Virchows Archiv A Pathol Anat (1993) 422:247–252

Virchows Archiv A
Pathological Anatomy and Histopathology

Case report

Adenomatous hyperplasia of the liver resembling focal nodular hyperplasia in patients with chronic liver disease

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Received October 5, 1992 / Received after revision November 9, 1992 / Accepted November 10, 1992

Abstract. Two nodules of hepatic adenomatous hyperplasia (AH) resembling focal nodular hyperplasia were found in two patients with cirrhosis or chronic active hepatitis. Imaging techniques suggested that the nodules were hepatocellular carcinoma. Pathological examination showed that the nodules (approximately 1.0 cm in diameter) were clearly demarcated from the surrounding liver tissue, and contained foci of scar-like fibrosis in the centre of the nodules. Microscopically, they contained portal tracts and fulfilled the criteria of AH. A large number of arteries were present in the central scar-like fibrosis as well as in the parenchyma of the nodules. There were foci of mildly atypical hepatocytes in one nodule but no cellular atypia in the other. Morphometric analysis showed that the cumulative luminal area of arteries per unit area was much greater in the nodules than in the extranodular liver tissues, while the cumulative luminal area of portal veins per unit area was much less in the nodules than in the extranodular liver tissues. Although the pathogenesis is unclear, these nodules might have developed through localized vascular changes associated with chronic liver disease, may have arisen from pre-existing arterial malformation, or may represent the early stages of angiogenesis in hepatocarcinogenesis.

Key words: Adenomatous hyperplasia – Liver – Focal nodular hyperplasia – Radiology – Pathology

Introduction

Recent advances in imaging have made it possible to detect small nodular lesions in the liver in patients with chronic liver disease. Although most such nodules are small hepatocellular carcinomas (HCC), a minority are large regenerative nodules or nodules of uncertain malignancy. Such large or equivocal nodules have been termed adenomatous hyperplasia (AH) or macroregenerative nodule (MRN) (Eguchi et al. 1992; Ferrell et al. 1992; Furuya et al. 1988; Nakanuma et al. 1990; Sakamoto et al. 1991; Terada and Nakanuma 1991; Terada and Nakanuma 1992; Theise et al. 1992; Ueda et al. 1992).

The term AH of the liver was originally coined by Edmondson (1976) for a sizable hepatocellular nodule which develops following acute or chronic liver injuries, especially in cirrhosis. Recently, AHs have been considered to be preneoplastic or early-neoplastic lesions in human hepatocarcinogenesis, because they occasionally contain malignant hepatocellular foci and frequently coexist with HCC (Furuya et al. 1988; Nakanuma et al. 1990; Ueda et al. 1992). Nodules of AH characteristically contain portal tracts with portal veins, hepatic arteries and bile ducts (Furuya et al. 1988; Nakanuma et al. 1990; Ueda et al. 1992). AHs show heterogeneous morphology, and can be divided into the following types: ordinary AH or MRN type 1, atypical AH or MRN type 2, and AH with focal malignancy (Furuya et al. 1988; Nakanuma et al. 1990; Ueda et al. 1992). Ordinary AH is devoid of hepatocellular atypia, atypical AH consists of atypical hepatocytes not regarded as malignant, and AH with focal malignancy contains overt HCC foci (Nakanuma et al. 1990; Ueda et al. 1992).

Focal nodular hyperplasia (FNH) of the liver, a term first coined by Edmondson (1956), is a nodular lesion occurring in the almost normal liver (Fechner and Roehm 1977; Kerlin et al. 1983; Knowles and Wolff 1976; Mays et al. 1974; Wanless et al. 1985). FNH is characterized macroscopically by the non-encapsulated nodule with central stellate scar. Microscopically, the central scar consists of fibrous tissue and many arterial or venous blood vessels. The hepatocytes surrounding the central scar are hyperplastic, and there are many ductular elements admixed with hyperplastic hepatocytes. Although several theories on the pathogenesis of FNH have been proposed such as inflammation, hamar-

