

Relationship between Histopathology in Cirrhosis of the Liver with or without Hepatocellular Carcinoma and Esophageal Varix Formation

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Abstract: A clinicopathological study using autopsy materials to find out the correlation between histological findings of cirrhosis of the liver (LC) with or without hepatocellular carcinoma (HCC) and morphological evidences of portal hypertension such as esophageal varix formation and splenomegaly. In all 79 cases of LC (accompanied with or without HCC) and HCC (with no LC) out of 1,112 autopsy cases at the Department of Pathology, Institute of Tropical Medicine, Nagasaki University during the period 1967 to 1989 were reviewed. All patients were from Nagasaki City and its suburbs. Histologically, the LC cases were divided into three types; Nagayo's A-type (Nagayo, 1914) which showed wide fibrous septum, Nagayo's B-type which showed thin fibrous septum and macronodular pseudolobule, and micronodular type which showed micronodular pseudolobule with fatty metamorphosis and thin fibrous septum. Five out of six cases (83%) of A-type LC were complicated with esophageal varix and four out of the five cases (80%) showed rupture of varix. Five out of eight cases (63%) of B-type LC were complicated with esophageal varix and two out of the five cases (40%) showed rupture of varix. Two out of five cases (40%) of micronodular type LC were complicated with ruptured esophageal varices and the remaining three cases had no varix. All 16 cases (100%) of A-type LC accompanied with HCC were complicated with esophageal varices. Ten cases (63%) of them showed rupture of varix. On the other hand 23 out of all 31 cases (74%) of B-type LC accompanied with HCC showed esophageal varices. However, only eight (35%) of the varix cases showed rupture of varices. As for HCC without LC, five out of all 13 cases (38%) were complicated with esophageal varices showing no rupture. These findings suggest that advanced and thick fibrosis of the liver in the LC cases with architectural distortion of the intrahepatic portal veins and the disturbance of blood flows is one of the most important factors which play an etiological role of portal hypertension followed by esophageal varix formation and splenomegaly. More advanced splenomegaly (mean weight, 470 g) and esophageal varix formation may be caused by more severe portal hypertension in A-type LC which shows wide fibrous septa than other types of LC. HCC may play an etiological role of portal hypertension, especially in the cases of occurrence

of intrahepatic portal invasion of tumor tissue, but less remarkably than LC cases.

Key words: Cirrhosis of the liver, Hepatocellular carcinoma, Portal hypertension, Esophageal varix, Splenomegaly

INTRODUCTION

Liver diseases are the wide-spread diseases, especially in the tropics and temperate areas. Nagasaki, situated in south west of Japan and one of the prevalent areas of hepatitis B virus infection, has a higher incidence of liver diseases including cirrhosis of the liver (LC) and hepatocellular carcinoma (HCC) than other parts of Japan. Although prevalency of LC and HCC in Nagasaki area have been published (Matsukuma, 1967; Toda *et al.*, 1984), no established study on correlation between histopathology and clinical features of the diseases has been reported.

The aim of the present study was to find out the correlation between the types of LC with or without HCC and the morphological evidences of portal hypertension such as esophageal varix formation and splenomegaly using autopsy materials.

MATERIALS AND METHODS

There were 79 cases of liver diseases (LC accompanied with or without HCC, and only HCC with on LC) out of 1,112 autopsy cases at the Department of Pathology, Institute of Tropical Medicine, Nagasaki University during the period 1967 to 1989. All patients were from Nagasaki City and its suburbs. Among them, 19 cases were LC with no HCC, 47 cases were LC accompanied with HCC, and 13 cases were HCC without LC. Autopsy protocols were reviewed for age and sex of the patients, weight of the liver and spleen, macroscopical findings of the liver and metastatic behavior of HCC, and serological test for hepatitis B virus surface antigen (HBsAg). Histological examinations were performed using hematoxylin-and-eosin, Mallory's for collagen fibers, periodic acid Schiff, Van Gieson's for elastic and collagen fibers, silver impregnation for reticulin fibers and histochemical orcein for HBsAg staining methods.

