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Unusual hepatocellular lesions in primary biliary cirrhosis resembling but unrelated to hepatocellular neoplasms

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Summary. Structural, cellular and nuclear abnormalities of hepatocytes are a histological hallmark of well-differentiated, small hepatocellular carcinoma (HCC) or its borderline lesion. This study revealed that several hepatocellular abnormalities found in these hepatocellular neoplasms were also found in non-cirrhotic stages of primary biliary cirrhosis (PBC) in which HCC is unlikely to develop. These changes are small cell changes, consisting of the appearance of small hepatocytes arranged in thin trabecular or compact patterns with increased cellularity and basophilic cytoplasm. This was found in 36%, 71% and 100% in specimens of stages 1, 2 and 3, respectively. Large cell changes occurred and consisted of large hepatocytes with large nuclei and prominent nucleoli, found in 27%, 47% and 22% of the stages, respectively. Finally, liver cell rosettes were seen, showing variable acinar formation and present in 0%, 41% and 33% of the stages, respectively. These lesions were identified microscopically as irregularly shaped areas or vague nodules of hepatocytes without a fibrous rim, in the hepatic lobules. They showed an expansive growth or shaggy border against the surrounding hepatic parenchyma. Follow-up studies, including autopsies, failed to show development of HCC or its borderline lesion in PBC cases. Pathologists must make a diagnosis of HCC and its borderline lesion bearing in mind the occurrence of such unusual hepatocellular lesions probably of a reactive nature.

Key words: Hepatocellular atypism – Reactive hyperplasia – Primary biliary cirrhosis – Borderline lesions – Hepatocellular carcinoma

Introduction

Recent advances in imaging have made it possible to detect small nodular lesions, including well-differentiated hepatocellular carcinoma (HCC) and adenomatous hyperplasia (AH) of the liver (Arakawa et al. 1986; Kondo et al. 1987, 1988; Nakanuma et al. 1990a; Okuda 1992; Takayama et al. 1990; Terada and Nakanuma 1991a, b). AH, coined by Edmondson (1976), implies a sizeable hepatocellular nodule in cirrhotic livers and has several synonyms. AH – especially atypical AH, which consists of atypical hepatocytes equivocal as to benignity and malignancy (Nakanuma et al. 1990a; Okuda 1992; Sakamoto et al. 1991; Tsuda et al. 1988) – is now regarded as a borderline lesion or early developmental stage of HCC arising in liver cirrhosis. The data accumulated so far suggest that well-differentiated, small HCC and atypical AH are histologically different from classical HCC, which is usually observed at autopsy or in surgically resected livers (Okuda 1992, 1988). At present, the following structural, cellular and nuclear changes are generally proposed as important in making a diagnosis of well-differentiated, small HCC or atypical AH: gland-like formation or liver cell rosettes, increased cellularity with nuclear crowding, increased cytoplasmic staining (basophilic or eosinophilic), irregularly arranged trabecular pattern of hepatocytes and infiltrative or expansive growth against the surrounding liver parenchyma (Arakawa et al. 1986; Kondo et al. 1987, 1988; Nakashima et al. 1990; Sakamoto et al. 1991; Tsuda et al. 1988).

The histological distinction between well-differentiated, small HCC and atypical AH, both of which may eventually give rise to overt HCC, remains controversial. Another important issue which should be resolved in making a diagnosis of these two neoplastic conditions is the degree and extent of cellular and structural abnormalities of hepatocytes unrelated to malignant neoplasia. Studies in this regard have not been reported in the English or Japanese literature.

Our study aims to clarify this issue, using primary biliary cirrhosis (PBC) of non-cirrhotic stages in which HCC is unlikely to occur (Scheuer et al. 1988).

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Materials and methods

A diagnosis of PBC was made by a combination of clinical, laboratory and histological findings (Scheuer 1980; Sherlock 1989). These cases of PBC were histologically classified into four stages according to the classic staging combining Scheuer's and Ludwig's staging system (Ludwig et al. 1978; Scheuer 1980). Briefly, stage 1 was portal hepatitis with intact limiting plates. Stage 2 was characterized by periportal changes (destruction of the limiting plates) associated with pathological changes such as ductular proliferation and lymphocytic piecemeal necrosis. Stage 3 showed a variable number of bridging necrotic and/or dense scar-like septa and stage 4 was characterized by the presence of regenerative nodules.

