J Hepatobiliary Pancreat Surg (2004) 11:215–219
DOI 10.1007/s00534-003-0878-z

Journal of HBP Surgery

Hepatocellular carcinoma associated with autoimmune hepatitis

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Abstract
Autoimmune hepatitis (AIH) is a disorder of unknown etiology, which often progresses to cirrhosis and carries a high mortality, even though its treatment with corticosteroids has become common. Hepatocellular carcinoma (HCC) has been reported as a rare complication of AIH. We describe herein a patient with HCC associated with AIH, in whom microwave coagulation therapy provided a means of definitive management, and we also review the literature. Male sex and longstanding cirrhosis seem to be the risk factors for hepatocarcinogenesis in AIH. The prognosis of this disease is extremely poor because of the low resectability caused by poor hepatic reserve. It is important to pay attention to hepatic disorders and the possible development of HCC at the time of diagnosis of AIH. Surgeons should select suitable treatment, without undue surgical stress, whenever the diagnosis of HCC has been established. Microwave coagulation therapy is a preferred option for the treatment of high-risk patients with poor hepatic reserve or unresectable multiple HCCs.

Key words Hepatocellular carcinoma · Autoimmune hepatitis

Introduction

Autoimmune hepatitis (AIH), as first reported by Mackay et al.,[1] is a chronic, but fluctuating, hepatitis with hypergammaglobulinemia and circulating autoantibodies. AIH is more frequent in females than males and its prognosis is poor. Hepatocellular carcinoma (HCC) has been reported as an unusual and sporadic complication of AIH.[2] As immunomodulatory therapy with corticosteroids improves the prognosis of AIH and has become commonplace,[3] cases of HCC associated with AIH have come to be reported.[4–29] The aims of this article are to report a 5-year survivor of surgery for HCC associated with AIH and to discuss some diagnostic and therapeutic approaches.

Offprint requests to: R. Nishiyama
Received: March 6, 2003 / Accepted: September 16, 2003

Case report

A 51-year-old Japanese man was admitted because of liver dysfunction. He had no significant symptoms and there was no history of alcohol abuse or blood transfusion. On admission, laboratory data were as follows: serum bilirubin, 0.97 mg/dl; glutamic oxaloacetic transaminase, 300 IU/l; glutamic pyruvic transaminase, 193 IU/l; plasma indocyanine green retention at 15 min, 27.5%; platelet count, $8.4 \times 10^4/\mu l$; gammaglobulin, 1840 mg/dl; and immunoglobulin G, 1190 mg/dl. Antinuclear antibody titer was 1/160. Lupus erythematosus (LE) test was negative, as were anti-smooth muscle, anti-DNA, anti-mitochondria, and anti-kidney-liver-microsome antibodies. Hepatitis B and C virus (HBV and HCV) markers were negative, including circulating HCV-RNA by polymerase chain reaction (PCR). Serum α-fetoprotein and protein-induced vitamin K absence II (PIVKA-II) levels were 17.9 ng/ml and 28 mAU/ml, respectively. Computed tomography (CT) showed a well-enhanced mass, 20 mm in diameter (Fig. 1A), which was ring-enhanced in the late phase on magnetic resonance imaging (MRI) with intravenous bolus injection of contrast medium (Fig. 1C), in the upper part of the right posterior segment. This lesion was not visible by ultrasound. Hepatic angiography demonstrated early staining with tumor vessels at the same site (Fig. 2A,B). The patient was diagnosed as having HCC due to liver cirrhosis arising from AIH. He did not consent to blood transfusion because of personal religious reasons.

At surgery, biopsy specimens were obtained and microwave coagulation therapy (MCT), instead of limited liver resection, was selected to avoid operative bleeding

