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Abstract

A comparison was made of the clinical findings of 59 patients with liver cirrhosis (LC) accompanied with hepatocellular carcinoma (HCC) (of which 35 had ascites and 24 did not at the time of admission) and 164 patients with LC, but without HCC (of which 39 had ascites and 125 did not). HCC patients were older and more often had hepatomegaly, vascular spider and pleural effusion than LC patients. Ascites was more frequently observed in HCC than in LC patients when the serum albumin level and the indocyanine green disappearance rate were relatively well maintained and when peripheral edema was absent. There was no difference in the ascitic protein concentration between LC and HCC patients. Malignant cells were detected in ascites only in 14% of the HCC patients. These facts indicate the presence of ascites-inducing factors in HCC patients which have no direct relation to serum colloid osmotic pressure and effective hepatic blood flow. Almost all of the HCC patients with ascites (96%) died with ascites, whereas 54% of the LC patients with ascites recovered from the ascitic condition.

KEYWORDS: liver cirrhosis, hepatocellular carcinoma, ascites

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CLINICAL STUDIES OF HEPATOCELLULAR CARCINOMA WITH LIVER CIRRHOSIS AND ASCITES

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Abstract. A comparison was made of the clinical findings of 59 patients with liver cirrhosis (LC) accompanied with hepatocellular carcinoma (HCC) (of which 35 had ascites and 24 did not at the time of admission) and 164 patients with LC, but without HCC (of which 39 had ascites and 125 did not). HCC patients were older and more often had hepatomegaly, vascular spider and pleural effusion than LC patients. Ascites was more frequently observed in HCC than in LC patients when the serum albumin level and the indocyanine green disappearance rate were relatively well maintained and when peripheral edema was absent. There was no difference in the ascitic protein concentration between LC and HCC patients. Malignant cells were detected in ascites only in 14 % of the HCC patients. These facts indicate the presence of ascites-inducing factors in HCC patients which have no direct relation to serum colloid osmotic pressure and effective hepatic blood flow. Almost all of the HCC patients with ascites (96 %) died with ascites, whereas 54 % of the LC patients with ascites recovered from the ascitic condition.

Key word : liver cirrhosis, hepatocellular carcinoma, ascites.

Reports of clinical and pathophysiological examinations of hepatocellular carcinoma (HCC) patients with ascites are few (1). The following four causes of ascites in liver cirrhosis (LC) patients have been proposed : portal hypertension, decreased colloid osmotic pressure, plasma transudation and primary renal plasma volume expansion (2-4). However, the cause of ascites in HCC patients remains unclear. The low incidence of malignant cells in the ascitic fluid of HCC patients suggests that cancerous peritonitis does not play a major role in ascites formation in HCC patients (5).

In this study, the clinical features of HCC with ascites (AHCC) were compared with those of LC with ascites (ALC) to understand the mechanism of ascites formation in HCC.

SUBJECTS AND METHODS

Fifty-nine LC patients with HCC and 164 LC patients without HCC were selected from patients who were admitted to our department during the 5-year period from January 1974 to December 1978. Patients with primary renal disease or biliary cirrhosis were excluded. Out of the 59 HCC patients, 35 had ascites at the time of admission, but seventeen of those ad-

mitted without ascites later developed the condition, making a total of 52 AHCC patients (88 %). HCC was diagnosed in 29 patients by autopsy or liver histology after death, in 11 patients by laparoscopy and liver biopsy and in 19 patients by alpha fetoprotein (AFP), celiac angiography or liver scintigram.

Out of the 164 LC patients, 39 (24 %) had ascites. Out of the 125 without ascites, 5 patients were admitted a second time after developing ascites. The diagnoses of all 125 patients without ascites were made by laparoscopy and liver biopsy. Of the patients with ascites, diagnoses were made by laparoscopy and liver biopsy in 22, by autopsy or liver histology after death in 12 and by clinical findings in 5.

Fifty items such as age, sex, physical findings, laboratory data on admission, clinical course and prognosis were studied. For the HCC patients who developed ascites after admission, both data on admission and at the time of ascites appearance were used. The data of both admissions were used for those patients admitted twice. Total and direct serum bilirubin, GOT, GPT, alkaline phosphatase, blood ammonia, urinary electrolytes, BUN and serum creatinine values were converted to logarithms and treated statistically. After converting to the antilogarithms, the data were shown as mean-SD $-$ mean $+$ SD. All data were treated by the t test or the chi-square test using the Yates modification.