A total of 37 wedge liver biopsy specimens of 36 PBC patients (age range, 28–76 years; 33 females, 3 males) were examined. These specimens were obtained from many institutions in Japan including the Kanazawa University Hospital (1966–1990). Antimitochondrial antibodies (AMA) were positive in all cases of PBC except one. The AMA-negative case showed a histologically florid duct lesion. Hepatitis B surface antigen (HBsAg) was negative in the serum of all these PBC patients, and orcein-positive hepatocellular inclusions of HBsAg (Shikata et al. 1974) were negative in the liver specimens. Anti-hepatitis C virus antibody was negative in 3 cases of PBC examined, though data about this HCV antibody were not available in the remaining cases. A total of 37 liver specimens of PBC were divided into four stages as follows: stage I (11 specimens), stage II (17 specimens), and stage III (9 specimens). In this study, liver specimens in stage IV in which development of HCC has been reported occasionally (Nakanuma et al. 1990b) were excluded. Among these 36 patients, 21 were followed up for more than 1 year and 9 of the 21 patients were autopsied.

AH was defined as a grossly recognizable hepatocellular nodule (>0.8 cm in its greatest diameter) in cirrhotic livers and histologically different from overt HCC, according to the original description of Edmondson (1967) and our previous study (Nakanuma et al. 1990a). They were subdivided into ordinary AH and atypical AH. The former, corresponding to macroregenerative nodule (MRN) type I (Furuya et al. 1988), consists of non-atypical hepatocytes and is basically similar to the surrounding cirrhotic livers. The latter, corresponding to MRN type II, is composed of atypical hepatocytes which are insufficient to be diagnosed as overt HCC. In this study 10 nodules of atypical AH found in surgically resected or autopsied livers were analysed histologically.

All of the liver specimens were fixed in 10% neutral formalin and embedded in paraffin. Several 4-μm sections from these specimens were stained with haematoxylin and eosin, Azan-Mallory, orcein and Gomori's reticulin stains (Sano 1976).

These liver specimens were examined with an emphasis on several histological changes: liver cell rosettes or gland-like formation, increased cellularity, nuclear crowding, increased cytoplasmic staining (basophilic or eosinophilic), irregularly arranged trabecular pattern of hepatocytes, and infiltrative or expansive growth pattern. These changes have been reported in well-differentiated, small HCC or atypical AH (Kondo et al. 1987; Nakanuma et al. 1990a; Nakashima et al. 1990; Wada et al. 1988).

Hepatocellular nuclei per unit area were counted according to the method of Nakashima et al. (1990) in six cases of PBC and in four nodules of atypical AH. Five photographs (6.8 × 10.4 cm, at a magnification of ×700) were taken at random in the affected areas as well as in the surrounding non-affected areas in the same specimen, and hepatocellular nuclei were counted in each photograph (range of nuclear numbers in the non-affected areas 39–112 and in the affected areas 117–223). The ratio of the nuclear number of each photograph in the affected area to the mean of nuclear number of the non-affected areas was calculated in each specimen. The mean and standard deviation of the ratio in each specimen were then evaluated.

Expression of alpha-fetoprotein (AFP) on hepatocytes and that of receptor of *Ulex europaeus* agglutinin I (UEA-I) on sinusoidal endothelial cells were examined on 4-μm-thick deparaffinized sections. This was done in 5 cases of PBC showing variable and unusual hepatocellular lesions (vide infra), using the avidin-biotin-peroxidase complex (ABC) method of Hsu et al. (1981). Our previous studies (Terada and Nakanuma 1991a, b; Terasaki et al. 1991) disclosed that AFP was frequently positive on HCC cells, and receptors of UEA-I were positive in HCC tissue and negative in non-carcinomatous hepatic parenchymal areas. Briefly, sections were pretreated with methanolic-H_2O_2 and then with diluted normal goat serum. Primary polyclonal rabbit antibodies against human AFP (Dako, Santa Barbara, Calif.) were applied overnight at 4° C. Sections were then treated with biotinylated secondary antibodies to rabbit IgG (Vector Laboratory, Burlingame, Calif.) for 30 min at room temperature. Biotinylated UEA-I (Vector) was also applied on other deparaffinized and methanolic-H_2O_2 treated sections from the same paraffin blocks for 30 min at room temperature. Then, the ABC method (Vector) was applied on both of these sections for 30 min. The histochemical reaction for peroxidase was carried out using a H_2O_2-3,3′-diaminobenzidine tetrahydrochloride (DAB) (Sigma, St. Louis, Mo.) solution.