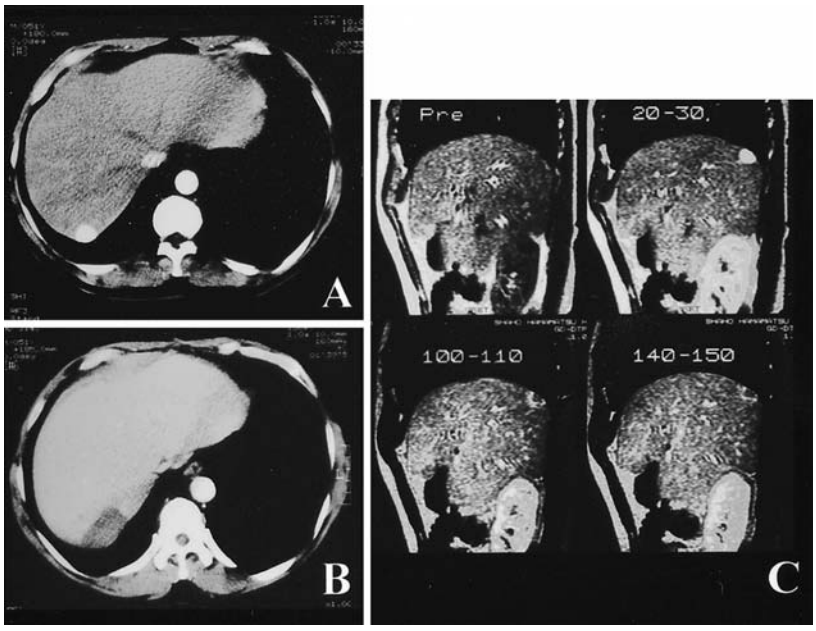

Fig. 1. A Preoperative computed tomography (CT) shows a low-density well-enhanced mass, 20 mm in diameter, in the upper part of the right posterior segment. **B** CT at 10 months after operation demonstrates a coagulated site, which can be seen as a nonenhanced area; the hepatocellular carcinoma lesion is completely coagulated. **C** Preoperative magnetic resonance imaging (MRI) of sagittal view shows an isodensity mass, which is ring-enhanced in the late phase with intravenous bolus injection of contrast medium

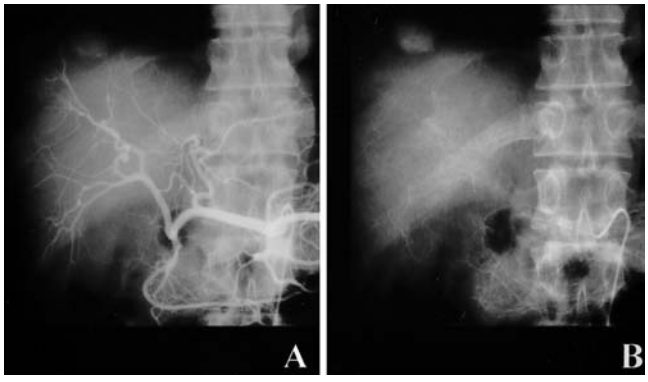

Fig. 2A,B. Hepatic angiography demonstrates early staining with tumor vessels, which remains in the late phase

and to maintain the hepatic reserve. Histology revealed chronic active hepatitis with plasma cell infiltration (Fig. 3A, arrows) and well-differentiated hepatocellular carcinoma (Fig. 3B) with CD34-positive endothelial cells in the sinusoid-like vessels (Fig. 3C), which indicated a relationship with the process of angiogenesis induced by hepatocarcinogenesis.[30] The postoperative course was uneventful. CT at 10 months after the operation demonstrated that MCT had been effective, and the HCC lesion was completely coagulated (Fig. 1B). Five years after the surgery the patient maintains good liver function, without HCC, and he takes ursodeoxycholic acid.

Discussion

AIH is a disorder of unknown etiology, in which progressive destruction of the hepatic parenchyma occurs. In more severe cases it often progresses to cirrhosis and carries a high mortality, even though immunosuppressive therapy for the condition has become common.

Although HCC has been described as a rare complication of AIH,[10] the incidence has recently increased. It has been suggested that longterm survival with liver cirrhosis[31] and a suppressed immune system resulting from corticosteroid therapy[32] might be responsible for carcinogenesis in AIH. It has been reported that a high proportion of patients with presumed AIH in southern Europe had evidence of hepatitis C virus (HCV) infection[33] and HCV infection induced autoantibodies.[34]

