Development of Hepatocellular Carcinoma in a Woman with HBV- and HCV-negative Autoimmune Hepatitis with Unsatisfactory Response to Corticosteroid

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Abstract

A 57-year-old woman was admitted due to a hemorrhage from esophageal varices. Laboratory tests showed liver dysfunction, elevated immunoglobulin G levels and positivity for anti-nuclear antibodies. Serum hepatitis B virus and hepatitis C virus markers were negative. The liver biopsy specimen was compatible with autoimmune hepatitis, and low-dose prednisolone was started. During the follow-up, her serum alanine aminotransferase levels continued to fluctuate between 40 and 60 IU/l. Nine years later, hepatocellular carcinoma 20 mm in diameter was detected. This case suggests that hepatocellular carcinoma develops even if serum alanine aminotransferase levels are maintained at less than twice the upper normal limit.

(Key words: autoimmune hepatitis, hepatocellular carcinoma, corticosteroid treatment, alanine aminotransferase)

Introduction

Autoimmune hepatitis is a chronic liver disease of unknown etiology, which is characterized by interface hepatitis upon microscopic examination, hypergammaglobulinemia, and autoantibodies in serum. The disease is more common in women than in men and most patients respond to immuno-suppressive treatment (1, 2).

Before the availability of hepatitis C virus testing, hepatocellular carcinoma reportedly occurred in 7% of patients with autoimmune hepatitis and cirrhosis of at least five year’s duration (3). However, with hepatitis C virus testing, many of the hepatocellular carcinomas once considered to have developed with autoimmune hepatitis were found to be influenced by the hepatitis C virus (4). According to a recent study, the occurrence of hepatocellular carcinoma is rare in autoimmune hepatitis in the absence of hepatitis B virus and hepatitis C virus infections (5).

Several cases of hepatocellular carcinoma associated with autoimmune hepatitis in which hepatitis B virus and hepatitis C virus infections were absent have been reported in the English literature since the availability of hepatitis C virus testing (4–12). Hepatocellular carcinoma has been suggested to occur with long-standing cirrhosis; however, the mechanism by which hepatocellular carcinoma develops in autoimmune hepatitis remains unknown.

In this report, we describe a woman whose serum alanine aminotransferase levels were consistently abnormal for 9 years after the diagnosis of autoimmune hepatitis without hepatitis B virus and hepatitis C virus infection in spite of immuno-suppressive treatment. This patient ultimately developed hepatocellular carcinoma.

Case Report

A 57-year-old woman was admitted to Okayama University Hospital due to a hemorrhage from esophageal varices in May 1990. Hemostasis was achieved with endoscopic injection sclerotherapy. No transfusion was performed. The subject had attended regular check-ups for liver dysfunction since 1983, during which time the etiology had not been proven. There was no history of alcohol abuse or blood transfusion. The results of liver function tests upon admission were as follows: aspartate aminotransferase 44 IU/l, alanine aminotransferase 19 IU/l, and total bilirubin 0.7 mg/dl. Serum immunoglobulin G level was 2,888 mg/dl.
Test results for hepatitis B surface antigen, anti-hepatitis B core antibodies, and anti-hepatitis C virus antibodies, as well as test results for anti-mitochondrial antibodies, were negative. However, anti-nuclear antibodies were positive with a titer of 1:320 (Table 1). Three months later, a liver biopsy specimen taken under laparoscopy showed severe bridging fibrosis with chronic inflammatory cell infiltration and piecemeal necrosis (Fig. 1). The patient was diagnosed with autoimmune hepatitis. In June 1993, alanine aminotransferase levels went up to 95 IU/l, and prednisolone was administered. Mild abnormalities in the liver function tests were continued (Fig. 2).

In September 1999, ultrasonography showed a hypoechoic lesion in the liver, and computed tomography revealed a low-density mass 20 mm in diameter in the right lobe (Fig. 3A, B). Serum hepatitis B virus markers, hepatitis B virus-DNA, anti-hepatitis C virus antibodies, and hepatitis C virus-RNA were all negative. The serum alpha-fetoprotein levels went up to 95 IU/l, and prednisolone was administered. Mild abnormalities in the liver function tests were continued (Fig. 2).

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level was 22.9 ng/dl (Table 1). The biopsy specimens of the tumorous and non-tumorous lesions were taken under ultrasonography. The tumorous lesion showed moderately-differentiated hepatocellular carcinoma (Fig. 3C). The non-tumorous lesion showed liver cirrhosis with minimal inflammatory cell infiltration. Hepatitis B virus-DNA was shown to be negative in both tumorous and non-tumorous lesions with reverse transcription-PCR (13). Selective hepatic angiography showed a hypervascular tumor at the same site (Fig. 3D), and transcatheter arterial chemoembolization was performed with 20 mg of epirubicin.

