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Case Report

Fibrolamellar Hepatocellular Carcinoma Coexistent with a Hepatocellular Carcinoma of Common Type: Report of a Case

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Abstract: A case of small fibrolamellar hepatocellular carcinoma (HCC) coexistent with a HCC of common type is herein reported. A 56-year-old man was diagnosed as having multi-nodular type HCC with liver cirrhosis. The serum alpha-fetoprotein (AFP) level was slightly increased. The patient underwent a partial caudate lobectomy and lateral segmentectomy. Histologically, both resected tumors were small HCCs measuring less than 2 cm in diameter. One was a fibrolamellar type located in the caudate lobe, while the other was the common type in the lateral segment of the liver. Positive immunohistochemical staining for AFP was observed in the tumor cells of the HCC of common type but was not observed in the fibrolamellar HCC. We also reviewed previously reported cases of fibrolamellar HCC in Japan, and discussed the clinicopathologic implications of this disease.

Key Words: fibrolamellar hepatocellular carcinoma (HCC), small HCC, double cancer, liver cirrhosis

Introduction

Fibrolamellar hepatocellular carcinoma (HCC) has recently been categorized as a distinct clinicopathologic entity with its own histologic pattern and a favorable prognosis.[1–3] The first case was described by Edmondson in 1956,[4] and in 1980 independent reports by Craig et al.[5] and Berman et al.[6] described the clinical and pathologic features of 35 cases. To our knowledge, however, only 3 cases have previously been reported in Japan,[7–9] with no instance of fibrolamellar HCC occurring simultaneously with a HCC of common type. More than 100 cases have since been described in the world literature.[2–11]

We herein report a rare case of small fibrolamellar HCC which occurred simultaneously with a HCC of common type in a Japanese man who had underlying cirrhosis.

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Case Report

A 56-year-old Japanese man had been found to have liver dysfunction approximately 10 years before ultrasonography at a local hospital disclosed a small nodular lesion in the left lobe of the liver. He was then referred to us for further evaluation and treatment and was admitted to the Oita Medical University Hospital with a diagnosis of hepatoma on September 3, 1986. The physical examination on admission revealed a moderately nourished man. The liver and spleen were not palpable and there was no observation of either ascites or jaundice. The results of the hematological studies were as follows: hemoglobin, 11.2 g/dl; white blood cell count, 3,900/mm^3; platelet count, 15.5 × 10^4/mm^3; and prothrombin time, 79%. Serum albumin was 3.2 g/dl. The serum alanine and aspartate aminotransferases were 77 IU/L and 53 IU/L, respectively. The serum bilirubin was 0.6 mg/dl, while the alkaline phosphatase was 110 IU/L. Although the carcinoembryonic antigen was within the normal range, the serum alpha-fetoprotein (AFP) was slightly elevated, to 123 ng/ml. The hepatitis B surface antigen (HBsAg) and antibody were negative. The anti-hepatitis C virus (HCV) antibody was positive. Subsequent radiologic studies confirmed a diagnosis of a multi-nodular type hepatoma in the lateral segment of the left lobe and caudate lobe of the liver. An enhanced computed tomography (CT) scan demonstrated two low density lesions with moderate-to well-defined margins in the lateral segment and caudate lobe of the liver. Each tumor measured less than 2 cm in diameter (Fig. 1). Selective arteriography showed a hypervascular tumor in the lateral segment, which was supplied by the left hepatic artery. No other tumors were detected in the

