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BRIEF ARTICLES

Features of hepatocellular carcinoma in cases with autoimmune hepatitis and primary biliary cirrhosis

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Abstract

AIM: To characterize the clinical features of hepatocellular carcinoma (HCC) associated with autoimmune liver disease, we critically evaluated the literature on HCC associated with autoimmune hepatitis (AIH) and primary biliary cirrhosis (PBC).

METHODS: A systematic review of the literature was conducted using the Japana Centra Revuo Medicina database which produced 38 cases of HCC with AIH (AIH-series) and 50 cases of HCC with PBC (PBC-series). We compared the clinical features of these two sets of patients with the general Japanese HCC population.

RESULTS: On average, HCC was more common in men than in women with AIH or PBC. While many patients underwent chemolipiodolization (CL) or transcatheter arterial embolization (TAE) (AIH-series: P = 0.048 (*vs* operation), P = 0.018 (*vs* RFA, PEIT); PBC-series: P = 0.027 (*vs* RFA, PEIT), others refused therapeutic interventions [AIH-series: P = 0.038 (*vs* RFA, PEIT); PBC-series: P = 0.003 (*vs* RFA, PEIT)]. Liver failure was the primary cause of death among patients in this study, followed by tumor rupture. The survival interval between diagnosis and death was fairly short, averaging 14 ± 12 mo in AIH patients and 8.4 ± 14 mo in PBC patients.

CONCLUSION: We demonstrated common clinical features among Japanese cases of HCC arising from AIH and PBC.

Key words: Autoimmune hepatitis; Autoimmune liver disease; Hepatocellular carcinoma; Literature review; Primary biliary cirrhosis

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INTRODUCTION

Autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerotic cholangitis (PSC) form the triad of autoimmune liver diseases. As defined by Mackay *et al*[1], AIH is a chronic active hepatitis resulting from several distinct autoimmune phenomena. While the anti-inflammatory effects of steroid therapy for this disease may inhibit the promotion of liver carcinogenesis, hepatocellular carcinoma (HCC) does occur rarely in patients with this condition (in about 0.5% of AIH cases)[2,3].

In contrast to AIH, PBC results from an autoimmune mechanism causing chronic cholestasis and chronic non-suppurative destructive cholangitis in medium sized intrahepatic bile ducts[4]. Rare cases of HCC arising from PBC have been reported to date. However,

this association is rare (affecting between 0.3% and 4.22% of cases)[5-11], because a PBC patient's ability to produce regenerative nodules is weak[5-9,12]. Additionally, PBC is pathologically characterized in chronic non-suppurative destructive cholangitis (CNSDC), and the main inflammatory lesions associated with PBC are not hepatocytes, but cholangiocytes, which may be one of the reasons why the incidence of HCC with PBC is low, especially at the early stage when cirrhotic and fibrotic changes do not progress. Recently, reports have suggested that the prevalence of HCC arising from both AIH and PBC is higher than previously believed. In 2001, Caballeria *et al*[13] found that the incidence of HCC in patients with advanced PBC (Scheuer histological stage Ⅲ or Ⅳ) was 11.1%, approximating the 15% incidence in patients with HCV-related cirrhosis (RR 0.812, 95% CI 0.229-2.883). The clinical features of HCC associated with AIH and PBC, however, have not yet been extensively described. Here, we performed a systematic literature review of HCC cases associated with AIH and PBC in Japan, a country with a high burden of autoimmune liver disease. We conducted a critical analysis of case reports to find common themes in the demographic and clinical histories of patients with HCC associated with AIH and PBC.

MATERIALS AND METHODS

We performed a systematic literature review of case reports published in Japan and listed in the Japana Centra Revuo Medicina database, version 3 (systematic literature search system through a computer web site for Japanese literature), using the keywords "hepatocellular carcinoma", "autoimmune hepatitis", and "primary biliary cirrhosis". The database search was limited to the period between 1990 (when the hepatitis C virus was first detected) to the present. The quality of this database available for analysis is thoroughly well-documented. In total, 38 cases of HCC associated with AIH, and 50 cases of HCC associated with PBC were identified. No cases were duplicated, and patients were identified across multiple Japanese medical centers. Most patients in the series had been diagnosed with autoimmune liver disease before HCC was identified. Several cases also presented with co-factors of liver damage and HCC development other than AIH or PBC, such as excessive alcohol intake, HBV, or HCV infection. However, no cases had evidence of hemochromatosis or α1-antitrypsin deficiency. The demographics of these two groups were recorded based on gender, age, period of medical observation, and history of blood transfusion or excessive alcohol intake. Clinical data was also recorded to determine noncancerous pathologies of the liver, HBV or HCV infection status, serum α-fetoprotein (AFP) level, maximal tumor size, history of HCC therapy, clinical outcomes, and cause of death. Cases that did not include a description of alcohol intake were assumed not to have histories of excessive alcohol intake.