RESULTS

Age and sex distribution. The average age of HCC patients was greater than that of LC patients by 5 years, and the average age of AHCC patients was greater than that of ALC patients by 6 years (Tables 1, 2). There was no difference in sex distribution, with males comprising about 88 % of the total.

Physical findings on admission. Ascites was found more often in HCC patients (88 %) than in LC patients (24 %). Hepatomegaly, pleural effusion and vascular spider were more frequent in HCC than in LC patients (Table 2). Though peripheral edema was more frequent in ALC (54 %) than in AHCC patients (31 %), hepatomegaly was more frequent in AHCC (79 %) than in ALC patients (46 %). Pleural effusion of the right pleural cavity occurred in 3 ALC patients (8 %). Effusion was present in one HCC patient not having ascites in either pleural cavity, and in 8 AHCC patients having ascites in the right (5 patients), left (2 patients) or both cavities (1 patient). Effusion from HCC lung metastases occurred in one patient in the right pleural cavity and 2 patients in both pleural cavities.

Laboratory data on admission. HBs antigen (determined by immunoelectrophoresis from 1974 to 1977 and by reversed passive hemagglutination thereafter) was positive in 21 % of the HCC and 17 % of the LC patients (Table 3). AFP was positive in 72 % of the HCC patients. Esophageal varices were observed in 88 % of the HCC and 86 % of the LC patients, and in 93 % of both the AHCC and ALC patients. There was no difference in the protein concentration of ascites between HCC and LC patients. The protein concentration of the ascitic fluid correlated with the total serum protein ($r=0.40$) and the serum albumin ($r=0.40$) in LC patients. However, no such correlations were observed in HCC patients. Chylous ascites was found in only 3 LC patients and bloody ascites in 3 HCC patients. Cytological examination of the ascitic fluid from 14 HCC patients re-

TABLE 1. AGE AND SEX DISTRIBUTION OF TOTAL AND ASCITIC CASES OF LIVER CIRRHOSIS WITH HEPATOCELLULAR CARCINOMA (HCC) AND LIVER CIRRHOSIS (LC)

Age	HCC Total	Male	Female	LC Total	Male	Female
10-19				1 (0)	1 (0)	0 (0)
20-29				6 (1)	5 (1)	1 (0)
30-39	2 (2)	2 (2)	0 (0)	18 (4)	17 (4)	1 (0)
40-49	20 (15)	18 (13)	2 (2)	72 (17)	63 (14)	9 (3)
50-59	21 (20)	19 (18)	2 (2)	43 (12)	34 (10)	9 (2)
60-69	12 (11)	11 (10)	1 (1)	21 (5)	11 (2)	10 (3)
70-80	4 (4)	2 (2)	2 (2)	3 (0)	3 (0)	0 (0)
Total	59 (52)	52 (45)	7 (7)	164 (39)	134 (31)	30 (8)

( ): cases with ascites

TABLE 2. COMPARISON OF AGE, SEX AND PHYSICAL FINDINGS BETWEEN CASES OF LIVER CIRRHOSIS WITH HEPATOCELLULAR CARCINOMA (HCC) AND THOSE OF LIVER CIRRHOSIS (LC)

	1) Total HCC	2) Total LC	3) HCC with ascites (AHCC)	4) LC with ascites (ALC)	1) vs. 2)	3) vs. 4)
No. of cases	76	169	52	39		
Age	54.5 ± 9.5 (39-80)	49.1 ± 10.3 (17-75)	55.1 ± 9.7 (39-80)	49.2 ± 9.9 (23-70)	≫	≫
Sex Male	52 (88 %)	134 (82 %)	45 (87 %)	31 (79 %)		
Female	7 (12 %)	30 (18 %)	7 (13 %)	8 (21 %)		
Physical findings						
Ascites	52/59 (88 %)	39/164 (24 %)			≫	
Peripheral edema	16 (21 %)	30 (18 %)	16 (31 %)	21 (54 %)		<
Vascular spider	49 (64 %)	84 (50 %)	34 (65 %)	24 (62 %)	>	
Encephalopathy	0	5 (3 %)	0	3 (8 %)		
Hepatomegaly	61 (80 %)	105 (62 %)	41 (79 %)	18 (46 %)	≫	≫
Splenomegaly	24 (32 %)	41 (24 %)	14 (27 %)	16 (41 %)		
Pleural effusion	9 (12 %)	3 (2 %)	8 (15 %)	3 (8 %)	≫	

$< >$: $p < 0.05$, ≫ : $p < 0.01$

vealed Class I in 3, Class II in 7, Class III in 2 and Class IV in 2 patients (14 %).

