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A Case of Acute Pancreatitis Associated with a Severe Acute HAV Infection and Compensated Liver Cirrhosis Type B

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Abstract：A 59-year-old male presented with general fatigue and appetite loss. He had a history of hepatitis B virus treatment when he was 37-years-old and was reaching a state of clinical cure. During a previous visit to a different clinic, his serum aspartate transaminase (AST) level was 1,608 IU/l ; alanine aminotransferase (ALT), 2,328 IU/l ; and prothrombin time (PT), 49%. In addition, he was IgM-hepatitis A antibody and hepatitis A virus-RNA positive. There was a sudden onset of epigastralgia, and his pancreatic enzyme levels were elevated on the 72nd day following hospitalization. Computed tomography (CT) revealed severe acute pancreatitis (grade D). Despite continuous regional arterial infusion of a protease inhibitor and an antibiotic along with plasma exchange therapy, the patient died due to multiple organ failure. The histopathological analysis during the autopsy revealed almost collapsed hepatocytes and fibrous bands with regenerative nodules (cirrhosis). HBV-DNA (PCR) was positive in the hepatic tissue. These results were important findings which confirmed the progression to compensated liver cirrhosis by an occult HBV infection. In conclusion, patients with chronic liver disease are considered to be at risk for severe disease, especially, patients that are HBc antibody positive might progress to liver cirrhosis during a latent HBV infection. This is a valuable case due to the occurrence of both HAV infection and acute pancreatitis with liver cirrhosis and HBsAg seroclearance.

Key words：**Acute Hepatitis A, HAV, HBV, Superinfection, Acute Pancreatitis**

Introduction

Hepatitis A virus (HAV) infection rarely has a fulminant course and is seldom fatal, with an estimated fatality rate of 0.14 to 2.0%. Acute HAV superimposed on chronic HBV infection results in a higher morbidity and mortality than isolated acute HAV infection. Two major risk factors of fulminant hepatic failure have been identified : age (over 40 years) and the presence of underlying chronic liver disease.[1)2)]

Occult HBV infection is characterized by undetectable HBsAg. The serum HBV DNA level is usually less than 10^4 copies/mL in patients with this infection. HBV-induced liver damage is directly related to active viral replication, which is usually investigated by determining serum viral DNA by direct hybridization techniques. Consequently, HBsAg-positive patients with suppressed

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viral replication and undetectable levels of viremia usually exhibit a low grade or absence of hepatocellular injury. Nevertheless, several observations suggest that an undefined amount of free viral genomes may persist in the hepatocytes of these subjects. This report presents a case of acute pancreatitis associated with severe acute HAV infection with compensated liver cirrhosis type B ; the patient was serum HBsAg and antibody negative (−), serum HBc antibody positive (+), serum HBV-DNA negative (−), and hepatic HBV-DNA positive (+).

Case Report

A 59-year-old male patient presented with compensated liver cirrhosis type B. He regularly visited a clinic for liver-function checkups. From the age of 37, he had been administered medication on steroid withdrawal for chronic hepatitis type B. As a result, he was reaching a state of clinical cure. According to the records from his last visit, serological testing revealed that his serum was HBc antibody positive (+), HBsAg and antibody negative (−), HBeAg negative (−), and HBe antibody positive (+) ; furthermore, his transaminase levels before the onset of liver damage were normal. Finally, he experienced general fatigue, appetite loss and fever from around mid-September 2001, and visited the clinic on September 27. Serum biochemical tests revealed liver damage. Thereafter, his liver enzyme levels gradually elevated, and the prothrombin time (PT) was gradually prolonged. He was then referred to this hospital for further investigation. On admission, his serum aspartate aminotransferase (AST) value was 1,608 IU/l ; alanine aminotransferase (ALT), value 2,328 IU/l ; and PT, 49% (September 15, 2001). Abdominal ultrasound and computed tomography (CT) revealed a pattern of liver cirrhosis without ascites at the time of admission. A flare-up of the HBV infection was not detected due to the negative serum HBsAg and negative serum HBV DNA (polymerase chain reaction, PCR) on admission. Furthermore, viral testing revealed that his serum was IgM-hepatitis A (HA) antibody and HAV

