Virchows Arch (1999) 434:511–515

ORIGINAL ARTICLE

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Sarcomatoid hepatocellular-carcinoma showing rhabdomyoblastic differentiation in the adult cirrhotic liver

Received: 19 November 1998 / Accepted: 12 February 1999

Abstract An unusual case of a massive liver tumour composed of rhabdomyosarcoma with a small focus of hepatocellular carcinoma in a 52-year-old man is presented. He had hepatitis B virus (HBV) surface antigen in his serum. Macroscopically, a large tumour with satellite nodules occupied the right lobe of the cirrhotic liver. Microscopically, the tumours were composed of small and short spindle-shaped undifferentiated cells, mixed with desmin-positive round rhabdomyoblasts and elongated striated muscle cells, strongly suggestive of rhabdomyosarcoma of the liver. Elevated levels of alpha-fetoprotein in the serum led us to examine the liver tumour closely in multiple sections, which disclosed a hepatocellular carcinoma component measuring 2 cm in diameter within the massive tumour. Immunohistochemically, the hepatocellular carcinoma cells were alpha-fetoprotein positive. There was neither a tumour capsule, nor distinct demarcation, and cytokeratin-positive clusters of undifferentiated cells were intermingled with the hepatocellular carcinoma and rhabdomyosarcoma at the border. The invading tumour outside the liver and metastatic tumours were pure rhabdomyosarcomas. It is suggested that the present case should be diagnosed as rhabdomyosarcoma transformed from hepatocellular carcinoma.

Key words Rhabdomyosarcoma · Hepatocellular carcinoma · Liver · Alpha-fetoprotein

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Introduction

Primary malignant liver tumours are mostly epithelial, originating from hepatocytes, and primary sarcomas in the liver are rare, except for rhabdomyosarcoma in children and angiosarcoma [2, 29]. Rhabdomyosarcomas in the liver are usually restricted to the paediatric age group, and are considered to derive from undifferentiated mesenchymal tissue in the biliary structures [15]. Rhabdomyosarcomatous components also appear within hepatic malignant mixed tumours or hepatoblastoma mixed with a carcinomatous component, and are considered to be the result of focal rhabdomyoblastic differentiation from multipotential tumour cells [13, 29]. In contrast, rare cases of primary rhabdomyosarcoma in the adult liver, which do not have a connection with the biliary system, have been reported [3, 7, 10, 14, 17, 20, 28, 31]. They occur as pure rhabdomyosarcomas, or as tumours co-existing with hepatocellular carcinoma and/or liver cirrhosis. Although the histogenesis is not understood, a high rate of coexistence of rhabdomyosarcoma with hepatocellular carcinoma and/or liver cirrhosis suggests that it does not grow independently [7, 10, 14]. Rhabdomyosarcoma in the adult liver may be dedifferentiated from a pre-existing hepatocellular carcinoma. We report an autopsy case of adult hepatic rhabdomyosarcoma in a cirrhotic liver in which the hepatocellular carcinoma component was found with difficulty. Cytokeratin-positive, undifferentiated cells favouring the histogenesis of a transformation from primary hepatocellular carcinoma were seen.

Clinical history

A 52-year-old Japanese man had been complaining of general malaise and easy fatiguability since the end of October 1996, and was admitted to the Kanazawa University Hospital on 16 December 1996. Fourteen years earlier, he had been found seropositive for the hepatitis B virus (HBV) surface antigen, and a liver biopsy had led to a diagnosis of chronic inactive hepatitis B. His condition was later reclassified as chronic hepatitis B with minimal activity and