RESULTS

LC:

Table 1 shows the age and sex of the patients of LC with no HCC, the types based on macroscopical and histological observations of LC, the incidence of esophageal varices, and the results of HBsAg serological test and/or staining methods. The high incidence of LC was found between the age of 50 and 59 (mean age; 51). The male to female ratio was 1.0: 0.2.

Histologically, six out of 19 cases (32%) of all LC with no HCC were A-type LC of "Nagayo's classification of cirrhosis of the liver" (Nagayo, 1914), which showed wide fibrous septum (Photo. 1), eight (42%) were Nagayo's B-type LC, which showed thin

fibrous septum and macronodular pseudolobules (Photo.2), and five (26%) were micronodular type of LC, which showed micronodular pseudolobules with fatty metamorphosis and thin fibrous septum (Photo. 3).

Table 1. Cirrhosis of the liver (LC) and esophageal varix formation

Type of cirrhosis	Mean Age (year old)	Sex	Esophageal varix		HBsAg(+)	
			absent	present(ruptured)		
A(n=6)	38 (1-69)	Male: 5 Female: 1	1 (17%)	5 (83%)	4 (80%)	2 (33%)
B(n=8)	58 (44-68)	Male: 5 Female: 3	3 (38%)	5 (63%)	2 (40%)	5 (62%)
M(n=5)	52 (43-62)	Male: 5 Female: 0	3 (60%)	2 (40%)	2 (100%)	0 (0%)
Total (n=19)	51 (1-69)	Male: 15 Female: 4	7 (37%)	12 (63%)	8 (67%)	7 (37%)

A: A-type LC, B: B-type LC, M: Micronodular type LC,
HBsAg(+): serologically and/or histologically positive.

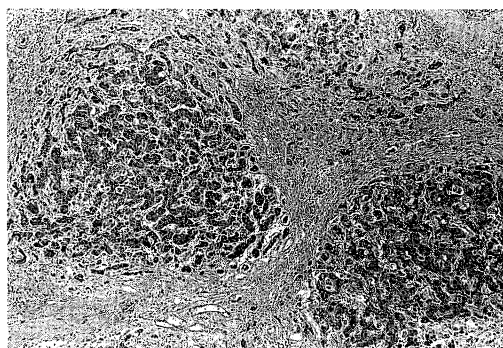


Photo. 1. A-type LC showing wide fibrous septum. (H.E. original mag., x40)

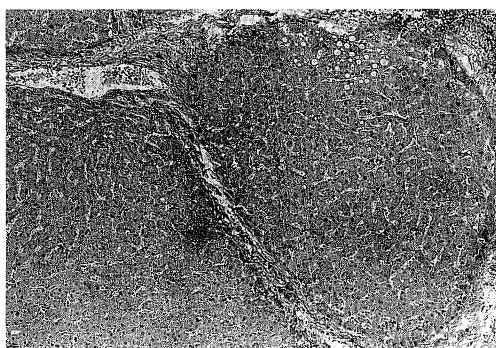


Photo. 2. B-type LC showing thin fibrous septum and macronodular pseudolobule. (H.E. original mag., x40)

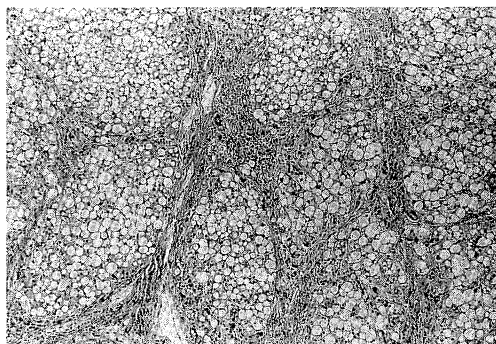


Photo. 3. Micronodular type LC showing micronodular pseudolobules with fatty metamorphosis and thin fibrous septum. (H.E. original mag., x40)

Five out of six cases (83%) of A-type LC were complicated with esophageal varix formation and four out of the five cases (80%) showed rupture of varix. Five out of eight cases (63%) of B-type LC were complicated with esophageal varices and two out of the five cases (40%) showed rupture of varix. Two out of five cases (40%) of micronodular type LC were complicated with esophageal varices followed by rupture and the remaining three cases had no varix.