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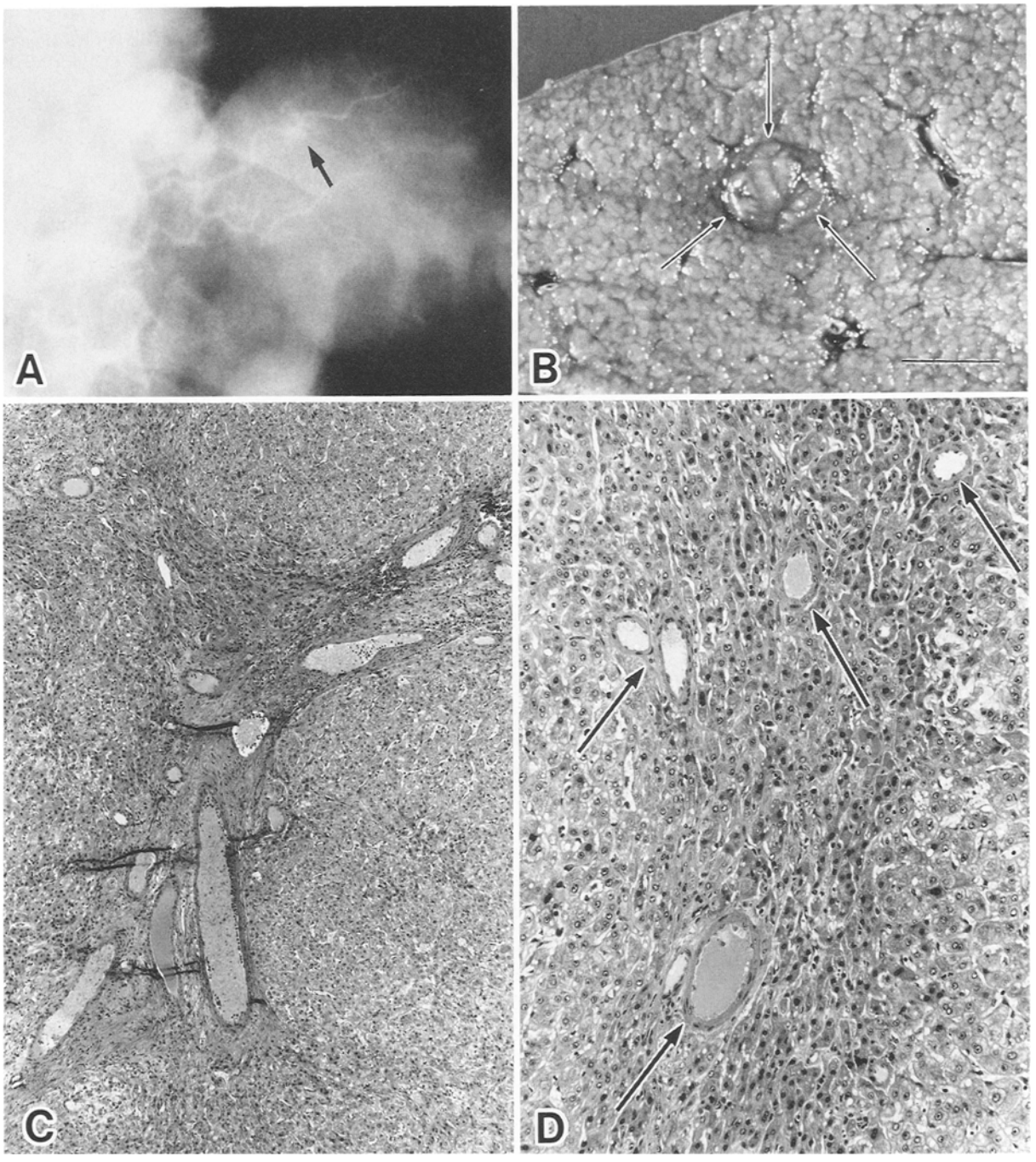