with mild fibrosis according to the recent classification published by Desmet et al. [5]. There was no history of blood transfusion, alcohol abuse or drug abuse. Physical examination revealed hepatomegaly and vascular spiders on the skin. There was no jaundice. Laboratory investigation revealed the following: red blood cells $404\times10^4/\mu l$, white blood cells 4,500/µl, platelet $10.2\times10^4/\mu l$, hepaplastin test 67%, C-reactive protein 5.5 mg/dl, serum total protein 7.7 g/dl (albumin 45.4%, α_1-globulin 4.5%, α_2-globulin 7.8%, β-globulin 7.5%, γ-globulin 34.8%), zinc sulfate turbidity test 29.2, thymol turbidity test 27.3, total bilirubin 1.6 mg/dl, direct bilirubin 0.8 mg/dl, glutamic oxaloacetic transaminase 169 IU/l, glutamic pyruvic transaminase 87 IU/l, alkaline phosphatase 821 IU/l, γ-glultamyl transpeptidase 341 IU/l, lactate dehydrogenase 894 IU/l, cholinesterase 2.48 IU/ml, carcinoembryonic antigen (CEA) 9.0 ng/ml. Alpha-fetoprotein (AFP) in the serum was markedly elevated at 9,090 ng/ml. Serological tests for the HBV surface antigen, HBV core antibody and HBV envelope antibody were positive. An indocyanine green test over 15 min was 50.0%. Ultrasonography, X-ray computed tomography (CT), magnetic resonance imaging of the abdomen and CT angiography showed a large hypervascular mass in the right lobe of the cirrhotic liver, small hypervascular nodules in the left lobe, and a tumour embolus in the portal vein. CT arterial-portography also confirmed the presence of a tumour embolus in the vein. All of these findings suggested hepatocellular carcinoma. Metastases in the hepatic hilar and para-aortic lymph nodes were detected by ultrasonography. Radioisotope scintigraphy detected no evidence of bone metastasis.

Chemotherapy was not performed because of rapid elevation of total bilirubin in the serum on the 10th day of admission. From 13 January 1997 onward the patient's renal function progressively deteriorated. He died of disseminated intravascular coagulation (DIC) on 19 January 1997.

Pathological findings

At autopsy, the body was found to be 166 cm in length and to weigh 49 kg. The skin was icteric. There was 360 ml of ascites. The liver was enlarged and weighed 2,370 g. A massive tumour measuring 19×12×11 cm occupied almost the entire right lobe, which was not encapsulated and had invaded the right adrenal gland, diaphragm, bilateral hepatic ducts and inferior vena cava. Several satellite nodules were shown in both lobes. The cut surface of the tumour was not icteric, and icteric nontumour cirrhotic areas were seen within the main tumour mass (Fig. 1). Multiple necrotic and haemorrhagic foci were found in the tumour. The portal vein and its branches were markedly distended, with an embolic tumour extending retrogradely to the confluence of the superior mesenteric and splenic veins. Multiple sections of several slices were resected for a microscopic examination. The tumour showed alternating densely packed, hypercellular areas and loosely textured myxoid areas. It was composed of small and short spindle-shaped undifferentiated cells (Fig. 2A). Rhabdomyoblasts with plump eosinophilic cytoplasm and eccentric hyperchromatic nuclei were scattered among the undifferentiated cells (Fig. 2B). Elongated cells which had abundant eosinophilic cytoplasm with cross-striations were also found (Fig. 2D). The cross-striated bands were clearly stained with phosphotungstic acid and haematoxylin. Immunostaining was performed using a standard avidin–biotin peroxidase complex (ABC) method with antibodies against AFP (DAKO, Denmark, 1:1000), CEA (Serotec, UK, 1:10), CAM 5.2 (Becton Dickinson, San Jose, Calif., 1:50), AE 3 (ICN Biomedicals, Aurora, Ohio, 1:800), desmin (DAKO, 1:200), myoglobin (DAKO, 1:2000), HHF 35 (ENZO Diagnostics, N.Y., 1:2000), S-100 (Nichirei, Tokyo, 1 :10) and chromogranin A (Boehringer Mannheim Biochemica, Germany, 1 :500). As listed in Table 1, rhabdomyoblasts were positive for desmin (Fig. 2C), myoglobin, and HHF 35, and negative for AFP, CAM 5.2, AE 3, S-100 and chromogranin A. HHF 35 was positive on the cross-striations of elongated cells. The tumour cells in the satellite nodules, in the portal vein and in the invaded areas outside the liver were also exclusively rhabdomyosarcomatous, showing the same features.

