Hepatocellular Carcinoma Arising from Autoimmune Hepatitis: Report of a Case

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Abstract
We describe an operative case of a 64-year-old woman with hepatocellular carcinoma (HCC) associated with autoimmune hepatitis (AIH) during a 4.8-year follow-up. Sixty-seven cases of HCC with AIH have been previously reported as a sporadic complication of AIH. The survival rate after diagnosis with HCC showed the 5-year survival rate to be 10.4%, thus indicating the majority of patients to have either extensive HCC or severe liver dysfunction. Immunosuppressant therapy helped to postpone the hepatocarcinogenesis but it did not improve the prognosis of the patients demonstrating HCC with AIH. A univariate analysis of factors associated with prognosis disclosed that the histology of nontumorous lesion at diagnosis with HCC, tumor size, tumor number, and treatment for HCC were independent prognostic predictors. Patients with AIH were not recognized to be a high-risk group for developing HCC because HCC occasionally occurred even in patients with long-standing cirrhosis in the absence of hepatitis B virus and hepatitis C virus infection.

Key words Hepatocellular carcinoma · Autoimmune hepatitis · Hepatitis virus

Introduction
Autoimmune hepatitis (AIH) rapidly develops into cirrhosis and causes liver failure, thus leading to early death in untreated patients.1,2 Hepatocellular carcinoma (HCC) developed in patients with AIH is reported to be sporadic at an incidence rate of 0.5%–7.0%.3–5 However, cases of HCC associated with AIH have been recently increasing because the treatment regimens of steroid monotherapy or combination therapy of azathioprine and steroids have achieved a high efficacy, thus leading to a decrease in the mortality rates and the achievement of 10-year survival rates of 90% or better.6 A search on MEDLINE indicated that only 67 cases of HCC associated with AIH have been published in international medical journals between 1980 and 2006, the vast majority of them being reports on Japanese patients. This study reports the curatively operative case of a 64-year-old woman who developed HCC with AIH, and also summarizes the clinicopathological features of 68 cases.

Case Report
A 64-year-old woman was diagnosed in 2000 as having AIH with a combination of biochemical [elevated aspartate aminotransferases (AST), alanine aminotransferases (ALT), and immunoglobulin G (IgG)] and serological [antinuclear antibody (ANA), ×40; anti-smooth muscle antibody, ×40] analyses. There was no history of blood transfusion, alcohol abuse, or drug ingestion. She refused both liver biopsy and steroid therapy and was thereafter followed at another clinic. She was referred to our hospital and diagnosed as having liver dysfunction. Pertinent laboratory data revealed AST 42 IU/l; ALT 33 IU/l; IgG 2050 mg/dl and showed negativity for hepatitis B virus (HBV) DNA, hepatitis C virus (HCV) RNA, anti-liver-kidney microsomal antibody type 1 (LKM-1), and antimitochondrial antibody. DR2 and DR4 among the human leukocyte-associated antigen were positive. The patient’s score according to the International Autoimmune Hepatitis Group criteria7 was 12 points, thus corresponding to a probable AIH. The serum α-fetoprotein and protein-induced by vitamin K absence II (PIVKA-II) levels were elevated at 37.0 ng/ml and 288 mAU/ml, respectively. The hepatic function of the patient was classified as...
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Child–Pugh A. The value of the indocyanine green clearance test at 15 min (ICGR_{15}) was 13%. Computed tomography showed a tumor located in the posterioinferior subsegment (S7) of the liver that measured 50 mm in diameter (Fig. 1). It showed a mosaic pattern and capsule, characteristics compatible with HCC. Selective hepatic angiography showed a hypervascular tumor. A mixture of iodized oil (Lipiodol Ultrafl uide; Laboratory Guerbet, Aulnay-sous-Bois, France) with 40 mg of epirubicin hydrochloride (Farmorubicin; Pharmacia, Tokyo, Japan) was selectively injected into the inferior branch of the right hepatic artery. Subsequently, a subsegmental resection of S7 of the liver was performed. The resected specimen showed coagulative necrosis of the encapsulated tumor nodules, measuring 52 × 42 mm in size. It was pathologically diagnosed to be moderately differentiated HCC (Fig. 2). The circumferential nontumorous lesion of the liver showed cirrhosis with moderate inflammatory cell infiltration. The conclusive TNM (tumor, node, metastasis)-staging was pT2, pN0, M0, stage II according to the general rule of Japanese Classifi cation of Liver Cancer Association.8 The curativity was judged to be B. There has been no sign of recurrence in the follow-up period of 8 months after the operation.

Discussion

The reported cases of HCC associated with AIH have recently increased, even though they have been expected to be quite rare. Wang et al.4 reported an incidence of HCC at a 7% occurrence after 5 years of cirrhosis. In contrast, Park et al.5 followed 212 patients with AIH for the development of HCC and reported only one person (0.5%) to develop HCC in the absence of HBV and HCV infection in an 8-year follow-up.5 The major difference in the evaluation between the two cohort studies was the testing of all patients for HBV and HCV and the elimination of infected patients from the study population. Ryder et al.3 revealed that six out of eight HCC patients (four patients, in the serum samples; two patients, in the liver tissues) associated with AIH had evidence of HCV infection. HCC could occur in AIH; however, it seldom occurred, even in patients with long-standing cirrhosis in the absence of HBV and HCV infection.

The clinicopathological features of the 68 cases reported are reviewed and summarized as follows: The values are expressed as the average ± SD. The men to women ratio was 1:2.7, thus indicating that sex was a risk factor for the development of HCC in AIH because AIH occurs predominantly in women, seven to ten times more often.2 The age at the detection of HCC was 61.0 ± 12.3 years. The duration from the diagnosis with AIH to the detection of HCC was 9.1 ± 6.7 years. Cirrhosis of circumferential nontumorous lesion of the liver accounted for 63.2% and ICGR_{15} was 24.8% ± 11.7%, thus supporting the theory that AIH rapidly develops into liver cirrhosis from chronic active hepatitis rather than being virus related.2 Ten of the cases (14.7%) were complicated by autoimmune diseases other than AIH. AIH score was 14.6 ± 2.6 points. Forty-five cases were treated with immunosuppressants for AIH (steroid monotherapy 31 cases; combination therapy 14 cases). Twenty-two cases were treated without immunosuppressants. It significantly took more time to develop HCC in patients with immunosuppressant therapy (123.5 ± 58.6 months) than those without immunosup-

Fig. 1. Computed tomography revealed a tumor, showing a mosaic pattern and capsule, located in the posterioinferior subsegment (S7) of the liver which measured 50 mm in diameter

Fig. 2. The resected specimen showed coagulative necrosis of the encapsulated tumor nodules, 52 × 42 mm in size. It was pathologically diagnosed to be moderately differentiated HCC