Table 1 Laboratory Findings

Urine		**Blood chemistry**		**Virus marker**	
Urinary protein	(−)	Total protein	6.6 g/dL	IgM-anti-HA	5.3 (+)
Urine bilirubin	(−)	Albumin	2.3 g/dl	HAV-RNA	(+)
Ketones in urine	(1+)	Total bilirubin	2.8 mg/dL		
		Direct bilirubin	2.0 mg/dL	HBs-Ag	(−)
		AST	1,680 IU/L	Anti-HBs	(−)
Stool		ALT	2,328 IU/L	HBe-Ag	(−)
Fecal occult blood	(−)	LDH	1,435 IU/L	Anti-HBe	(+)
		ALP	367 IU/L	Anti-HBc	(+)
		GGT	318 IU/L	IgM-anti-HBc	(−)
Peripheral blood		ChE	205 IU/L	HBV DNA	
WBC	$2.8\times10^3/\mu L$	TTT	11.0 kunkel	<2.6 log copies/m	
RBC	$2.8\times10^6/\mu L$	ZTT	15.5 kunkel		
Hemoglobin	14.3 g/dL	Amylase	94 IU/L	Anti-HCV	(−)
Hematocrit	43.7%	Glucose	261 mg/dL	HCV-RNA	(−)
Platelet count	$153\times10^3/\mu L$	BUN	11 mg/dL		
		Creatinine	0.9 mg/dL	HSV IgM	(−)
		Total cholesterol	128 mg/dL	HSV IgG	160.0
Coagulation test		CRP	2.3 mg/dL	CMV IgM	(−)
Prothrombin activity	49%	NH_3	66 μg/mL	CMV IgG	29.5
		IgM	105 mg/dL	EBVCA IgM	(−)
				EBVCA IgG	40

WBC ; white blood cell, RBC ; red blood cell, AST ; aspartate aminotransferase, ALT ; alanine aminotransferase, LDH ; lactate dehydrogenase, ALP ; alkaline phosphatase, GGT ; gamma-glutamyl transpeptidase, ChE ; cholinesterase, TTT ; thymol turbidity test, ZTT ; zinc sulfate turbidity test, BUN ; blood urea nitrogen, CRP ; C-reactive protein

RNA positive ; hence, he was diagnosed to have an HAV superinfection with compensated liver cirrhosis.

There was no history of alcohol intake, ingestion of any form of drug, herbal medicine, or smoking. He was not on a diet and not sexually active. Furthermore, he had not recently traveled outside Japan. Moreover, he had not undergone a dental examination or surgery for the last 6 months. These findings indicated the following diagnosis ; first, the liver disease in this patient had been progressing to compensated liver cirrhosis due to an occult HBV infection (HBc antibody positive (+), HBsAg and antibody negative (−), HBeAg negative (−), and HBe antibody positive (+)), furthermore he had developed into severe hepatitis due to superinfecting HAV.

Ursodeoxycholic acid (600 mg/d) and stronger neo-minophagen C (SNMC) was used to treat the acute hepatitis HAV. Lamivudine (100 mg/d) was used to treat the occult HBV infection (chronic hepatitis HBV). Intravenous hyperalimentation (IVH) was used to treat the electrolyte abnormality and malnutrition. As a result, the hepatic enzymes (AST, ALT) were improved, but liver function (PT, albumin (Alb), total bilirubin (T-Bil), ascites) gradually deteriorated. A sudden onset of epigastralgia was observed on the 72nd day of hospitalization. The pancreatic enzyme levels were elevated (serum amylase, 2,912 IU/l ; urine amylase, 5,220 IU/l ; pancreatic secretory trypsin inhibitor (PSTI), 657.1 ng/ml). A CT scan revealed severe extrapancreatic changes as well as fluid accumulation (CT severity index : CT grade D). The presence of typical abdominal pain (continuous epigastralgia and dorsal pain) and high serum and urine amylase along with the CT scan results indicated severe acute pancreatitis. Moreover, with severe acute pancreatitis, he went into fulminant hepatic failure and renal failure. He was treated with continuous regional arterial infusion of a protease inhibitor (nafamostat mesilate, 120 mg) as well as an antibiotic (imipenem, IPM/CS ; 2,000 mg) for 5 days along with plasma exchange therapy for the severe acute pancreatitis. Furthermore, he underwent plasma exchange therapy (PE) for fulminant hepatic failure and by continuous hemodiafiltration (CHDF) for renal failure.

On the 87th day, the patient died due to multiple organ failure. The histopathological analysis following the autopsy revealed almost totally collapsed hepatocytes and fibrous bands with regenerative nodules (cirrhosis). HBV-DNA (PCR) was positive in the liver instead of in the serum. These results were thus considered to be important findings that confirmed the progression to compensated liver cirrhosis due to an occult HBV infection.