We confirmed that all 38 identified cases of HCC associated with AIH met generally accepted international criteria for diagnosis of AIH[14]. Scoring was performed prior to AIH therapy initiation; all scores were greater than 10, and thereby classified as either "probable AIH" or "definite AIH".

Because no internationally accepted diagnostic criteria yet exists for PBC, we utilized the Japanese standard criteria for PBC diagnosis, a standard first proposed in 1992 by a clinical study group supported by the Japanese Ministry of Welfare. According to this standard, PBC diagnosis requires that cases meet at least one of the following criteria: (1) pathologic evidence of CNSDC and positive anti-mitochondrial antibody (AMA) or anti-PDH antibody titers, (2) positive AMA or anti-PDH antibody titers and non-CNSDC pathology compatible with PBC, or (3) no liver biopsy, but, positive AMA or anti-PDH antibody titers and a clinical picture and clinical course compatible with PBC. We confirmed that all 50 identified cases of HCC associated with PBC met the above diagnostic criteria. Six of 50 (12.0%) HCC cases with PBC met the third criteria for PBC, and 44 of 50 (88.0%) cases met the first or second criteria for PBC. The third criteria for PBC remain ambiguous, and it is really hoped that internationally accepted criteria will be determined for PBC diagnosis.

If a case met both generally accepted international criteria for diagnosis of AIH, and the Japanese standard criteria for PBC diagnosis, we diagnosed the case as overlap syndrome. We had two cases of overlap syndrome, and excluded these cases from our analysis.

We did not include a control group, but used the general HCC population in Japan for comparison[15].

Statistical analysis

Intention-to-treat analyses were used throughout, and statistical analysis for categorical comparisons of the data was performed using the program ystat2006.xls for Windows/Macintosh (Igaku Tosho Shuppan Corporation, Tokyo, Japan). We used the χ^2 test and Fisher's exact test for categorical comparisons between patients with HCC associated with AIH or PBC and HCC patients without associated autoimmune disease[15]. The following variables were assessed: gender, HBV or HCV co-infection, history of blood transfusions, history of excessive alcohol intake, positivity for serum-AFP and clinical outcomes. Because the baseline male to female ratio of AIH and PBC was 1:7 and 1:9, respectively, we performed the χ^2 test for males and females separately. We also used the χ^2 test with or without the Yates correction for categorical comparisons of pathological findings of noncancerous lesions of the liver, HCC therapy choices, and cause of death. Where significant differences were noted, χ^2 tests or Fisher's exact tests were repeated with all categorical combinations, using Bonferroni corrections for multiple comparisons. Two tailed Mann-Whitney *U*-tests and *F*-tests were performed at the 5% significance level only for comparisons between HCC patients with AIH and PBC, as the following variables were unavailable for the general HCC

Table 1 Developement period of reported cases of hepatocellular carcinoma associated with autoimmune hepatitis and primary biliary cirrhosis, compared to cases of general hepatocellular carcinoma in Japan

Clinical status	Compiled numbers			*P*-values		
	HCC patients with AIH (AIH-series)	HCC patients with PBC (PBC-series)	General-HCC patients	AIH-series/ General-HCC patients	PBC-series/ General-HCC patients	AIH-series/ PBC-series
Observation period (mean ± SD)	Total: 38 1 yr 1 mo-23 yr (10 yr 6 mo ± 6 yr 7 mo)	Total: 49 3 mo-24 yr (9 yr 4 mo ± 6 yr 4 mo)	NA	NA	NA	$P = 0.307$ ($P = 0.815$)
Interval between liver damage and HCC diagnosis (mean ± SD)	Total: 34 0-22 yr 9 mo (10 yr 2 mo ± 6y 5 mo)	Total: 40 0-24 yr (9 yr 9 mo ± 7 yr 0 mo)	NA	NA	NA	$P = 0.740$ ($P = 0.688$)
Period from HCC development to death (mean ± SD)	Total: 18 2 mo-3 yr (1 yr 2 mo ± 12 mo)	Total: 16 0-5 yr (8.4 ± 14 mo)	NA	NA	NA	$P = 0.047$[a] ($P = 0.401$)

The *P*-value above was calculated from the Mann-Whitney *U*-test and the *P*-value below, indicated in parentheses, was calculated from the *F*-test. [a]$P < 0.05$, Statistically significant. HCC: Hepatocellular carcinoma; AIH: Autoimmune hepatitis; PBC: Primary biliary cirrhosis; SD: Standard deviation; NA: Not available.