In order to investigate the involvement of HCV in hepatocarcinogenesis in AIH, we reviewed the reported cases of HCC associated with AIH in which HCV antibody tests had been performed (Table 1). Thirty-five patients, (10 men and 25 women) were examined for HCV antibody tests, and 27 patients (10 men and 17 women), had had polymerase chain reaction (PCR) examination of circulating HCV RNA. Although the average AIH score[33] in these patients was probable AIH (score, 15.7), their conditions conformed to AIH in all other respects. Four women (11.4%) were seropositive for HCV antibody and no patient had serological evidence of HBV infection. Six patients (22.2%), 2 men and 4 women, had evidence of positive HCV RNA by PCR. Forty percent of the patients who had negative HCV RNA results were men, despite the about seven-times female predominance reported for AIH.[35] The duration from the diagnosis of AIH to the detection of HCC ranged from 0 to 26 years, with a mean of 9.8 years. There was no significant difference between this duration in the HCV-positive patients (12.0 years) and the HCV-negative patients (9.2 years). Therefore, HCV

Table 1. Reported cases of hepatocellular carcinoma (HCC)-associated autoimmune hepatitis (AIH)

Ref. no.	Year of publication	M/F	Age (years)	Duration between diagnosis of AIH and detection of HCC (years)	Treatments for AIH	HBsAg	HCVAb	HCV-RNA (blood/tissue)	AIH score	Treatment for HCC	Cause of death	Survival (months)
4	1991	F	76	0	P	(−)	(−)		18	Op	LF	27
5	1991	F	65	3	(−)	(−)	(+)		15	TAE − op	LF	5
6	1992	M	57	9	P + A	(−)	(−)	(−)	19	5-FU	LF	3
7	1993	F	71	15	(−)	(−)	(−)	(−)	16	PEI	LF	20
8	1993	F	81	3	(−)	(−)	(+)		17	(−)	LF	22
9	1994	F	68	13	P	(−)	(−)	(−)	11	TAE	LF	16
10	1995	F	mean, 56	14	P + A	(−)	(−)	(+/+)				
10	1995	F		19	P + A	(−)	(+)	(+/+)				
10	1995	F		7	P + A	(−)	(−)	(−/+)				
10	1995	M		24	P + A	(−)	(−)	(−)				
10	1995	M		22	P + A	(−)	(−)	(+/+)				
10	1995	M		24	P + A	(−)	(−)	(−)				
10	1995	F		10	P + A	(−)	(+)	(+/+)				
10	1995	M		18	P + A	(−)	(−)	(−/+)		LTx		24
11	1995	F	56	5	P	(−)	(−)	(−)	16	Op − TAE		74
12	1996	F	68	13	P	(−)	(−)	(−/−)	21	TAE	LF	23
13	1996	F	62	2	(−)	(−)	(−)	(−)	18	Op	LF	30
14	1996	F	67	1.5	(−)	(−)	(−)	(−)	14	Op		
15	1997	F	69	5	(−)	(−)	(−)		17	(−)	LF	2
16	1997	F	59	14	P	(−)	(−)		20	(−)	LF	7
17	1997	M	56	1.5	P	(−)	(−)	(−)	15	Op		
18	1997	F	61	11	P	(−)	(−)	(−)	15	TAE − PEI	HCC	31
19	1998	F	80	10	(−)	(−)	(−)	(−/−)	16	TAE		2
20	1999	F	71	14	P	(−)	(−)		17	TAE		
21	1999	F	58	9	P	(−)	(−)	(−)	18	TAE − PEI		
22	1999	M	82		(−)	(−)	(−)	(−)	12	TAE	LF	3
23	2000	F	58	9	(−)	(−)	(−)	(−)	13	(−)	HCC	1
24	2000	M	77	5	(−)	(−)	(−)	(−)	10	TAE	GIB	6
25	2000	F	73	10	P	(−)	(−)	(−)	14	TAE	HCC	8
25	2000	F	72	7	(−)	(−)	(−)		17	TAE	LF	22
26	2000	M	49	26	P	(−)	(−)	(−)		Op		
27	2001	F	66	10	P	(−)	(−)	(−/−)	12	Op		18
28	2001	F	59	0	P	(−)	(−)		16	MCT + RFA − LTx		
29	2003	F	89	0	(−)	(−)	(−)	(−)	16	(−)	LF	25
Our patient	2004	M	51	0	(−)	(−)	(−)	(−)	14	Op		60