The ratio of weight of the liver to spleen was 1.0: 0.32 (mean weight; liver, 1130g, spleen, 360g) in all LC without HCC cases. Among them, 1.0: 0.47 (mean weight; liver, 1,000g, spleen, 470g) in A-type LC, 1.0: 0.38 (mean weight; liver, 960g, spleen, 360g) in B-type LC, and 1.0: 0.15 (mean weight; liver, 1,550g, spleen, 230g) in micronodular type of LC.

Seven cases (37%) of all LC with no HCC showed positive HBsAg by serological test and/or orcein staining methods. Higher positivity of HBsAg was seen in B-type LC than A-type LC. No HBsAg positive case was observed in micronodular LC.

LC accompanied with HCC:

Table 2 indicates the age and sex of the patients, types of LC accompanied with HCC, the incidence of esophageal varices, macroscopical portal invasion and extrahepatic metastases of HCC nests, and the results of HBsAg serological test and/or staining methods.

The high incidence of LC accompanied with HCC appeared between the age of 50 and 59 (mean age; 57). The male to female ratio was 1.0: 0.3. As for histological type of all 47 cases of LC accompanied with HCC, 16 cases (34%) showed A-type and 31 (66%) cases showed B-type. No case of micronodular type was observed.

Macroscopically, 29 out of 47 cases (62%) of HCC within LC showed nodular pattern (Photo. 4), 12 (26%) showed massive pattern (Photo. 5), three (6%) showed diffuse pattern (Photo. 6), two (4%) showed nodular with massive pattern, and one (2%) showed diffuse with massive pattern of "Eggel's macroscopical classification of hepatocellular carcinoma" (Eggel, 1901). Histologically, 38 out of 47 cases (81%) of HCC within LC showed trabecular pattern of tumor cell arrangement (Photo. 7), four (9%) showed pseudoglandular

Table 2. Cirrhosis of the liver (LC) accompanied with hepatocellular carcinoma (HCC) and esophageal varix formation

Type of cirrhosis	Mean Age (year old)	Sex	Esophageal varix			MPI(+)	MEM(+)	MPI(+) + MEM(+)	HBsAg(+)
			absent	present	(ruptured)				
A(n=16)	48 (41-70)	Male:13 Female:3	0 (0%)	16 (100%)	10 (63%)	8 (50%)	6 (38%)	1 (6%)	6 (38%)
B(n=31)	58 (40-75)	Male:23 Female:8	8 (26%)	23 (74%)	8 (35%)	12 (39%)	20 (65%)	5 (16%)	10 (32%)
Total(n=47)	57 (40-75)	Male:36 Female:11	8 (17%)	39 (83%)	18 (46%)	20 (43%)	26 (55%)	6 (13%)	16 (34%)

A: A-type LC, B: B-type LC, MPI(+): macroscopical portal invasion, MEM(+): macroscopical extrahepatic metastasis, HBsAg(+): serologically and/or histologically positive.

pattern (Photo. 8), three (6%) showed trabecular with pseudoglandular pattern, one (2%) showed compact pattern (Photo. 9) and one (2%) showed compact with trabecular pattern. According to "Edmondson's classification on the histological degree of cellular atypism of hepatocellular carcinoma" (Edmondson and Steiner, 1954), 29 out of 47 cases (62%) of HCC within LC were grade II (Photo. 10), 11 (23%) were II to III, eight (17%) were III (Photo. 11).

Eight out of 16 cases (50%) of HCC within A-type LC showed macroscopical portal invasion and six (38%) showed macroscopical extrahepatic metastases of HCC tissue. Twelve out of 31 cases (39%) of HCC within B-type LC showed macroscopical portal invasion and 20 (65%) showed macroscopical extrahepatic metastases. Twenty out of all 47 cases (43%) of HCC within LC showed macroscopical portal invasion and 26 (55%) showed macroscopical extrahepatic metastases of HCC tissue.