The total and direct bilirubin, GOT, GOT/GPT, alkaline phosphatase (ALP), cholesterol, BUN and serum creatinine values were higher in HCC than in LC patients. The choline esterase, indocyanine green disappearance rate (KICG), serum albumin, A/G, serum sodium, serum chloride and fasting blood glucose values were lower in HCC than in LC patients. The prothrombin time was more prolonged in LC than in HCC patients. Urine protein was positive more frequently in HCC than in LC patients.

The direct bilirubin, GOT, GPT, GOT/GPT and ALP values were higher in

TABLE 3. COMPARISON OF LABORATORY DATA BETWEEN CASES OF LIVER CIRRHOSIS WITH HEPATOCELLULAR CARCINOMA (HCC) AND THOSE OF LIVER CIRRHOSIS (LC)

	1) Total HCC	2) Total LC	3) HCC with ascites (AHCC)	4) LC with ascites (ALC)	1) vs. 2)	3) vs. 4)
No. of cases	76	169	52	39		
Liver function tests						
HBs antigen	14/68 (21%)	26/153 (17%)	10/48 (21%)	8/37 (22%)		
α-fetoprotein	52/72 (72%)		36/50 (72%)			
Total bilirubin (mg/dl)	2.9, 1.1-7.5	1.4, 0.7-3.2	3.3, 1.3-8.1	2.4, 0.9-6.6	≫	
Direct bilirubin (mg/dl)	1.7, 0.5-5.1	0.6, 0.2-1.7	2.0, 0.7-5.8	1.2, 0.4-4.1	≫	>
GOT (u.)	191, 97-375	94, 51-173	217, 111-423	89, 51-153	≫	≫
GPT (u.)	77, 41-148	75, 33-171	79, 42-151	56, 28-111		>
GOT/GPT	3.0±2.5	1.4±0.8	3.4±2.9	1.7±0.8	≫	≫
Alkaline phosphatase (BL u.)	5.6, 3.3-9.6	3.0, 1.8-4.8 (165)	5.6, 3.4-9.2	3.3, 2.0-5.4	≫	≫
Choline esterase (Δ pH)	0.43±0.16 (70)	0.58±0.20 (159)	0.38±0.14 (47)	0.39±0.16	≪	
Cholesterol (mg/dl)	183±75	160±42	184±88	141±43	>	≫
TTT (u.)	4.6±2.3 (69)	4.6±2.4 (165)	4.6±2.2 (46)	4.7±2.0		
ZTT (u.)	12.2±3.9 (70)	12.1±3.5 (165)	12.5±3.9 (47)	12.8±3.4		
ICG disappearance rate	0.069±0.028 (41)	0.089±0.037 (148)	0.063±0.024 (21)	0.065±0.028 (30)	≪	
Prothrombin time (sec.)	14.4±1.7 (61)	15.1±2.1 (161)	14.2±1.7 (39)	16.6±2.3	<	≪
Blood ammonia (μg/dl)	104, 63-170 (53)	95, 55-164 (111)	112, 71-177 (34)	106, 61-185		
Total protein (g/dl)	6.9±0.8	6.9±0.8	6.8±0.7	6.5±1.0		
Albumin (g/dl)	3.1±0.5	3.5±0.6	3.0±0.5	2.9±0.6	≪	
γ-globulin (g/dl)	2.1±0.6	2.0±0.6	2.1±0.7	2.3±0.7		
A/G	0.9±0.2	1.0±0.3	0.8±0.2	0.8±0.2	≪	
Renal function tests and electrolytes						
Serum Na (mEq/l)	134±5	137±5 (157)	133±5	133±6	≪	
Serum K (mEq/l)	4.2±0.5	4.1±0.5 (157)	4.2±0.5	4.2±0.6		
Serum Ca (mg/dl)	9.0±0.8	8.9±0.4 (154)	9.0±1.0	8.6±0.5		≫
Serum Cl (mEq/l)	101±6	105±5 (156)	100±6	102±6	≪	
Urine Na (mEq/l)	73, 41-133 (47)	65, 26-162 (56)	69, 37-129 (39)	49, 22-111 (27)		
Urine K (mEq/l)	31, 17-56 (47)	29, 17-49 (56)	29, 17-48 (39)	26, 16-42 (27)		
Urine Ca (mg/dl)	8, 5-15 (44)	10, 6-16 (53)	9, 5-15 (37)	9, 5-14 (25)		
Urine Cl (mEq/l)	70, 32-152 (45)	67, 30-151 (56)	66, 29-150 (37)	49, 22-111 (27)		
Urine Na/K	3.1±2.3 (47)	3.0±1.8 (55)	3.3±2.4 (39)	2.6±2.1 (27)		
Urine specific gravity	1,018±6 (60)	1,017±6 (83)	1,017±6 (46)	1,017±6		
BUN (mg/dl)	17, 12-25 (58)	15, 9-24 (126)	18, 12-27 (44)	17, 9-34 (36)	>	
Serum creatinine (mg/dl)	1.3, 1.0-1.8 (35)	1.0, 0.8-1.4 (81)	1.4, 1.0-1.9 (26)	1.3, 0.8-1.9 (23)	≫	
Creatinine clearance (ml/min.)	71±22 (14)	77±24 (21)	67±24 (10)	67±23 (8)		
PSP (%, 15 min.)	33±13 (10)	36±10 (34)	30±14 (7)	35±11 (10)		
Urine protein ≥ +	9/74 (12%)	7/164 (4%)	9/50 (18%)	5/39 (13%)	>	
Urine sediment RBC ≥ 5/hpf	4/74 (5%)	10/164 (6%)	4/50 (8%)	6/39 (15%)		
Urine cast ≥ +	8/74 (11%)	11/164 (7%)	7/50 (14%)	8/39 (21%)		
Others						
Fasting blood glucose (mg/dl)	104±20 (58)	117±47 (155)	104±22 (38)	133±77	≪	<
Hematocrit (%)	37.1±5.9 (68)	37.4±5.4 (167)	36.3±6.1	34.7±4.7		
Ascites protein conc. (g/dl)			1.5±1.0 (39)	1.1±0.7 (26)		
Esophageal varices	38/43 (88%)	113/132 (86%)	25/27 (93%)	25/27 (93%)		