P, prednisolone; A, azathioprine; TAE, transcatheter arterial embolization; PEI, percutaneous ethanol injection; LTx, liver transplantation; Op, operation; MCT, microwave coagulation therapy; RFA, radiofrequency ablation; LF, liver failure; GIB, gastrointestinal bleeding; 5-FU, 5-fluorouracil; HBsAg, hepatitis B virus surface antigen; HCVAb, hepatitis C virus antibody

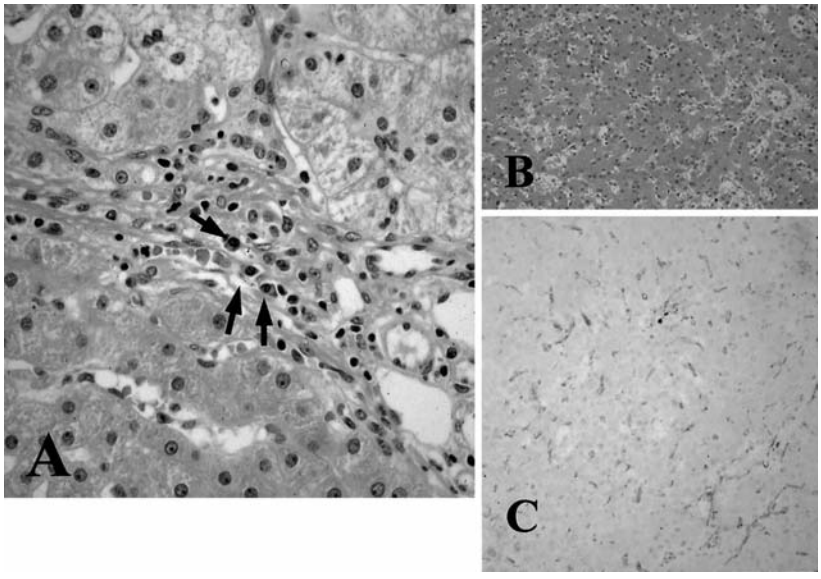

Fig. 3. **A** Non-neoplastic portion of the specimen shows chronic active hepatitis with piecemeal necrosis of hepatocytes and plasma cell infiltration (*arrows*). **B** Hepatocellular carcinoma of grade I–II by Edmondson's classification. **C** Immunohistochemical staining for CD34 demonstrates widespread capillarization in hepatocellular carcinoma. **A** H&E, ×50; **B** H&E, ×10; **C** H&E, ×10

seems to have no influence on the development of HCC in AIH. In contrast, HCC needs more time to develop in patients with corticosteroid therapy (12.4 years) than in patients without corticosteroid therapy (5.0 years). This means that liver cirrhosis had a greater effect on carcinogenesis in AIH than corticosteroid. Male sex and longstanding cirrhosis are the risk factors for the development of HCC in AIH, as reported for chronic viral hepatitis.[36] In 4 patients (11.4%), as well as our patient, HCC was detected at the time of diagnosis of AIH. Therefore, careful attention should be paid to the potential development of HCC from the time of diagnosis of AIH. Screening for HCV RNA should be considered in AIH patients with a previous history of parenteral exposure to blood.

The prognosis of HCC associated with AIH was very poor. The survival of the reported patients ranged from 1 to 74 months, with a mean of 19.5 months. With regard to therapeutic approaches, the resection rate was extremely low. The reasons that patients were diagnosed as having unresectable HCC were extension of HCC or severe liver dysfunction. In 11 patients (31.4%), hepatectomies, including two liver transplantations, were performed. The survival of resected patients ranged from 5 to 74 months, with a mean of 34.0 months, and that of unresected patients ranged from 1 to 31 months, with a mean of 12.3 months. For the improvement of prognosis, surgeons should endeavor to remove HCC and to reduce surgical stress. MCT was introduced as a low-invasive adjunctive treatment for HCC in Japan; however, this procedure has now be come a definitive modality.[37] Radiofrequency ablation has also been used recently to treat HCC.[38] Because MCT and radiofrequency ablation can be done through laparotomy, laparoscopy, and percutaneous approaches, these techniques are preferable for high-risk patients with poor hepatic reserve or unresectable multiple HCCs.

In conclusion, careful attention should be paid not only to hepatic disorders but also to the potential development of HCC at the time of diagnosis of AIH. It is important to select suitable treatment, without undue surgical stress, whenever the diagnosis of HCC has been established.

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