All 16 cases (100%) of A-type LC accompanied with HCC were complicated with esophageal varices and 10 cases (63%) of them showed rupture of varix. On the other hand 23 out of all 31 cases (74%) of B-type LC accompanied with HCC showed esophageal varices. However, only eight of them (35%) of the varix cases showed rupture of varices.

The ratio of weight of the liver to spleen was 1.0: 0.17 (mean weight; liver, 1800g, spleen, 300g) in the total cases of LC accompanied with HCC, 1.0:0.14 (mean weight; liver,

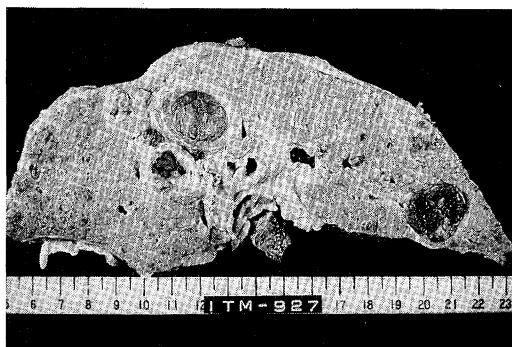


Photo. 4. Nodular type HCC.

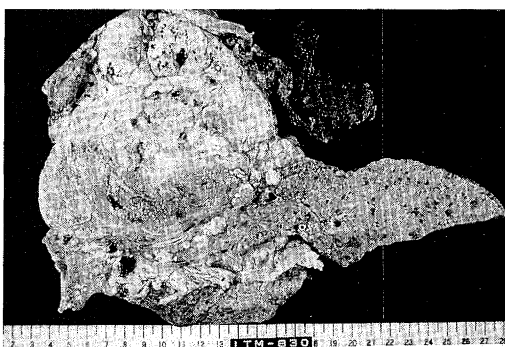


Photo. 5. Massive type HCC.

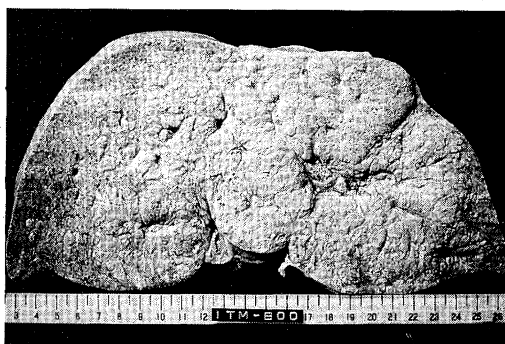


Photo. 6. Diffuse type HCC.

1700g, spleen, 240g) in cases of A-type LC with HCC, and 1.0: 0.18 (mean weight; liver, 1820g, spleen, 330g) in cases of B-type LC with HCC. About 35% of both A-type and B-type LC with HCC showed HBsAg positive.

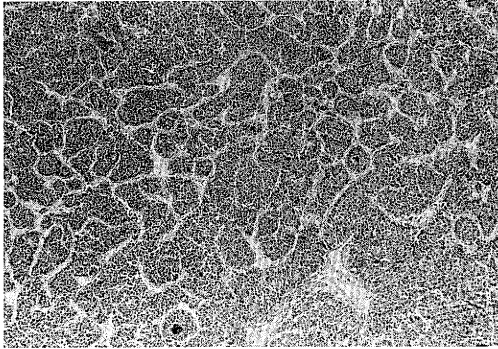


Photo. 7. Trabecular pattern of HCC.
(H.E. original mag., x40)

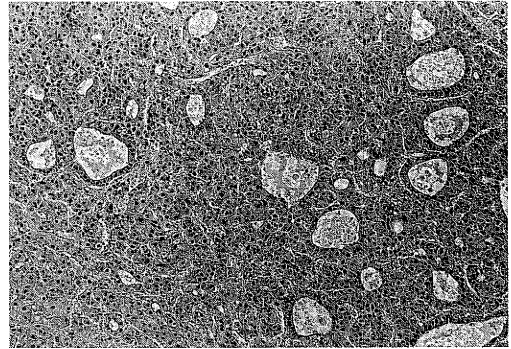


Photo. 8. Pseudoglandular pattern of HCC.
(H.E. original mag., x40)