Several staining and specificity controls were performed. HCC

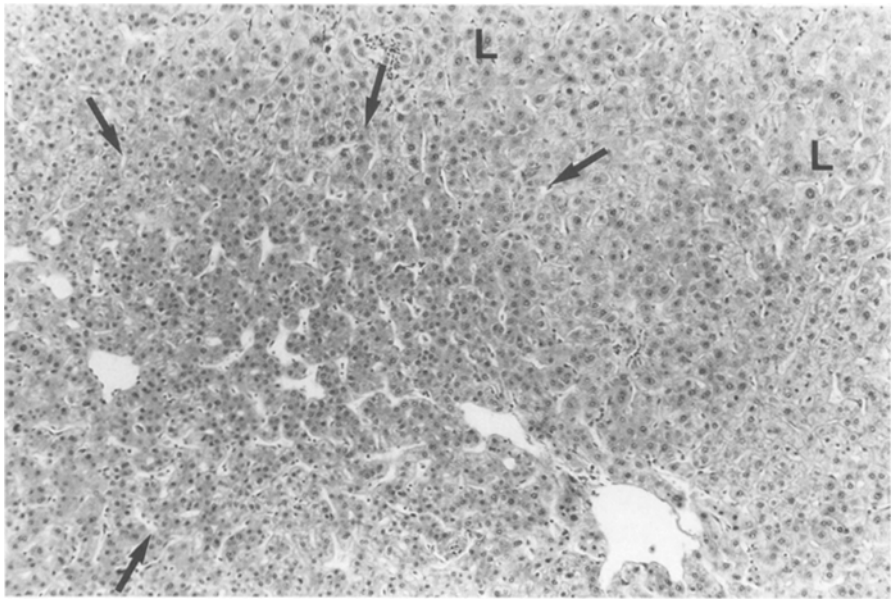

Fig. 1. An area of small cell change of thin trabecular pattern is seen (*arrows*). Hepatocytes show hyperchromatic nuclei, nuclear crowding and basophilic cytoplasm. Surrounding hepatic parenchyma is composed of large hepatocytes with hyperchromatic nuclei (large cell change) (*L*). Primary biliary cirrhosis (stage II). H & E, ×200

