Clinical Significance of Liver Cell Dysplasia in Chronic Liver Diseases

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ABSTRACT

In an attempt to determine the clinical significance of liver cell dysplasia (LCD) arising in the course of chronic liver diseases, studies were made on the incidence of LCD among various liver diseases, on persistence of LCD in chronic hepatitis and liver cirrhosis, and on the prognosis of LCD-positive patients with chronic hepatitis or liver cirrhosis. The incidence of LCD was significantly higher in liver cirrhosis with hepatocellular carcinoma than in normal liver, chronic hepatitis, liver cirrhosis or metastatic liver cancer. LCD persisted for years in some cases of chronic hepatitis and liver cirrhosis while in others it disappeared in a relatively short period of time. In patients who subsequently developed hepatocellular carcinoma, however, LCD never disappeared throughout the follow-up period. The incidence of hepatocellular carcinoma developing over a period of 5 years was significantly higher in LCD-positive than in LCD-negative patients. These observations suggest that a close relationship exists between LCD and development of hepatocellular carcinoma and that LCD may serve as a morphological indicator of the premalignant condition for hepatocellular carcinoma.

Key Words: *liver cirrhosis*; *liver cell dysplasia*; *premalignant lesion*; *hepatocellular carcinoma*

Frequent association of hepatocellular carcinoma with liver cirrhosis has led to the general belief that liver cirrhosis is a premalignant status for hepatocellular carcinoma[1-4]. However, what specific morphological features of liver cells represent a premalignant lesion has not yet been demonstrated.

In 1973, Anthony et al.[5] suggested that liver cell dysplasia (LCD) represents a precursor state for hepatocellular carcinoma because of the

frequent occurrence of LCD in cirrhotic livers complicated by hepatocellular carcinoma.

This study was designed to determine the clinical significance of LCD developing in the course of chronic liver diseases by investigating the incidence of LCD in the liver of patients with various liver diseases, its persistence in chronic hepatitis and liver cirrhosis and prognosis of LCD-positive patients with chronic hepatitis or liver cirrhosis.

MATERIALS AND METHODS

Specimens obtained by needle biopsy or at autopsy from 162 cases of chronic persistent hepatitis, 183 cases of chronic active hepatitis, 143 cases of liver cirrhosis, 61 cases of hepatocellular carcinoma with liver cirrhosis, 15 cases of hepatocellular carcinoma without liver cirrhosis, 31 cases of metastatic liver cancer without chronic liver diseases and 16 cases of normal liver were used for the examination of the incidence of LCD. For biopsy, Vim-Silverman needle was used, and specimens not smaller than 1.5 cm in length were subjected to investigation. At least five lobules or an equivalent area was studied microscopically in H & E-stained sections. LCD was defined according to the criteria of Anthony