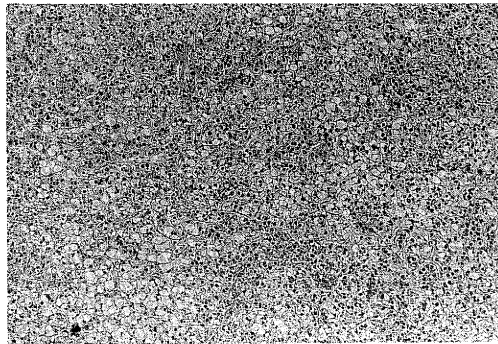


Photo. 9. Compact pattern of HCC.
(H.E. original mag., x40)

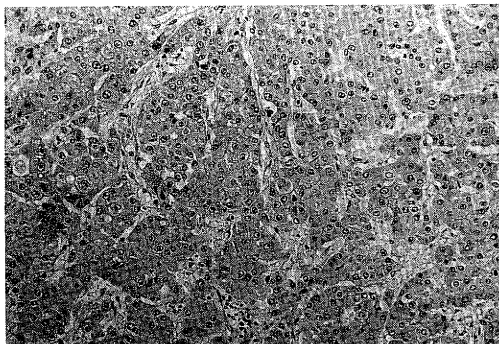


Photo. 10. Grade II, cellular atypism of HCC.
(H.E. original mag., x100)

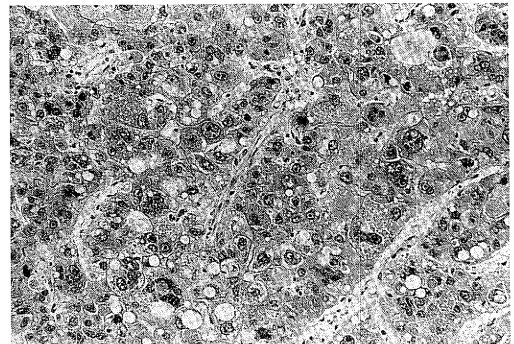


Photo. 11. Grade III, cellular atypism of HCC.
(H.E. original mag., x200)

HCC without LC:

Table 3 shows the age and sex of the patients, the incidence of esophageal varices, macroscopical portal invasion and extrahepatic metastases of HCC nests, and the results of HBsAg serological test and/or staining method. The high incidence of HCC was found between the age of 50 and 59 (mean age; 56). The male to female ratio was 1.0: 0.1.

Macroscopically, four out of 13 cases (31%) of all HCC cases showed nodular pattern, four (31%) showed massive pattern, three (23%) showed nodular with massive pattern, one (8%) showed nodular with diffuse pattern and one (8%) showed massive with diffuse pattern of Eggel's classification.

Histologically, nine out of 13 cases (69%) of HCC showed trabecular pattern, one showed trabecular with pseudoglandular pattern, one showed trabecular with compact pattern, and one showed only compact pattern. On the degree of histological cellular atypism of HCC of Edmondson's classification, four out of 13 cases (31%) of HCC were grade II, five (38%) were grade II to III, two (15%) were grade III.

The incidence of macroscopical portal invasion of HCC was 7 out of 13 cases (54%), and macroscopical extrahepatic metastases was 6 out of 13 cases (46%). Five out of all 13 cases (38%) of HCC without LC were complicated with esophageal varices showing no rupture.

The ratio of weight of the liver to spleen was 1.0: 0.07 (mean weight; liver, 2600g, spleen, 170g). Three cases (23%) were positive for HBsAg with serological test and/or staining methods.

Table 3. Hepatocellular carcinoma (HCC) and esophageal varix formation

	Mean Age (year old)	Sex	Esophageal varix			MPI(+)	MEM(+)	MPI(+) + MEM(+)	HBsAg(+)
			absent	present(ruptured)					
Total (n=13)	56 (41-80)	Male:12 Female:1	8 (62%)	5 (38%)	0 (0%)	7 (54%)	6 (46%)	1 (8%)	3 (23%)

MPI(+): macroscopical portal invasion, MEM(+): macroscopical extrahepatic metastasis, HBsAg(+): serologically and/or histologically positive.

