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Fatty macroregenerative nodule in non-steatotic liver cirrhosis

A morphologic study

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Summary. We here describe the morphologies of 9 macroregenerative nodules (MRNs) showing moderate to marked fatty change (fatty MRN) from 6 cases of non- or minimally-steatotic cirrhotic livers. In most of these cases, no obvious steatogenic factors of the liver were obtainable. These fatty MRNs showed more or less a sharp border. Seven of these fatty MRNs showed a variable degree of unusual morphological alterations suggestive of neoplasia: atypical and hyperchromatic nuclei, abnormal blood vessels, foci of clustering Mallory bodies, numerous hyaline globules, α-fetoprotein-positive hepatocytes, resistance to iron accumulation, infiltration into the portal tracts within MRN, and occurrence of hepatocellular carcinoma without fatty change. These observations suggest that at least some of the fatty MRNs are neoplastic or belong to a borderline lesion, and that the fatty change in the MRNs may be one of hepatocellular expressions related to human hepatocarcinogenesis.

Key words: Fatty change of the liver – Macroregenerative nodule of the liver – Borderline lesion – Hepatocellular carcinoma

Introduction

Fatty change of the liver is generally recognized as a diffuse process involving the entire organ, although it may be accentuated in central or peripheral portions of the hepatic lobules depending on its etiology. Localized fatty change in otherwise normal livers is a rare phenomenon (Simon 1934; Young 1951; Ramchand et al. 1970; Shojania and Hogg 1975; Brawer et al. 1980).

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Recently, hepatocellular nodules appreciably larger than the surrounding regenerative nodules in liver cirrhosis have been suspected to be a putative precancerous lesion in human hepatocarcinogenesis, because emergence of malignant foci have been reported within such nodules (Arakawa et al. 1986; Ohta and Nakanuma 1987; Furuya et al. 1988; Tsuda et al. 1988). Such hepatocellular nodular lesions in liver cirrhosis have been variously called such as adenomatous hyperplastic nodule (Arakawa et al. 1986), adenomatous hyperplasia (Sasaki 1980; Tsuda et al. 1988), adenomatoid hyperplasia (Ohta and Nakanuma 1987), hepatocellular pseudotumor (Nagause et al. 1984) and macroregenerative nodule (MRN) (Furuya et al. 1988).

We have recently observed an autopsy case of liver cirrhosis containing a MRN. It was of interest that the majority of hepatocytes of this MRN showed marked fatty change whereas other regenerative nodules showed no or minimum steatosis. This experience prompted us to survey fatty change in MRNs, and the pathologic significance of MRN showing moderate to marked fatty change (fatty MRN) was evaluated in this study.

Materials and Methods

MRNs were defined as hepatocellular nodules in cirrhosis appreciably larger than and different in color and texture from the surrounding regenerative nodules. The smallest diameter of MRNs was defined as 0.8 cm or more. "Fatty MRNs" were defined as the MRNs which occur in non- or minimally-steatotic cirrhotic livers as well as those in which more than 50% of hepatocytes showed fatty change. MRNs were surveyed from surgical and autopsy livers of our Laboratory and affiliated hospitals during the period between 1972 and 1988, and a total of 9 MRNs from 6 cirrhotic livers (2 surgically resected cases and 4 autopsy cases) were found to belong to the fatty MRNs.

Liver tissue specimens containing MRNs were fixed in 10% formalin and embedded in paraffin. Five μm sections were stained with hematoxylin and eosin, Gomori's silver impregna-

Table 1. Clinical summary of 6 cases with fatty macroregenerative nodules

Case no.	Age	Sex	Source	Clinical diagnosis	Liver steatogenic factor	Suspected etiology of cirrhosis
1	71	F	Autopsy	LC+HCC	None	Positive HBsAg
2	69	F	Surgery	LC+HCC	None	Unknown
3	59	M	Surgery	LC+HCC	None	Alcohol
4	65	M	Autopsy	LC	None	Unknown
5	57	M	Autopsy	LC	Diabetes Mellitus	Alcohol
6	56	F	Autopsy	LC+Diabetes Mellitus	Diabetes Mellitus	Unknown

