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CASE REPORT

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Cholangiocarcinoma arising in bile duct adenoma with focal area of bile duct hamartoma

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Abstract A 59-year-old male with history of sigmoid colon cancer had a high serum-CEA level and was referred for the evaluation of metastatic liver disease. Ultrasonography and computerized tomography showed two tumours in the liver. Macroscopically, these were in segment 4 (S4) and 2 (S2). Histologically, the tumour in S4 showed a number of bile ductules with variable amounts of stroma, an appearance compatible with bile duct adenoma (BDA). There were markedly atypical ductules of various sizes, the epithelium of which had coarsely granular/hyperchromatic large nuclei, in some areas of the lesion. These atypical ductules showed invasive growth into the liver parenchyma. Some cystically dilated ductules with bile plugs resembling bile duct hamartoma (BDH) were also seen. The other tumour in S2, was a metastatic adenocarcinoma from sigmoid colon and showed strongly positive staining for CEA. Since the lesion in S4 of our case is solitary and most of histological features are similar to those of BDA with markedly atypical bile ductules, we consider that this may be the first case of cholangiocarcinoma associated with BDA with focal area of BDH. It is possible that the adenoma-carcinoma sequence occurs in biliary tumours.

Key words Bile duct adenoma · Cholangiocarcinoma · Bile duct hamartoma · Proliferating cell nuclear antigen

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Introduction

Benign bile duct tumours and tumour-like lesions of the liver are rare [4, 10]. Malignant transformation of biliary tumours and tumour-like lesions is even rarer. There have been a few reports describing cholangiocarcinoma associated with multiple bile duct hamartoma (MBDH), also referred to as "Meyenburg complex" [2, 3, 7]. We describe a case of bile duct adenoma (BDA) in which a focal area had histological features indistinguishable from those of bile duct hamartoma (BDH). The latter element contained an area with markedly atypical bile ductules with invasive growth, which were interpreted as cholangiocarcinoma.

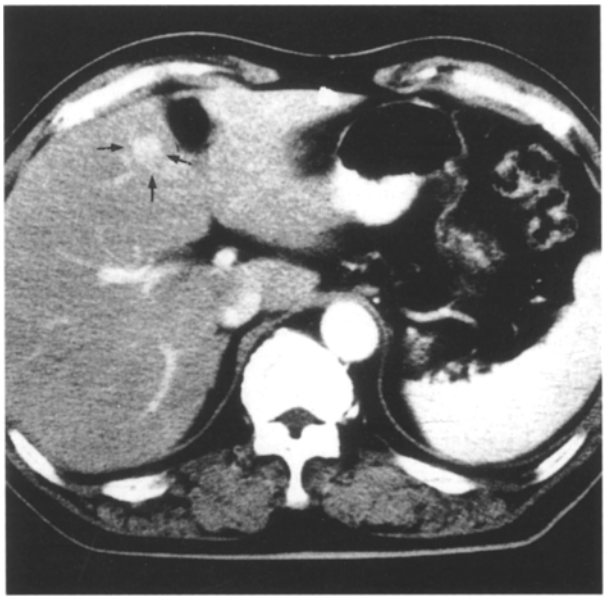

Fig. 1 Computerized tomography of the liver. There is a high-density area (*arrows*) in segment four

Clinical history

A 59-year-old man with a history of rectosigmoidectomy for advanced sigmoid colon cancer was referred to the National Cancer Center Hospital East for evaluation of liver metastasis of colon cancer. Ultrasonography (US) showed two mass lesions in segment two (S2) of the left lobe and segment four (S4) of the right lobe of the liver. The former had low echogenicity and the latter had central high and peripheral low echogenicity. Computerized tomography (CT) after intravenous bolus injection of iopamidol (Schering Co., Osaka, Japan) showed that the former tumour was stained in the late phase, while the latter was stained in the rapid phase (Fig. 1). On the basis of these findings, the former was considered to be metastatic colon cancer as was the latter, although a primary tumour of the liver could not be excluded. The rest of the liver, biliary tract, spleen, pancreas, and kidneys were unremarkable. The level of serum carcinoembryonic antigen (CEA) was 143.7 ng/ml (<50 ng/ml), but all other laboratory data, including SGOT/SGPT, alkaline phosphatase, bulirubin, albumin, and prothrombin time, were normal. Laboratory tests for hepatitis B and C were negative. The patient underwent partial resection of S2 and S4 of the liver in December 1992.

