Sequential Occurrence of Hepatocellular Carcinoma Following Waldenström's Macroglobulinemia: The Pathogenetic Role of Chronic Liver Disease

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We report a case of sequential occurrence of hepatocellular carcinoma (HCC) following Waldenström's macroglobulinemia (WM) in the course of chronic liver disease. The diagnosis of WM was made in a 55-year-old man with a history of alcohol abuse. He developed HCC in the course of WM, and hepatitis C virus (HCV) infection was detected by enzyme-linked immunosorbent assay. Recent reports suggest that persistent HCV infection is related to the pathogenesis of B cell malignancy. Chronic liver disease may be associated with the pathogenesis of the double malignancies in the present case.

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Key words: B cell malignancy, hepatitis C virus, alcohol abuse

Introduction

Hepatocellular carcinoma (HCC) is frequently associated with other malignancies (1). We present a case of sequential occurrence of HCC following Waldenström's macroglobulinemia (WM) in the course of chronic liver disease, and discuss the pathogenesis of the double malignancies in the present case.

Case Report

A 55-year-old man was admitted to the hospital because of slight fever in February 1988. He had no previous exposure to blood transfusion. His daily intake of alcohol was about 200 ml. Physical examination showed hepatosplenomegaly. Hematological findings were as follows; hemoglobin 9.4 g/dl, leukocytes 5,300/ μ l (1% metamyelocytes, 67% neutrophils, 18% lymphocytes, 12% monocytes and 2% eosinophils), and platelets 30.5 $\times$ 10⁴/ μ l. Other laboratory findings were as follows; aspartate aminotransferase (AST) 52 mU/ml (normal range, 11–30), alanine aminotransferase (ALT) 67 mU/ml (normal range, 4–30), alkaline phosphatase (ALP) 485 mU/ml (normal range, 89–285), total protein 9.9 mg/dl [26.6% albumin, 5.6% α_1 -globulin, 12.6% α_2 -globulin, 9.4% β -globulin

and 45.5% γ -globulin with monoclonal protein (IgM-k)], total bilirubin 0.4 mg/dl (normal range, 0.2–1.0), and IgM 2,890 mg/dl. Hepatitis B surface antigen (HBsAg) and antibody against HBsAg were negative. Ultrasonography of the abdomen showed mild hepatomegaly without a space-occupying lesion and marked splenomegaly (135 $\times$ 54 mm). Bone marrow examination revealed normocellularity with an increase of lymphoplasmacytic series (Fig. 1). Cryoglobulin and pyroglobulin were negative. He was diagnosed as having WM. He had two courses of melphalan and prednisolone (MP) in combination with vincristine. After his discharge from hospital in March 1988, forty-four courses of MP were administered until November 1991. No blood transfusion was administered before the second admission. The accumulative dose of melphalan was 1,002 mg.

Three months before the second admission a high fever developed. He was admitted again in December 1991. Table 1 shows the laboratory data on the second admission. The antibody against HCV (HCVAb) was detected by the second generation enzyme-linked immunosorbent assay (ELISA) (2). Ultrasonography of the abdomen showed splenomegaly (147 $\times$ 48 mm) and a high echoic mass in the 5th and 8th segments of the liver. Aspiration biopsy of the liver revealed hepatocellular carcinoma (Fig. 2). His condition soon changed adversely. He

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Figure 1. Bone marrow examination demonstrated an increase of lymphoplasmacytic series (Wright-Giemsa stain, ×1,000).

Figure 2. Aspiration biopsy of the liver revealed hepatocellular carcinoma with pseudoglandular pattern (HE stain, ×100).

died of hepatic failure in March 1992. No autopsy was performed. Figure 3 summarizes the clinical course.

Discussion

Only a few cases of WM accompanied by HCC have been reported, most of the patients were Japanese (3, 4). WM is a rare B-cell neoplasia, the pathogenesis of which is little known.

