient (HVPG), indocyanine green (ICG), serum-ascites albumin gradient (SAAG), sinusoidal epithelial cell (SEC), total bilirubin (T-BIL), thyroid stimulating hormone (TSH), white blood cell (WBC)

CONSENT

Written informed consent was obtained from the patient for the 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 man diagnosed with alcoholic liver cirrhosis complained of abdominal distention due to massive ascites. The ascites did not resolve with diuretic agents. The serum-ascites albumin gradient value of 1.9 g/dl and the total protein level in the ascites of 3.1 g/dl indicated the ascites to have been caused by portal hypertension. Hypothyroidism was detected, and the patient received supplementation with levothyroxine. The ascites dramatically decreased after supplementation with levothyroxine. We herein conclude that the ascites in the present case had thus been strongly influenced by portal hypertension, which was induced by liver dysfunction associated with liver cirrhosis and hypothyroidism.

Introduction

Ascites in the patients with portal hypertension is considered to originate from the lymph at the space of Disse, which contains approximately the same concentration of protein because the physiological sinusoidal epithelium has numerous fenestrations (1, 2). In contrast, the extrasinosoidal lymph in the patients with liver cirrhosis contains only a small amount of plasma protein because the sinusoidal fenestrations disappear and a fibrous basement membrane surrounds the epithelium in the cirrhotic liver, such as the general capillary wall, resulting in a phenomenon referred to as capillarization (3). Therefore, the total protein (TP) level of ascites tends to be high in the patients with post-sinusoidal portal hypertension, such as that seen in association with Budd-Chiari syndrome and cardiac failure, while it tends to be low in the patients with liver cirrhosis (4). Conversely, the serum-ascites albumin gradient (SAAG) correlates positively with the hepatic sinusoidal pressure. Moreover, an SAAG of 1.1 g/dl or more is the threshold for distinguishing exudative from transudative ascites (5, 6). Previous reports have demonstrated that hypothyroidism may induce ascites (7, 8), although the underlying mechanism remains unknown.

We herein report the case of a patient with alcoholic liver cirrhosis combined with hypothyroidism, which induced ascites with a high concentration of TP. A hemodynamic study before the treatment for hypothyroidism revealed sinusoidal portal hypertension. The supplementation of levothyroxine markedly reduced not only the ascites, but also portal hypertension. The electron microscopic findings of a liver tissue specimen showed a fenestrated SEC, as speculated by the high ascetic TP level. A hemodynamic study and the electron microscopic findings suggested that the ascites in the present patient had been caused by hypothyroidism-induced sinusoidal hypertension. Furthermore, the diagnostic criteria of cirrhotic ascites, SAAG and the TP level in ascites clearly demonstrated the mechanism of ascites in this case.

Case presentation

A 71-year-old Japanese man complained of abdominal distension and edema in his legs. The patient had regularly consumed 100 g of ethanol per day for the previous 40 years, had been diagnosed with alcoholic liver cirrhosis and was being followed without any medication for liver cirrhosis. Both abdominal computed tomography and abdominal ultrasound revealed massive ascites with splenomegaly and a small hepatocellular carcinoma (HCC) at segment 8 (Figures 1A and B). The occurrence of ascites was considered to be due to portal hypertension caused by liver cirrhosis. Because the ascites did not sufficiently decrease after sodium restriction, the use of diuretics and paracentesis, the patient was referred to our department to control the ascites and to receive treatment for the HCC. The biochemistry data revealed a mild elevation of the AST level (Table). Thyroid function studies revealed a thyroid stimulating hormone (TSH) level of 106.92 μIU/mL, a free T4 of 0.68 ng/dl and a free T3 of 1.9 pg/mL (Figure 2 and Table). To obtain a differential diagnosis, paracentesis was conducted. The white cell count was 400 /μL, 75% of which were neutrophils. The ascites culture was negative. The ascitic fluid had a total protein level of 3.0 g/dL, an

albumin level of 1.4 g/dL and a SAAG of 1.9 g/dl. Because the TP level of 3.0 g/dL in the ascites was high for a patient with liver cirrhosis-induced ascites, it was necessary to rule out the presence of cardiac ascites or vascular occlusion as the causes of ascites in the present case. Therefore, a hepatic venous pressure measurement was performed to evaluate the hemodynamics. The hemodynamic study revealed a hepatic venous pressure gradient (HVPG) of 21 mmHg and a right atrium pressure of 6 mmHg, both of which suggested that hepatic portal hypertension existed in the present case (Figure 2). Furthermore, no pericardial effusion was observed on abdominal CT. According to a right atrium pressure within the normal range and no evidence of pericardial effusion, we therefore excluded right arterial failure in the present case.