Table 2 Analysis on gender and age of reported cases of hepatocellular carcinoma associated with autoimmune hepatitis and primary biliary cirrhosis, compared to cases of general hepatocellular carcinoma in Japan

Clinical status	Compiled numbers (%)			*P*-values		
	HCC patients with AIH (AIH-series)	HCC patients with PBC (PBC-series)	General-HCC patients	AIH-series/ General-HCC patients	PBC-series/ General-HCC patients	AIH-series/ PBC-series
Gender						
Actual number	Total: 38	Total: 50	Total: 16743			
Male	7 (18.4)	13 (26.0)	12025 (71.8)			
Female	31 (81.6)	37 (74.0)	4718 (28.2)	$P = 0.149$[1]	$P = 0.512$[1]	$P = 0.244$
Relative number	Total: 38	Total: 50				
Male	23.3 (61.3)	38.0 (76.0)				
Female	14.7 (38.7)	12.0 (24.0%)				
Age at HCC diagnosis	Total: 38	Total: 50	Total: 16743			
(mean ± SD)	(67.61 ± 8.58)	(68.54 ± 9.30)	NA			
< 40 s	0 (0)	2 (4.0)	761 (4.6)	NA	NA	$P = 0.410$
50 s	8 (21.0)	6 (12.0)	2818 (16.8)			($P = 0.614$)
60 s	16 (42.1)	21 (42.0)	6179 (36.9)			
70 s	9 (23.7)	14 (28.0)	5976 (35.7)			
< 80 s	5 (13.2)	7 (14.0)	1009 (6.0)			

The *P*-value above was calculated from the Mann-Whitney *U*-test and the *P*-value below, indicated in parentheses, was calculated from the *F*-test. [1]The *P*-value was calculated from the relative numbers. HCC: Hepatocellular carcinoma; AIH: Autoimmune hepatitis; PBC: Primary biliary cirrhosis; SD: Standard deviation; NA: Not available.

population: interval between liver damage and HCC diagnosis, interval from HCC diagnosis to death, age at HCC diagnosis, serum-AFP levels, maximum tumor size and number of HCC loci. Because the patient sample size in each group was greater than 20, we chose to use *P*-values calculated from the asymptotic distribution. The total number of cases in each patient group did not include cases for which categorical data were unknown (Table 1).

The statistical analysis for survival among HCC patients with AIH and PBC was performed on a personal computer with the statistical package SPSS for Windows (version II, SPSS Inc., Chicago, IL, USA). Because there were too few published cases of HCC arising from AIH or PBC, however, differences in survival between patient groups could not be calculated.

RESULTS

The intervals between HCC diagnosis and death for HCC patients with AIH (14 ± 12 mo) and PBC (8.4 ± 14 mo) was notably shorter than among general HCC patients in Japan (77.5% 1-year survival, 52.5% 3-year survival, and 35.4% 5-year survival)[15]. As shown in Table 1, the survival interval for HCC patients with PBC was also significantly shorter than that for patients with AIH ($P = 0.047$).

Among HCC cases associated with AIH, the actual male to female ratio was 7:31. Because AIH patients in Japan are predominantly female (7:1), the corrected risk ratio for HCC among male AIH patients was 1.6:1 relative to females, and the male to female ratio of the relative numbers was 23.3:14.7 (Table 2). The majority of Japanese PBC patients are also female, outnumbering

Table 3 Clinical status of reported cases of hepatocellular carcinoma associated with autoimmune hepatitis and primary biliary cirrhosis, compared to cases of general hepatocellular carcinoma in Japan

