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Hepatocellular carcinoma in adenomatous hyperplasia of the liver

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Summary. A hepatocellular carcinoma (HCC) measuring 0.2 cm in diameter was found in the center of an adenomatous hyperplasia (AH) measuring 1.7 cm in diameter in a cirrhotic liver. The liver cells of the AH showed a marked fatty change and contained many Mallory bodies. The AH and HCC were studied in relation to liver cell dysplasia in 108 surgically resected livers. The AH was mainly associated with fully developed cirrhosis in 5 (71%) of the 7 cases. The liver cell dysplasia, however was accompanied largely by fibrosis and early-stage incomplete septal cirrhosis in 10 (67%) of the 15 cases. As far as the active inflammatory change was concerned, a fairly active inflammation was found in only 3 (20%) of the 15 livers with liver cell dysplasia, but in 4 (57%) of the 7 livers with AH.

Introduction

Hepatocellular carcinoma (HCC) in situ and its precancerous condition in the course of hepatocarcinogenesis have not yet been established. Liver cell dysplasia, described by Anthony et al. [1] is important as a possible premalignant lesion [8]. Furthermore, a large regenerative nodule, adenomatous hyperplasia described by Edmondson [3], has become worthy of note as a possible precancerous or borderline lesion in recent years. Operations on small liver cancer, less than 2 cm in diameter, are increasing because of the remarkable advances in imaging modalities. It has therefore become a problem to distinguish between adenomatous hyperplasia and early-stage HCC. Since a microscopic HCC in adenomatous hyperplasia can be found as "nodules in nodule" [2, 5, 7, 9], adenomatous hyperplasia (AH) seems to have a closer lesion to HCC than liver cell dysplasia (LCD).

The relationships between LCD, AH, and HCC have been studied on the basis of livers surgically resected for HCC at our institute and affiliated hospitals.

Materials and methods

One-hundred and eight liver resections in 106 cases with HCC, performed from December 1969 to July 1987 at Osaka University Hospital, were studied. Of the livers resected from December 1969 to September 1980, 16 were not treated by transcatheter chemoembolization before surgery. The remaining 92 livers, resected from October 1980 to July 1987, underwent transcatheter chemoembolization before surgery. Two of the 106 cases underwent a liver resection twice, the intervals between the two operations being 7 years 7 months and 4 years 4 months. One was on a 50-year-old man and the other on a 59-year-old woman (ages at the time of initial surgery). The former operation revealed LCD in both resections but the latter did not.

Serum HBsAg and a history of alcoholism correlated with liver cell dysplasia and adenomatous hyperplasia of the liver. In 103 of the 108 cases, both the serum HBsAg and HBsAb were known. They were correlated with LCD and AH as shown in Table 1. The serum HBsAg was positive in 21 (20.4%) of the 103 cases at the time of surgery. LCD was found in 5 (23.8%) of the 21 HBsAg-positive cases and in 10 (12.2%) of the 82 HBsAg-negative cases. On the other hand, alcoholics occurred more frequently in the HBsAg-negative group than in the positive group: 8 (38.1%) in the HBsAg-positive group of 21, and 38 (46.3%) in the HBsAg-negative group of 82.

Recurrence of HCC in livers with LCD. On the 15 HCCs with LCD, 3 showed no cirrhosis, 7 were accompanied by early-stage incomplete septal cirrhosis (B'type cirrhosis), and 5 were associated with fully developed cirrhosis (A and B type), as shown in Table 2. Two of the three non-cirrhotics and three of the twelve cirrhotics were HBsAg-positive. As far as the active inflammatory change was concerned, only 3 of the 15 were fairly active; 12 of the 15 were inactive or only mildly active. The prognosis of the

Table 1. Serum HBsAg and alcoholic history correlated with liver cell dysplasia (LCD) and adenomatous hyperplasia (AH) of liver

Presence or absence of HBsAg	No. of cases	LCD	AH	Alcohol over 3 Go/day[a]
+	21	5 (23.8%)	0	8 (38.1%)
−	82	10 (12.2%)	7	38 (46.3%)
Total	103	15 (14.6%)	7	46 (44.7%)

[a] 1 Go = 180 ml

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Table 2. Recurrence of hepatocellular carcinoma and prognosis of cases with liver cell dysplasia