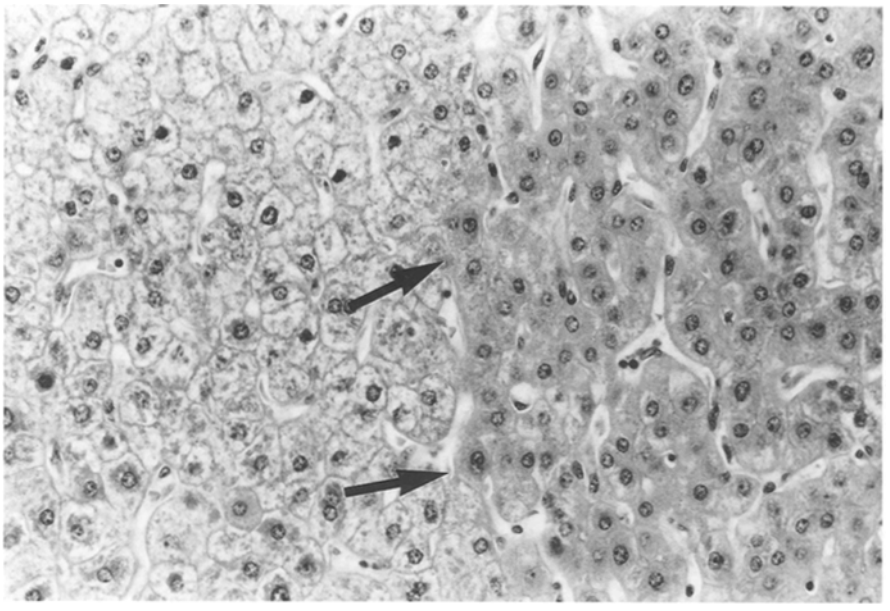

Fig. 2. Small cell change (*right*) shows basophilic cytoplasm, nuclear crowding and hyperchromatic nuclei and irregular cord pattern. There is an abrupt transition between this atypical area and the non-affected area (*arrows*). There is an apparent increased number of sinusoidal lining cells. Primary biliary cirrhosis (stage II). H & E, ×750

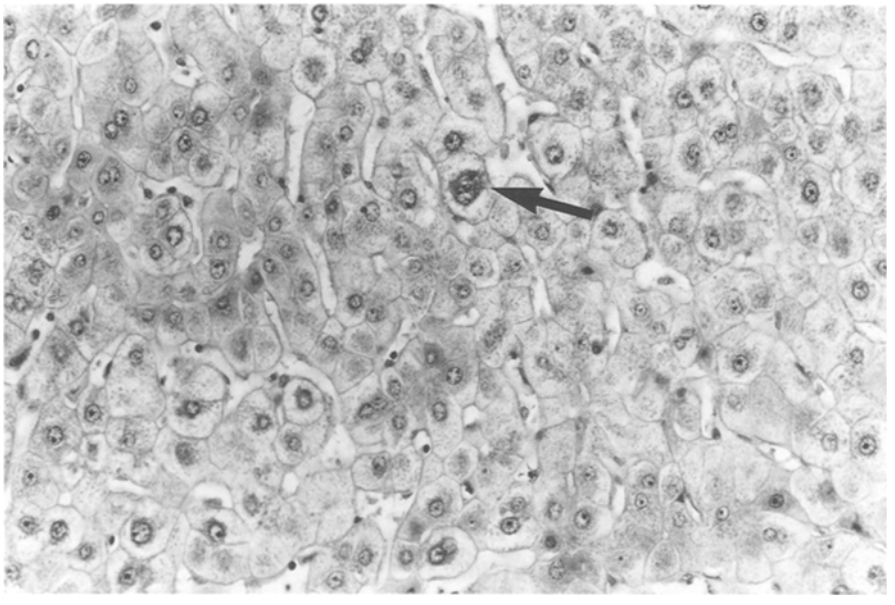

Fig. 3. Relatively large hepatocytes with large nuclei and prominent nucleoli show irregular cord pattern (large cell change). There are occasional binucleated cells (*arrow*). Primary biliary cirrhosis (stage II). H & E, ×750

tissues were used as a positive control for AFP. No positive stain was obtained when H_2O_2 without DAB or DAB without H_2O_2 was applied. Positive stain was abolished when phosphate-buffered saline or non-immune serum was used as the first layer.

Results

There were irregularly shaped or round areas (appearing as poorly defined nodules) of hepatocytes without fibrous rim, which showed variable, unusual structural and cellular patterns with hyperchromatic nuclei. These unusual lesions were histologically classifiable into three categories, as follows.

Small cell change (Figs. 1, 2) was characterized by foci or irregularly shaped areas of small hepatocytes showing basophilic cytoplasm and hyperchromatic nuclei with rather thickened nuclear membranes. Increased

Table 1. Nuclear count per unit area in the foci showing small cell change in six cases of primary biliary cirrhosis (PBC) and four cases of adenomatous hyperplasia of the liver (AH). Ratio of nuclear count per unit area in the affected areas (small cell change) to that of the non-affected areas (mean ± SD)

PBC	
Case 1	2.29 ± 0.17
Case 2	1.99 ± 0.17
Case 3	1.97 ± 0.26
Case 4	1.85 ± 0.17
Case 5	1.66 ± 0.19
Case 6	1.63 ± 0.17
AH	
Case 1	2.33 ± 0.30
Case 2	2.04 ± 0.55
Case 3	1.67 ± 0.23
Case 4	1.66 ± 0.20