Fig. 1A–D. Case 1. **A** Hepatic angiography demonstrates that the nodule is hypervascular (*arrow*). **B** The nodule (*arrows*) measuring 1.0 × 1.2 cm in diameter is different from surrounding regenerative nodules in size, colour and texture. Scar-like discolorations are present in the nodule. The background liver exhibits micronodular cirrhosis. *Bar* = 1 cm. **C** The central scar-like area consists of fibrous tissue and many arteries. Haematoxylin and eosin, × 50. **D** Arteries (*arrows*) are abundant in the hepatocytes of the nodule. There is mild hepatocellular atypia, but the hepatocytes are not malignant. Haematoxylin and eosin, × 100

toma, and an association with oral contraceptive pills, it is now believed that FNH is an arterial malformation accompanied by hepatocellular hyperplasia (Wanless et al. 1985).

We recently encountered two nodules of AH in two patients with cirrhosis or chronic active hepatitis. Interestingly, the AH nodules of the patients shared features of FNH.

Case reports

Case 1

A 44-year-old man was admitted to our University Hospital because of headache and fever. He had drunk alcohol (45 g/day) for 20 years. He denied a history of blood transfusion. Laboratory data revealed severe liver dysfunction. Hepatitis B surface antigen (HBsAg), antibody to HBsAg, and antibody to hepatitis B core