( ) : Number of examined cases < > : $p < 0.05$ ≪ ≫ : $p < 0.01$

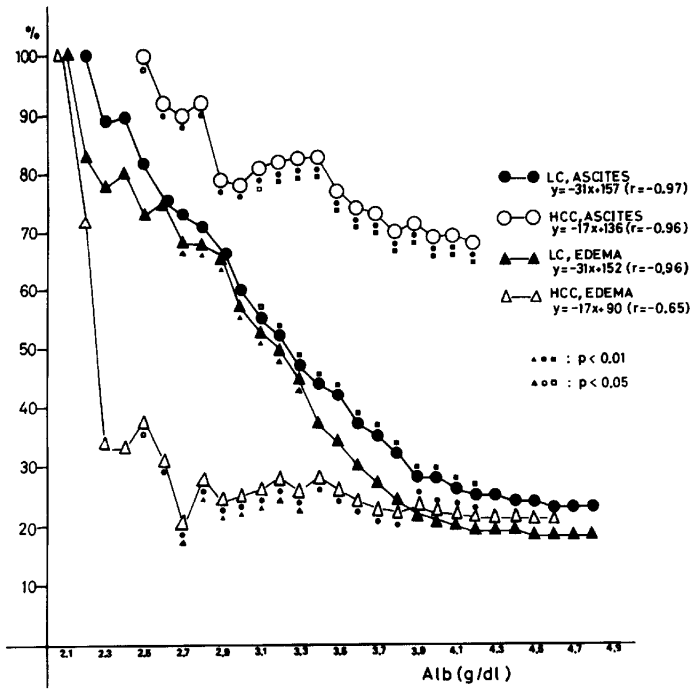

Fig. 1. Appearance rate of ascites and peripheral edema in relation to serum albumin in cases of liver cirrhosis with hepatocellular carcinoma (HCC) and those of liver cirrhosis (LC)

AHCC than in ALC patients. Cholesterol and serum calcium levels were lower in ALC than in AHCC patients. The fasting blood glucose value was higher and the prothrombin time was longer in ALC than in AHCC patients.

