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Histopathological and morphometric analysis of atypical adenomatous hyperplasia of human cirrhotic livers

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Abstract. Atypical adenomatous hyperplasia (AAH) is a hyperplastic parenchymal nodular change in the cirrhotic liver, in which overt hepatocellular carcinoma (HCC) occasionally arises. AAH is defined as a sizable hepatocellular nodule with a variable degree of hepatocellular atypia not regarded as HCC, and is different from ordinary adenomatous hyperplasia in which hepatocellular atypia is absent. In the present study, we attempted to evaluate carcinogenetic processes and to find histological variables which indicate malignant transformation in AAH, using 49 surgically resected or autopsied nodules. AAH frequently showed morphological heterogeneity. Atypical lesions within AAHs were divisible into the following three categories from overall histopathological appearances: malignant (A), equivocal (B), or non-malignant (C) lesions. Analysis of combination of these three lesions, which were frequently intermixed in a given AAH, suggested that B lesions appear subsequent to C lesions, and A lesions finally appear in AAH nodules. Among the 14 histological variables, enlargement, hyperchromasia and irregular contour of nuclei were found to correlate well with A lesions. Increased nuclear density, iron resistance, reduction of reticulin fibres, clear cell change, sinusoidal dilatation and presence of abnormal arteries were suggestive of A or B lesions. Nuclear deviation toward the sinusoids, acinar and compact arrangements, fatty change and Mallory's hyaline alone were not useful indicators of A or B lesions. These results indicate that AAH is a preneoplastic or borderline lesion in which overt HCC is likely to evolve through several steps. Although a needle liver biopsy is a useful tool for diagnosis of benign, equivocal and malignant hepatocellular nodular lesions, the needle biopsy specimen should be carefully evaluated by considering the morphological heterogeneity of the AAH and a variable combination of 14 histological variables.

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Key words: Atypical adenomatous hyperplasia of the liver – Hepatocellular carcinoma – Histopathology – Morphometry

Introduction

Adenomatous hyperplasia (AH) of the liver, a term coined by Edmondson (1976), implies a sizable parenchymal nodule which develops following acute or chronic liver injuries, especially in cirrhosis. AH is synonymous with macroregenerative nodule (Ferrell et al. 1992; Furuya et al. 1988; Theise et al. 1992). Recently, AHs have been considered to be among the preneoplastic or early-neoplastic lesions in human hepatocarcinogenesis; AHs occasionally contain overt malignant hepatocellular lesions, and frequently coexist with hepatocellular carcinoma (HCC) (Arakawa et al. 1986; Eguchi et al. 1992; Ferrell et al. 1992; Furuya et al. 1988; Grigioni et al. 1989a, b; Nakanuma et al. 1990; Okuda 1992; Sakamoto et al. 1991; Terada and Nakanuma 1991, 1992; Theise et al. 1992; Tsuda et al. 1988; Ueda et al. 1992; Wada et al. 1988). In addition, a recent clinicopathological follow-up study has demonstrated that AHs occasionally undergo malignant transformation (Takayama et al. 1990).

Our recent studies have demonstrated that AHs are divisble into two types morphologically: ordinary and atypical (Nakanuma et al. 1990; Terada and Nakanuma 1991, 1992; Ueda et al. 1992). The former lacks hepatocellular atypia, while the latter shows a varied degree of structural and cytological atypia. This atypia is not pronounced and is not regarded as HCC. Atypical AHs (AAHs) also occasionally contain unequivocally malignant lesions, while ordinary AHs never harbour malignant lesions (Nakanuma et al. 1990). In our previous study, we mentioned that AAHs often show morphological heterogeneity (Nakanuma et al. 1990). This heterogeneity and the occasional presence of malignant foci may cause histopathological diagnostic problems, when a part of the AAH is taken by needle biopsy. However,

the morphologic heterogeneity of AAHs has not been fully investigated.

In order to evaluate the heterogeneity and evolution of AAH and to look for valuable histological variables indicating malignant change within AAHs, we conducted a histopathological and morphometric study of AAHs.

Materials and methods

AHs were defined both grossly and microscopically. Grossly, they were hepatocellular nodules (>8 mm in diameter), clearly larger than the surrounding regenerative nodules in cirrhotic livers (Fig. 1). Microscopically, AHs were defined as hepatocellular nodules containing portal tracts with bile ducts, portal veins and hepatic arteries. Hepatocellular nodules composed totally of malignant cells were defined as HCC. AHs were classified, according to our previous studies, into two types: ordinary and atypical (Nakanuma et al. 1990; Terada and Nakanuma 1991, 1992; Ueda et al. 1992). Ordinary AHs are devoid of hepatocellular atypia, while AAHs consist of atypical hepatocytes. The degree of hepatocellular atypia of AAHs is milder than that of HCC and is not regarded as HCC. AAHs occasionally contain overt HCC foci.