In November 2000, a mass 10 mm in diameter suggestive of recurring hepatocellular carcinoma was detected in the left lobe by ultrasonography and computed tomography. Transcatheter arterial chemoembolization was performed with 10 mg of epirubicin.

In April 2001, a mass 33 mm in diameter in the right lobe and portal vein tumor thrombosis were detected by ultrasonography and computed tomography. Transcatheter arterial chemoembolization was performed with 20 mg of epirubicin, but the patient died of hepatic failure 6 months later.

**Discussion**

A variety of immunological abnormalities have been described in patients with chronic hepatitis C, and in particular, a high prevalence of positivity for autoantibodies was reported (14, 15). Furthermore, patients with autoantibodies had more severe portal-periportal necroinflammation (15). Many patients diagnosed with autoimmune hepatitis before the availability of hepatitis C virus testing were thought to have hepatitis C virus infection (2). Hepatitis C virus infection is a risk factor for the development of hepatocellular carcinoma worldwide. In order to clarify whether hepatocellular carcinoma develops with autoimmune hepatitis, the possibility of hepatitis C virus infection must be excluded.

A recent report indicates that decreased alanine aminotransferase with medical treatment prevents the development of hepatocellular carcinoma in patients with chronic hepatitis C (16). In addition, no significant differences in the development of hepatocellular carcinoma after interferon treatment are found between virological responders with the persistent absence of hepatitis C virus-RNA from serum and biochemical responders with persistent alanine aminotransferase normalization in spite of positivity for hepatitis C virus-RNA in serum (17). Based on these findings, we consider that long-term continuous inflammation rather than existence of hepatitis C virus-RNA contributes to the development of hepatocellular carcinoma. In most of the patients with autoimmune hepatitis that developed hepatocellular carcinoma, the disease had already progressed to cirrhosis at the time of the diagnosis of hepatocellular carcinoma (4–12). In the present case, although hepatitis C virus-RNA was not tested in the liver tissue, serum anti-hepatitis C antibody and hepatitis C virus-RNA were negative, and alanine aminotransferase levels were persistently abnormal in spite of prednisolone.
treatment. Recently, we found that, of 84 patients with autoimmune hepatitis followed up for the median duration of 6 years, hepatocellular carcinoma did not develop in 44 patients with serum alanine aminotransferase levels maintained at less than 40 IU/l, although it developed in 2 of 40 patients without serum alanine aminotransferase levels maintained at less than 40 IU/l (unpublished observation). In autoimmune hepatitis, long-term continuous inflammation may contribute to the development of hepatocellular carcinoma.

Occult hepatitis B virus infection is reported to be a risk factor for the development of hepatocellular carcinoma (18). Occult hepatitis B virus may play a direct oncogenic role through both its integration into the host genome and its maintained transcriptional activity, which may facilitate the synthesis of proteins (such as X protein) with potential pro-oncogenic properties. In the present case, hepatitis B virus-DNA was negative in hepatocellular carcinoma tissue with reverse transcription-PCR (13); thus, the hepatitis B virus did not seem to play a role in the development of hepatocellular carcinoma.

It is reported that corticosteroid treatment may be related to the development of hepatocellular carcinoma by suppressing tumor immunity in patients with autoimmune hepatitis (19). But, in the present case, sufficient corticosteroid treatment was not performed, and mild abnormalities in the liver function tests continued. We speculate that corticosteroid treatment did not affect the development of hepatocellular carcinoma in the present case.

In the present case, autoimmune hepatitis had already progressed to pre-cirrhosis at the time of diagnosis. In cases of autoimmune hepatitis, long-standing cirrhosis is reported to be a risk factor for the development of hepatocellular carcinoma (5); however, the presence of cirrhosis at the beginning of therapy does not affect the response to treatment or long-term life expectancy (20). In the present case, to avoid disease progression and to prevent the development of hepatocellular carcinoma, we should have recommended increasing the prednisolone dose or adding azathioprine. Based on the findings in this study as well other reports on the hepatitis C virus-related liver disease after interferon therapy, transaminase levels in patients with autoimmune hepatitis should be maintained within normal limits to avoid disease...
progression and to prevent further development of the hepatocellular carcinoma.

References