Clinical course and prognosis. Only 2 (4 %) of the 52 AHCC patients were relieved of ascites and discharged from the hospital. Five patients moved to another hospital and 45 patients died in the hospital. The causes of death of the 45 patients were gastrointestinal bleeding (58 %), renal failure (16 %), intraperitoneal bleeding (9 %), hepatic coma (9 %), cachexia (7 %) and heart failure (2 %).

Twenty-two (56 %) out of the 39 ALC patients were relieved of ascites which lasted 1-24 weeks (median, 3 weeks) in these patients. Seventeen patients died in our hospital, one of bacterial encephalitis after the disappearance of ascites and the other 16, still having ascites, of gastrointestinal bleeding (56 %), hepatic coma (19 %), renal failure (13 %) and shock other than hemorrhagic shock (13 %).

Incidence of ascites and peripheral edema in relation to serum albumin in HCC and LC patients. The incidence of ascites and peripheral edema correlated inversely with serum albumin in both HCC and LC patients (Fig. 1). In HCC patients, the rate of occurrence of ascites was higher than that of peripheral edema when the serum albumin level was over 2.5 g/dl, while in LC patients the rates were not different. The rate of occurrence of ascites was not different between HCC (78 %) and LC

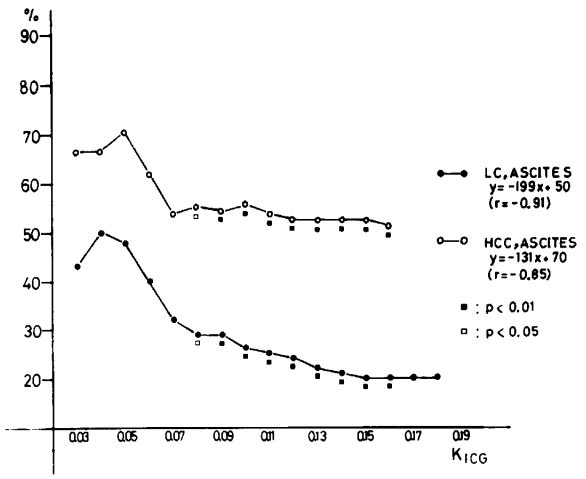

Fig. 2. Appearance rate of ascites in relation to ICG disappearance rate in cases of liver cirrhosis with hepatocellular carcinoma (HCC) and those of liver cirrhosis (LC)

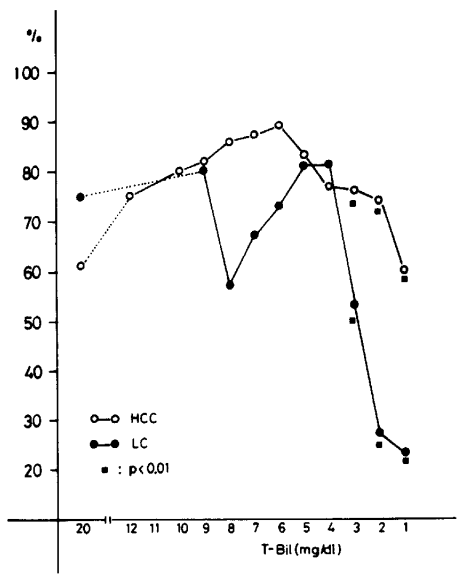

Fig. 3. Appearance rate of ascites in relation to total bilirubin in cases of liver cirrhosis with hepatocellular carcinoma (HCC) and those of liver cirrhosis (LC)

patients (60 %) when the serum albumin level was under 3.0 g/dl, but it was higher in HCC (58 %) than in LC patients (11 %) when the serum albumin level was over 3.1 g/dl. The rate of occurrence of peripheral edema was higher in LC (43 %) than in HCC patients (22 %) when the serum albumin level was 2.6-3.3 g/dl.

Retention rate of ascites in relation to KICG and total bilirubin in HCC and LC patients. The retention rate of ascites increased in both HCC and LC patients as KICG decreased (Fig. 2). Ascites was retained more frequently in HCC than in LC patients when KICG was over 0.08 (47 % vs. 12 %). The ascites retention rate was 81 % in both HCC and LC patients when the total bilirubin level was over 4 mg/dl (Fig. 3). When the total bilirubin level was 3 mg/dl or less, the ascites retention rate was higher in HCC (62 %) than in LC patients (14 %).