Clinical status	Compiled numbers (%)			*P*-values		
	HCC patients with AIH (AIH-series)	HCC patients with PBC (PBC-series)	General-HCC patients	AIH-series/General-HCC patients	PBC-series/General-HCC patients	AIH-series/PBC-series
History of blood transfusion	Total: 29	Total: 38	Total: 12602	$P = 0.040$[a]	$P = 0.581$	$P = 0.041$[a]
+	3 (10.3)	13 (34.2)	3633 (28.8)			
-	26 (89.7)	25 (65.8)	8969 (71.2)			
History of excessive alcohol intake	Total: 38	Total: 50	Total: 14694	$P = 0.812$	$P = 0.056$	$P = 0.352$
+	1 (2.6)	5 (10.0)	3271 (22.3)			
-	37 (97.4)	45 (90.0)	11423 (77.7)			
Co-infection	Total: 33	Total: 40	Total: 4121			
HBV (prior) +	2 (6.1)	10 (25.0)	2138 (51.9)	$P < 0.001$	$P < 0.001$	$P = 0.025$
HBV (prior) –	31 (93.9)	30 (75.0)	1983 (48.1)			
Co-infection	Total: 38	Total: 49	Total:16492			
HCV +	3 (7.9)	10 (20.4)	11488 (69.7)	$P < 0.001$	$P < 0.001$	$P = 0.044$
HCV -	35 (92.1)	39 (79.6)	5004 (30.3)			
Pathological findings of noncancerous lesion of the liver	Total: 31	Total: 44	Total: 4941	$P = 0.163$	$P = 0.007$[b]	$P = 0.489$
NL, CH, LF	13 (41.9)	15 (34.1)	2691 (54.5)			
LC	18 (58.1)	29 (65.9)	2250 (45.5)			

HCC: Hepatocellular carcinoma; AIH: Autoimmune hepatitis; PBC: Primary biliary cirrhosis; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NL: Normal liver; CH: Chronic hepatitis; LF: Liver fibrosis; LC: Liver cirrhosis.

males by 9:1. The relative risk ratio for HCC among males with PBC was 3.2:1 relative to females, and the male to female ratio of the relative numbers was 38:12 (Table 2). No significant differences in male to female ratios were noted between the three patient groups ($P = 0.149$, $P = 0.512$, $P = 0.244$, respectively).

Among the HCC cases associated with AIH, only three (10.3%) had a history of blood transfusions, while 13 (34.2%) of the cases with PBC had such a history. Among all Japanese patients with HCC, 3633 (28.8%) had a history of blood transfusions[15]. The proportion of HCC cases associated with AIH having a history of blood transfusions was significantly lower than that of the general HCC cases in Japan ($P = 0.040$), and the proportion of HCC cases associated with PBC having a history of blood transfusions was significantly greater than that of the HCC cases associated with AIH ($P = 0.041$, Table 3).

Similarly, only one case (3.1%) of HCC associated with AIH had a history of excessive alcohol intake, while five (20.0%) cases associated with PBC had such a history ($P = 0.352$, Table 3). Among all Japanese patients with HCC, 3271 (22.3%) had a history of excessive alcohol intake[15].

While prior infection with HBV was relatively rare among AIH patients (6.1%), it was much more prevalent among patients with PBC (25.0%, $P = 0.025$). Similarly, 7.9% of AIH patients tested positive for HCV, as compared to 20.4% of PBC patients ($P = 0.044$). The population of Japanese HCC patients without autoimmune liver disease had significantly higher rates of both HBV and HCV co-infection ($P < 0.001$, Table 3).

Among the HCC cases associated with AIH, 18/31 (58.1%) were found to have cirrhosis on examination of liver biopsy samples or resected samples at operation. In contrast, 29/44 (65.9%) of the HCC cases associated with PBC were found to have cirrhotic liver tissue. Within the general HCC population in Japan, 2250 of the 4941 cases for which liver specimens were available (45.5%) showed evidence of cirrhosis[15]. While the proportion of liver cirrhosis among HCC cases associated with PBC was significantly greater than that in the general HCC population in Japan ($P = 0.007$), no statistical significance in the prevalence of cirrhosis was found between AIH-associated HCC and general HCC patients ($P = 0.163$, Table 3).

The numbers and positive ratios of the AIH-series, PBC-series and general-HCC patients were 22/37 (59.5%), 34/47 (72.4%) and 10075/15831 (63.6%), respectively. No significant differences in positive ratios of serum-AFP were noted between the three patient groups ($P = 0.597$, $P = 0.216$, $P = 0.214$, respectively, Table 4). AFP levels at diagnosis were 2340.2 ng/mL (range 1-49100 ng/mL) among patients with AIH, and 854.2 ng/mL (range 4.2-14646 ng/mL) among patients with PBC. The maximum size of the primary hepatic tumor at diagnosis was 3.97 cm (range 1.0-10.0 cm) among patients with AIH and 3.51 cm (range 1.0-8.8 cm) among PBC patients (Table 4). Due to lack of available data, we could not compare serum AFP levels, tumor sizes and numbers of HCC loci between the autoimmune-associated HCC cases and the general HCC cases in Japan. However, we found that serum AFP level did not vary widely, and that maximum tumor size and number of HCC loci were considerably lower in patients with autoimmune liver disease than in general HCC patients (Table 4).