Postoperatively the patient recovered without complications and CEA decreased to a normal level. The patient is currently alive and well without any signs of recurrent malignant disease 19 months after surgery.

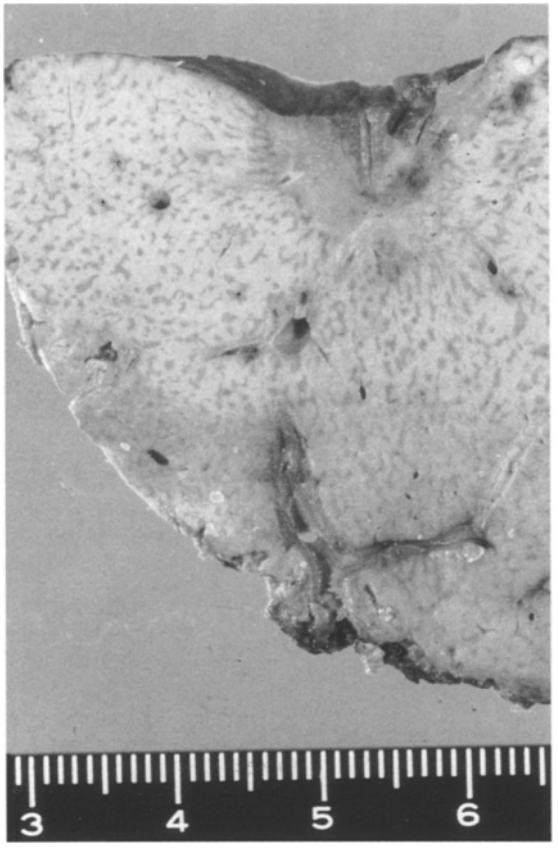

Fig. 2 Cut section of segment four of the liver. A well circumscribed, nonencapsulated tumour is evident in the subcapsular area

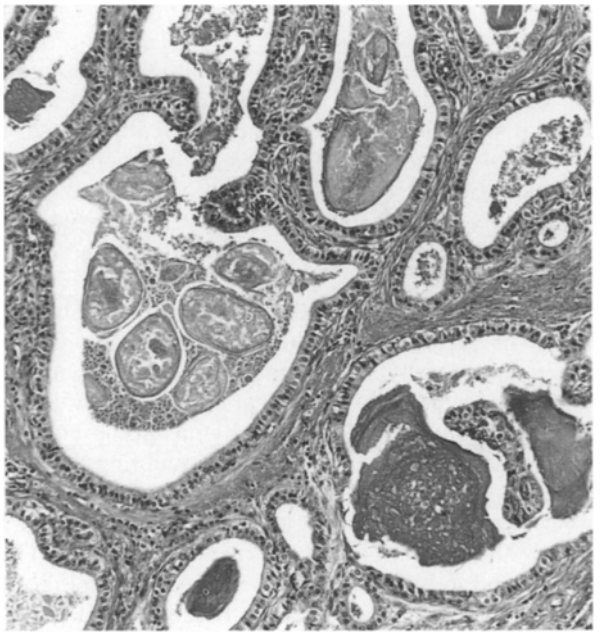

Fig. 4 Area with features of bile duct hamartoma. Some cystically dilated bile ductules have bile plugs within their lumina. H&E, ×100