Abbreviations: LC, liver cirrhosis; HCC, hepatocellular carcinoma

Table 2. Pathological findings of fatty macroregenerative nodules

Case no.	Size of MRN (cm)	Steatosis of MRN	Steatosis of liver	Background lesions	Mallory bodies in MRN	Globular hyaline in MRN	Abnormal vessels in MRN	AFP in MRN	Iron resistance in MRN
1	1.0×1.0	marked	minimal	LC+HCC	absent	numerous	present	positive	present
2	2.0×1.3	moderate	none	LC	present	absent	present	negative	u.k.
3	1.0×1.0	marked	none	LC+HCC	absent	absent	absent	negative	u.k.
4	2.5×1.5	marked	none	LC+HCC	present	absent	present	negative	u.k.
	1.8×1.6	moderate			absent	absent	present	negative	u.k.
	1.1×1.0	marked			present	absent	absent	negative	u.k.
5	2.0×1.8	moderate	none	LC+HCC	absent	absent	present	negative	u.k.
6	1.8×1.4	marked	minimal	LC	absent	absent	absent	negative	u.k.
	1.0×1.0	marked			absent	absent	absent	negative	u.k.

Abbreviations: MRN, macroregenerative nodule; AFP, alpha-fetoprotein; LC, liver cirrhosis; HCC, hepatocellular carcinoma; u.k., unknown because background liver was not siderotic; "marked", almost all hepatocytes of macroregenerative nodule show fatty change; "severe", more than 80% of hepatocytes show fatty change, and "moderate" that 50–80% of hepatocytes show fatty change

tion, Mallory-Azan, elastica van Gieson, Perls' iron as well as an immunostain for α-fetoprotein using the avidin-biotin-peroxidase method as described by Hsu et al. (1981).

Results

The main clinical data of the 6 cases with the fatty MRNs were shown in Table 1. The age ranged 56 to 71 years, and male to female ratio was 1:1. No steatogenic factors were obtainable in the 4 cases while the remaining 2 cases were diabetic. In cases 3 and 5 who had been heavy drinkers, alcohol was not considered as a steatogenic factor because they had abstained from alcohol for 2 to 3 years before the surgical resection or autopsy. The suspected etiology of cirrhosis was hepatitis B virus infection in 1 case, chronic alcoholism in 2 cases and unknown in the remaining 3 cases.

The pathologic findings of the 9 fatty MRNs were shown in Table 2. The fatty MRNs were pale yellow and rather soft, and relatively well-demarcated from the surrounding liver. The fatty MRNs lacked fibrous capsule. The number of fatty MRNs in a cirrhotic liver ranged from 1 to 3, and their size from 1.0×1.0 to 2.5×1.5 cm (Table 2). The fatty change was of macrovesicular type in all cases. The degree of fatty change varied from case to case and also from area to area. More than 80% of hepatocytes of MRNs showed steatosis in 7 MRNs (Fig. 1), and 50–80% of hepatocytes showed steatosis in the remaining 2 ones (Fig. 2). The remaining livers showed no steatosis in 4 cases and minimum steatosis in the remaining 2 cases. Background hepatic lesions were liver cirrhosis with hepatocellular carcinoma in 4 cases, and cirrhosis alone in the remaining 2 cases.

Microscopically, portal tracts and fibrous septa were present within all of these fatty MRNs (Fig. 3), especially in the peripheral portions. There were unusual histologic changes suggestive of neoplasia or recent hepatocellular replication in 7 fatty MRNs in cases 1–5; Clustering of Mallory bodies was seen in 2 fatty MRNs (Fig. 4). Numerous hyaline globules were present in fatty hepatocytes in one fatty MRN (Fig. 5). Hepatocytes showing variable fatty changes revealed nuclear