Among both the AIH and PBC patient groups,

Table 4 Serum AFP levels, tumor sizes and number of HCC loci of reported cases of hepatocellular carcinoma associated with autoimmune hepatitis and primary biliary cirrhosis, compared to cases of general hepatocellular carcinoma in Japan

Clinical status	Compiled numbers (%)			*P*-values		
	HCC patients with AIH (AIH-series)	HCC patients with PBC (PBC-series)	General-HCC patients	AIH-series/ General-HCC patients	PBC-series/ General-HCC patients	AIH-series/PBC-series
Serum-AFP	Total: 37	Total: 47	Total: 15831			
AFP – (< 15 ng/mL)	15 (40.5)	13 (27.7)	5756 (36.4)	$P = 0.597$	$P = 0.216$	$P = 0.214$
AFP + (⩾ 15 ng/mL)	22 (59.5)	34 (72.3)	10075 (63.6)			
Serum-AFP (ng/mL)	Total: 37	Total: 47	Total: 15831			
(mean ± SD)	(2340.21 ± 8823.45)	(854.18 ± 2263.83)	NA			
< 15	15 (40.5)	13 (27.6)	5756 (36.4)			
15-199	12 (32.5)	16 (34.0)	5786 (36.5)	NA	NA	$P = 0.106$
200-399	1 (2.7)	6 (12.8)	902 (5.7)			($P < 0.001^b$)
400-999	3 (8.1)	2 (4.3)	907 (5.7)			
⩾ 1000	6 (16.2)	10 (21.3)	2480 (15.7)			
Maximum tumor size	Total: 36	Total: 48	Total: 15788			
of HCC				NA	NA	$P = 0.744$
(mean ± SD) (cm)	(3.75 ± 2.42)	(3.51 ± 1.69)	NA			($P = 0.028^a$)
< 2	14 (38.9)	11 (22.9)	5123 (32.4)			
2.1-5.0	16 (44.4)	29 (60.4)	7434 (47.1)			
⩾ 5.1	6 (16.7)	8 (16.7)	3231 (20.5)			
Number of HCC loci	Total: 38	Total: 49	Total: 16187			
(mean ± SD)	(1.58 ± 2.05)	(1.74 ± 1.97)	NA	NA	NA	$P = 0.418$
Single	33 (86.8)	38 (77.6)	9365 (57.9)			($P = 0.805$)
Double	2 (5.3)	7 (14.3)	2850 (17.6)			
Multiple	3 (7.9)	4 (8.1)	3972 (24.5)			

The *P*-value in the first row was calculated from the χ^2 test and Fisher's exact test. The *P*-value in the following row was calculated from the Mann-Whitney *U*-test and the *P*-value below, indicated in parentheses, was calculated from the *F*-test. $^aP < 0.05$, $^bP < 0.01$, Statistically significant. HCC: Hepatocellular carcinoma; AIH: Autoimmune hepatitis; PBC: Primary biliary cirrhosis; AFP: α-fetoprotein; SD: Standard deviation; NA: Not available.

the most commonly selected forms of treatment were chemolipiodolization (CL) and transcatheter arterial embolization (TAE); other options included percutaneous ethanol injection therapy (PEIT) and radiofrequency ablation (RFA). Differences in the choice of therapeutic procedures were noted as follows, although no comparisons reached statistical significance following the Bonferroni correction: (1) The rate of CL or TAE among HCC patients with AIH was greater than the rate of operations among general HCC patients ($P = 0.048$), (2) The rate of CL or TAE among HCC patients with AIH was greater than the rate of PEIT and RFA among general HCC patients ($P = 0.018$), and (3) The rate of CL or TAE in HCC patients with PBC was greater than the rate of PEIT and RFA among general HCC patients ($P = 0.027$). Additionally, the frequency with which HCC patients with PBC chose to forgo treatment was significantly higher than the frequency with which general HCC patients chose to undergo PEIT or RFA ($P = 0.003$). Although not statistically significant, the frequency with which HCC patients with AIH refused therapeutic interventions was also higher than the frequency of PEIT or RFA in the general HCC population ($P = 0.038$, Table 5). Ideally, data on survival by treatment modality should be presented. However, the number of patients receiving each treatment modality who were able to be followed up to death was small. Hence, the mean period from HCC development to death was calculated from patient survival following all treatment options. Future prospective studies are needed to further analyze mean survival for each treatment alternative.

