Two Cases of Adult Varicella Accompanied by Hepatic Dysfunction

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Introduction

Varicella is a typical acute exanthematous viral infection caused by varicella-zoster virus (VZV)¹⁾. In recently years, as far as hepatic dysfunction caused by viruses other than the hepatitis virus is concerned, there have been a few reports on hepatic dysfunction accompanying varicella following organ transplantation of Europe and America²⁾³⁾ and another report on an immunocompromized adult following treatment for Systemic lupus erythematosus (SLE) in Japan⁴⁾. Nonetheless, we searched the MEDLINE and J MEDICINE listing the publications between 1986 and 1996 and found one report on healthy adults with varicella accompanied by hepatic dysfunction in Europe and America⁵⁾ and two reports in Japan^{6,7)}. Only Noguchi *et al.* dealt with the findings of liver biopsy⁶⁾. We examined two healthy adults with varicella and mild-to-moderate hepatic dysfunction, and referred to the results of their liver biopsies. The present paper discusses this issue, citing some references.

Cases

Case 1. The patient was a 37-year-old man who received a leg burn in 1985 and had been drinking Shochu (Japanese spirit), 0.27 liter a day, for 10 years. He was admitted to our department with chief complaints of general malaise, fever and exanthema on April 13. Five days before admission, he had a fever of about 39°C and a rash appeared all over his body on April 10. There was no past history of varicella.

Physical examination showed a height of 172 cm; weight, 63 kg; blood pressure, 148/72 mmHg, and pulse rate, 80/min. Diffuse vesicles and ulcers were found on the trunk and all extremities. In the abdominal region, the liver was palpable at two fingerbreadths above the right midclavicular line. Neither tenderness nor knock pain was confirmed.

Laboratory data on admission are shown in the Table 1. An elevated white blood cell count and atypical lymphocytes (3%) were detected in the peripheral blood. There were mild-to-moderate increases in the levels of transaminase, LDH and biliary enzymes. The patient was negative for the following virus markers: HBs antigen, HCV antibody (second generation), herpes-simplex virus (HSV) and VZV antibody. Also, it was found that he had been exposed to Epstein-Barr virus (EBV)

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Table 1 Laboratory data on admission

	Case 1	Case 2		Case 1	Case 2
Peripheral blood			Viral markers		
WBC(/mm ³)	10,600	7,900	HBaAG	(-)	(-)
Neut(%)	81	46	HCV-Ab(2nd)	(-)	(-)
Eos(%)	0	1	IgG-anti-EB-VCA	×320	×80
Lymph(%)	12	18	EBNA	×40	×20
Mono(%)	4	42	IgM-anti-CMV		(-)
Baso(%)	0	1	anti-VZV (CF)	<×4	×16
Atyp. lymph(%)	3	2	anti-HCV (CF)	<×4	<×4
RBC(×10 ⁴ /mm ³)	459	510			
Hb(g/dl)	13.2	15.1	Coagulation test		
Ht(%)	40.4	48.9	PT(%)	94	68
PLt(×10 ⁴ /mm ³)	21.3	31.6	HPT(%)	115	82
Blood chemistry			Urinalysis		
Tp(g/dl)	5.9	7.6		n.p.	n.p.
alb(g/dl)	3.1	4.7			
TB(mg/dl)	0.8	0.8			
GOT(IU/l)	113	57			
GPT(IU/l)	132	193			
LDH(IU/l)	805	396			
AL-P(IU/l)	121	225			
γ-GTP(IU/l)	159	52			
LAP(G.R.U)	429	266			

n.p.: nothing in particular, CF: complement-fixation test, EBNA: Epstein-Barr virus-associated nuclear antigen

in the past. Furthermore, the patient was negative for HCV antibody on September 8, five months after the onset of hepatic dysfunction. A chest X-ray taken on admission did not show any abnormalities.

Case 2. The patient was a 26-year-old man who had been drinking three bottles of beer a day for 10 years. He was admitted to the Department of Dermatology with chief complaint of fever and rash on October 30, 1995. On October 29, he had a fever of 39°C, and a rash and vesicles appeared all over the body the next day. After hospitalization, 780 mg of acyclovir per day was administered from October 30 to November 6 based on the diagnosis of varicella. On November 8, the 11th day from the onset, the levels of sGOT and sGPT suggested hepatic dysfunction (64 and 194 IU/l, respectively). Consequently, for the purpose of close examination, he was transferred to our department on November 10, the 13th day from the onset. There was no past history of varicella.

Physical examination showed a height of 167 cm; weight, 63 kg; blood pressure, 140/70 mmHg and pulse rate 70/min. Incrustation was detected on the trunk. In the abdominal region, the liver was palpable at one fingerbreadth above the right midclavicular line and two fingerbreadths in the epigastrium. The liver was elastic firm. Neither tenderness nor knock pain was detected.