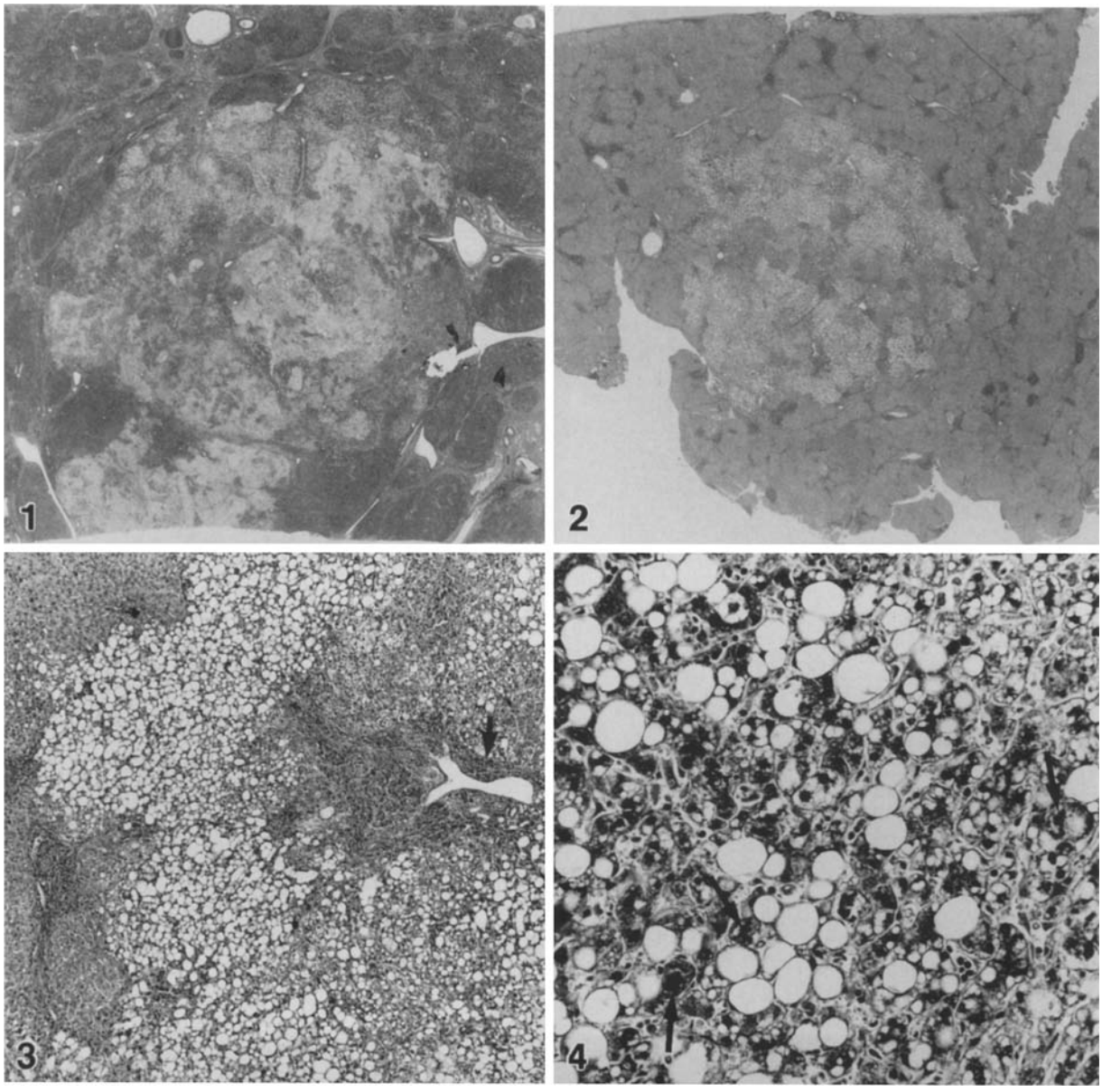

Fig. 1. Fatty macroregenerative nodule (2.5 × 1.5 cm) in case 4. About 90% of hepatocytes of the macroregenerative nodule shows fatty change. Elastica van Gieson, × 2.5

Fig. 2. Fatty macroregenerative nodule (1.0 × 1.0 cm) in case 3. About 70% of hepatocytes of the nodule shows fatty change. Hematoxylin and eosin, × 2

Fig. 3. The edge of fatty macroregenerative nodule. The fatty nodule (*right*) compresses the surrounding liver (*left*), and contains the portal tract (*arrow*). Hematoxylin and eosin, × 40

Fig. 4. Mallory bodies (*arrows*) are present in hepatocytes of the fatty macroregenerative nodule (case 4). Hematoxylin and eosin, × 100

enlargement and hyperchromasia (Fig. 6), which were more evident in hepatocytes with mild fatty deposition. Nonfatty hepatocellular foci with a variable degree of structural and cellular atypia including nuclear crowding and hyperchromasia were seen in 7 fatty MRNs, and at least one such nonfatty focus showing trabecular arrangement (case 2) was considered as malignant (Fig. 7). These fatty hepatocytes infiltrated into the portal tracts including the subendothelial regions of the portal vein within MRNs. Reticulin fibers were much more sparse in all fatty MRNs than in the