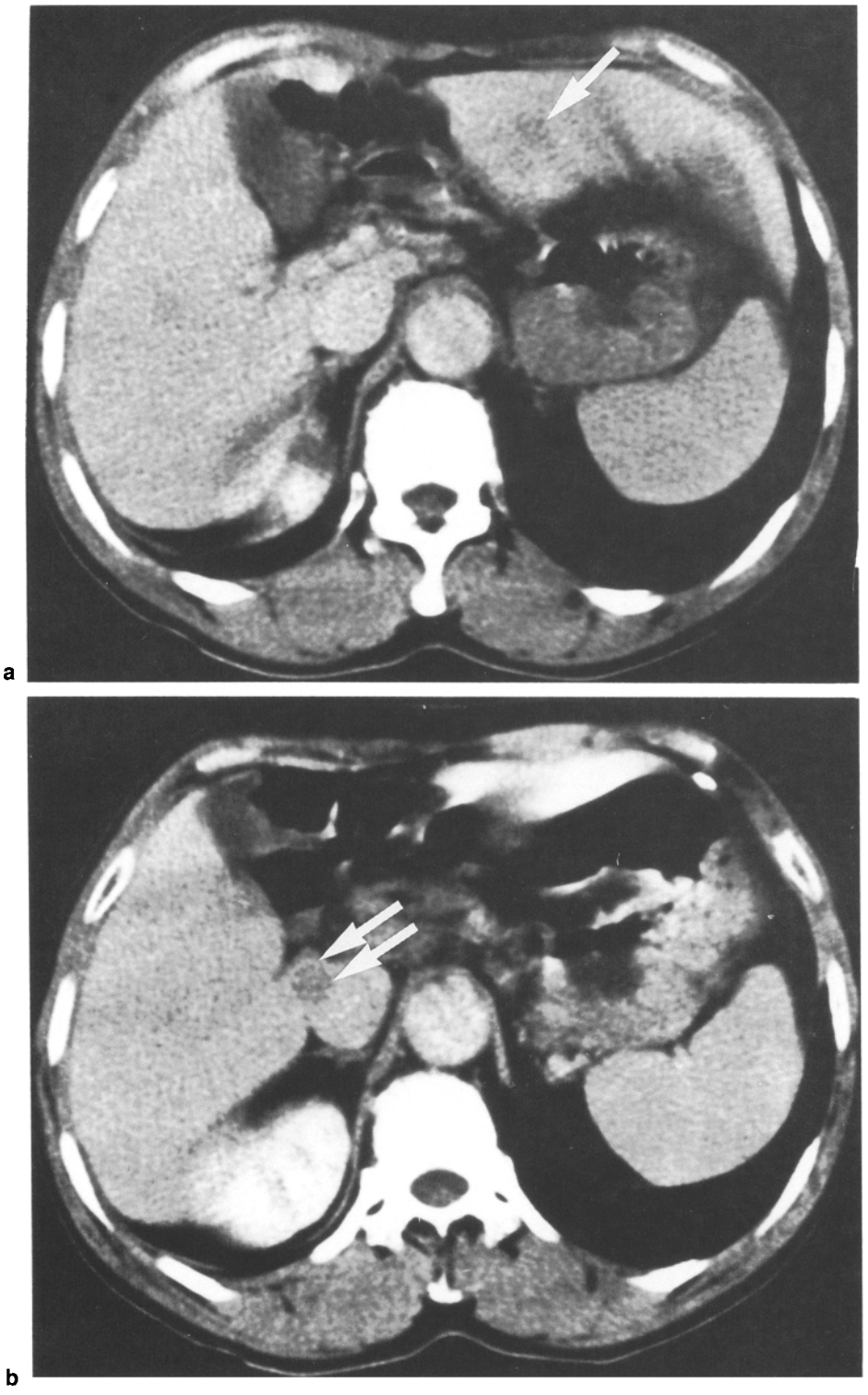

Fig. 1a,b. A contrast-enhanced CT scan showing two small lesions in the liver. **a** One is a slightly low density mass in the lateral segment (*arrow*); **b** the other is a low density mass in the caudate lobe (*arrows*)

caudate lobe by selective arteriography. On October 30, the patient underwent a lateral segmentectomy and partial caudate lobectomy.

Macroscopically, the tumors were well circumscribed from the adjacent liver tissue. One tumor in the lateral segment was solid, encapsulated, elastic soft, yellowish-white in color, and 1.9 cm in diameter (Fig. 2a). The other tumor in the caudate lobe was solid, non-capsulated, elastic hard, grayish-white in color, and 1.8 cm in diameter (Fig. 2b).