Because there was no evidence of congestive liver injury in this patient, hypothyroidism was thus suspected to be the cause of the ascites. Therefore, levothyroxine supplementation was initiated on the 5th hospital day (Figure 2). After 45 days of levothyroxine supplementation, in combination with one-third of the previous dose of diuretics, the ascites thereafter dramatically decreased (Figures 1C-F). A 99mTc-Galactosyl sialyl

albumin (GSA) scintigram and indocyanine green (ICG)-based diagnosis were performed to assess the liver function, and the liver function was suspected to be depressed. To evaluate the liver histology, a liver biopsy was performed on the 40th hospital day. The liver biopsy specimen revealed pericellular fibrosis without bridging fibrosis in the light microscopic findings and fenestrated SECs in the electron microscopic findings (Figure 3). The patient selected radiofrequency ablation (RFA) for the treatment of HCC and underwent RFA 50 days after admission (Figures 1G and H). The patient was discharged without any complications on the 58th hospital day.

Discussion

Hypothyroidism is a well-known cause of ascites. Hypothyroidism-induced ascites, referred to as “myxedema ascites,” has been previously reported by others (7, 9, 10). However, the pathogenesis of myxedema ascites remains unclear. In contrast, liver cirrhosis is one of the most common causes of ascites and most frequently induces transudative ascites.

In order to determine the cause of the ascites, both the SAAG value and TP level in the ascites are useful for making a diagnosis of cirrhotic ascites. In particular, a SAAG value of 1.1 g/dl or more suggests transudative ascites caused by portal hypertension. Additionally, a low TP level in transudative ascites is explained by the electron microscopic findings, which are characterized by the capillarization of SECs (11).

The present case demonstrated a SAAG value of 1.1 or more. Moreover, other laboratory data, including the low platelet count, elevation of the fibrotic markers, slow ICG elimination and a delay in the GSA uptake, in the liver suggested that ascites in the present patient was induced by liver cirrhosis (12-15). However, previous reports have demonstrated a

discrepancy in the high TP level in the ascites if the ascites is caused by liver cirrhosis (4, 10, 16, 17). A high TP concentration in the ascites suggests exudative ascites or ascites due to non-cirrhotic portal hypertension. Furthermore, the ascites in the present case persisted despite treatment based on presumed cirrhotic ascites, and it decreased after supplementation with thyroid hormones. Although a diagnosis of hypothyroidism-induced ascites in the patients with liver cirrhosis is often difficult, we were able to accurately diagnose the cause of the ascites in this case using the laboratory data from both the ascites and the blood. We concluded that the ascites in the present case was mediated by portal hypertension, which had been induced by not only liver dysfunction associated with liver cirrhosis, but also hypothyroidism.

Two remarkable findings were observed in the present study. First, the HVPG was significantly lower on the 40th hospital day than on the 5th hospital day, and the percentage of HVPG on the 40th hospital day decreased by 27% compared with that on the 5th hospital day. An improvement of 20% or more in portal hypertension is defined as a successful intervention (18-20). During the significant decrease in the portal pressure in the present case,

the patient was also administered levothyroxine. We therefore considered that hypothyroidism induced portal hypertension in this case and that the supplementation of levothyroxine decreased the portal pressure. Second, there was a fenestrated wall in the sinusoidal epithelial cells on the electron microscopic findings, although the histological findings revealed fibrosis in the liver. These two findings suggested that the sinusoidal epithelial cells had not yet capillarized, thus the ascites in the present case was not induced by liver cirrhosis alone. Taken together, these findings indicate that hypothyroidism can induce reversible portal hypertension. We hypothesize that hypothyroidism-induced edematous changes influence the sinusoid, thus resulting in portal hypertension. Indeed, translational research has demonstrated that hypothyroidism decreased the activity of the bile acid transporter (21) and additionally diminished the cell membrane fluidity and the Na, K- ATPase activity (22). As a result of the impairment of the Na, K-ATPase activity, the sinusoid may become swollen.