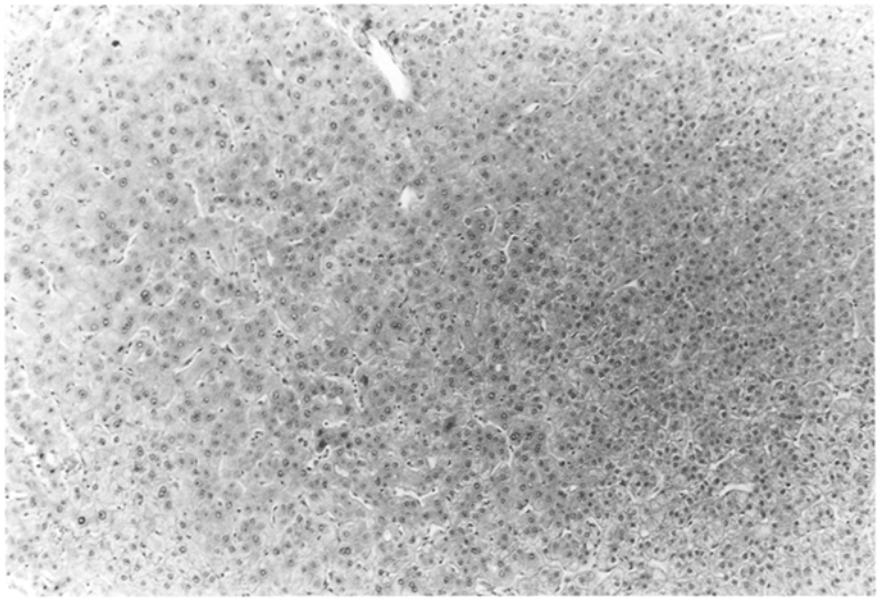

Fig. 4. Left half shows large cell change and right half small cell change with compact pattern. Transition of these two areas is gradual. Primary biliary cirrhosis (stage II). H & E, ×250

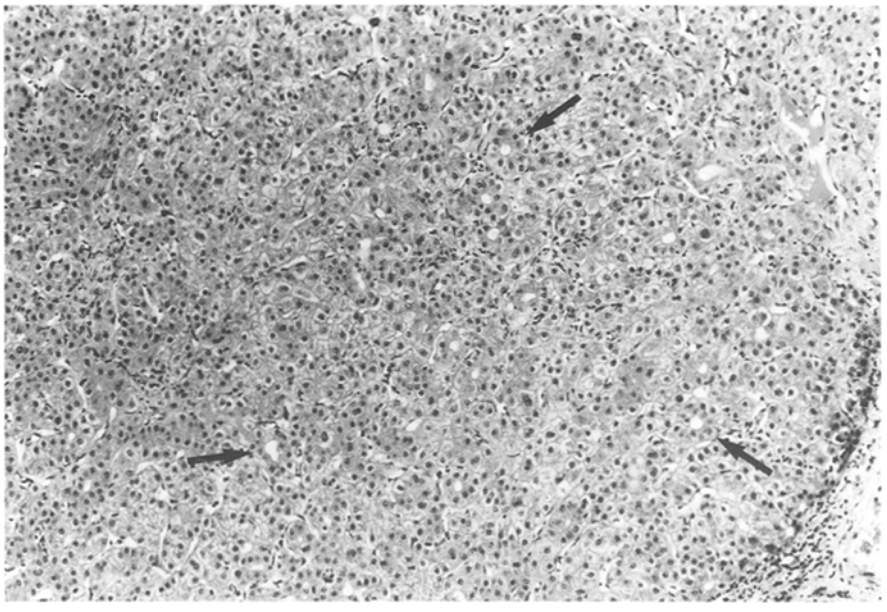

Fig. 5. This hepatic parenchymal area shows numerous pseudoglandular formations (*arrows*). Primary biliary cirrhosis (stage II). H & E, ×200

cellularity was recognizable quantitatively as an increased nuclear count (Table 1). These areas were irregularly arranged as "clear-cut trabecular pattern" of two or four cell thickness or compact features (Figs. 1, 2). There was, on occasion, abrupt transition in the same hepatocellular cords between the hepatocytes of these small cell changes and of the adjoining hepatocytes (Fig. 3). Some of the hepatocytes within this lesion showed rosette formation.