Since the histological and immunohistochemical findings did not account for the elevated level of AFP in the serum, we examined further multiple sections of the tumour. Finally, a hepatocellular carcinoma measuring about 2.0 cm in diameter was disclosed in the hepatic hilar region within the massive tumour. It was difficult to detect the tumour macroscopically even by retrospective examination, because it was not encapsulated and the boundary was not clear (Fig. 1). The polygonal tumour cells with epithelial connections exhibited solid proliferation in a glandular arrangement (Fig. 2E). The epithelial element and undifferentiated cells were intermingled at the boundary. The epithelial tumour cells were positive for AFP (Fig. 2F), CAM 5.2 and AE 3. Desmin, myoglobin, HHF 35, S-100 and chromogranin A were negative. Using anti-AFP antibody, the hepatocellular carcinoma cells were distinctly distinguished from the rhabdomyoblastic and undifferentiated cells. CAM 5.2- and AE 3-positive undifferentiated cells were shown as clusters around the hepatocellular carcinoma (Fig. 2G), although the cell clusters were also found at locations distant from the tumour. Metastatic rhabdomyosarcoma in the lymphatic vessels was seen in the lungs and the gallbladder. All the metastatic tumours in the superior mesenteric arterial, fundic, subcarinal, right paratracheal, right cervical, and poststernal lymph nodes were also rhabdomyosarcoma. Hepatocellular carcinoma was not found outside the liver. A few small and short spindle-shaped undifferentiated cells were positive for S-100 and chromogranin A, which are markers of neuroectodermal or neuroendocrine differentiation. Cirrhosis was macronodular, and the HBV surface antigen evaluated by orcein staining was positive for the hepatocytes.

An haemorrhagic diathesis was manifest in the lungs, pericardium, endocardium, peritoneum, stomach, duodenum, small intestine, colon, rectum, gallbladder, and uri-

Fig. 2 **A** Medullary pattern in small undifferentiated tumour cells. Most of the tumour is composed of this type of cell. Haematoxylin and eosin, ×135 **B** Rhabdomyoblasts with eosinophilic cytoplasm and eccentric hyperchromatic nuclei. Haematoxylin and eosin stain, ×360 **C** Desmin-positive rhabdomyoblasts. Immunoperoxidase, ×360 **D** Elongated cells with thick eosinophilic cytoplasm and distinct cross-striation. Haematoxylin and eosin, ×540 **E** Hepatocellular carcinoma detected in a small focus within the tumour mass. Solid proliferation and gland formation were observed. Haematoxylin and eosin, ×180 Alpha fetoprotein-positive hepatocellular carcinoma. Immunoperoxidase, ×180 **G** CAM 5.2-positive undifferentiated tumour cells. Immunoperoxidase, ×135 ▶