There are two limitations associated with the present study. First, the microscopic findings did not show the exact pathogenesis of the hypothyroidism-induced ascites because the liver specimen was obtained on

the 40th hospital day. Second, the examinations of the liver function, including the GSA and ICG, showed a decreased liver function during hospitalization although levothyroxine supplementation was initiated. In contrast, the patient's prothrombin and albumin levels were better than the levels obtained on admission. We speculate that the observed decreased liver function may have been due to a decrease in the portal flow. In fact, Merkel et al. previously reported that an improvement of portal hypertension by beta blockers decreased ICG (23). We therefore speculated that the worsening of the liver function after the supplementation of levothyroxine may indicate the "true" capacity of the liver in the present case. Although the reason(s) why some patients with hypothyroidism exhibit ascites remains unclear, the importance of hypothyroidism as a cause of ascites was demonstrated in the present report. Furthermore, the present study is the first report which demonstrates hypothyroidism-induced portal hypertension proven by a hemodynamic study, while also showing that hypothyroidism-induced portal hypertension may be reversed by the supplementation of levothyroxine.

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Figure Legends

Figure 1. Abdominal computed tomography of the present patient during the treatment period. (A) and (B) Abdominal computed tomography (CT) at admission showed massive ascites. The white arrow indicates a high density mass in segment 8 detected by the enhanced study. (C-F) A dynamic CT study on the 30th hospital day showed a small amount of ascites and a high density region in segment 8. (G) and (H) CT showed a low density area in segment 8, which was an indication for post-locoregional therapy for hepatocellular carcinoma.

Figure 2. The time course of the laboratory data, hemodynamics and medications. The bar charts above the figure indicate the dose of each medication administered and the duration of the treatment with each medication. The upper line graph shows the thyroid hormone parameters, including the levels of thyroid-stimulating hormone (TSH), free triiodothyronine (FT3) and free thyroxine (FT4). The lower line graph shows the body weight (BW) and several laboratory data, including the total protein (TP) level and albumin (Alb) level. The central tables show each of

the values from several examinations, including the indocyanine green (ICG), the hepatic uptake ratio of Tc - GSA (LHL15), the hepatic vein pressure (HVP) and the wedged hepatic vein pressure (WHVP).

Figure 3. The electron microscopic findings of the liver obtained on the 40th hospital day. The white arrows indicate the fenestration of the sinusoidal epithelial cells. The gray arrows indicate the space of Disse.