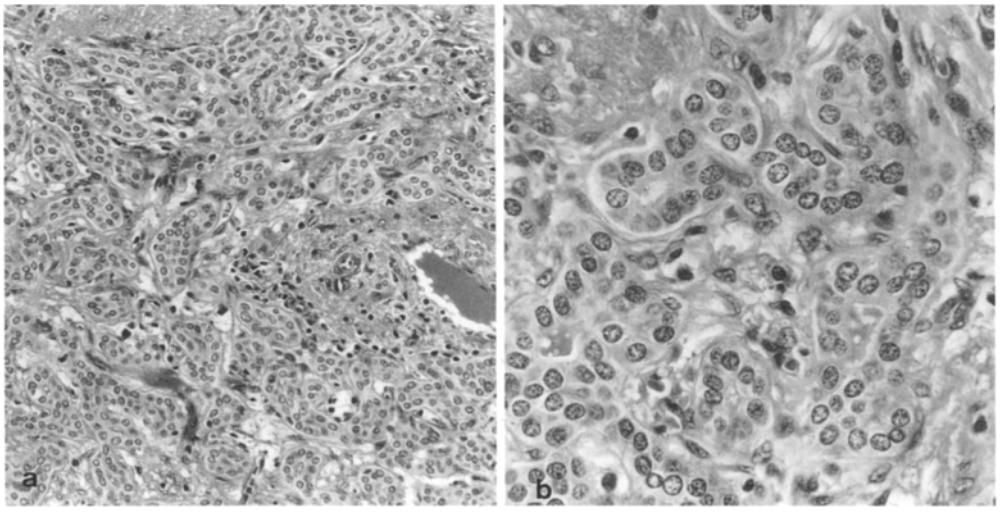

Fig. 3a, b Microscopic appearance of the tumour in segment four. **a** Highly packed bile ductules are present in a scanty to moderate amount of surrounding connective tissue. H&E, ×100 **b** Higher power view of the bile ductules. The epithelial cells have a moderate amount of cytoplasm and small round to oval nuclei with finely granular chromatin. H&E, ×200