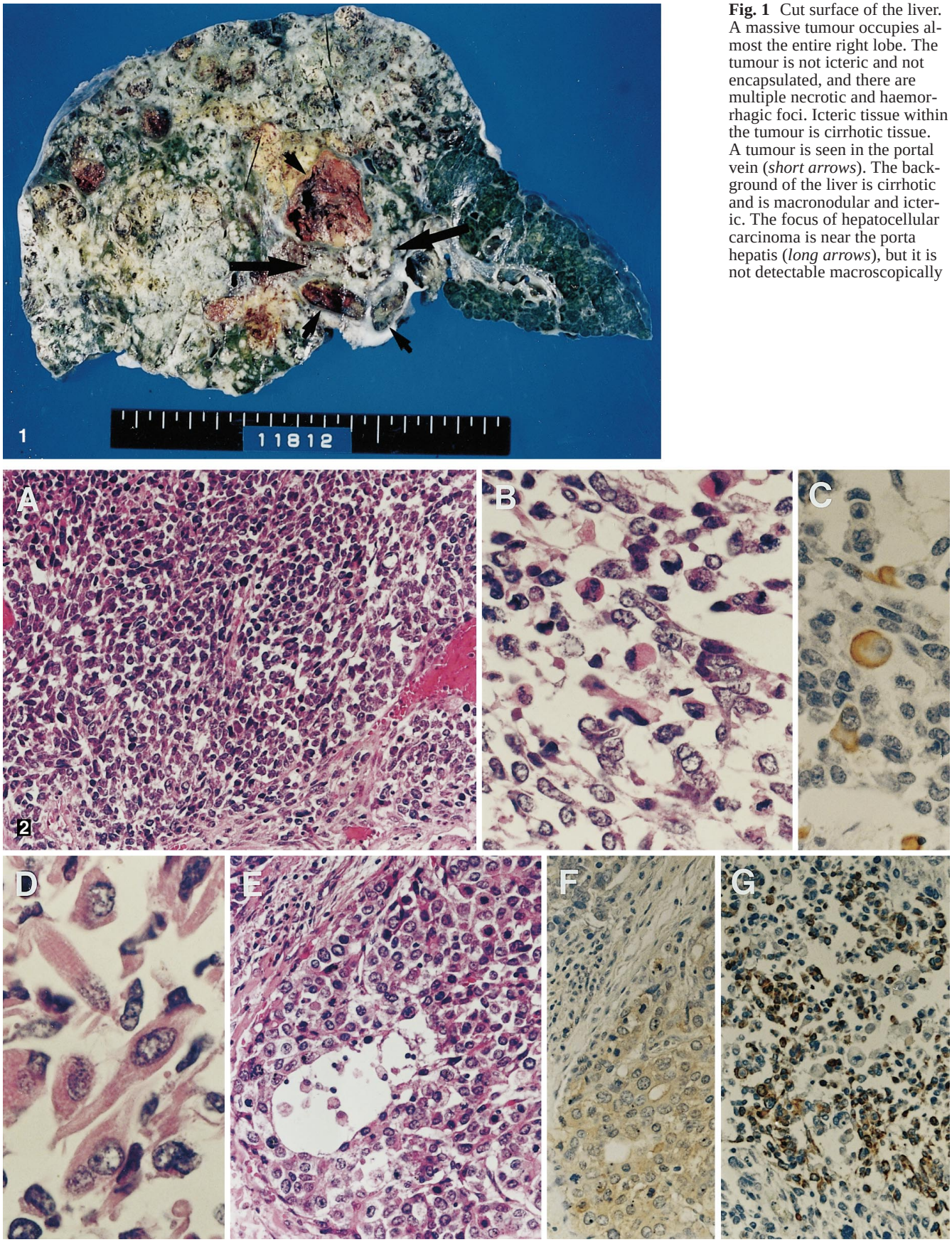

Fig. 1 Cut surface of the liver. A massive tumour occupies almost the entire right lobe. The tumour is not icteric and not encapsulated, and there are multiple necrotic and haemorrhagic foci. Icteric tissue within the tumour is cirrhotic tissue. A tumour is seen in the portal vein (*short arrows*). The background of the liver is cirrhotic and is macronodular and icteric. The focus of hepatocellular carcinoma is near the porta hepatis (*long arrows*), but it is not detectable macroscopically

Table 1 Results of Immunohistochemistry (*AFP* alpha-fetoprotein, *CEA*, carcinoembryonic antigen, – negative, + focally positive, ++ diffusely and constantly positive)

	Desmin	Myoglobin	HHF 35	CAM 5.2	AE 3	AFP	CEA	S-100	Chromogranin A
Rhabdomyosarcomatous component	++	++	++	–	–	–	–	–	–
Small and short spindle -shaped undifferentiated cells	+	–	–	+	+	–	–	+	+
Carcinomatous component	–	–	–	++	++	++	–	–	–

nary bladder. The spleen was enlarged (140 g), but there was no distinct oesophageal varix.