DISCUSSION

There have been few, if any reports of comparative study between the pathological findings of the liver and the clinical features of portal hypertension in the cases of cirrhosis of the liver. In our study we attempted to get any correlations in the cases of liver diseases (LC with no HCC, LC accompanied with HCC, and HCC without LC) between the histological findings; such as liver fibrosis, parenchymal regenerative nodules and tumor growth within the liver and the clinical evidences of portal hypertension; such as esophageal varix formation and splenomegaly (Okuda *et al.*, 1977; Nakashima *et al.*, 1983; Okuda *et al.*, 1984; Nakashima *et al.*, 1984; Jimi, 1984).

A-type LC showed a higher incidence of esophageal varix formation and its rupture than B-type LC or micronodular type LC. A-type LC showed more marked splenomegaly

than others. Two cases of micronodular type LC which caused rupture of esophageal varices showed similar histological findings to A-type LC; wide fibrous septa and micronodular pseudolobules. These cases were negative for HBsAg and could have been complicated with non-A non-B hepatitis virus (hepatitis C virus) infection. Other three cases of micronodular type LC were typical alcoholic LC, histologically showing fatty metamorphosis, Mallory's hyaline bodies, liver cell ballooning, thin and irregular fibrosis, and indistinct margin between pseudolobules and fibrous septa. These cases had no esophageal varices and non-remarkable splenomegaly. A-type LC accompanied with HCC showed a high tendency of esophageal varix formation and its rupture. The degree of varix formation was similar to A-type LC without HCC cases.

Tumor tissues in the cases of HCC accompanied with A-type LC showed a high tendency of macroscopical portal invasion. As for HCC accompanied with B-type LC, tumor nests showed a high tendency of macroscopical extrahepatic metastases than the case of HCC with A-type LC. Generally, remote metastases of HCC should be hematogenous (Nakashima *et al.*, 1982; Kojiro *et al.*, 1984). Therefore, the altered blood channels in A-type LC could be architecturally different from B-type LC. According to macroscopical classification of HCC, over half of the HCC cases accompanied with LC were nodular type, followed by massive and diffuse type. Although we noticed that nodular and diffuse type of HCC had a high tendency of macroscopical portal invasion, and massive type had a high tendency of macroscopical extrahepatic metastases, we could not explain the reason for the difference between them (Nakashima *et al.*, 1982; Jimi, 1982; Nakashima *et al.*, 1984).

All HCC cases without LC showed more marked hepatomegaly than LC cases accompanied with or without HCC, because of more easier tumor growing in the liver. Although more than half of the HCC cases without LC showed a slight esophageal varix formation, no rupture case was found. The fact might be due to less disturbance of portal blood flow within the liver with rather slight liver fibrosis and non-remarkable architectural distortion of the intrahepatic portal veins (Nakashima *et al.*, 1984). In massive type HCC without LC, a high tendency of macroscopical portal invasion and extrahepatic metastases was noted. Also in massive type of HCC cases, tumor nodules were not surrounded by fibrous septa contrary to nodular type of HCC. Therefore, such type of HCC might have a high tendency of intravascular invasion with remote metastases. The relation between HBsAg positivity and portal hypertension in LC cases was not clear in this study.

These findings suggest that advanced and thick fibrosis of the liver in the LC cases with architectural distortion of the intrahepatic portal veins and the disturbance of blood flows is one of the most important factors which play an etiological role of portal hypertension followed by esophageal varix formation and splenomegaly. More advanced splenomegaly (mean weight, 470g) and esophageal varix formation may be caused by more severe portal hypertension in A-type LC which shows wide fibrous septa than other types of LC. HCC with or without LC may play an etiological role of portal hypertension, especially in the cases of occurrence of intrahepatic portal invasion of tumor tissue, but less remarkable than LC cases.

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