We surveyed AHs from surgical and autopsy files at our laboratory and affiliated hospitals during the period January 1972 to December 1991. In this period, there were 222 autopsies of liver cirrhosis with or without HCCs, and 92 surgically resected livers with cirrhosis and HCC or AH. Each liver with cirrhosis was cut into several slices approximately 1 cm in thickness, and the liver slices were carefully searched for AHs. A total of 105 AHs were found in 62 cirrhotic livers (30 surgically resected livers and 32 autopsy livers). Among the 105 AHs, 49 AHs (31 cases) were AAHs and 66 AHs (31 cases) were ordinary AHs. The present study examined these 49 nodules of AAH. The background liver disease of the 31 cases with AAHs was primary biliary cirrhosis at stage IV in 2 cases, and liver cirrhosis of varying aetiology in the remaining 29 cases; alcoholic (3 cases), hepatitis B virus-associated (6 cases) and cryptogenic (20 cases). Among the 31 cirrhotic livers

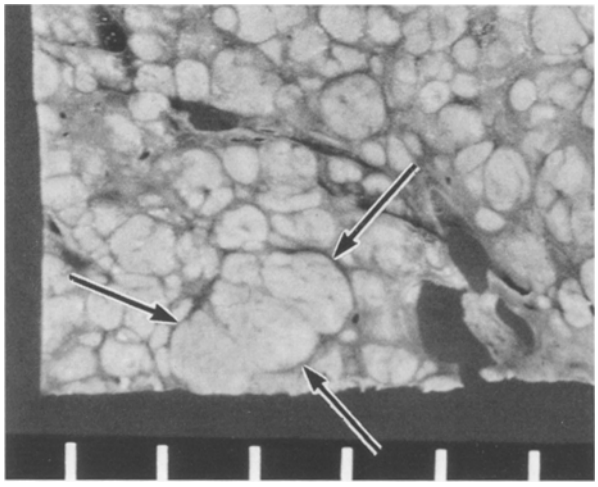

Fig. 1. Gross features of a nodule of adenomatous hyperplasia in a cirrhotic liver. The nodule of adenomatous hyperplasia (*arrows*) is clearly larger than the surrounding regenerative nodules

Table 1. Main clinical features of the patients and number and size of nodules of atypical adenomatous hyperplasia and small hepatocellular carcinoma

Histology	Number of patients	Age (years; mean ± SD)	Sex (M:F)	Number of nodules	Size (mm; mean ± SD)
AAH	31	60.7 ± 7.1	21:10	49	12.9 ± 4.4
HCC	20	61.4 ± 7.3	15:5	20	20.5 ± 3.2

AAH, Atypical adenomatous hyperplasia; HCC, hepatocellular carcinoma; SD, standard deviation; M, male; F, female

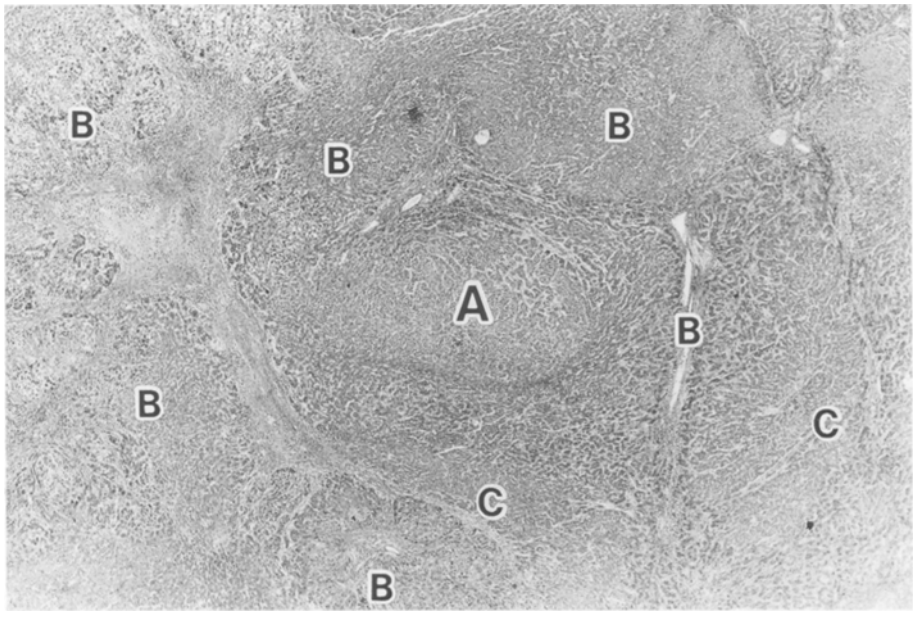

Fig. 2. Morphological heterogeneity in a nodule of atypical adenomatous hyperplasia. The nodule shows morphological heterogeneity consisting of A, B and C lesions. A lesion (A) is the malignant (hepatocellular carcinoma) lesion with marked atypia. B lesion (B) is equivocal as to benignity and malignancy with moderate atypia. C lesion (C) is non-malignant with mild atypia. Haematoxylin and eosin, ×20