Laboratory data on admission revealed that the levels of transaminase and biliary enzymes were increased slightly (Table 1). Increases in white blood cell count and eosinophil count were not found and atypical lymphocytes (2%) were detected in the peripheral blood. As for changes in the coagulation system, prothrombin time (PT) and hepaplastin test (HPT) were slightly decreased. The patient was negative for virus markers such as HBs antigen, HCV antibody (second generation), and cytomegalovirus. It was found that the patient had been exposed to EBV in the past, and he was positive for VZV antibody but negative for HSV by the complement-fixation test (CF). The result of

Fig. 1 Clinical course of Case 1.

Fig. 2 Clinical course of Case 2.

the chest C-ray taken on admission was normal.

Clinical course (Fig. 1 and 2): Although in Case 1 VZV antibody was negative on admission, the patient was diagnosed as having varicella based on clinical symptoms, and administration of 750 mg of acyclovir per day started on April 13, the 6th day from the onset. In Case 1, the levels of sGOT and sGPT were increased to 285 and 539 IU/l, respectively, on April 17, the 10th day from the onset. At this time, an increase in the eosinophil count, dermal pruritus and a rash were not detected. Even though acyclovir was administered until April 21, the level of transaminase started to decrease before this date. Then, the levels of sGOT and sGPT became normal (both 29 IU/l) on May 8, the 31st day from the onset. Also, in Case 2, the levels of sGOT and sGPT had decreased to 28 and 31 IU/l, respectively, on November 15, the 18th day from the onset. The Case 1 patient was found to be positive for VZV antibody by CF on April 19. To determine the cause of hepatic dysfunction, liver biopsies were performed in both patients on April 28, the 21st day from the onset, and on November 17, the 20th day from the onset.

Liver biopsy (Fig. 3 and 4): In both cases, focal necrosis and neutrophil infiltration were noted in the center of the lobe, suggesting mild acute hepatitis. Also mild cellular infiltrations, consisting mainly of neutrophils, were also detected in the portal area. Neither internuclear inclusions nor coagulative necrosis, which are typical of VZV and HSV²⁾ were found. There was slight proliferation of Kupffer cells in Case 2.

Discussion

When people are first exposed to VZV, they experience varicella as a rash. VZV establishes latent infections in the sensory ganglions during the onset of the rash. In adult patients over the age of 40 and those whose immune system is compromised, VZV in the sensory ganglions is reactivated and induces herpes zoster¹⁾. Reye's syndrome⁸⁾ is known to be one of the complications of varicella in children. Pneumonitis⁵⁾ is known as one of the complications of varicella in adults, and can cause death in patients suffering from varicella. Schleussing *et al.*⁹⁾ first reported varicella accompanied by hepatic dysfunction in 1927, and since then there have been several reports on hepatic dysfunction among children⁸⁾ and immunocompromized adults following transplantation²⁾³⁾. Nonetheless, to the best of our knowledge, there have been only four reported cases of adult varicella patients with hepatic dysfunction who had not undergone organ transplantation^{4)~7)}. One of these patients⁴⁾

Fig. 3 Histology of liver biopsy specimen (Case 1, on the 21st day from onset). In the portal area, mild inflammatory cell infiltration is seen. Focal necrosis is also seen. Inflammatory cells are composed mainly of neutrophils. (H & E stain $\times 200$).

Fig. 4 Histology of liver biopsy specimen (Case 2, on the 20th day from onset). Mild focal necrosis and inflammatory cell infiltration are seen in sinusoids. Inflammatory cells are composed mainly of neutrophils. There is no findings of fatty liver. (H & E stain $\times 200$)

was diagnosed having as SLE and received more than 15 mg of prednisolone per day for about six months. When this patient had a varicella-induced rash, 20 mg of the drug per day was administered, so the immune system of this patient was believed to be compromised. Therefore, only three otherwise healthy adults have had varicella accompanied by hepatic dysfunction^{5,7)}. However, Kobayashi *et al.*⁷⁾ reported that, of 79 adult patients with varicella, hepatic dysfunction was confirmed in 59 patients (71%) who did not have an underlying disease or receive drugs that might cause the dysfunction, suggesting that the rate of healthy adults with varicella accompanied by hepatic dysfunction is not low. We examined two otherwise healthy patients with varicella accompanied by mild-to-moderate hepatic dysfunction who not have pneumonitis, and live biopsies were performed on these patients.

There was no family history of liver diseases in either of the two patients in the present study, and they were negative for both HBs antigen (RIA; Dainabot Co., Ltd., Tokyo, Japan) and HCV antibody (Ortho HCV-RIA II, Ortho Diagnostic System Inc, Raritan, New Jersey, USA). Also, it was found that they had not been exposed to EBV or cytomegalovirus recently. Although the two patients regularly drank alcohol, the results of their liver biopsies did not show conditions associated with alcoholic hepatitis, such as ballooning of hepatocytes, Mallory body¹⁰⁾ and perihepatocytic fibrosis. Also, based on their medical history, it was determined that they did not have alcoholic hepatitis. Only acyclovir was administered to these patients. Therefore, we deny the possibility that the hepatic dysfunction was caused by acyclovir. In Case 1, an increase in eosinophil, and the onset of the rash or dermal pruritus were not found during acyclovir administration. Also, in Case 2, even though the level of transaminase peaked at the completion of acyclovir administration, increases in white blood cell count and eosinophils were not detected in the peripheral blood when the patient was transferred to our department. Furthermore, in both of these patients, the liver biopsy did not show the eosinophil infiltration¹¹⁾ that is seen in patients with drug-induced hepatic dysfunction. Based on these findings, it was concluded that acyclovir did not cause the hepatic dysfunction. The titer of HSV antibody determined by CF did not increase during the follow-up observation period in either patient; therefore, it was thought that the hepatic dysfunction experienced by the two patients was associated with VZV infection from the characteristic clinical symptoms and the increase in the titer of VZV antibody detected by CF.