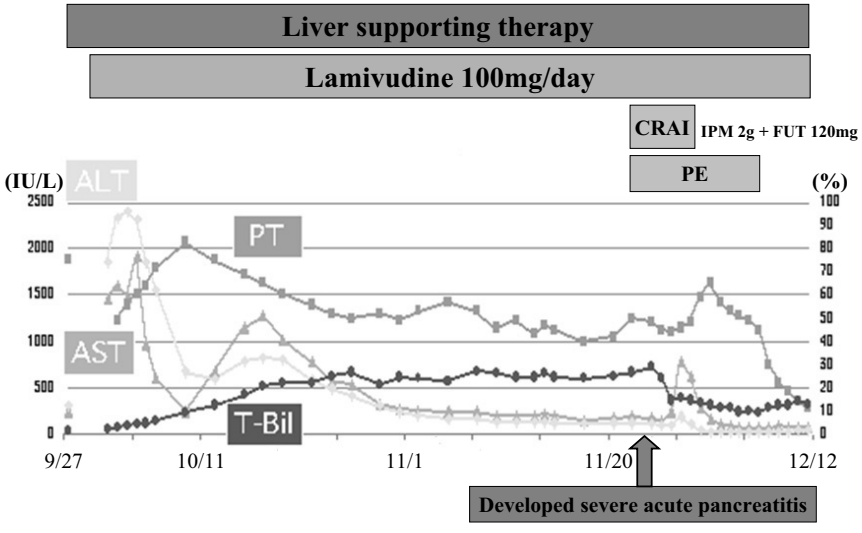

Figure 1. Clinical course
PT ; prothrombin activity, AST ; aspartate aminotransferase, ALT ; alanine aminotransferase, T-Bil ; total bilirubin, CRAI ; continuous regional arterial infusion, PE ; plasma exchange

Discussion

This report presents a case of acute pancreatitis associated with severe acute HAV infection with compensated liver cirrhosis type B. The patient had a medical history of steroid withdrawal for chronic hepatitis type B around 20 years ago. Thereafter, he tested negative for the HBsAg and HBs antibody, and no HBV DNA was detected in the serum. In other words, he was reaching a state of clinical cure. However, HBV DNA was detected in the liver instead of in the serum. Arase et al. reported that thirteen patients were examined for histological changes of the liver after HBsAg seroclearance, all patients showed marked improvement of necroinflammation of the liver, but only 2 of the 13 patients showed no liver fibrosis.[5] If patients with HBV have reached a state of clinical cure, chronic hepatitis gradually might progress to liver cirrhosis during the latent HBV infection in the liver.

Most patients with chronic hepatitis B who acquire an HAV infection have an uncomplicated course.[3] However, patients with cirrhosis are at a substantial risk of fulminant hepatitis and death associated with HAV superinfection can occur.[4] In Shanghai with the occurrence of a large outbreak of HA over 300,000 cases of acute HA were reported, and 30,000 of these cases probably occurred in HBV carriers. According to the Shanghai data, the fatality rate was shown to be 5.6 times higher in HBsAg carriers (0.05%) than in HBsAg-negative patients (0.009%).[6] Moreover, 15/47 deaths were caused by HA superimposed on chronic hepatitis B.[7]

Acute liver failure (ALF) due to HAV infection is uncommon, but is a potentially lethal illness. The U.S. Acute Liver Failure Study Group proposed a prognostic model incorporating 4 features (serum ALT<2,600 IU/L, creatinine>2.0 mg/dL, intubation, pressors) that predicted the likelihood of transplant/death.[8] Our case did not manifest any of the above features.

The HAV vaccine is currently recommended for three groups：communities with endemic HAV infection (>20/100,000), individuals at increased risk of HAV exposure, and individuals with increased risk of severe disease.[4] Furthermore, in Japan, 6% experience side effects of hepatitis A vaccine, and no serious side effects are reported.[9] Patients with chronic liver disease are considered to be at risk for severe disease, and also have an increased risk of HAV exposure. Hence, vaccination against HAV is recommended for anti-HAV antibody negative patients who have mild to mild chronic liver disease in HBV.

The etiology of acute pancreatitis is diverse, and unusual causes include HAV.[10] Although pancreatitis has been observed during the autopsy in patients with fulminant hepatic failure, there have been only a few reports of an association between mild to moderate acute viral hepatitis and acute pancreatitis.[11][12] Basaranoglu et al. speculated that HAV might induce hypomotility and/or dysmotility of the gallbladder that might lead to sludge formation, and a partial blockage due to the flow of bile might occur when sludge blocks any part of the biliary ductal system.[12] HAV-associated pancreatitis may be due to the formation of biliary sludge during the acute phase of the viral illness. In this case, biliary sludge in the gallbladder was detected by abdominal ultrasonographic examination at the time of the diagnosis of acute pancreatitis. The cause of the pancreatitis was not identified, aside from the biliary sludge. Consequently, as reported by Basaranoglu et al., the pancreatitis may have been due to the formation of biliary sludge during the acute phase of HAV. One of the late complications of severe acute pancreatitis is pancreatic necrosis. The necrotic pancreas become secondarily infected up to 40% to 60% of the time.[13] Moreover, mortality increases when necrotic lesions become infected.[14] Antibiotics have been shown to improve patient outcomes in severe acute pancreatitis. Continuous arterial infusion of a protease inhibitor along with antibiotic therapy is considered to be useful for the treatment.[15] The arterial injection of a protease inhibitor might be effective for the control of abdominal pain, and arterial injection of antibiotics also might have advantages for the prevention of infectious pancreatic necrosis. The current patient did not recover despite treatment with the combined modality therapy for fulminant hepatic failure and severe pancreatitis. No previous case

reports have noted the occurrence of both HAV infection and acute pancreatitis in liver cirrhosis with HBsAg seroclearance. Patients with chronic liver disease are considered to be at risk for severe disease. In particular, patients who are HBc antibody positive might progress to liver cirrhosis during a latent HBV infection.

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