Case no.	Age, sex	Diameter of HCC (cm)	Cirrhosis[b]	HBs-Ag, Ab	α-Fetoprotein (ng/ml)	Alcohol/day (years)	Prognosis[c] (July 1987)
1	48, M	4.0	A −	+, −	26000	1 Sho[d]	10y6m ASD
2[a]	52, M	6.0	−	+, −	20	1 bottle of beer	7y11m DWD
3	46, M	12.0	B'+	+, −	−	/[e]	7m DWD
4	63, M	3.5	B'+	−, −	8	5 Go	4y DSD
5	68, F	5.2	B +	−, /	24000 −1625	−	2y11m DWD
6	53, M	11.5	B'+	−, /	>1000	/	9.5m DWD
7	49, M	2.3	B'+	−, /	/	6 Go (30)	5y ASD
8	67, F	1.0	B++	−, −	<5	−	3y5m ASD
9	72, M	1.6	B'+	−, −	<5	2 glasses whiskey 1 Go (30)	3y2m AWD
10	63, M	1.3	−	+, −	<5	4 Go (45)	1y2m ASD
11[a]	58, M	4.8	B'−	−, −	826	1 bottle of beer	4m DWD
12	50, M	1.6 AH (1.0)	−	−, −	230	3 Go (20)	36 days DSD
13	53, M	2.0	B++	−, +	10.5	1 bottle of beer	
14	60, M	4.2	B'+	+, −	11	5 Go (20)	4m ASD
15	53, M	2.0	B++	−, −	113	3 Go	4m ASD

[a] Cases no. 2 and 11 are the same patient
[b] Classification of cirrhosis by Nagayo-Miyake [4]: −, inactive; +, mildly active; ++, moderately active; +++, markedly active for inflammation
[c] ASD, alive without disease; AWD, alive with disease; DSD, dead without disease; DWD, dead with disease; y, year; m, month
[d] Sho = 10 Go = 1.800 ml [e] not determined

cases with LCD was fairly good, showing that 6 of the 15 lived for 3–10 years.

Adenomatous hyperplasia and alcohol. Adenomatous hyperplasia was found in 7 (6.8%) of the 103 resected livers. It was found in 6 (9.0%) of the 67 cirrhotics with HCC and in 1 (2.8%) of the 36 non-cirrhotics with HCC. All of the seven cases with AH were HBsAg-negative. LCD was present in only one of the seven cases of AH (case 12 in Table 2, which is the same as case 7 in Table 3). Six of the seven were accompanied by cirrhosis, of which five had fully developed cirrhosis (A and/or B type) and only one had incomplete septal (B' type) cirrhosis. One of the seven showed no signs of cirrhosis, which was the only case associated with LCD. A fairly active inflammatory change was found in four of the seven cases, with mild inflammation in three. A history of alcoholism in seven cases showed that six cases were more than 3 Go per day (1 Go = 180 ml) of whom four were over 5-Go drinkers. Their prognosis was rather poor, and three of them died between 36 days and 7 months following surgery. Two deaths were from liver failure and one from an HCC recurrence. HCC was proved in five of the AH cases. Two AH patients were on the borderline of being well-differentiated Edmondson's grade I HCC (cases 3 and 5 in Table 3). The other two AH patients showed a marked fatty change and many Mallory bodies (cases 2 and 6 in Table 3). Case 2 in Table 3 is the case of HCC in AH as nodule in nodule. The HCC

Table 3. Adenomatous hyperplasia (AH), hepatocellular carcinoma (HCC) and alcohol consumption

Case no.	Age, sex	Diameter of HCC (cm)	Diameter of AH (cm)	Cirrhosis	HBs-Ag, Ab	α-Fetoprotein (ng/ml)	Alcohol/day (years)	Prognosis[c] (July 1987)
1	46, M	−	1.4	B++	−, −	1270	5 Go (10)	2y5m ASD
2	57, F	0.2	1.7[a]	B+	−, +	2969	heavy drinker	1m DSD
3	63, M	7.6	0.7[b]	B+	−, −	16413	5 Go	6m DWD
4	49, M	0.9	0.8	B'++	−, −	554	3 Go (25)	1y1m ASD
5	54, M	/	2.7[b]	B++	−, −	<5	5 Go (30)	1y1m ASD
6	50, M	3.1	1.5[a] 1.0[a]	BA'+++	−, −	112	social	1y1m ASD
7	50, M	1.6	1.0[b]	−	−, −	230	3 Go (20)	36 days DSD