Microscopically, the tumor in the lateral segment (Fig. 3) was diagnosed as a thin-trabecular type, grade

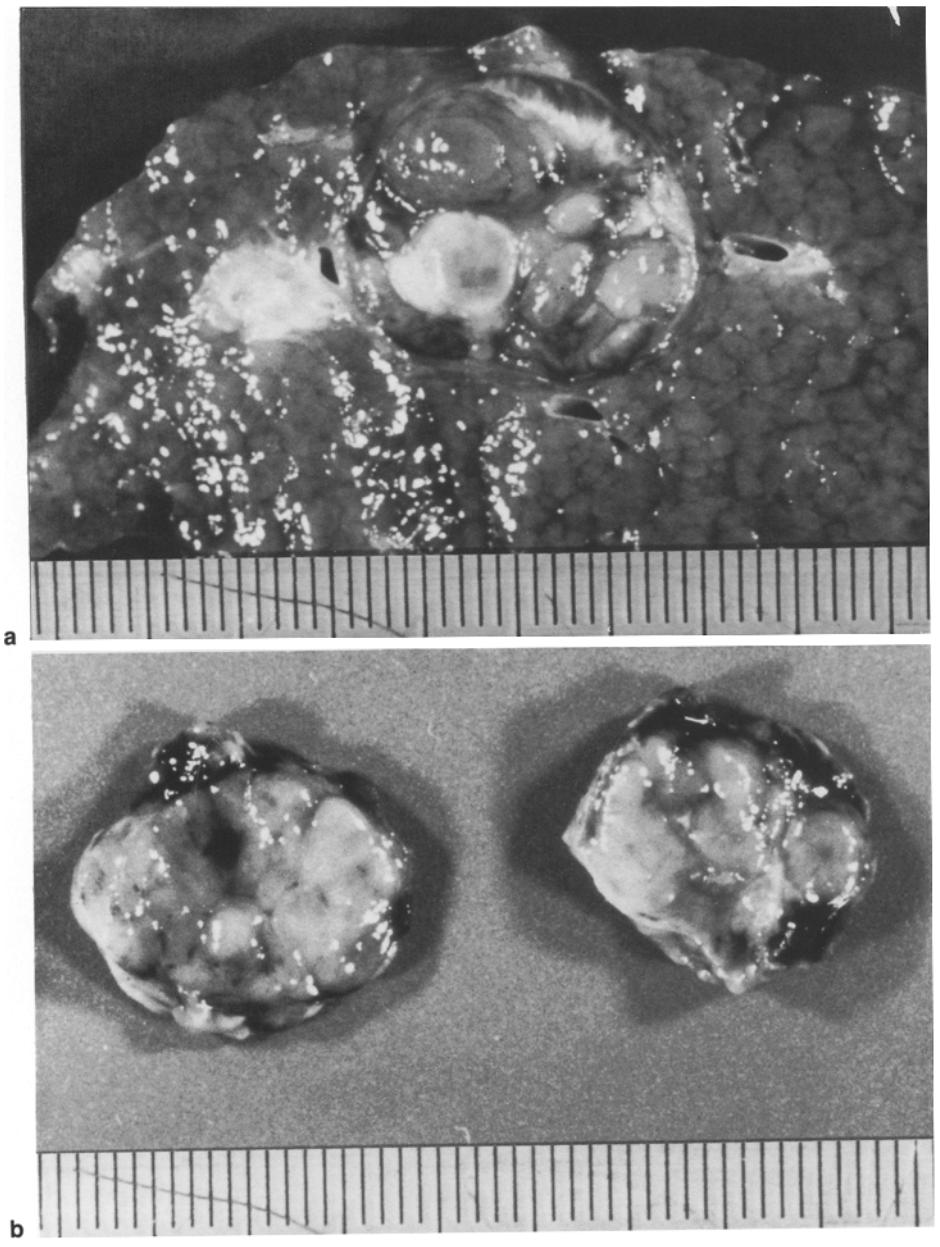

Fig. 2a,b. The cut surface of two tumors. **a** One is an encapsulated tumor in the lateral segment; **b** The other is a non-capsulated tumor in the caudate lobe