Patti *et al.*³⁾ studied hepatic dysfunction in children and adult suffering from varicella between 1975 and 1988, and reported that when the immune system was compromised, the mortality rate was high in both children and adults, nonetheless, when the immune system was not compromised, varicella was asymptomatic. This finding suggested that varicella might cause hepatic dysfunction in healthy adults whose immune system was not compromised. In the present study, the chest X-ray taken on admission showed that the two patients did not suffer from pneumonitis and their immune system was not compromised.

In the present cases, the maximum level of sGOT was 285 and 64 IU/l (average 174.5 IU/l) in Cases 1 and 2, and the maximum level of sGPT was 539 and 194 IU/l (average 366.5 IU/l), respectively. Thus, the levels of the two transaminases showed mild-to-moderate abnormalities. Also, Kobayashi *et al.*⁷⁾ reported that the maximum levels of sGOT and sGPT were 93 and 162 IU/l, respectively, in 56 adult varicella patients with hepatic dysfunction, and that the level of sGPT exceeded 100 IU/l in three of the 56 patients (5.8%). Furthermore, Schlossberg *et al.*⁵⁾ found that the level of sGOT was mildly or moderately increased in three of six adult varicella patients whose disease was complicated by pneumonia. The results of the present study also showed mild or moderate increases in the level of two transaminases.

In the present cases, the level of LDH was increased moderately to 805 IU/l in one patient. Kobayashi *et al.*⁷⁾ found that the maximum level of the LDH in the 56 adult varicella patients with hepatic dysfunction was 522 U/l, and that the level of LDH exceeded 350 IU/l nine of the 56 patients (16.1%). Schlossberg *et al.*⁵⁾ reported that the level of LDH was mildly or moderately increased in five of six adult varicella patients. Therefore, their findings were in agreement with ours.

Kobayashi *et al.*⁷⁾ reported that the level of sGPT normalized within 18 days from the onset in the nine adult varicella patients. The number of days that is required for sGPT to normalize has not been determined. Also, Noguchi *et al.*⁶⁾ stated that the change in transaminase levels was mono-peaked and was not prolonged in two adult patients who developed liver injury after varicella and herpes zoster. These findings suggested that hepatic dysfunction accompanied by varicella takes a favorable clinical course in adults who do not have pneumonitis or in those whose immune system is not compromised. The level of sGPT in the two patients in the present study normalized on the 31st and the 18th day from the onset, respectively, and these data are in agreement with the results of Kobayashi's study.

Kusne *et al.*²⁾ stated that, like hepatic dysfunction caused by HSV, the histopathological findings of hepatic dysfunction accompanying varicella was coagulative necrosis caused by a mild inflammatory reaction, and that the inflammatory cellular infiltration consisted mainly of neutrophils. In the present study, focal necrosis and inflammatory cellular infiltration were also found in the center of the lobe, and the infiltrating cells consisted mainly of neutrophils. These findings are in agreement with the result of the study conducted by Kusne *et al.*²⁾.

At present, the mechanism of onset of hepatic dysfunction accompanying varicella is unclear. Noguchi *et al.*⁶⁾ performed liver biopsies on two adult patients with hepatic dysfunction following the onset of varicella and herpes zoster to determine the subsets of infiltrating lymphocytes. They found Leu 2a (cytotoxic/suppressor) and Leu 15 (suppressor, natural killer/killer) positive cells in the hepatocyte necrotic regions. On the other hand, it is reported that VZV particles are located in hepatic tissue¹²⁾, and it is known that VZV has a cytopathic effect on human nephrocyte and fetal pulmonary blasts¹⁾. These findings show that the hepatic dysfunction which accompanies varicella might directly correlate with hepatic dysfunction caused by VZV. The results of the present study also showed that the degree of inflammatory cellular infiltration in hepatic tissue was mild and that the infiltrating cells consisted mainly of neutrophils. Thus, these findings suggest that VZV may

directly cause hepatic dysfunction.

In studies of more cases in the future, it will be important to investigate the clinical characteristics and histopathological findings of patients with varicella accompanied by hepatic dysfunction.

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水痘に合併した肝障害の2例

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要 旨

肝機能異常を伴った成人水痘の2例を経験した。sGOT, sGPT値, 及びLDH値は共に一過性の軽度から中等度の上昇を認めた。sGPT値は2

例共に発症後8週間以内に正常化した回復期の肝生検組織像では小葉中心部の focal necrosis と好中球を主体とした炎症細胞浸潤を認め、軽い急性肝炎の所見を呈していた。