DISCUSSION

The ascites retention rate was higher in HCC than in LC patients in this study. The high rate of ascites retention in HCC patients in this study, 88 %, compared with 44-56 % in previous papers (6, 7), may be due to the fact that all of the present cases of HCC were complicated with LC. The present retention rate of 24 % in LC patients was much lower than the 60-70 % reported in a previous paper (8), probably because more than 75 % of the patients were diagnosed in the early stage of LC by laparoscopy and liver biopsy in the present study. As would be expected from the observation that HCC usually develops after LC in Japan (6), HCC patients of this study were older than LC patients by 5 years, which coincides with a survey and follow-up study of primary liver cancer in Japan (6). However, the severity of the HCC-complicated LC did not decide the ascites retention rate.

The ascites retention rate was studied with regard to serum albumin, which is known as a factor of ascites formation in LC (9). The ascites retention rate increased in both HCC and LC patients as serum albumin levels decreased (Fig. 1). The rate was not significantly different between HCC and LC patients when the serum albumin level was under 3.0 g/dl, but the rate was higher in HCC than in LC patients when the level was over 3.1 g/dl. Therefore, serum albumin seems to be less important for ascites formation in HCC than in LC patients.

The incidence of peripheral edema increased parallel to that of ascites in LC patients as serum albumin levels decreased, but the incidence of peripheral edema was markedly lower than that of ascites in HCC patients (Fig. 1). Peripheral edema increased as serum albumin levels decreased in both HCC and LC patients (Fig. 1). The incidence of peripheral edema was higher in LC than in HCC patients in the range of 2.6-3.3 g/dl of serum albumin which indicates that peripheral edema seldom occurs in HCC patients even when their serum albumin level is relatively low. Ascites occurs more often than peripheral edema in HCC than in LC patients at most levels of serum albumin (Fig. 1).

KICG and total bilirubin are believed to represent the degree of severity of LC (10, 11). The ascites retention rate increased in both HCC and LC patients as KICG decreased. Ascites was retained more often in HCC than in LC patients, when KICG was over 0.08 and total bilirubin was in the range of 1-3 mg/dl (Figs. 2, 3). However, the ascites retention rate did not differ when total bilirubin

was over 4 mg/dl. These results suggest that the severity of LC does not play a major role in the retention of ascites in HCC patients, and that factors other than the hepatic blood flow are involved in the formation of ascites in HCC patients.

Biochemical and cytological analyses of ascitic fluid from HCC and LC patients were performed. Ascitic protein concentration did not differ between HCC and LC patients. A wide range in protein content of ascitic fluid is known to occur among patients with liver disease, and the protein concentration is useless for diagnostic purposes (12, 13). Bloody ascites was found only in HCC patients and chylous ascites only in LC patients. Bloody ascites, in the absence of trauma, usually indicates malignant disease (14). Chylous ascites is caused by lymphatic obstruction and is usually due to lymphoma or other malignancies, but may occasionally be found in cirrhosis (15). Malignant cells in the ascitic fluid were observed in only 14 % of the HCC patients in this study. Motoki *et al.* suggested that the low incidence of HCC metastasis to the peritoneum (6 %) might be attributable to the fact that few malignant cells are found in HCC ascitic fluid (5). However, Kusakabe *et al.* have recently reported that after careful and repeated examinations malignant cells were observed in 39 % of the samples of ascitic fluid from HCC patients (16).

In summary, hepatomegaly and ascites were observed more frequently in HCC than in LC patients when serum albumin and KICG were relatively well maintained and when peripheral edema was absent. Therefore, ascites-inducing factors which are not directly correlated with serum colloid osmotic pressure, severity of LC or hepatic blood flow are likely to exist in HCC patients. Hepatomegaly and elevation of serum ALP and GOT often observed in cases of HCC (17) indicate that congestion of the liver due to the spread of the carcinoma to the hepatic or portal veins or the inferior vena cava could be an ascites-inducing factor. Another possible factor is the elevation of serum calcium in HCC. It is well recognized that hypercalcemia may be associated with a depression of GFR and azotemia (18).