I–II HCC according to Edmondson's classification,[10] while the tumor in the caudate lobe (Fig. 4) was a fibrolamellar type, grade II HCC, accompanied by liver cirrhosis. Both tumors had neither any distinctive vascular invasions nor intrahepatic metastases. The latter tumor showed the following characteristic features: (1) large polygonal-shaped neoplastic hepatocytes with eosinophilic granular cytoplasm and/or pale bodies and (2) fibrosis arranged in a lamellar fashion around the tumor cells (Fig. 5). The tumor was sharply defined with a compression of the adjacent liver tissue. In the immunohistochemical staining for AFP by the indirect peroxidase labeled antibody method,[13] some AFP-positive tumor cells were observed in the HCC of common type, while there were no positive cells in the fibrolamellar HCC.

The postoperative course was uneventful, and the patient was discharged on the 31st day after the operation. The AFP declined to less than 10.0 ng/ml. Five years and 6 months after the operation, the patient is still alive with recurrent disease.

Discussion

Fibrolamellar HCC is a recently recognized histological variant of HCC that occurs predominantly in young people; it does not occur preferentially in either sex. It

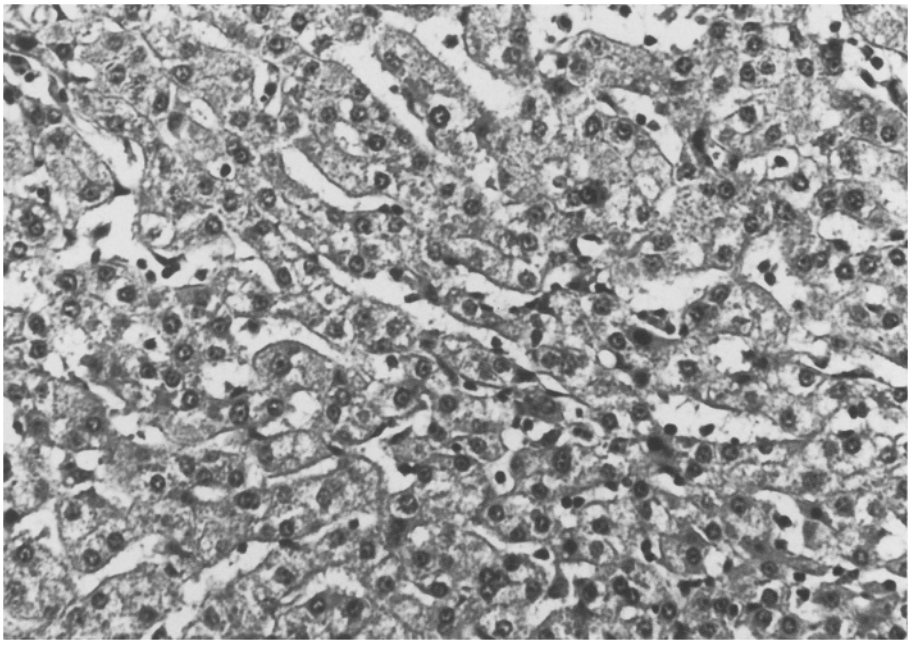

Fig. 3. Low-power view of one tumor in the lateral segment showing a thin-trabecular HCC of common type. (H&E, ×160)