Table 2. Prevalence of ten histological variables in three atypical lesions within nodules of atypical adenomatous hyperplasia

Histological variables	Atypical lesions within AAH		
	A lesion	B lesion	C lesion
Hyperchromasia	19/26 (72%) >	8/37 (22%) >	1/43 (2%)
Resistance to iron accumulation[a]	11/11 (100%) =	2/2 (100%) >	6/10 (60%)
Clear cell change	9/26 (35%) =	10/37 (27%) >	3/43 (9%)
Sinusoidal dilatation	11/26 (42%) =	19/37 (51%) >	9/43 (21%)
Abnormal arteries[b]	10/26 (38%) =	24/37 (65%) >	5/43 (12%)
Mallory's hyalin	4/26 (15%) <	14/37 (38%) >	4/43 (9%)
Nuclear deviation toward the sinusoids	9/26 (35%) =	17/37 (46%) =	23/43 (54%)
Fatty change	4/26 (15%) =	11/37 (30%) =	11/43 (26%)
Acinar pattern	7/26 (27%) =	3/37 (8%) =	5/43 (12%)
Compact pattern	6/26 (23%) =	11/37 (30%) =	6/43 (14%)

Number of lesions positive for each histological variable/number of total lesions: A lesion, overt hepatocellular carcinoma lesion with severe atypia; B lesion, equivocal lesion as to malignancy and benignity with moderate atypia; C lesion, non-malignant lesion with mild atypia; AAH, atypical adenomatous hyperplasia

>, former is significantly greater than latter ($P<0.05$); <, the latter is significantly greater than the former ($P<0.05$); =, difference is not significant ($P>0.05$)

[a] Only siderotic nodules of atypical adenomatous hyperplasia were examined for resistance to iron accumulation, and resistance to iron accumulation is a phenotypic marker for malignant or equivocal lesions in siderotic AAH

[b] Abnormal arteries are arteries not accompanying portal vein and bile ducts

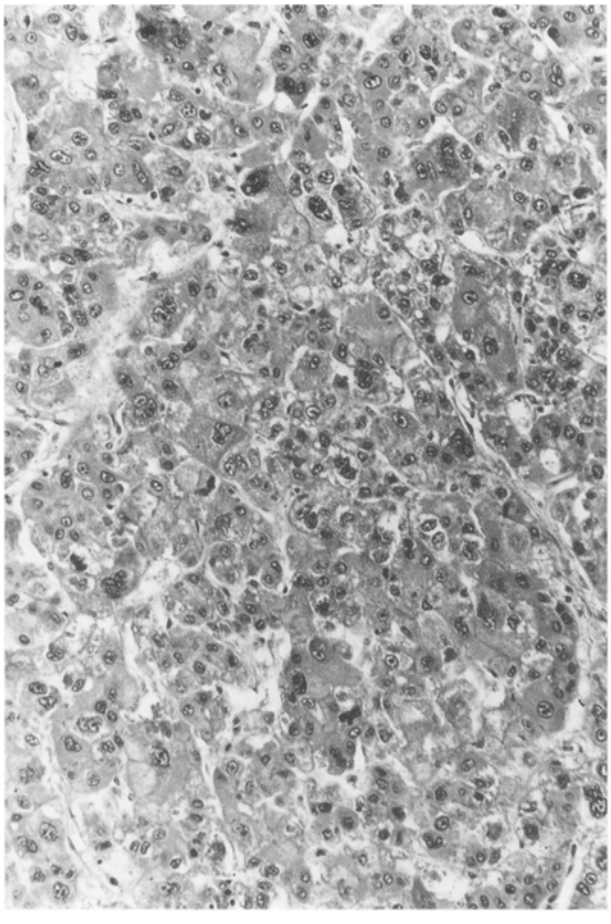

Fig. 3. A lesion within the nodule of atypical adenomatous hyperplasia showing nuclear enlargement, hyperchromasia and irregularity of nuclear contour. These features are consistent with hepatocellular carcinoma. Haematoxylin and eosin, ×200