Large cell change (Figs. 3, 4) was characterized by cellular and nuclear enlargement of variable degrees. This type of lesion is unusual. Nuclei were vesicular and pleomorphic and nucleoli were rather prominent (Fig. 3). The nuclei with prominent nucleoli and thickened nuclear membrane were vesicular and the cytoplasm was acidophilic. There were binucleated cells on occasion (Fig. 3). Foci of these lesions were occasionally admixed with small cell change (Fig. 4).

Foci or areas of hepatocytes disclosed a considerable number of rosettes or gland-like formation (Figs. 5, 6). A majority of these liver cell rosettes were small and immature, while some were well-formed (Fig. 5). Some foci of this unusual lesion were totally composed of liver cell rosettes (Fig. 5), while the other foci showed scattered liver cell rosettes. Hepatocytes in these areas had rather hyperchromatic nuclei, and some parts were composed of rather small hepatocytes usually seen in the small cell change type mentioned above.

Either of these three lesions generally showed an expansile growth or shaggy border to each other or the surrounding hepatic parenchyma (Figs. 1, 2, 5). At the shaggy border, unusual hepatocytes occasionally showed

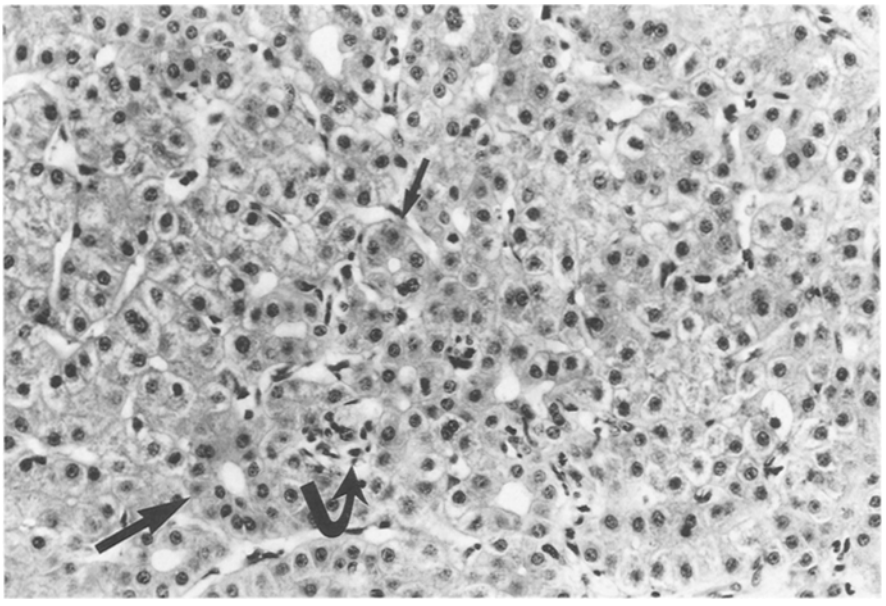

Fig. 6. Higher mangification of Fig. 5. There are microacinar formations (*small arrow*) and well-developed pseudogland formation (*large arrow*). There is focal hepatocellular necrosis (*curved arrow*) and also an apparently increased number of sinusoidal lining cells. Primary biliary cirrhosis (stage II). H & E, ×750