Figure 1

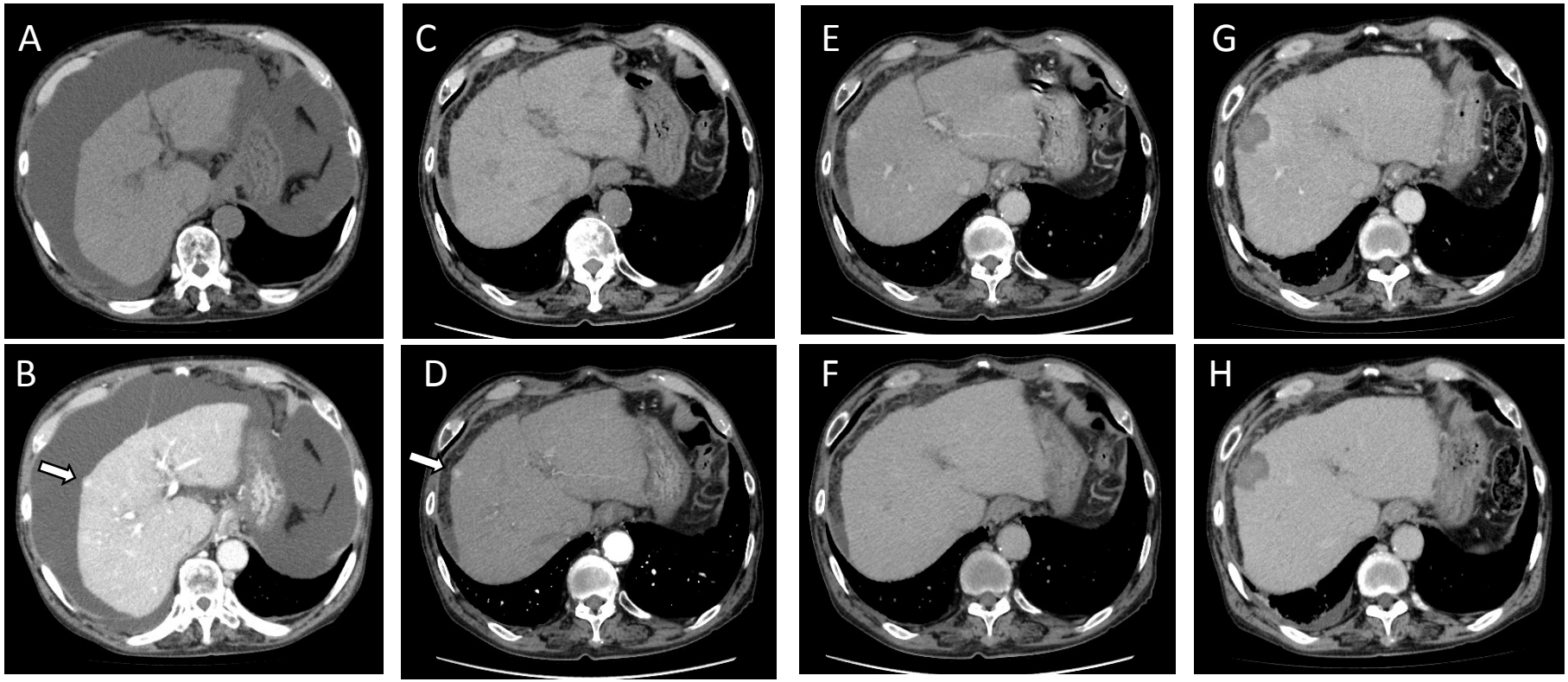

Figure 2

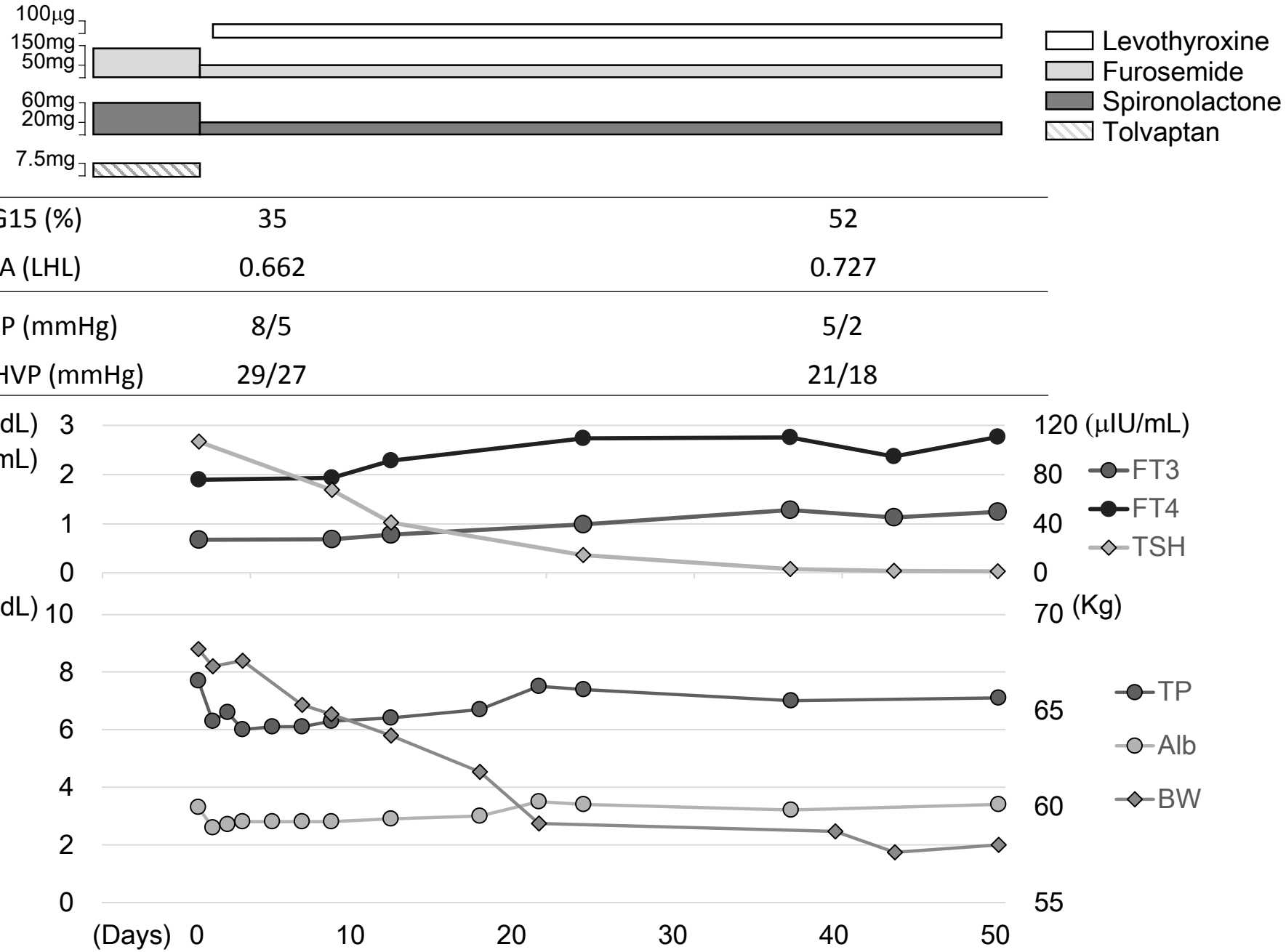
100μg
150mg
50mg
60mg
20mg
7.5mg
Levothyroxine
Furosemide
Spironolactone
Tolvaptan
ICG15 (%) 35 52
GSA (LHL) 0.662 0.727
HVP (mmHg) 8/5 5/2
WHVP (mmHg) 29/27 21/18
(ng/dL)
(pg/mL)
3
2
1
0
120 (μIU/mL)
80
40
0
FT3
FT4
TSH
(g/dL)
10
8
6
4
2
0
70 (Kg)
65
60
55
TP
Alb
BW
(Days) 0 10 20 30 40 50