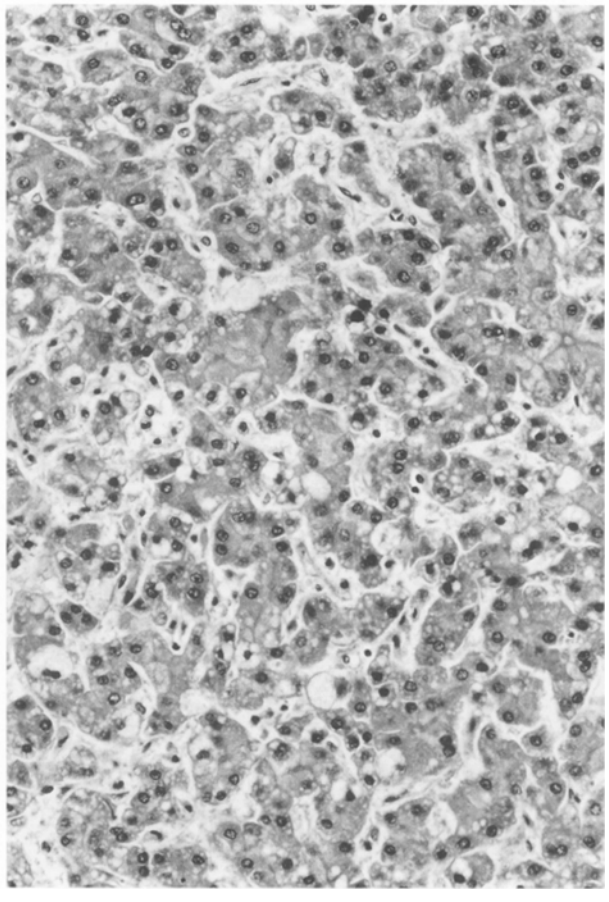

Fig. 4. B lesion within the nodule of atypical adenomatous hyperplasia showing mild nuclear hyperchromasia and nuclear crowding. These features are equivocal as to benignity and malignancy. Haematoxylin and eosin, ×200

with AAHs, 15 were complicated by HCC. We also collected 20 small HCCs (< 3 cm in diameter; 13 surgically resected livers and 7 autopsy livers) from our recent surgical and autopsy files. All small HCCs used were complicated by liver cirrhosis. Brief clinicopathological data about the material are shown in Table 1.

Liver specimens containing AHs or small HCCs and surrounding regenerative nodules were fixed in 4% formaldehyde solution and embedded in paraffin. Several sections (5 μm thick) were obtained from each paraffin block, and stained with haematoxylin and eosin, elastic van Gieson, Gomori's silver impregnation, and Prussian blue for iron.

Three pathologists (the authors) examined each nodule of AAH. From the standpoint of overall histopathology, areas within the AAHs were divided into the following three categories by consensus of the three pathologists: A lesions, malignant lesions (overt HCC); B lesions, equivocal lesions as to malignancy and benignity; and C lesions, non-malignant lesions.

Ten histological variables indicating cellular and structural atypia were selected. These are shown in Table 2. The prevalence of each of these variables in A, B, and C lesions within AAHs was examined.

Nuclear area, nuclear density, nuclear form factor, and reticulin fibre density were morphometrically examined in all atypical lesions within AAHs, in all surrounding cirrhotic parts of the 49 nodules of AAH, and in all 20 small HCCs, using an image analyser (Nexus 6400; Kashiwagi Lab., Tokyo, Japan), personal computer PC 9801 (Nihon Electric, Tokyo, Japan), and video camera BK5001 (Hitachi, Tokyo, Japan). In each atypical lesion of AAH, each cirrhotic part surrounding the AAH, and each small HCC, 100 nuclei were examined for nuclear areas and nuclear perimeters. In each lesions, nuclear density, i.e. the number of nuclei per square micrometre was analysed by the image analyser. Nuclear form factor was expressed as $4\pi \times$ nuclear area/nuclear perimeter squared. This nuclear form factor represents the degree of irregularity of the nuclear contour; the value of a complete circle is 1, and the more irregular the nuclear contour is, the lower the factor. Ellipsoid nuclei also have a value less than 1.0. Reticulin fiber density was evaluated as the length of reticulin fibres per square micrometre.

The Chi-square test was used for comparison of the prevalence of the 10 histologic variables in A, B, and C lesions of AAHs. Student's *t*-test was used for comparison of nuclear area, nuclear density, nuclear form factor, and reticulin fibre density in A, B, and C lesions of AAHs, small HCC, and cirrhotic parts surrounding the AAHs. A *P* value less than 0.05 was considered as significant.

Results

The nodules of AAH frequently showed morphological heterogeneity (Fig. 2). A (Fig. 3) and B (Fig. 4) lesions were admixed in 8 nodules of AAH (Table 3). B and C (Fig. 5) lesions coexisted in 18 nodules of AAH (Table 3). A, B, and C lesions were admixed in 8 nodules of AAH (Fig. 2, Table 3). Only C lesions were present in the remaining 15 nodules of AAH (Table 3). The AAHs consisting of only C lesion were different from ordinary AHs in that hepatocytes of AAHs had mild