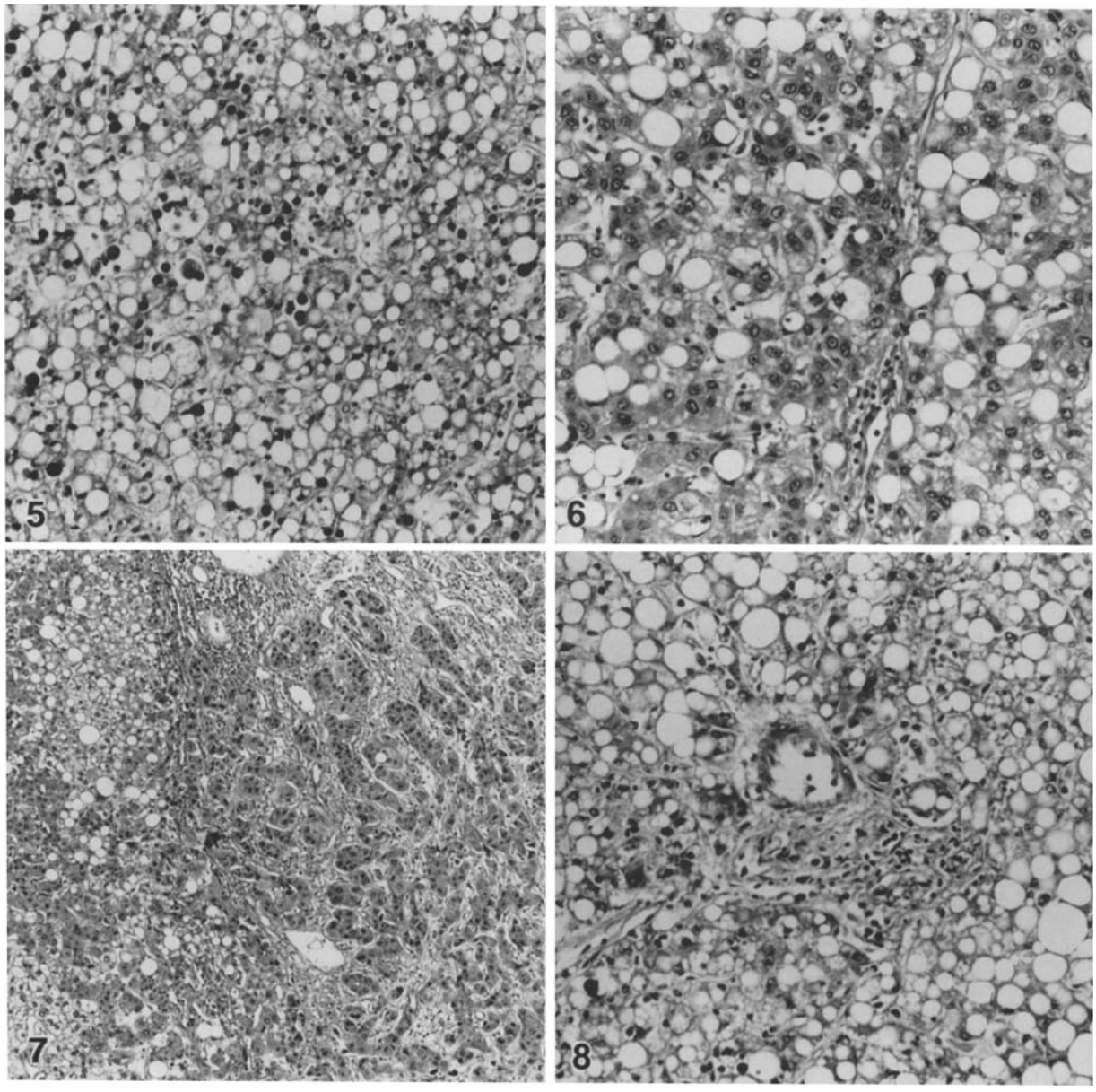

Fig. 5. Many hyaline glibules are present in fatty hepatocytes. Hematoxylin and eosin, ×100

Fig. 6. Nuclear hyperchromasia and atypia are seen in hepatocytes with a variable fatty changes. Case 5. Hematoxylin and eosin, ×200