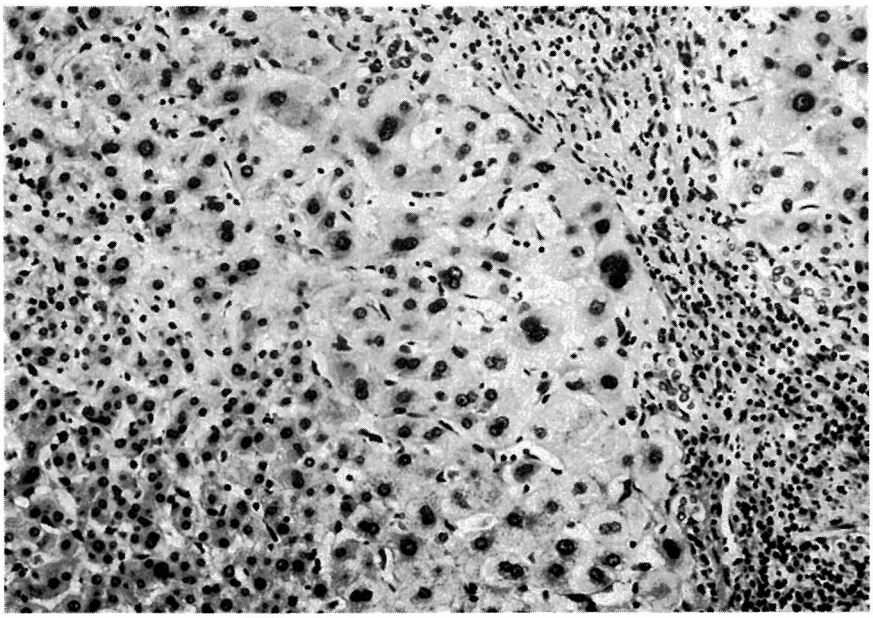

Fig. 1. Liver cell dysplasia showing nuclear and cytoplasmic enlargement, gross nuclear pleomorphysm with hyperchromasia, and multinucleation. Hematoxylin and eosin stain. ×370.

et al.[5], namely cellular enlargement, nuclear pleomorphism, and multinucleation of liver cells (Fig. 1). It was graded as follows: (1+)-several single dysplastic cells in a lobule, (2+)-at least 20 dysplastic cells in cluster in a lobule, (3+)-numerous dysplastic cells in whole lobule. A study was made on the persistence of LCD in 38 cases of chronic active hepatitis or liver cirrhosis in which histologic examinations could be made twice or more. A follow-up study was also made over a period of 5 years in 24 LCD-positive and 46 LCD-negative cases of chronic hepatitis or liver cirrhosis to compare the incidence of hepatocellular carcinoma developing during the follow-up period in these 2 groups.

RESULTS

· Prevalence of LCD

Table 1. Frequency of liver cell dysplasia in chronic liver diseases and liver cancer

Disease	No.	Dysplasia				%
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Chronic persistent hepatitis	162	2	0	0	2	1.2
Chronic active hepatitis	183	21	7	3	31	16.9
Liver cirrhosis	143(16)	16	11	9	36(6)	25.1(37.5)
Hepatocellular carcinoma with cirrhosis	61(31)	19	14	12	45(23)	73.7(74.1)
Hepatocellular carcinoma without cirrhosis	15(5)	7	1	2	10(2)	66.6
Metastatic liver cancer without chr. liver diseases	31(12)	2	0	0	2	6.4
Normal liver*	16(7)	0	0	0	0	0.0

*Includes disease of other organs.
( ) Autopsy material
Liver cell dysplasia is graded on a 1+ (several in a lobule) to 3+ (numerous in whole lobule) scale.

The incidence of LCD in the liver of the patients with various liver diseases is shown in Table 1. LCD was present in 2 (1.2%) of 162 cases of chronic persistent hepatitis, in 31 (16.9%) of 183 cases of chronic active hepatitis, in 36 (25.1%) of 143 cases of liver cirrhosis, in 45 (73.7%) of 61 cases of hepatocellular carcinoma with liver cirrhosis, in 10 (66.6%) of 15 cases of hepatocellular carcinoma without liver cirrhosis and in 2 (6.4%) of 31 cases of metastatic liver cancer, whereas it was observed in none of the cases with normal liver. LCD found in cases of chronic persistent hepatitis, chronic active hepatitis, hepatocellular

carcinoma without liver cirrhosis or metastatic liver cancer was often of grade 1. Grade 2 or 3 LCD was more frequent in cases of liver cirrhosis or hepatocellular carcinoma with liver cirrhosis. A significant difference was observed in the incidence of LCD between the cases of hepatocellular carcinoma with liver cirrhosis and those of chronic active hepatitis, liver cirrhosis or metastatic liver cancer ($P>0.01$).

Follow-up study

A study was made on the persistence of LCD in 15 cases of chronic active hepatitis and in 23 cases of liver cirrhosis in which LCD was