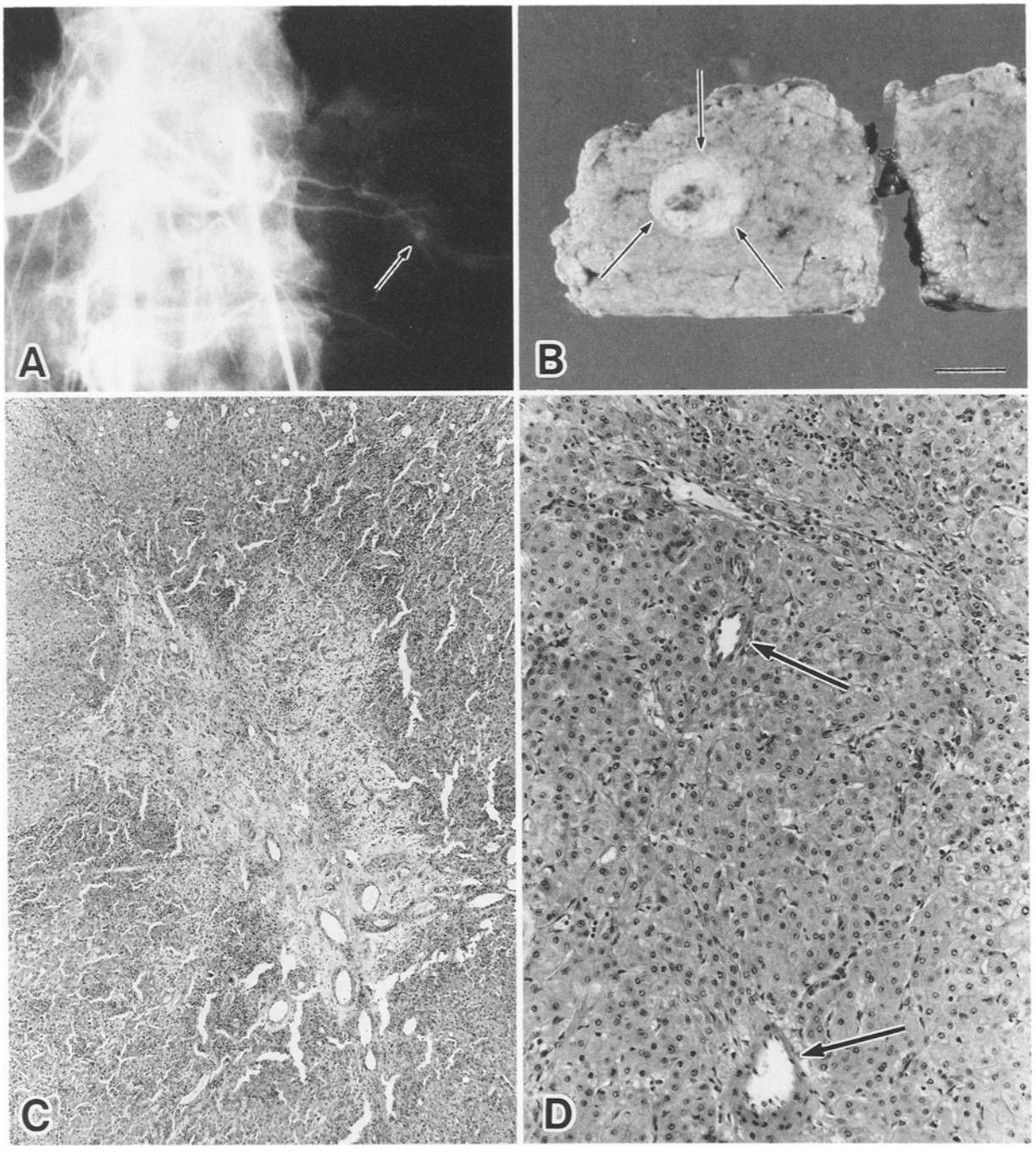

Fig. 2A–D. Case 2. **A** Hepatic angiography shows that the nodule is hypervascular (*arrow*). **B** The nodule (*arrows*) measuring 1.2 × 1.2 cm in diameter is different from the surrounding liver tissue in colour and texture. Scar-like discolorations are present in the centre of the nodule. The background liver is fibrotic (chronic active hepatitis). *Bar* = 1 cm. **C** The central scar-like area consists of fibrous tissue, many arteries and ductular elements. Haematoxylin and eosin, × 50. **D** Arteries (*arrows*) are abundant in the hepatocytes of the nodule. There is no hepatocellular atypia. Haematoxylin and eosin, × 100

antigen were negative. Antibody to hepatitis C virus (anti-HCV) was not available. A diagnosis of cirrhosis was made. Ultrasound of the liver revealed a poorly echogenic nodular lesion (approximately 1 cm in diameter) in the external inferior segment in the left lobe. The nodular lesion was also detected as a low-density area by computed tomography (CT). Hepatic arteriography disclosed that the lesion was hypervascular (Fig. 1A), and showed a perfusion defect by CT during arterial portography (CT-AP). CT during arteriography (CT-A) showed that the lesion was perfused by arterial blood. These findings suggested that the nodule was HCC. Surgical resection of the hepatic left lobe was performed.

Case 2

A 59-year-old man was admitted to our University Hospital because of general malaise. He had drunk alcohol (54 g/day) for 20 years. There was no history of blood transfusion. Laboratory

data indicated moderate liver dysfunction. HBsAg and anti-HCV were negative. Alpha-fetoprotein was within the normal range (2.5 ng/ml). He was diagnosed as having chronic active hepatitis. Ultrasound of the liver revealed a poorly echogenic nodular lesion (approximately 1 cm in diameter) in the external inferior segment in the left lobe. CT revealed that the lesion was low in density and hepatic angiography disclosed that it was hypervascular (Fig. 2A). The lesion showed a perfusion defect by CT-AP and was stained by CT-A. These findings suggested that the nodule was HCC. Partial resection of the hepatic left lobe was performed.

Materials and methods

The resected specimens were fixed in 4% neutral formaldehyde solution and liver blocks containing the nodular lesions and those without nodular lesions were obtained. They were embedded in paraffin, and stained with routine staining methods. As controls, we obtained ten nodules of ordinary AH with cirrhosis, ten nodules of atypical AH with cirrhosis, and ten nodules of small HCC with cirrhosis from recent surgical files of our laboratory, and processed them as described above.