Fig. 7. A focus of atypical nonfatty hepatocytes within a fatty macroregenerative nodule (case 2). The atypical cells (*right*) show nuclear atypia and thin trabecular pattern in rather fibrous tissue. Fatty hepatocytes (*left*) lie adjacent to this focus. Hematoxylin and eosin, ×100

Fig. 8. An abnormal vessel within fatty macroregenerative nodule (case 1). Hematoxylin and eosin, ×200

surrounding regenerative nodules. One fatty MRN (case 1) showed resistance to stainable iron against siderotic background. Abnormal blood vessels which were not accompanied by portal veins nor bile ducts, were scattered in 5 fatty MRNs (Fig. 8). α-fetoprotein was positive in a few fatty hepatocytes in one MRN (case 1). These morphological alterations were varied from one MRN to another in the seven fatty MRNs of cases 1–5, while these changes were absent or minimum in the remaining two fatty MRNs of case 6.

Discussion

Fatty change of the liver is generally a diffuse process. Localized or focal fat deposit in the liver has

been sporadically reported as "lipoma of the liver" (Young 1951; Ramchand et al. 1970), "focal fatty infiltration" (Simon 1934), "isolated liver nodules" (Shojania and Hogg 1975) and "focal fatty change of the liver" (Brawer et al. 1980). These focal fatty lesions were reported to occur in otherwise normal livers (Simon 1934; Young 1951; Ramchand et al. 1970; Shojania and Hogg 1975; Brawer et al. 1980), and local ischemia under the steatogenic conditions is considered as an important pathogenetic factor of these lesions (Shojania and Hogg 1975; Brawer et al. 1980). Localized fatty change of the present cases differs from above-mentioned entities in that the fatty change was confined to the MRNs in cirrhotic livers. Such fatty MRNs have not yet been reported in the English literature to our knowledge. It is well known that hepatocellular carcinoma cells occasionally show fatty change (Gibson and Sobin 1978), and thus fatty change is recognized as a cytoplasmic expression of hepatocellular carcinoma, particularly small hepatocellular carcinoma (Nakanuma et al. 1981).

Recently, MRNs or adenomatous hyperplasia have been suspected as a putative precancerous lesion in human hepatocarcinogenesis. Arakawa et al. (1986) first described emergence of malignant hepatocellular lesions within adenomatous hyperplastic nodules. Furuya et al. (1988) described clinicopathological findings of 86 MRNs, and divided them into type I without atypia and type II with proliferative foci regarged as cancer. Tsuda et al. (1988) reported a case of liver cirrhosis with 2 nodules of adenomatous hyperplasia, one of which contained malignant hepatocellular foci. These data suggest that MRNs are one of important precancerous lesions in human hepatocarcinogenesis.

In the present study, fatty MRNs showed a well-demarcated border, and portal tracts were sparse within MRNs, suggesting that the fatty MRNs are rather proliferating hepatocellular nodules. It is of interest that several morphological alterations suggestive of neoplasia were found in these fatty MRNs, although they were minimal or absent in 2 fatty MRNs of case 6. Among these alterations, Mallory bodies and hyaline globules are a well known cytoplasmic expression of hepatocellular carcinoma (Gibson and Sobin 1978; Nakanuma et al. 1981; Nakanuma and Ohta 1986). Resistance to hemosiderin accumulation is also known to be a marker for hepatic preneoplasia or neoplasia in chemical hepatocarcinogenesis of rodents overloaded with iron (Williams and Yamamoto 1972; Williams 1980) as well as in human hepatocellular carcinoma (Hirota et al. 1982). α-fetoprotein is a well known marker of hepatocellular carcinoma. The sparsity of reticulin fibers and emergence of abnormal vessels are well known in hepatocellular carcinoma (Anthony et al. 1973). These cellular alterations, therefore, strongly suggest that the fatty MRNs of cases 1–5 are already neoplastic or belong to a borderline lesion, rather than reflect the ischemic changes which are speculated important in "focal fatty change" occurring in otherwise normal livers (Shojania and Hogg 1975; Brawer et al. 1980). Focal occurrence of non-fatty hepatocellular clusters with nuclear hyperchromasia and trabecular arrangement within the fatty MRN in case 2 (Fig. 6), supports the above-mentioned suggestion. In this context, the fatty change in fatty MRNs may be a hepatocellular expression occurring in human hepatocarcinogenesis.

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