REFERENCES

1. Mas, A., Arroyo, V., Rodes, J. and Bosch, J.: Ascites and renal failure in primary liver cell carcinoma. *Br. Med. J.* **1**, 629, 1975.
2. Schober, O., Mariβ, P., Schmidt, F.W. and Hundeshagen, H.: Total body water, extracellular water, plasma volume, and total body potassium in cirrhosis of the liver. *Klin. Wsht.* **57**, 757-761, 1979.
3. Lieberman, F.L., Denison, E.K. and Reynolds, T.B.: The relationship of plasma volume, portal hypertension, ascites, and renal sodium retention in cirrhosis: The overflow theory of ascites formation. *Ann. N.Y. Acad. Sci.* **170**, 202-206, 1970.
4. Witte, M.H., Witte, C.L. and Dumont, A.E.: Progress in liver disease: Physiological factors involved in the causation of cirrhotic ascites. *Gastroenterology* **61**, 742-750, 1971.
5. Motoki, T., Terano, A., Katamoto, T., Inagaki, T., Okano, K., Hirano, M., Matsumoto, K., Kamisaka, K., Kamii, K. and Murao, S.: A study in cytologic examination of ascitic fluid

in primary liver cancer. *Naika* **45**, 656-658, 1980 (in Japanese).
6. Okuda, K. and the Liver Cancer Study Groups of Japan : Primary liver cancers in Japan. *Cancer* **45**, 2663-2669, 1980.
7. Kondo, T., Arataki, Y., Hirota, S., Murakami, T., Takabe, S., Imafuku, T., Ishikawa, Y. and Kawasaki, M. : Clinical studies on 27 cases with hepatoma. *Iryo* **34**, 61-64, 1980 (in Japanese).
8. Ichida, F. and Kawamura, T. : Liver cirrhosis. *Nihon Rinsho* **41**, 551-558, 1982 (in Japanese).
9. Cherrick, G.R., Kerr, D.N.S., Read, A.E. and Sherlock, S. : Colloid osmotic pressure and hydrostatic pressure relationships in the formation of ascites in hepatic cirrhosis. *Clin. Sci.* **19**, 361-375, 1960.
10. Itoshima, T. : Significance of ICG test for diagnosis of liver cirrhosis. Evaluation by computer diagnosis using discriminant function. *Acta Hep. Jpn.* **10**, 45-56, 1969 (in Japanese).
11. Itoshima, T., Kawaguchi, K., Morichika, S., Ito, T., Kiyotoshi, S., Ogawa, H., Yuasa, S., Hattori, S., Kitadai, M., Ukida, M. and Nagashima, H. : Differential diagnosis of liver parenchymal disease by likelihood method using 12 laboratory data and age. *Gastroenterol. Jpn.* **17**, 453-462, 1982.
12. Boyer, T.D., Kahn, A.M. and Reynolds, T.B. : Diagnostic value of ascitic fluid lactic dehydrogenase, protein and WBC levels. *Arch. Intern. Med.* **138**, 1103-1105, 1978.
13. Bar-Meir, S., Lerner, E. and Conn. H.O. : Analysis of ascitic fluid in cirrhosis. *Dig. Dis. Sci.* **24**, 136-144, 1979.
14. Sherlock, S. : Ascites, In *Diseases of the Liver and Biliary System*, ed. S. Sherlock, Blackwell Scientific Publications, London, pp. 116-133, 1981.
15. Willkinson, S.P. and Williams, R. : Ascites, electrolyte disturbances and renal failure, In *Liver and Biliary Diseases*, ed. R. Wright, K.G. Alberti, S. Karren and G.H. Millward-Sadler, Saunders, London, pp. 1060-1086, 1979.
16. Kusakabe, A., Yoshioka, K., Kuwahara, Y., Kusugami, K., Kurokawa, S., Miwa, S., Oka, Y., Itoh, S., Uno, Y., Nishiyama, T. and Ichihara, M. : Clinical significance of cytology of ascitic fluid in diagnosis of hepatocellular carcinoma. *Saishin Igaku* **37**, 1586-1591, 1982 (in Japanese).
17. Miyake, S. : The mechanism of the release of hepatic enzymes in various liver diseases. 1. Alterations in cytoplasmic and mitochondrial enzyme activities in serum. *Acta Med. Okayama* **33**, 287-304, 1979.
18. Levy, M. : The kidney in liver disease, In *Sodium and Water Homeostasis*, ed. B.M. Brenner and J.H. Stein, Churchill Livingstone, New York, pp. 105-106, 1978.