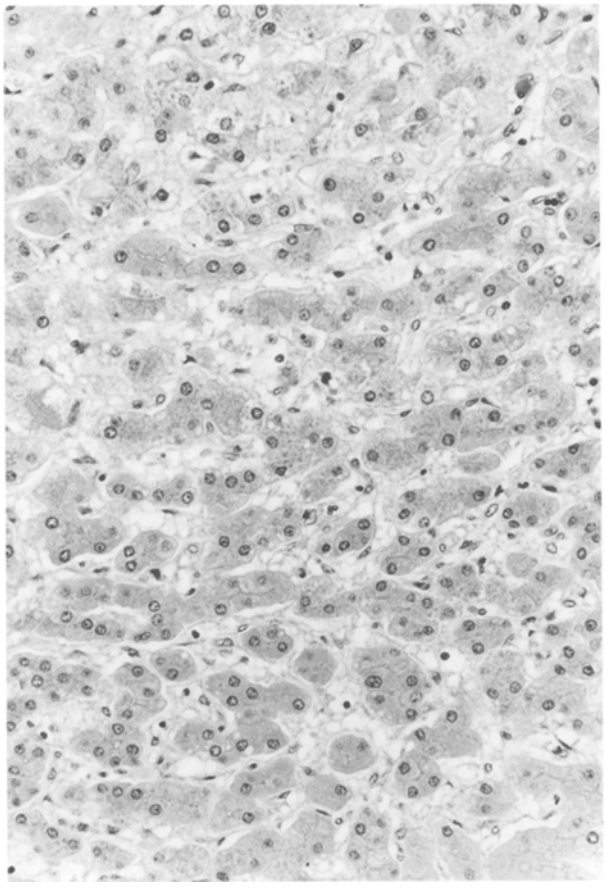

Fig. 5. C lesion within the nodule of atypical adenomatous hyperplasia showing mild or little nuclear atypia. These features are interpreted as non-malignant. Haematoxylin and eosin, ×200

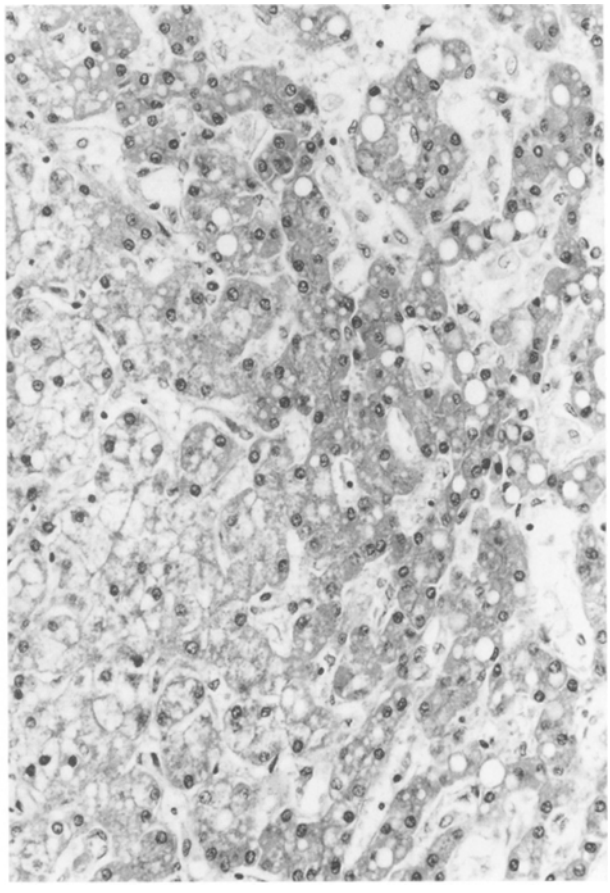

Fig. 6. Sinusoidal dilatation (right) and clear cell change (left) of hepatocytes in a B lesion. Nuclear atypia is mild to moderate. Haematoxylin and eosin, ×200

Table 3. The number of nodules of atypical adenomatous hyperplasia consisting of marked, moderate and mild atypical lesions

Atypical lesions within AAH	Number of nodules of AAH
A lesion only	0
B lesion only	0
C lesion only	15
A + B lesions	8
B + C lesions	18
C + A lesions	0
A + B + C lesions	8

A lesion, over hepatocellular carcinoma lesion with severe atypia; B lesion, equivocal lesion as to malignancy and benignity with moderate atypia; C lesion, non-malignant lesion with mild atypia; AAH, atypical adenomatous hyperplasia

structural and cytological atypia while hepatocytes of ordinary AHs had no such atypia. There were no nodules of AAH consisting of only A lesions, only B lesions, or A plus C lesions (Table 3). In a nodule of AAH, these atypical lesions were single or multiple; A and B lesions appeared as oval or irregular geographic areas within AAHs. Among the 49 nodules of AAH, A lesions were seen in 16 nodules (33%), B lesions in 34 nodules (69%) and C lesions in 41 nodules (84%). In total, there were 26 A lesions, 37 B lesions and 43 C lesions within the 49 nodules of AAH.