Across all three patient groups, we found that liver failure was the leading cause of death, followed by rupture of HCC. Among general HCC patients, neoplastic death was most common (1487/2700, 55.1%), although differences between causes of death did not reach statistical significance. Comparisons between patient groups showed that: (1) The rate of neoplastic death in general HCC patients was higher than the rate of variceal rupture in HCC patients with AIH ($P = 0.050$), (2) The rate of neoplastic death in general HCC patients was higher than the rate of gastrointestinal bleeding in HCC patients with AIH ($P = 0.013$), and (3) The rate of neoplastic death in general HCC patients was greater than the rate of variceal rupture in HCC patients with PBC ($P = 0.050$, Table 5).

DISCUSSION

While autoimmune liver disease is more common among women than men in Japan, HCC in our group of patients with autoimmune liver disease was more common in men than women (Table 2). Men with AIH had a 1.6-fold greater risk of HCC than women, while men with PBC had a 3.2-fold greater risk of HCC than women with PBC. Moreover, when we followed AIH and PBC patients during HCC surveillance, we noted that the rate of HCC development was higher in male patients with autoimmune liver disease than in female patients with autoimmune liver disease.

Cirrhosis was found in only 18/31 (58.1%) of HCC

Table 5 Therapy and outcome of reported cases of hepatocellular carcinoma associated with autoimmune hepatitis and primary biliary cirrhosis, compared to cases of general hepatocellular carcinoma in Japan

Clinical status	Compiled numbers (%)			*P*-values		
	HCC patients with AIH (AIH-series)	HCC patients with PBC (PBC-series)	General-HCC patients	AIH-series/ General-HCC patients	PBC-series/ General-HCC patients	AIH-series/ PBC-series
Therapy choices for HCC	Total: 38	Total: 47	Total: 17005	Operation *vs* CL or TAE $P = 0.048$[1]	RFA, PEIT *vs* CL or TAE	
CL or TAE	18 (47.4)	17 (36.2)	4636 (27.2)	RFA,PEIT,MCT *vs*	$P = 0.027$[1]	
Operation	8 (21.0)	16 (34.0)	5268 (31.0)	CL or TAE	RFA, PEIT *vs*	
RFA, PEIT, MCT	6 (15.8)	6 (12.8)	4890 (28.8)	$P = 0.018$[1]	No therapy	
Chemotherapy	0 (0)	0 (0)	765 (4.5)	RFA,PEIT,MCT *vs*	$P = 0.003$[2]	
Others	0 (0)	0 (0)	122 (0.7)	No therapy		
No therapy	6 (15.8)	8 (17.0)	1324 (7.8)	$P = 0.038$[1]		
Clinical outcome	Total: 37	Total: 49	Total: 16646			
Alive	20 (54.1)	31 (63.3)	13946 (83.8)	$P < 0.001$[b]	$P < 0.001$[b]	$P = 0.389$
Dead	17 (45.9)	18 (36.7)	2700 (16.2)			
Cause of death	Total: 16	Total: 18	Total: 2700	Neoplastic death	Neoplastic death	
Liver failure	8 (50.0)	8 (44.4)	581 (21.5)	*vs* variceal rupture	*vs* variceal rupture	
HCC rupture	3 (18.8)	4 (22.2)	172 (6.4)	$P = 0.050$[1]	$P = 0.050$[1]	
Variceal rupture	1 (6.2)	1 (5.6)	85 (3.1)	Cancer death *vs* GI		
GI bleeding	1 (6.2)	2 (11.1)	55 (2.0)	bleeding		
Neoplastic death	0 (0)	0 (0)	1487 (55.1)	$P = 0.013$[1]		
Others	3 (18.8)	3 (16.7)	320 (11.9)			

[b]$P < 0.01$, Statistically significant. [1]The calculated *P*-values did not reach statistical significance with Bonferroni correction; without the correction, however, *P*-values were below 0.05. [2]The calculated *P*-values reached statistical significance with Bonferroni correction. HCC: Hepatocellular carcinoma; AIH: Autoimmune hepatitis; PBC: Primary biliary cirrhosis; CL: Chemolipiodolization; TAE: Transcatheter arterial embolization; RFA: Radiofrequency ablation therapy; PEIT: Percutaneous ethanol injection therapy; MCT: Microwave coagulation therapy; GI: Gastrointestinal.