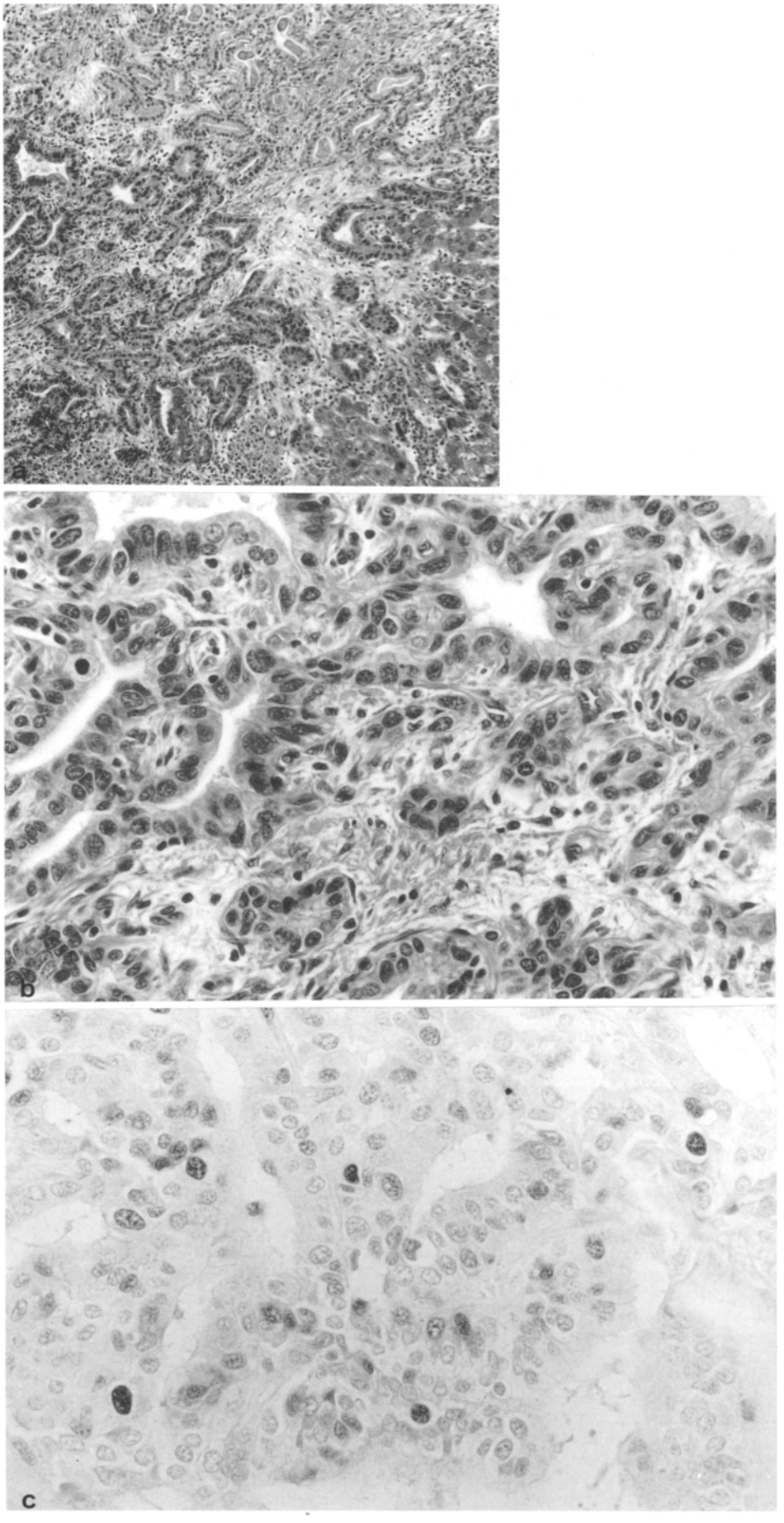

Fig. 5a–c Area of cholangiocarcinoma. **a** Irregularly shaped atypical bile ductules are seen adjacent to apparently benign ones. Some of them invade adjacent liver parenchyma (right lower corner). H&E, ×100 **b** Epithelial cells of atypical bile ductules have irregularly shaped and various-sized nuclei with coarsely granular chromatin and some of atypical bile ductules showed stromal invasion. H&E, ×200 **c** Cells of atypical bile ductules show positive nuclear staining for PCNA on immunohistochemistry. ×200

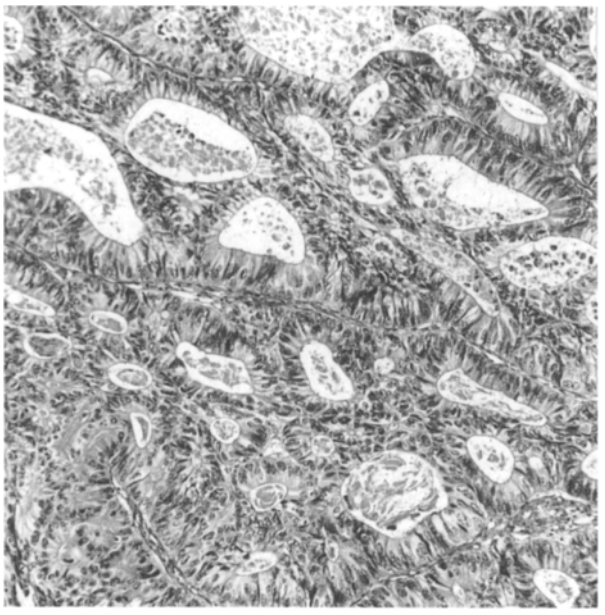

Fig. 6 Tumour in segment two of the liver. The histological features are different from the tumour in segment four and similar to the well differentiated adenocarcinoma of the colon primary. H&E, ×100

Pathological findings

Macroscopic

The specimen from S4 weighed 70 g and measured 5.5×4.0×4.5 cm. There was a tumour measuring 2.2×2.0×1.0 cm located in the subcapsular area (Fig. 2). It had no capsule, but was well circumscribed from the surrounding liver parenchyma. The cut surface of the tumour was light tan to greenish-white without foci of necrosis or haemorrhage.

The specimen from S2 measured 7.0×6.5×3.5 cm and weighed 100 g. There was a greyish-white, well circumscribed, tumour measuring 3.5×3.0×2.4 cm in the liver parenchyma. The remainder of the liver parenchyma was remarkable.

Microscopic

The tumour in S4 was fairly well circumscribed, but not encapsulated. It was composed of a number of bile ductules with a scanty to moderate amount of surrounding connective tissue (Fig. 3a). The lumena of the bile ductules were narrow or occasionally dilated slightly. These ductules were lined with small cuboidal cells having uniform small round to oval, finely granulated, nuclei and a moderate amount of light eosinophilic cytoplasm (Fig. 3b). There was no hyperchromasia of the nuclei or mitotic activity. These histological features were those of BDA [1, 6]. In some areas, cystically dilated ductules with brown bile plugs whose histological features resembled BDH were seen (Fig. 4). There was no mucous plugs in this lesion. Inflammatory cell infiltration was observed, composed predominantly of lymphoid cells sometimes forming lymph follicles in the surrounding connective tissue. In addition, markedly atypical and irregularly shaped bile ductules of various sizes were noted in some areas of the lesion and some of them invaded the stoma and extended into the adjacent liver parenchyma (Fig. 5a). There were bile ductules with atypical epithelium in the areas of transition between the markedly atypical bile ductules and apparently benign bile ductules. The epithelium of the markedly atypical bile ductules had coarsely granular and hyperchromatic irregularly shaped large nuclei (Fig. 5b). Mitotic figures were seen occasionally. The tumour in S2 consisted of tall columnar neoplastic cells quite typical of well-differentiated adenocarcinoma (Fig. 6), and the histological features were mostly similar to those of sigmoid colon cancer and clearly different from those of the S4 tumour. This was diagnosed as a metastasis from colon cancer.