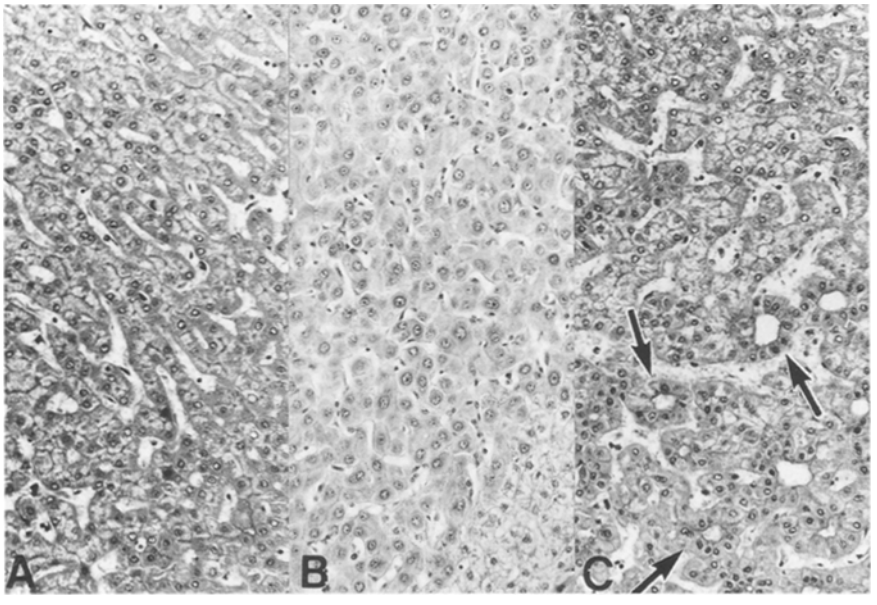

Fig. 7A–C. Unusual hepatocellular lesions in adenomatous hyperplasia of the liver. **A** Small cell change of hepatocytes showing thin trabecular pattern and basophilic cytoplasm. H & E, ×300. **B** Hepatocytes show large cell change with large nuclei and prominent nucleoli and increased sinusoidal lining cells are also seen. H & E, ×300. **C** Hepatocytes show many pseudoglandular formations (*arrows*) in the lower half. H & E, ×300

an abrupt transition in the same hepatocellular cords (Fig. 2). Otherwise, there was gradual transition between two areas (Fig. 4). The sizes of these unusual areas were variable, though a majority of them were equal to or smaller than a hepatic lobule. These changes were found in any part of a hepatic lobule. These three unusual lesions were generally found in a variable combination in the same specimen. A reticulin framework of hepatic parenchyma was well preserved in these unusual lesions. There were constantly hyperplastic Kupper cells and also sinusoidal lymphoid cell infiltration, and focal necrosis of hepatocytes was occasionally found within these unusual lesions (Fig. 6).

There was no expression of AFP in unusual hepatic parenchymal areas showing any of the three types or in adjoining parenchymal areas in PBC livers. Receptors of UEA-I were constantly expressed on the endothelium of blood vessels within the portal tracts and focally on sinusoidal endothelium around the portal tracts. However, these receptors were negative on the sinusoidal endothelial cells in the unusual parenchymal areas as well as in adjoining surrounding parenchyma.

The unusual hepatocellular features mentioned above were frequently seen in stages II and III of PBC (small cell change, large cell change and liver cell rosettes were found in 71%, 47% and 41% in stage II, and 100%, 22% and 33% in stage III, respectively), but were infrequent in stage I (small cell change, large cell change and liver cell rosettes were found in 36%, 27%, and 0%, respectively). The exent of these lesions was rather focal in stage I when compared with stages II and III. Although the degree, extent and combination pattern

Table 2. Frequency and degree of three types of unusual hepatocellular lesions in primary biliary cirrhosis

	Small cell change	Large cell change	Liver cell rosettes
Stage I (11 cases)			
−	7	8	11
+	2	3	0
++	2	0	0
Stage II (17 cases)			
−	5	9	10
+	3	7	5
++	9	1	2
Stage III (9 cases)			
−	0	7	6
+	6	1	3
++	3	1	0

−, No or minimal foci of unusual hepatocellular hepatocytes; +, focal occurrence of unusual hepatocellular lesions; ++, moderate to marked occurrence and widespread distribution of unusual hepatocellular lesions

of these features were variable from one case to another, small cell changes were most frequent and widespread relative to other two types (see Table 2). In two cases of stage II and one case of stage III, almost all hepatic parenchyma examined showed small cell change and/or large cell change.

Follow-up studies failed to detect or result in a diagnosis of HCC in 21 cases of PBC. Nine cases were autopsied and the livers showed advanced histological stages of PBC but failed to harbour HCC or atypical AH.

The three types of unusual hepatocellular lesions were also found in 10 cases of atypical AH in varying degrees and extent (Fig. 7), though nuclear hyperchromasia and thickening of nuclear membranes were more prominent in atypical AH relative to those in PBC. Increased cellularity represented by increased nuclear counts was also shown in the small cell changes in atypical AH nodules (Table 1).