patients with AIH, 29/44 (65.9%) of HCC patients with PBC, and in only 2250/4941 (45.5%) of the general Japanese HCC population. We did not add cases with liver fibrosis (LF) to the incidence of liver cirrhosis (LC) in the general Japanese HCC population, which may be one of the reasons why the incidence of liver cirrhosis was surprisingly low. Additionally, we think that the HCC cases with PBC and AIH and with non-cirrhotic liver, in which sufficient examinations and successful treatments were performed because of their higher hepatic reserve, were likely to be reported and submitted for publication. The possibility of bias in the selection of the reported cases should be raised.

Another interesting finding was that the interval between HCC diagnosis and death was shorter for patients with autoimmune liver disease than for the general HCC population of Japan[15]. Furthermore, although we found that serum AFP level did not vary widely, the maximum tumor size and number of HCC loci were considerably lower in patients with autoimmune liver disease than in general HCC patients (Table 4). One explanation for this finding may be a selection bias, as cases which were detected earlier and treated successfully were more likely to be submitted for publication. Despite a smaller tumor size and a lower number of HCC loci in patients with HCC arising in the setting of autoimmune liver disease at the time of HCC diagnosis, a shorter reported survival was not attributed to late detection of HCC and failure to survey patients with autoimmune liver disease for HCC, but was more likely to be due to advanced liver disease and cirrhosis. Future prospective studies will be needed to verify or refute these findings.

Although CL and TAE were the most frequently selected treatment modalities across all patient groups (Table 5), many patients ultimately refused treatment due to advanced age or social circumstances. Medical treatments using CL or TAE may be common because HCC cases are often inoperable due to cirrhotic liver disease in these patients. While survival may be related to the choice of therapeutic options, inconsistencies in data reporting over multiple decades and across multiple medical centers made the calculation of survival data difficult.

Several mechanisms explaining the development of HCC from autoimmune liver diseases have been proposed: enhanced progression to cirrhosis through progressive autoimmune hepatitis, decreased antitumor immune responses caused by long-term administration of steroids and immunosuppressants, or virus-mediated hepatitis[16,17]. In this study, we found significantly higher rates of HBV and HCV among PBC patients with HCC than among AIH patients with HCC. This finding may be attributable to the higher rates of blood transfusion in HCC patients with PBC ($P = 0.041$, Table 3). This result is supported by the findings of Shimizu *et al*[18], who reported that 3/16 (19%) HCC patients with PBC tested positive for prior HBV and present HCV infections. Given the high rates of prior HBV infections among HCC patients with PBC, it is possible that prior HBV infection predisposes patients to HCC through HBV-DNA becoming integrated into hepatocyte DNA. It has been reported that even in patients who test negative for serum HCV-RNA and serum HBV-DNA (less

than the sensitivity of HBV-DNA), liver tissue samples frequently test positive for HCV-RNA or HBV-DNA. This suggests a possible role for positive HCV-RNA or HBV-DNA in hepatic tissue in the development of HCC[19-23]. In the present study, however, only six HCC patients with AIH and two HCC patients with PBC were found to have detectable HBV-DNA and HCV-RNA in liver tissue samples. Aggressive liver biopsies should be taken to allow genetic analysis for HBV and HCV in liver tissue, in order to further study HCC cases with non-B, non-C hepatitis.

We reported high rates of HBV or HCV infection among HCC patients with PBC (Table 3); however, this is less surprising because international diagnostic criteria for AIH allocate negative points for positive HBV or HCV diagnostic tests[14]. Furthermore there are no definitive histological features that allow a clinician or pathologist to distinguish AIH from chronic viral hepatitis. Thus, HBV or HCV infected patients are rarely classified as having AIH in the modern era. In contrast, the unique histological features of PBC and the relative specificity of AMA tests allow clinicians to diagnosis and report cases of concurrent PBC and chronic viral hepatitis with a greater degree of confidence.

It has been reported that HCC develops significantly more often in patients with concurrent PBC and HCV infection than in patients with AMA-positive PBC[9]. The incidence of HCC associated with PBC has been suggested to have increased recently due to prolonged periods of liver cirrhosis resulting from longer survival on steroid therapy, concurrence of the hepatitis virus or alcohol intake with HCC, and the administration of immunosuppressants which may disturb immunoregulatory function[24,25]. In a proportional hazards analysis of patients with PBC, Shibuya *et al*[11] found 3 factors to be independently associated with the development of HCC: age at time of diagnosis, male gender, and a history of blood transfusion. Our findings showed that HCC cases arising from PBC were more common in men and those with liver cirrhosis.