On the haematoxylin- and -eosin-stained sections, we measured the cumulative areas of blood vessel lumens (arteries and portal veins) per unit area in the two nodules and control AH and HCC nodules as well as in the surrounding liver tissue, using a computed imaging analytical apparatus (Nexus 6400, Kashiwagi Laboratory, Tokyo, Japan), personal computer (PC-9801, NEC, Tokyo, Japan) and video camera (BK5001, Hitachi Electronics, Tokyo, Japan). Only vessels of 10 μm or more in minimum diameter were examined. The ratio of cumulative luminal areas of vessels per unit area in the nodules to those in the surrounding liver parenchyma was calculated.

Results

Case 1

Grossly, the resected left hepatic lobe contained a nodular lesion measuring 1.0×1.2 cm in diameter (Fig. 1B). The liver showed micronodular cirrhosis (Fig. 1B). The nodule bulged from the cut surface, and was different from the surrounding cirrhotic part as regards size, texture and colour (Fig. 1B). Scar-like discolorations were observed in the nodule (Fig. 1B).

Microscopically, it was partially demarcated from the surrounding cirrhotic parts by a thin fibrous band (pseudocapsule), while other parts of the nodule gradually merged with the surrounding cirrhotic parts. In the central portion of the nodule, there were areas of spider-like fibrosis, in which many arterial vessels and a few biliary elements were present (Fig. 1C). The spider-like fibrosis subdivided the parenchyma of the nodule into several lobules with ductular proliferation. Many arteries were also present in the parenchyma of the nodule (Fig. 1D). Venous vessels were very sparse. There were a few portal tracts with portal veins, arteries and bile ducts in the nodule. Most hepatocytes of the nodules lacked atypia, and resembled those of the surrounding cirrhotic part. However, there were a few foci of hepatocytes with mild atypia such as nuclear crowding, hyperchromasia and irregular contour (Fig. 1D). There were no overt malignant hepatocellular lesions in the nodule. The background liver showed micronodular cirrhosis with thin fibrous septa. Histological diagnoses were atypical AH resembling FNH and liver cirrhosis.

Table 1. The ratio of cumulative luminal areas of arteries and portal veins per unit area in the nodule to those in the liver tissue surrounding the nodule

Nodule	Arteries	Portal veins
Case 1	9.02	0.03
Case 2	3.28	0.18
Controls		
Ordinary AH ($n=10$)	0.73 ± 0.42	0.41 ± 0.38
Atypical AH ($n=10$)	1.03 ± 0.65	0.27 ± 0.25
Small HCC ($n=10$)	6.45 ± 7.54	0.01 ± 0.02

AH, Adenomatous hyperplasia; HCC, hepatocellular carcinoma

Case 2

Grossly, a nodule measuring 1.2×1.2 cm was seen in the resected specimens (Fig. 2B). The liver showed mild fibrosis, but no regenerative nodules were seen (Fig. 2B). The nodule bulged from the cut surface, and was different from the surrounding part as regards texture and colour. In the central part of the nodule, scar-like areas were seen (Fig. 2B).

Microscopically, the nodule was well demarcated from the surrounding liver tissues by thin, fibrous capsule. A few areas of scar-like fibrosis were present in the central portion of the nodule (Fig. 2C). The scar-like fibrosis contained many arteries and a few biliary elements (Fig. 2C). Many arteries were also present in the parenchyma in the nodule (Fig. 2D). Portal veins were few. Several foci of atypical bile ductular proliferation with inflammatory infiltrates and occasional cholestasis were present in the nodule. There was a portal tract with portal vein, hepatic arteries and bile ducts in the nodule. The hepatocytes of the nodules showed no atypia (Fig. 2D). The background liver showed chronic active hepatitis. Histological diagnosis was ordinary AH resembling FNH, and chronic active hepatitis.