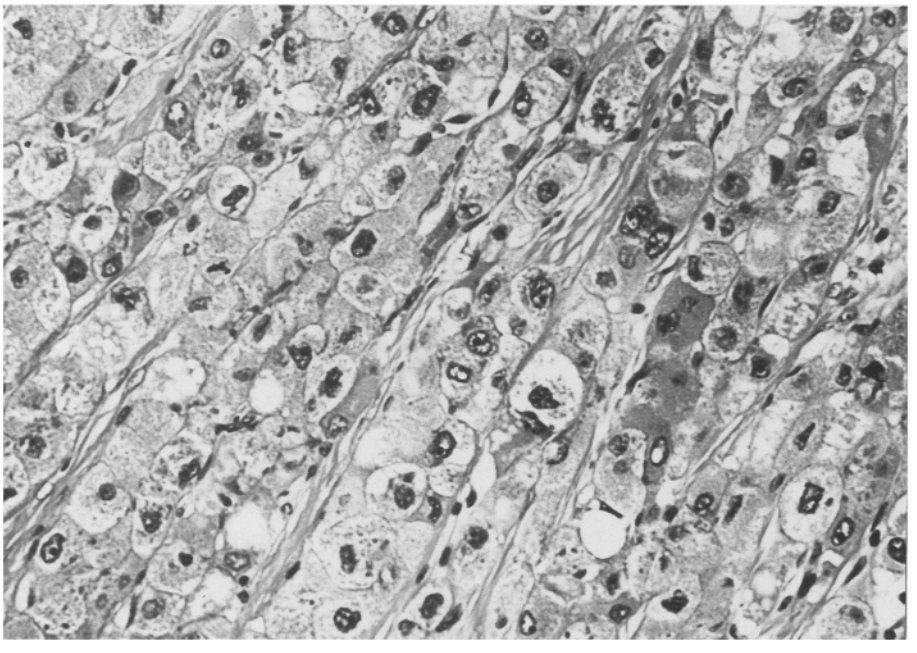

Fig. 4. Low-power view of another tumor in the caudate lobe, showing the characteristic features of fibrolamellar HCC, composed of large oncocytic polygonal-shaped neoplastic hepatocytes segregated by lamellar collagen. (H&E, ×160)

is rarely associated with positive HBsAg, a high level of serum AFP, or preexisting liver disease, such as cirrhosis, in particular.[1] Eight cases (5.4%) with HBsAg, 12 cases (8.2%) with a high level of serum AFP, and 8 cases (5.4%) with cirrhosis were observed to have been reported in a review of the literature of 147 cases, including the present one.[5–7,9,16,18,19] This disease has a better prognosis than HCC of common type because of its higher resectability. The mean survival time is 68 months.[6] Moreover, this tumor has been most commonly seen in Caucasians and appears to be very rare in Asians who have a high incidence of HCC of common type.[7–11] In Japan, to our best knowledge, only four cases of fibrolamellar HCC, including the present one, have previously been reported (Table 1).[7–9] The first was a 56-year-old Korean man with chronic hepatitis B who underwent a partial resection of the liver. The second was a 17-year-old Japanese boy with a normal liver who underwent a hepatic arterial ligation and cannulation for chemotherapy, and where