While the number of HCC cases arising from PBC is stated to be small, it has been reported that the calculated crude incidence of HCC was 492.4/100 000 person years, and that HCC has a relatively high prevalence in PBC[7]. Furthermore, there is a dramatically increased risk for development of hepatobiliary malignancies in patients with PBC, with a relative risk of 46 ($P < 0.0001$) in women and 55 ($P < 0.0001$) in men[26].

Finally, several questions remain for the clinician. Namely, should AIH and PBC patients be screened for HCC? Should screening be limited to cirrhosis? Does the clinical course after diagnosis differ from other HCC patients? Late-stage AIH and PBC patients should be screened for HCC just as in HCV-related cirrhosis, given the similar reported incidence of HCC development in late-stage PBC[13]. Furthermore, Suzuki *et al*[27], reported very recently that patients of older age, male sex, history of blood transfusion, and any signs of portal hypertension or cirrhosis should be considered for HCC screening. A prospective study or a case control study for AIH patients is needed similar to that conducted for PBC patients.

At present, HCC transformation in early-stage pre-cirrhotic AIH and PBC were thought to be very rare. However, a high incidence of HCC development was observed in AIH and PBC patients with overlapping HCV and HBV infection, including occult HBV infection[9,19,20]. These patients should be closely followed using ultrasonography, CT-scanning and MRI of the abdomen, as well as tumor markers for HCC. Reports of HCC cases arising from "pure" AIH and PBC (with no history of blood transfusion, excessive alcohol intake, immunosuppressant administration, and with negative HBV and HCV serotyping) are rare[2,27-31]. El-Serag *et al*[32], in a multivariate analysis reported that AIH itself is not significant; however, our study indicates that early-stage AIH and PBC patients also have the potential to develop HCC. We advocate that "pure" or "early-stage" AIH and PBC cases should also be regularly screened for HCC.

Our data also indicate that the clinical course after diagnosis of HCC with AIH and PBC differs from virus-associated HCC, although prospective studies are needed to confirm these results. Clinicians should note the common clinical features of HCC cases with AIH and PBC at diagnosis, treatment, and follow-up of these patients.

Lastly, our findings also beg the question of why HCC rupture is the second most common cause of death in both groups of patients examined. We have recently reported a pelioid-type HCC patient with PBC, who died from rupture of HCC[33]. A peliotic change was observed more frequency in large poorly-differentiated and encapsuled HCC[34], and the features of pelioid-type HCC were high blood flow into the HCC, high pressure in the tumor and fibrous capsular formation. It is unknown whether the ruptured HCCs in the present study had these features, as this study had severe limitations because it was retrospective. Tumors in such patients may grow rapidly, and pathophysiological factors shared by both patient groups may trigger the rupture of HCC. A prospective study on the cause of death and a pathologic study of ruptured HCC with AIH and PBC is awaited with great interest.

Further clinical and laboratory studies are needed to describe which pathological, biological and genetic features are common among HCC cases arising from AIH and PBC. How HCC in these patients relates to viral hepatitis also requires further clarification. The present study was retrospective; however, this is the first study to date that highlights the importance of these future research topics. Future prospective studies on these important subjects are required.

COMMENTS

Background

Hepatocellular carcinoma (HCC) development in autoimmune hepatitis (AIH) as well as in primary biliary cirrhosis (PBC) is a rare event. The common clinical features of HCC associated with AIH and PBC have not yet been extensively

described.

Research frontiers

In this study, we characterized these common features through a systematic review of the literature conducted using the Japana Centra Revuo Medicina database. We demonstrated common clinical features among cases of HCC arising from AIH and PBC in Japan.

Innovations and breakthroughs

We found common clinical features in HCC cases with AIH and PBC as follows, (1) HCC was more common in men than in women with AIH or PBC. (2) Many patients underwent chemolipiodolization (CL) or transcatheter arterial embolization (TAE). (3) Liver failure was the primary cause of death among patients in this study, followed by tumor rupture. (4) The survival interval between diagnosis and death was fairly short.

Applications

The present study was retrospective; however, this is the first study to date that highlights the common clinical features in HCC cases with AIH and PBC. Future prospective studies of these important subjects are required.

Peer review

This is a systematic literature review of HCC cases with AIH and PBC published throughout Japan. The review is clearly written and highlights a very interesting topic.

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