Among the ten morphological variables, one (nuclear hyperchromasia, Fig. 3), showed significant differences both between A and B lesions and between B and C lesions (Table 2). The prevalence of this change was high in A lesions, intermediate in B lesions, and low in C lesions (Table 2). Four other variables, namely resistance to iron accumulation, clear cell change (Fig. 6), sinusoidal dilatation (Fig. 6) and abnormal arteries (Fig. 7), showed significant differences either between A and B lesions or between B and C lesions (Table 2). The remaining five variables [Mallory's hyaline (Fig. 8), nuclear deviation toward the sinusoids, fatty change, acinar arrangement, and compact arrangement] showed no significant differences among A, B and C lesions (Table 2).

Nuclear area, nuclear density, nuclear form factor, and reticulin fibre density in A, B, and C lesions within AAHs, in small HCCs, and in cirrhotic parts are shown in Table 4. Nuclear area was high in A lesions, intermediate in B lesions and low in C lesions; the differences were statistically significant (Table 4). Nuclear density was high in A lesions, intermediate in B lesions, and low in C lesions; although there was a significant statistical difference between A and B lesions, there was no significant statistical difference between B and C lesions

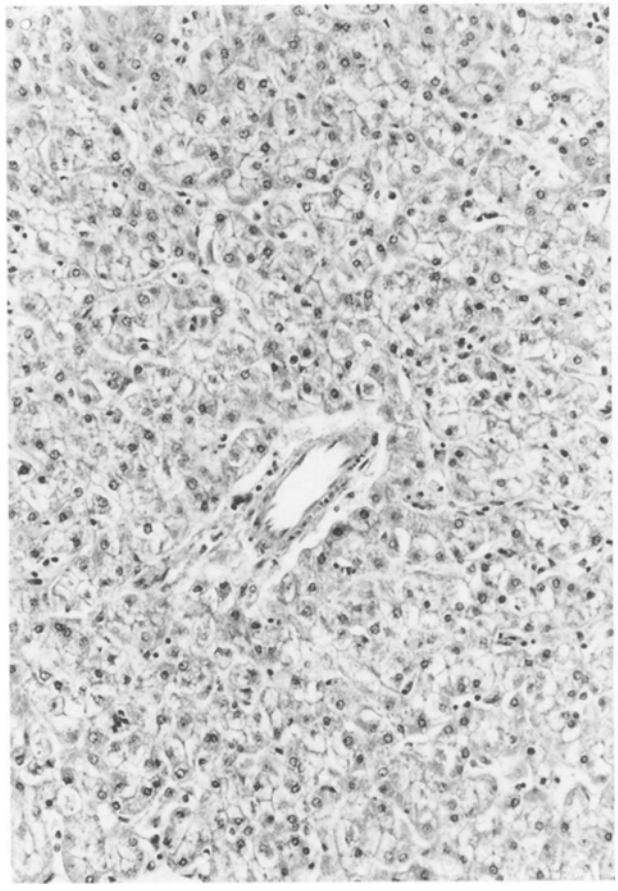

Fig. 7. An abnormal artery in a B lesion. The abnormal artery is not accompanied by portal veins or bile ducts. Haematoxylin and eosin, × 180

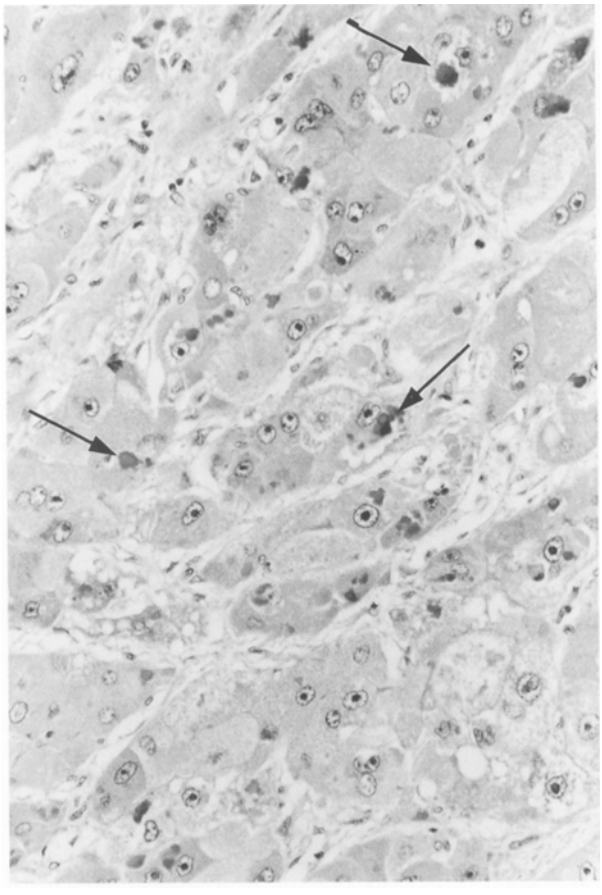

Fig. 8. Mallory's hyaline in a B lesion. There are many Mallory bodies (*arrows*). Haematoxylin and eosin, × 200