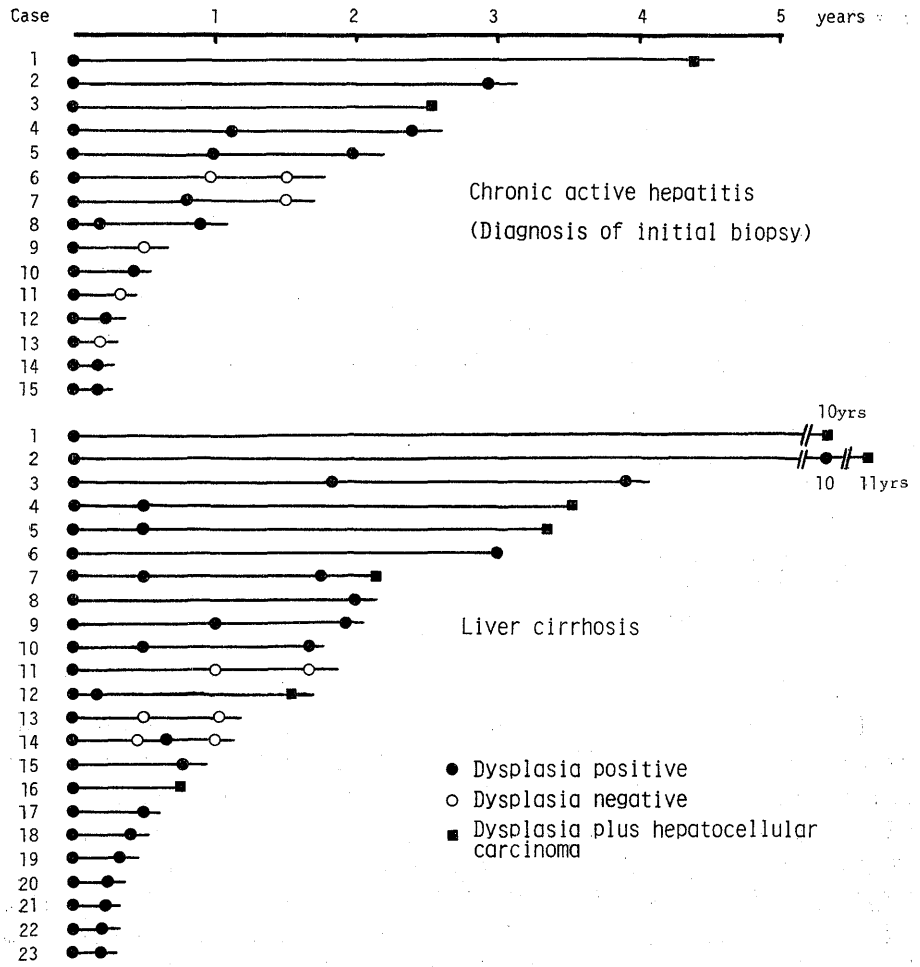

Fig. 2. Follow-up examinations of liver cell dysplasia

positive in the initial liver biopsy (Fig. 2). LCD became negative in the course of the disease in 5 of 15 cases of chronic active hepatitis and in 3 of 23 cases of liver cirrhosis. In 9 of these 38 cases hepatocellular carcinoma was detected during a period between 9 months and 11 years of observation. In these cases LCD was always positive, either remaining unaltered or becoming more marked.

Incidence of hepatocellular carcinoma in patients with LCD

A comparison was made of the incidence of hepatocellular carcinoma arising during the 5-year study period between LCD-positive and LCD-negative patients with chronic active hepatitis or liver cirrhosis (Fig. 3). During this period hepatocellular carcinoma became detectable in 7 of 24 LCD-positive cases and in 3 of 46 LCD-negative cases, with a significant difference between the two groups in the incidence at 3, 4 and 5 years. Two of the 3 patients in the LCD-negative group became LCD-positive in the course of observation.