Table 1. Laboratory Data on the Second Admission

Peripheral blood		IgG	2,389 mg/dl
Leucocytes	2,400/ μ l	IgM	1,490 mg/dl
Neutrophils	67.0%	IgA	106 mg/dl
Eosinophils	1.0%	C3	61 mg/dl
Monocytes	7.0%	C4	16 mg/dl
Lymphocytes	25.0%	Antinuclear antibody	160×
Hemoglobin	11.6 g/dl	Rheumatoid arthritis	
Hematocrit	35.0%	hemagglutination	
Reticulocytes	12%	(RAHA)	1,280×
Platelets	84,000/ μ l	PIVKA-II	1.6 AU/ml
Prothrombin time	69%	(normal range <0.1)	
Biochemistry		HBsAg	negative
Total bilirubin	2.1 mg/dl	Anti-HBs	negative
Direct bilirubin	1.2 mg/dl	Anti-HCV	positive
AST	150 mU/ml	Cryoglobulin	negative
ALT	138 mU/ml	Pyroglobulin	negative
Lactate dehydrogenase		Bone marrow (BM) biopsy	
(LDH)	519 mU/ml	Hypocellular bone marrow	
ALP	188 mU/ml	with focal plasmatoid cells	
Amylase	120 mg/dl	and lymphocyte aggregation	
Cholinesterase	0.17 Δ pH	Chromosomal analysis (BM)	
Urea nitrogen	8.4 mg/dl	Normal karyotype (46,XY)	
Creatinine	0.5 mg/dl		
Calcium	8.6 mg/dl		
Phosphate	3.4 mg/dl		

Therapy	Melphalan (Total dose 1,002 mg)								<div><div></div><div></div><div></div></div>
	Prednisolone								
	↓ Vincristine ↓ ↓ ↓ ↓								
Symptom	Fever								<div><div></div><div></div><div></div></div>
	Jaundice								
AST (mU/ml)	67	51	43	192	88	151	43	93	102
IgM (mg/dl)	2,890	650	394	309	297	276	225	643	1,079
Hb (g/dl)	9.6	13.3	14.5	14.3	14.7	13.5	13.2	14.1	8.2
WBC (/μl)	3,300	4,400	4,200	4,100	2,700	3,500	2,300	2,900	4,900
Lymphocyte (/μl)	1,100	880	1,200	900	430	7670	690	610	980
PLT (×10 ⁴ /μl)	18.4	13.4	12.6	10.8	7.4	7.5	9.1	8.3	1.3
Finding of ultrasonography	Marked splenomegaly (135×54 mm) Mild hepatomegaly with no space occupying lesion						Marked splenomegaly (147×48 mm) Hepatocellular carcinoma		
Month/year	II/1988		I /1989		I /1990		I /1991		III/1992

Figure 3. Clinical course.

Heimann et al (5) reported a high incidence of liver cirrhosis in the patients with chronic lymphoproliferative disorders. The present study suggests the relationship between the occurrence of WM and chronic liver disease. The cause of chronic liver disease was not determined in the present case. The history of alcohol abuse was pointed out, and might have been the primary cause of the liver dysfunction. Alcohol may be related to some types of solid cancer such as HCC (6), and WM (7). In the present case, alcohol might have affected the natural course of WM and HCC. However, other causes of chronic liver disease can not be ruled out, such as hepatitis A and C. Unfortunately, no antibodies against hepatitis A virus were examined. HCVAb was detected in December 1991, although HCVAb was not examined at the onset of WM in this patient. HCV infection might have preceded the onset of WM, because liver dysfunction coexisted with WM in February 1988, and there was no evidence of exposure to HCV such as a blood transfusion before December 1991.

A high incidence of HCV infection has been reported in patients with lymphoid malignancy, such as WM (8), non-Hodgkin's lymphoma (NHL) (9, 10) and monoclonal gammopathies with cryoglobulinemic activity (11) in Italy. We also reported a high incidence of HCV infection in patients affected with B cell malignancies (12). These studies suggest that HCV infection is involved in the pathogenesis of WM. HCV replicates in the B lymphocytes in patients with WM (8), nevertheless, the direct relationship between B cell malignancies and HCV infection is unknown. HCV may induce *p53* transitional mutation in HCC, and may be involved in hepatocarcinogenesis (13). Persistent HCV infection might influence the growth of B lymphocytes in the case of WM, which is similar to HCC.

As the previous studies on WM associated with HCC were carried out before the serological assay for HCV became available, the involvement of HCV infection in the pathogenesis of the double malignancies was not discussed (3, 4). Recently, Ono et al (14) reported a case of primary splenic lymphoma (B cell type) associated with HCC. Interestingly, HCV infection and history of alcohol abuse were documented in that case.

Chlorambucil and cyclophosphamide are widely used for the treatment of WM (15). However, chlorambucil is not available in Japan, and cyclophosphamide may induce liver dysfunction (16). In contrast, melphalan at usual doses rarely causes hepatotoxicity (16). Therefore, we used melphalan as the alternative to the above drugs in this case. Melphalan is known to induce secondary myelodysplastic syndrome and acute myeloid leukemia (17), however, the association of

melphalan with the occurrence of HCC is not well known.

Several factors including alcohol abuse and HCV infection may be responsible for the occurrence of WM and HCC in the present case. Further studies are needed to clarify the pathogenesis of WM.

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