In both nodules, the ratio of cumulative luminal areas of arteries per unit area in the nodule to those in the surrounding cirrhotic liver was high (case 1, 9.02; case 2, 3.28), while the comparable ratio for portal veins was low (case 1, 0.03; case 2, 0.18) (Table 1). When compared with control AHs and HCCs, the ratio of cumulative luminal areas of arteries in the nodule to those in the surrounding liver was much higher in the two nodules than in the control ordinary and atypical AHs, and the ratio in the two nodules was similar to the ratio in HCCs (Table 1). In contrast, the ratio of cumulative luminal areas of portal veins in the nodule to those in the surrounding liver was much lower in the two nodules than in the control ordinary and atypical AHs, and the ratio in the two nodules was similar to the ratio in HCCs (Table 1).

Discussion

These nodules were found in livers with chronic liver disease, and were composed of non-malignant hepatocytes with portal tracts. Thus, the two nodules fulfil the criteria of AH or MRN (Edmondson 1976; Furuya et al. 1988; Nakanuma et al. 1990; Ueda et al. 1992). However, they were somewhat different from usual AHs or MRNs in that they contained scar-like fibrosis, abundant arteries and few portal veins. Morphometric analysis confirmed that the vasculature of our nodules are different from usual AHs. The scar-like fibrosis and abundant arteries are characteristics of FNH, but FNH occurs in otherwise normal livers and does not contain portal tracts. Thus, the nodules of the present study are not FNH of the liver, and we made the diagnosis of AH resembling FNH. A similar case was recently reported by Sugihara et al. (1990).

Radiologically, CT-AP reflects portal blood flow (Matsui et al. 1983), while CT-A represents hepatic arterial flow (Prando et al. 1979). Radiological examinations revealed that the nodules were supplied exclusively by arterial blood, and portal flow was scant. The radiological findings of our nodules were compatible with those of HCC (Matsui et al. 1991), indicating the difficulty of distinguishing them from HCC radiologically. A histological and morphometrical analysis confirmed that the nodules were supplied exclusively by arterial blood vessels, and portal veins were very sparse in the nodules. Radiologically, it has been reported that AHs are supplied by both arterial and portal vessels, although the blood flow of arteries and portal veins of AHs is scanty relative to the surrounding liver tissues (Matsui et al. 1991). FNH has been reported to be supplied by arterial blood (Fechner and Roehm 1977; Kerlin et al. 1983; Wanless et al. 1985), although portal supply of FNH is unclear. Thus, it must be stressed that when hepatic nodules with exclusive arterial blood supply are encountered, AH resembling FNH must be considered and FNH in addition to HCC. In this situation, the presence of underlying chronic liver disease may indicate HCC or AH resembling FNH, although their radiological distinction is very difficult.

Although the pathogenesis of the nodules of the present study is unclear, there are three hypotheses. First, it is well known that the hepatic vascular architecture alters dramatically in chronic liver disease, especially cirrhosis. In our nodules, this altered hepatic vascular architecture might have aggregated arteries in an area of the liver. The aggregated arteries in turn might have caused hepatocellular hyperplasia, thus giving rise to AH resembling FNH. Secondly, it is possible that arterial anomalies had been present and had caused FNH in our patients. Subsequently, the patients had developed chronic liver disease, thus causing AH resembling FNH. Thirdly, our nodules might have been initially usual AHs in which, subsequently, arteries might have developed in the nodules, causing AH resembling FNH. Thus, the many arterial elements of our nodules may represent early stages of angiogenesis in carcinogenesis of HCC. Angiogenesis in a tumour is known to appear even in the stage of hyperplastic lesions before tumour formation (Folkman et al. 1989). This angiogenetic hypothesis may be supported by the fact that AHs are considered to be preneoplastic lesions and by the fact that atypical AH in case 1 had more arterial elements than did ordinary AH in case 2.

Finally, both of our nodules were present in the external inferior segment of the hepatic left lobe. This may be coincidental, since this part of the liver is not different in its vascular anatomy from other parts and is not a preferential site for AHs.

Acknowledgements. This work was supported in part by a Grant-in-Aid from the Ministry of Education, Science and Culture of Japan (no. 04454179) and the fund for medical treatment of the elderly of Kanazawa University School of Medicine.

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