The liver parenchyma of S4 and S2 surrounding the tumours showed mild fatty change of hepatocytes without hepatitis or cirrhosis. No adult worms or eggs of parasites or intrahepatic stones were found.

An immunohistochemical study was performed on paraffin-embedded tissue sections. Antibodies against CEA (Mochida, Tokyo, Japan, ×500) and PCNA (PC10, Novocastra, Newcastle, UK, ×100) were used with the avidin-biotin-peroxidase complex (ABC) technique [8]. Appropriate positive and negative controls were used for the two antibodies. Sections were counterstained with haematoxylin. To obtain the PCNA index, at least 1000 epithelial cells in ductules were counted at random in high-power fields (×400). PCNA index was calculated as the percentage of cells with positively stained nuclei among all cells counted. Brown to dark brown staining of the cell nuclei was considered as positive. The PCNA index of epithelial cells in markedly atypical bile ductules was 27.2% and higher than that (3.5%) of apparently benign epithelial cells of narrow to slightly dilated bile ductules (Fig. 5c). The metastatic tumour cells in S2 showed strongly positive staining for CEA. BDA was negative for CEA.

Discussion

BDA is usually a solitary lesion located in the subcapsular region, ranging in size from 1 to 20 mm, and well circumscribed without a capsule [1, 6]. Histologically, it is composed of small or slightly dilated ductules with various degrees of inflammatory cell infiltration and fibrosis. The macroscopic appearance and histological features of most of the liver tumour found in S4 in the present case corresponded to those of BDA. However, the histological features of ductules showing cystic dilatation or containing bile plugs were similar to those of BDH rather than BDA [6]. BDH is typically multiple, varying in diameter from 0.1 to 0.5 cm, and referred to as von Meyenburg complexes or MBDH. Multiplicity, cystic change of bile ductules and the presence of bile plugs are useful criteria for differentiating BDH from BDA [6]. Since the tumour in the present case was solitary and its main histological features were those of BDA, this unusual lesion was considered to be BDA with a focal area of BDH.

PCNA is present in the nuclei of cells in late G1 and S phase [11, 13], thus serving as a marker of proliferation. It has been demonstrated that the PCNA index is useful for the grading of malignancy [12, 16]. In the present case, the PCNA index of markedly atypical bile ductules with large hyperchromatic nuclei was higher than that of apparently benign bile ductules and some of the atypical bile ductules showed invasive growth. Therefore, we considered that the area containing markedly atypical bile ductules was cholangiocarcinoma.

Malignant transformation of von Meyenburg complex as has been reported [2, 3, 7] but malignant transformation in BDA has not. There has been only one report of a massive tumour consisting of atypical bile ductules that showed a histological resemblance to BDA. This was considered to be a cholangiocarcinoma with a compo-

nent of undifferentiated carcinoma with a long clinical course [5]. It was concluded that the tumour was a well differentiated peripheral cholangiocarcinoma, which had developed areas of anaplastic carcinoma in the late course of the disease. The present case appears to be the first reported case of cholangiocarcinoma developing from BDA.

It has been considered that epithelial atypia of the bile ducts may be a precursor lesion of cholangiocarcinoma [9, 15, 17, 18], and that persistent exposure of the biliary epithelium to bile may induce malignant transformation through an intermediate stage of epithelial atypia [14]. However, the present case is interesting insofar as the early stage of development of cholangiocarcinoma was observed in BDA, suggesting the possibility that the adenoma-carcinoma sequence occurs in biliary tumours.

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