Table 4. Nuclear area, nuclear density, nuclear form factor and reticulin fibre density in small hepatocellular carcinoma and in atypical lesions within atypical adenomatous hyperplasia

Histology	Number of specimens	Nuclear area (μm^2)	Nuclear density (per μm^2)	Nuclear form factor	Reticulin fibre density (μm per μm^2)
HCC	20	83.4 ± 31.4	2940 ± 871	0.80 ± 0.048	0.064 ± 0.055
AAH					
A lesion	26	81.0 ± 29.7^{a}	3317 ± 1003^{d}	0.79 ± 0.051^{f}	0.067 ± 0.044^{i}
B lesion	37	$68.8 \pm 19.6^{a,b}$	2239 ± 884^{d}	$0.85 \pm 0.042^{f,g}$	0.095 ± 0.045^{i}
C lesion	43	$53.2 \pm 13.9^{b,c}$	2112 ± 699^{e}	$0.87 \pm 0.035^{g,h}$	0.101 ± 0.048^{j}
Cirrhosis	49	38.0 ± 8.7^{c}	1642 ± 394^{e}	0.90 ± 0.019^{h}	0.121 ± 0.032^{j}

HCC, Hepatocellular carcinoma; AAH, atypical adenomatous hyperplasia; A lesion, overt hepatocellular carcinoma lesion with severe atypia; B lesion, equivocal lesion as to malignancy and benignity with moderate atypia; C lesion, non-malignant lesion with mild atypia; [a] $p<0.025$, [b,c,d,e,i,j] $p<0.01$, [f] $p<0.005$, [g,h] $p<0.05$. Nuclear form factor $=4\pi \times$ nuclear area/nuclear perimeter^2, nuclear density is the number of nuclei/μm^2, reticulin fibre density is the length (μm) of reticulin fibre/μm^2

(Table 4). Nuclear form factor was low in A lesions, intermediate in B lesions, and high in C lesions; there were significant statistical differences between A and B lesions and between B and C lesions (Table 4). Reticulin fibre density (Fig. 9) was low in A lesions, intermediate in B lesion and high in C lesion; although there was a significant statistical difference between A and B lesions, there was no significant statistical difference between B and C lesions (Table 4).

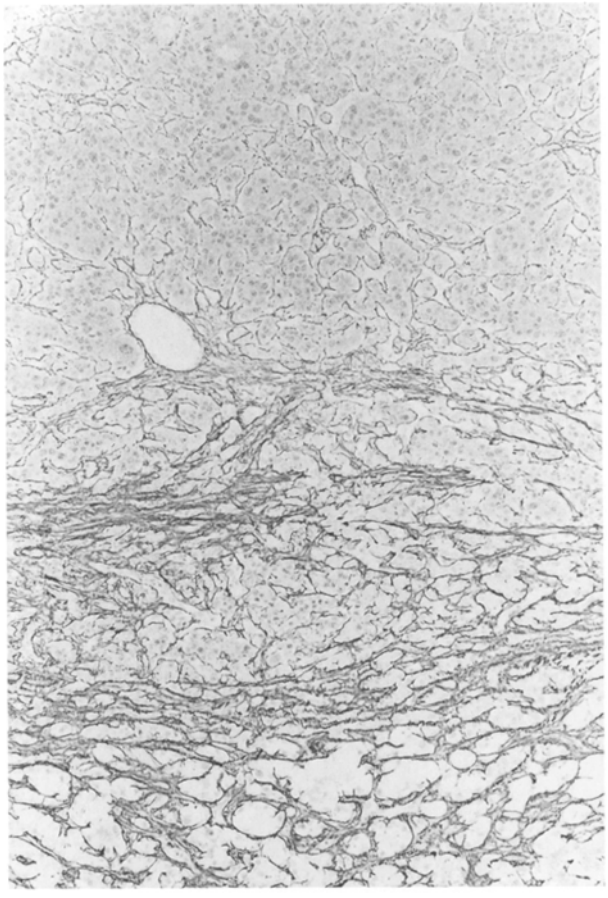

Fig. 9. Reduction of reticulin fibre in an A lesion (upper half). The A lesion (upper half) shows reduction of reticulin fibre relative to the surrounding parts of B lesion (lower half). Gomori's silver impregnation, $\times 100$

Discussion

Human HCC is now thought to progress in several steps, and AAH is suspected to correspond to the most important change predisposing to overt HCC (Arakawa et al. 1986; Eguchi et al. 1992; Ferrell et al. 1992; Furuya et al. 1988; Grigioni et al. 1989a, b; Nakanuma et al. 1990; Sakamoto et al. 1991; Theise et al. 1992; Tsuda et al. 1988; Wada et al. 1988). It seems conceivable that certain parts of the AAH are undergoing malignant transformation, giving rise to AAH with over malignant foci. However, we are still short of reproducible and objective histopathological criteria for malignant transformation or malignant foci in AAH.