[a] Fatty change and Mallory bodies
[b] Borderline lesion
[c] Abbreviations as in Table 2

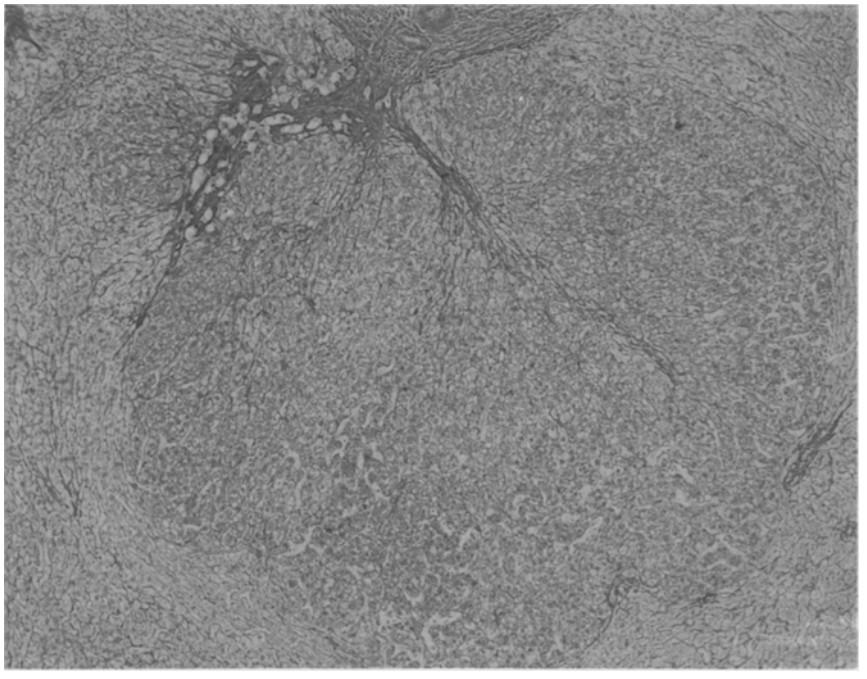

Fig. 1. A well-demarcated hepatocellular carcinoma is found in the center of the adenomatous hyperplasia. Silver impregnation. ×50

measured 0.2 cm in diameter, showing acinar and a thin trabecular pattern. It belonged to Edmondson's grade II and was located in the center of the AH (Figs. 1 and 2). The AH measured 1.7 cm in diameter, and was located subcapsularly. It showed a diffused markedly fatty change and numerous Mallory bodies (Fig. 3). The liver cells showed marked atypism. It was thought to be another incidental HCC during surgery, because preoperative angiography, the ultrasound echoes, and computed tomography scanning were all negative for AH. The remaining cirrhotic liver also showed a fatty change, since the patient was a heavy drinker, but not Mallory bodies were found.

Discussion

Liver cell dysplasia and adenomatous hyperplasia are thought to be paraplastic lesions. It is not certain whether they are premalignant or not. LCD is defined on a histological basis by Anthony et al. [1] and AH is defined grossly by Edmondson [3]. Peters used the words, adenomatous regeneration [6], as the histological counterpart of AH.

Patients with LCD and AH seem to have a different clinical history. LCD is more probably related to HBsAg and early-stage incomplete septal cirrhosis, as well as to the inactive inflammation of the liver. AH, on the other