Discussion

Small cell change with increased cellularity or large cell and gland-like formation of hepatocytes with hyperchromasia collectively constitute small, well-differentiated HCC or its borderline lesions, including atypical AH (Arakawa et al. 1986; Furuya et al. 1988; Kondo et al. 1987, 1988; Nakanuma et al. 1990a; Nakashima et al. 1990; Sakamoto et al. 1991). This study confirmed the presence of three such types of lesions in atypical AH. The aim of this study was to clarify the degree and extent of unusual structural and cellular patterns of hepatocytes of reactive natures relevant to the histological diagnosis of well-differentiated, small HCC or its borderline lesion.

The current study disclosed that the three types of unusual structural and cellular patterns of hepatocytes with hyperchromatic nuclei resembling well-differentiated, small HCC and its borderline lesions were found in a considerable number of non-cirrhotic stages of PBC. Small cell changes with increased nuclear density and hyperchromasia in PBC livers resemble small cell dysplasia, well-differentiated normotrabecular HCC and also atypical AH (Kondo et al. 1987, 1988; Nakanuma et al. 1990a; Tsuda et al. 1988; Watanabe et al. 1983). We found that the nuclear density in these foci of PBC livers was comparable to that of atypical AH, reflecting the fact that the increased cellularity was similar in these foci in PBC and atypical AH. Large cell change apparently resembles the large cell dysplasia of Anthony (Anthony et al. 1973; Watanabe et al. 1983) and also resembles atypical AH (Nakanuma et al. 1990a). Several studies have disclosed that large dysplastic cells actively proliferate and may play a role in the evolution of HCC (Roncalli et al. 1988; Thomas et al. 1992). Liver cell rosettes or gland-like formation with hyperchromatic nuclei are reported in well-differentiated small HCC and atypical AH (Kondo et al. 1987, 1988; Nakanuma et al. 1990a).

Of interest is the finding that these unusual hepatocellular changes were rather frequent in stages II and III relative to stage I in PBC. This suggests that the changes are secondary to periportal hepatocellular injuries occurring in stages II and III, and that they are not of a neoplastic nature. Failure to detect HCC and atypical AH nodules in the follow-up study of PBC, the absence of hepatocellular expression of AFP, sinusoidal expression of receptors of UEA-I, and preserved reticulin pattern in these unusual areas in PBC livers support this suggestion. Portmann et al. (1985) also briefly reported regenerative features of hepatocytes with unusual cellular and structural features in PBC, i.e. grouping of enlarged hepatocytes with prominent nucleoli and two-cell thickness and also a rosette formation of hepatocellular cords.

Tarao et al. (1991), using imaging analysis of liver volume and incorporation study of bromodeoxyuridine, disclosed that PBC livers were enlarged in stages II and III. They also reported that DNA synthetic activities of hepatocytes were significantly increased in these stages compared to normal livers, chronic active hepatitis and compensated liver cirrhosis. They suggested that active hepatocellular hyperplasia, probably a reflection of regeneration, is considerably raised in these stages. The reasons why the DNA synthetic potency of hepatocytes is markedly increased in certain stages of PBC remain unclear but may correspond to the unusual histological findings of regenerating hepatocytes in PBC which were found in this study. Nodular regenerative hyperplasia of the liver in PBC in early histological stages may also represent such an active hepatocellular proliferation of non-cirrhotic PBC livers (Colina et al. 1992; Nakanuma and Ohta 1987).

It is also of interest that unusual hepatocellular lesions formed variably sized areas, some of which showed vague nodularities without a fibrous rim. Furthermore, such areas or nodules showed compressive growth or abrupt or gradual transition against the adjoining hepa-

tocytes in the same hepatocellular cords. The compressive growth and abrupt transition at their borders resemble the growth patterns of HCC. In particular, the latter feature may well be in accordance with the "replacing" growth pattern of HCC proposed by Nakashima et al. (1982). These features of hepatocytes at their borders probably reflect an epiphenomenon of active growth of neoplastic as well as non-neoplastic hepatocytes within the hepatocellular cords.

This study has shown that non-cirrhotic hepatic parenchyma of PBC shows unusual hepatocellular lesions resembling but unrelated to well-differentiated, small HCC or its borderline lesions.

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