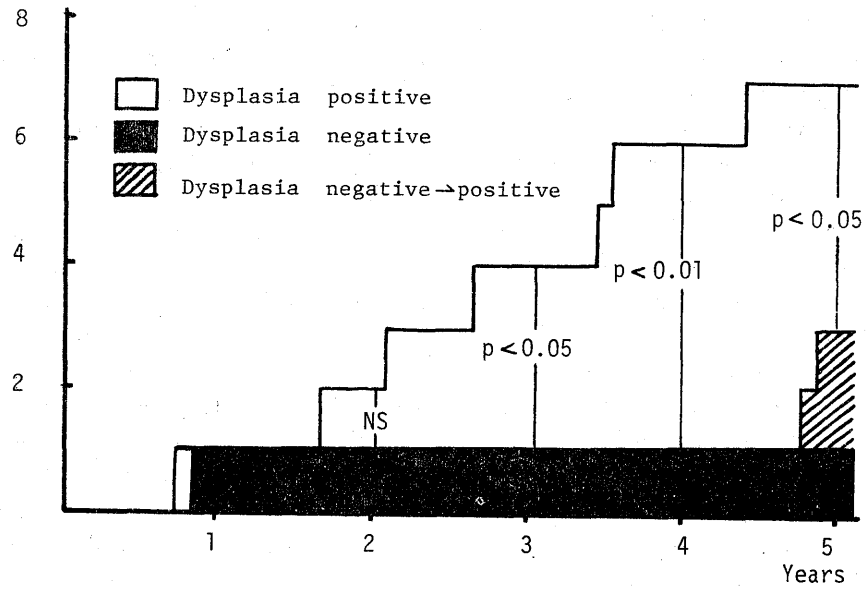

Fig. 3. Frequency of hepatocellular carcinoma in 24 dysplasia positive and 46 negative patients with chronic liver diseases.

DISCUSSION

Our results as to the incidence of LCD in patients with various liver diseases were much the same as those reported by Anthony et al.[5] LCD

occurred significantly more frequently in liver cirrhosis eventually complicated by hepatocellular carcimona than in chronic hepatitis, liver cirrhosis or metastatic liver cancer. Furthermore, LCD found in liver cirrhosis complicated by hepatocellular carcinoma was often of high grades. A histological follow-up of LCD was also made in patients to determine whether this condition was transient or persistent, and it was found that the condition disappeared in a relatively short period of time in some cases while it persisted long in others. Of great interest is the fact that LCD never became negative throughout the follow-up period in patients who subsequently developed hepatocellular carcinoma, and that the incidence of hepatocellular carcinoma over a period of 5 years was significantly higher in LCD-positive than in LCD-negative patients with chronic hepatitis or liver cirrhosis.

These results suggest that there exists a close relationship between LCD and development of hepatocellular carcinoma and that LCD could serve as a morphological indicator for hepatocellular carcinoma. However, it is uncertain whether or not normal liver cells transform into cancer cells via LCD, in other words, dysplastic cells are truly premalignant. It is sometimes difficult to distinguish LCD from 'morpholigically well-differentiated hepatocellular carcinoma[6]. Anthony et al.[5] made a distinction between LCD and hepatocellular carcinoma based on the following: 1) in LCD, there is cytoplasmic as well as nuclear enlargement with the nuclear/cytoplasmic ratio remaining within normal limits, 2) cytoplasmic staining or granularity is normal in LCD whereas cytoplasmic basophilia is present in hepatocellular carcinoma, and 3) the reticulin pattern is normal in LCD whereas reticulin is either deficient or completely lost in hepatocellular carcinoma. Steiner and Davis[7] also stated that liver cell atypia is different from liver cell carcinoma and that no relationship exists between them. However, the possibility that dysplastic cells have undergone a qualitative change (dedifferentiation) at the molecular biologic level cannot be completely ruled out, in consideration of close relationship between the presence of LCD and positive serum alpha-fetoprotein[8,9] or HB_sAg[5] as well as the localization of alpha-fetoprotein[9] or HB_sAg in dysplastic cells in some instances.

It has been suggested that the hyperplastic liver nodule induced by a chemical carcinogen, such as N-2-fluorenylacetamide or ethionine in rats, is a population of hepatocytes from which hepatocellular carcinomas derive[10)-13)]. In addition, it is known that the nodules which occur early during carcinogenesis regress after withdrawal of the carcinogen but those which occur later during carcinogenesis persist long after the discontinuation of the carcinogen and are associated with a high incide-

nce of hepatocellular carcinoma[13,14]. It is unclear at the moment what relationship exists between the nodular hyperplasia in an experimental model and LCD in man. However, if there were two kinds of dysplastic cells, reversible and irreversible, it would be reasonable and would well have importance to our understanding of clinical significance of LCD in chronic liver diseases to clarify morphological, biochemical and biological differences between them.

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