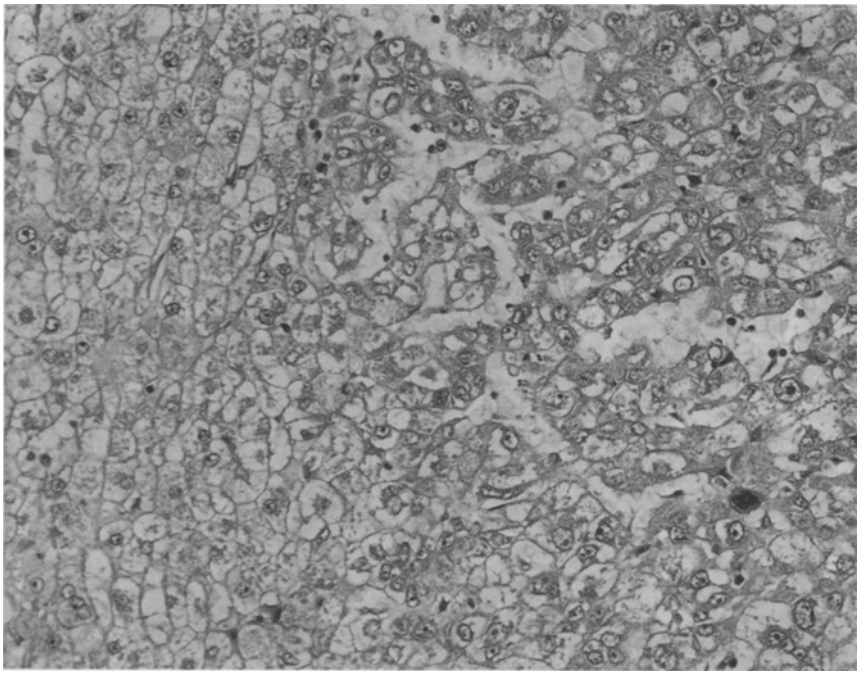

Fig. 2. The expansive growth of the hepatocellular carcinoma on the right and the adenomatous hyperplasia on the left of the picture. Hematoxylin/Eosin ×250

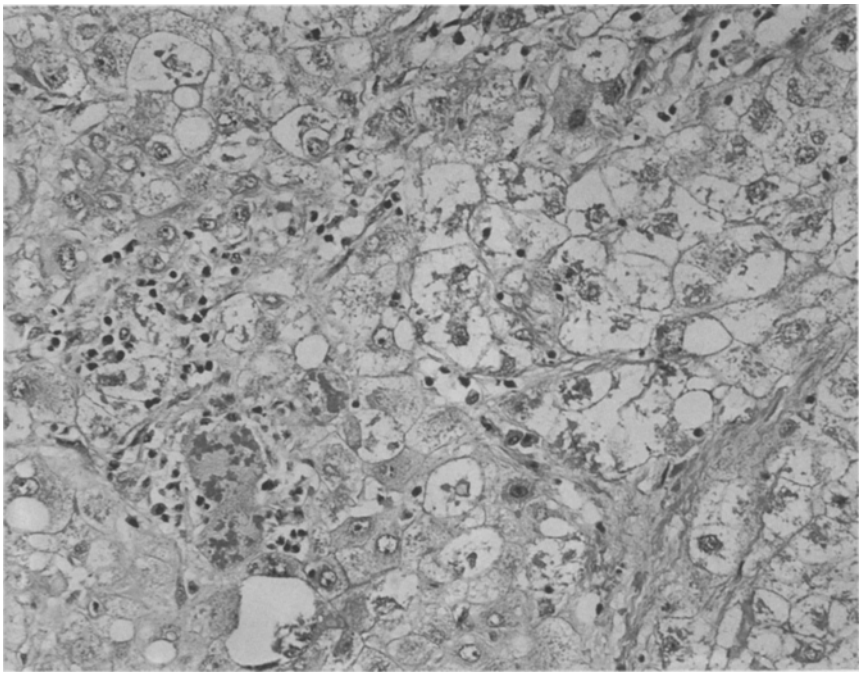

Fig. 3. The adenomatous hyperplasia shows a fatty change, ballooning, Mallory bodies, and polymorphonuclear leukocytic infiltration. Hematoxylin/Eosin ×250

hand, relates more to a history of heavy alcoholism and fully developed cirrhosis, as well as to the fairly active inflammatory change of the liver. As far as the prognosis is concerned, it is fairly good in the case of LCD but rather poor in AH.

The fatty change and the Mallory bodies in AH seem to offer an unique way of finding a premalignant condition and appear to be related to alcohol. LCD and AH seem to develop under a different mechanism, but both indicate a high risk of HCC.

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