Figure 3

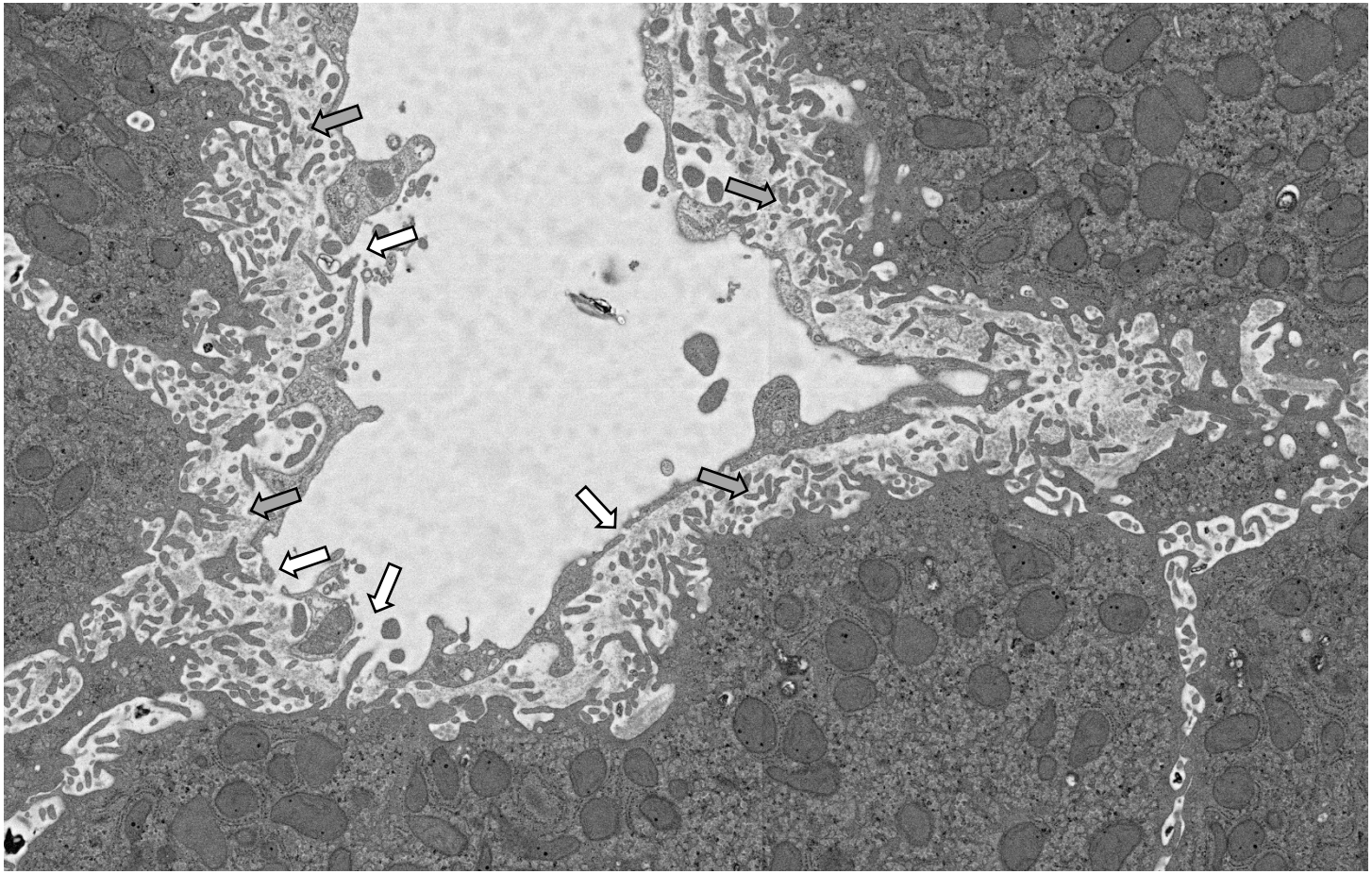

Table. Laboratory data of the present patient at admission.

Hematology		**Virus markers**		**Urine**	
WBC	7.27 10^3/mL	IgM HAVAb	(-)	Uric protein	(-)
Neutro	57.4%	IgMHBcAb	(-)	Urinal sugar	(-)
Lympho	31.6%	HBsAg	(-)		
Mono	7.9%	HBsAb	(-)	**Ascites**	
Eosino	1.8%	HBcAb	(+)	TP	3.1 g/dL
Baso	0.3%	HCVAb	(-)	Albumin	1.4 g/dL
RBC	397 10^6/mL	EBVCA IgG	(-)	WBC	0.4 10^3/mL
Hb	13.3 g/dL	EBVCA IgM	(-)		
Plt	205 10^3/mL	EBNA Ab	(-)	pH	7.8
Renal function		CMV IgG	(+)	Rivalta	(+)
BUN	**23.3** mg/dL	CMV IgM	(-)	SAAG	1.9 g/dL
CRNN	**1.24** mg/dL	**Autoantibodies**			
Blood chemistry		ANA	<x40	Culture	(-)
T-Bil	0.8 mg/dL	AMA	(-)	Cytology	No malignancy
AST	**35** IU/L				
ALT	19 IU/L	**Tumor markers**			
g-GTP	62 IU/L	CEA	**5.1** ng/mL		
ALP	423 IU/L	CA19-9	**47.5** U/mL		
TP	7.7 g/dL	AFP	4.8 ng/mL		
Albumin	**3.3** g/dL				
FBS	94 mg/dL				
HbA1c	5.5%	**Fibrosis marker**			
Ferritin	**1518** ng/mL	Hyaruronic acid	**300** ng/mL		
CRP	1.6 mg/dL	Type IV collagen	**11** ng/mL		
Blood coagulation					
PT-INR	1.06	**Endocrine**			
APTT	33.9 sec.	TSH	**106.92** mIU/mL		
Fib	**452** mg/dL	FT4	**0.68** ng/dL		
FDP	**25** mg/mL	FT3	**1.9** pg/mL		

WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; Plt, pletelets; BUN, blood urea nitrogen; **CRNN, creatinine**; T-Bil., total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; TP, total protein; CRP, C-reactive protein; PT, prothrombin time; HPT, hepaplastin test; Fib, fibrinogen; FDP, fibrin degradation products; Ab, antibody; Ag, antigen; HA, hepatitis A virus; HB, hepatitis B virus; HCV, hepatitis C virus; EB, Epstein–Barr virus; VCA, Virus capside antigen; NA, Nucleus antigen; CMV, cytomegalovirus; ANA, anti-nuclear antibody; AMA, anti-mitochondrial antibody; CEA, Carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; AFP, α-fetoprotein; TSH; Thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; SAAG, serum-ascites albumin gradient.