We have found that the nodules of AAH show a heterogeneous morphology consisting of atypical lesions. The present study divided these lesions into three categories from the overall histopathological appearances; malignant (A), equivocal (B) and non-malignant (C) lesions. The prevalence of these lesions was high in C lesions, intermediate in B lesions, and low in A lesions. As to the combination of these lesions, A and B lesions frequently coexisted with C lesion. There were no nodules of AAH consisting only of the A or B lesion while there were 15 nodules of AAH consisting only of C lesions, suggesting that a nodule of AAH consisting only of the C lesion is the initial lesion in human hepatocarcinogenesis. Co-existence of B and C lesions was seen in 18 nodules of AAH, while coexistence of A and C lesions was not found in any nodules of AAH, suggesting that B lesions appear subsequent to C lesions. A lesions invariably coexisted with B lesions, suggesting that A lesions finally appear in hepatocarcinogenesis. It seems, therefore, likely that B and A lesions appear sequentially in the nodule of AAH consisting only of C lesions, thus causing morphological heterogeneity. The heterogeneity may reflect the morphological marker of early steps of multi-step hepatocarcinogenesis in humans. This situation is similar to the well-known ad-

enoma-carcinoma sequence in carcinogenesis of colon in humans (Muto et al. 1975).

The morphological heterogeneity of the nodules of AAH may cause some diagnostic problems in needle biopsy specimens. For example, in the nodules of AAH with A, B, and C lesions, if the needle biopsy is taken from a C lesion, the diagnosis may be AAH, borderline lesion or no malignancy, while if the biopsy is taken from an A lesion, the diagnosis may be HCC. Thus, one must be aware that AAHs may show morphological heterogeneity, and should take into consideration that a needle biopsy taken from a hepatocellular nodule may only represent non-malignant areas even if the hepatocellular nodule is overtly malignant. For accurate evaluation of hepatocellular lesions multiple or periodic needle biopsies are necessary for precise diagnosis.

With regard to the histopathological variables used in making a diagnosis of well-differentiated HCC, there have been several reports in the English literature. Kondo et al. (1987, 1988, 1989) suggested that a combination of nuclear crowding, acinar structures and nuclear basophilia provided morphological clues indicative of well-differentiated HCC. Nagato et al. (1991) recently reported that nuclear area, nucleo-cytoplasmic ratio, and nuclear density were useful criteria for distinguishing well-differentiated HCC from borderline lesions and cirrhosis. In addition, localized fatty change (Terada et al. 1989b), Mallory body clustering (Terada et al. 1989a), resistance to iron accumulation (Terada and Nakanuma 1989), pseudoglandular pattern, clear cell change of hepatocytes, and irregular nuclear contour are listed as findings favouring malignancy or malignant transformation (Giannini et al. 1987; Motohashi et al. 1992). However, not all of these histopathological findings or variables have been generally accepted as signs of malignancy.

We have therefore attempted to analyse histological features or variables reflecting or constituting malignant, equivocal or non-malignant lesions in AAH in surgically resected or autopsied livers. In this study, the 14 histological variables were selected because many of them have been suspected to be useful markers in the discrimination of malignant and non-malignant lesions (Giannini et al. 1987; Kondo et al. 1987, 1988, 1989; Motohashi et al. 1992; Nagato et al. 1991; Terada and Nakanuma 1989; Terada et al. 1989a, b). Three variables; increased nuclear area, nuclear hyperchromasia, and nuclear irregular contour, have been found to be important clues for malignant lesions within AAHs. Each of an additional six variables (nuclear density, resistance to iron accumulation, reduction of reticulin fibres, clear cell change, sinusoidal dilatation and presence of abnormal arteries) is suggestive of malignant or equivocal lesions within AAHs. The remaining five (nuclear deviation toward the sinusoids, fatty change, acinar arrangement and compact arrangement, and Mallory's hyaline) may define AAH itself, but any of these parameters alone may be fail to help in the critical discrimination between malignant and non-malignant lesions within AAHs. This suggests that a combination of these variables in a given biopsy specimen may be helpful in making a diagnosis of AAH, HCC or AAH with malignant or equivocal lesions.

In conclusion, nodules of AAH frequently show morphological heterogeneity possibly related to the evolution of HCC in multi-step hepatocarcinogenesis. Among various cytological and structural variables, nuclear enlargement, nuclear hyperchromasia and irregular nuclear contour are most useful in the discrimination between malignant and non-malignant lesions within the nodule of AAH. Although less valuable, increased nuclear density, resistance to iron accumulation, reduction of reticulin fibres, clear cell change, sinusoidal dilatation and presence of abnormal arteries may also be variables with diagnostic utility in AAH.

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