Discussion

This is a unique tumour, being predominantly rhabdomyosarcoma with a small focus of hepatocellular carcinoma in a cirrhotic adult liver. The origin of the rhabdomyosarcoma reported here is unclear, but rhabdomyoblastic differentiation of undifferentiated cells derived from hepatocellular carcinoma is the most likely origin. This supposition is based on our precise examination, which showed the transition between the hepatocellular carcinoma and rhabdomyosarcomatous component.

Focal rhabdomyoblastic differentiation occurs on occasion as a feature in a variety of malignant liver tumours referred to as malignant hepatic mixed tumour, hepatoblastoma and hepatic teratoma [13, 19, 29]. Otherwise, rhabdomyoblastic liver tumours presumably have their origin in the primitive precursor cells in the undifferentiated mesenchymal tissue and represent unidirectional differentiation. In general, rhabdomyosarcomas develop in the areas in which the striated muscle tissue is scanty or absent, exemplified by the genitourinary tract, head and neck region, common bile duct and retroperitoneum [6, 9, 15, 16, 21, 24]. In the liver of children it arises from the submucosa of the major hepatic or common bile duct [4, 15]. The present tumour, however, had no apparent connection with the common bile duct and the gallbladder, and the patient had no jaundice on admission.

In the adult liver, three cases of rhabdomyosarcomas coexisting with hepatocellular carcinoma have been reported [7, 10, 14]. Kubosawa et al. found an encapsulated tumour of hepatocellular carcinoma in a rhabdomyosarcoma case, and they suggested that the rhabdomyosarcoma had differentiated from hepatocellular carcinoma [14]. Goldman et al. presented a case in which hepatocellular carcinomas were mixed with rhabdomyosarcoma, and the authors referred to the lesion as rhabdomyosarcohepatoma [7]. The present case resembled Goldman's case, because the tumour was composed of rhabdomyosarcoma and hepatocellular carcinoma and the two were intimately intermingled. In addition, rhabdomyoblastic transformation from carcinoma has been also reported in several organs, including the lung, the oesophagus, the anorectal junction and the breast [8, 23, 25, 30].

In the present case, the boundary between the rhabdomyosarcoma and the hepatocellular carcinoma was blurred and the two components were intermingled. The transitional feature, that is to say the expression of cytokeratin around the hepatocellular carcinoma by undifferentiated cells in this area, should be noted. Miettinen and Rapola [18] assumed that epithelial differentiation occurred in rare cytokeratin-positive rhabdomyosarcomas in the soft tissue, suggesting they retained an epithelial nature during a gradual transformation, resulting in the development of rhabdomyosarcoma. Both hepatocytes and hepatocellular carcinoma cells in general express cytokeratin 8 and 18, which are recognized by the CAM 5.2 antibody and AE 3 antibody [1]. An AFP-positive small focus in the present case was also positive for CAM 5.2 and AE 3. A few positive foci for such cytokeratin-positive cells in the rhabdomyosarcomatous component suggested transition to rhabdomyosarcoma from hepatocellular carcinoma. We regard the present case as an example of sarcomatoid hepatocellular carcinoma showing rhabdomyoblastic differentiation. Taken together with the previous reports [14], hepatocellular carcinoma cells may have changed themselves into immature multipotential cells, which in turn dedifferentiated into rhabdomyoblastic cells. In addition, it is interesting that the markers of neuroendocrine differentiation were positive in a few undifferentiated cells, since such differentiation has been observed in biphasic tumours with a rhabdomyoblastic component [25].

It is evident that the hepatocellular carcinoma with a small focus was discovered in the present massive rhabdomyoblastic tumour because of a high level of AFP in the serum. The present case is thus instructive, since the high level of AFP in the serum led us to examine the present tumour minutely. A small focus of cytokeratin-positive immature cells was also found in the massive rhabdomyoblastic tumour. The serum level of AFP is a useful tumour marker in the diagnosis of hepatocellular carcinoma and yolk sac tumours in the testis and ovary [11, 26, 27]. Although AFP-producing carcinoma in the stomach or lung shows a certain morphological feature referred to as hepatoid differentiation [12, 22], no primary tumour besides the one in the liver was found in our case.

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