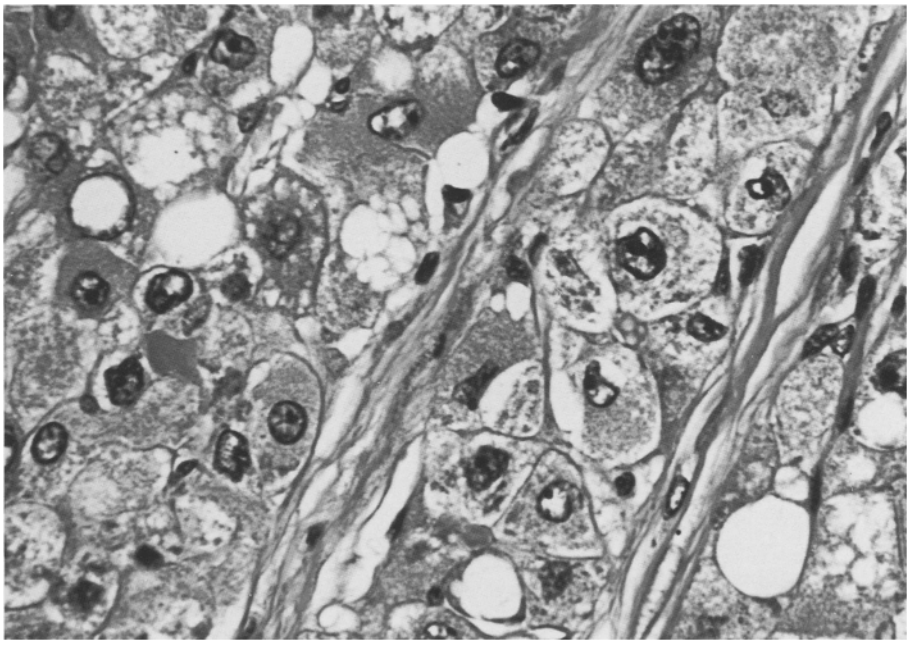

Fig. 5. High-power view of fibrolamellar HCC showing large oncocytic neoplastic hepatocytes and pale bodies. (H&E, ×330)

Table 1. Fibrolamellar hepatocellular carcinoma in Japan

Case	Author	Age/Sex (years)	Nationality	Tumor size and lobe	AFP (ng/ml)	HB	Liver disease	Surgery
1.	Yoshida et al.[7]	56/M	Korean	4 cm R	65	sAg (+) eAg (+) cAb (+)	Chronic hepatitis	Partial resection
2.	Taniura et al.[8]	17/M	Japanese	8 cm R	5>	(−)	(−)	(−)[a]
3.	Imai et al.[9]	36/F	Japanese	1.9 cm R	200	sAg (+) cAb (+)	Liver cirrhosis	Partial resection
4.	Present case	56/M	Japanese	1.8 cm C	123	(−)[b]	Liver cirrhosis	Partial resection

R, right hepatic lobe; *L*, left hepatic lobe; *C*, caudate lobe; *AFP*, alpha-fetoprotein; *HB*, hepatitis B
[a] chemotherapy and autopsy, [b] anti-HCV Ab (+)

a histological diagnosis of fibrolamellar HCC was confirmed at autopsy. The third was a 36-year-old Japanese woman with liver cirrhosis who underwent a partial hepatectomy and splenectomy. In the present case, the patient was a 56-year-old Japanese man with liver cirrhosis. The tumor in the caudate lobe was histologically diagnosed as typical fibrolamellar HCC due to its distinct characteristic features. Including the present case, however, three of the four cases from our country showed atypical clinical findings including: (1) the patients consisted of adult men, (2) elevated serum AFP levels, (3) positive HBsAg or anti-HCV antibodies, and (4) accompanying chronic hepatitis or liver cirrhosis.

Our case is interesting in that fibrolamellar HCC occurs in the cirrhotic liver simultaneously with a HCC of common type. For this multi-nodular type of HCC, it is difficult to determine whether each tumor represents transportal metastases or a multicentric emergence.[14,15] Two HCCs, 1.9 cm and 1.8 cm in diameter, were seen in different lobes. Histologically, the two tumors showed different patterns; that is, one was a HCC of common type, while the other was fibrolamellar. Both tumors showed no vascular invasion and intrahepatic metastases in close approximation. Therefore, judging from the difference in histology and tumor location, in addition to the similarity in tumor size, it seems that these tumors represent multicentric HCC rather than transportal metastases.

Serum markers such as AFP and HBsAg are negative in fibrolamellar HCC, with only rare exceptions. Negative serum markers and the rarity in countries with a high incidence of HCC of common type suggest that the pathogenesis of fibrolamellar HCC is different from that of HCC of common type.[1,16] Although the exact pathogenesis of fibrolamellar HCC still remains unclear, serum unsaturated vitamin B_{12} binding capacity and neurotensin have been reported to be tumor-

associated products of fibrolamellar HCC.[17,18] A possible relation of fibrolamellar HCC to focal nodular hyperplasia has also been speculated as a unique pathogenesis.[6,19] In the present case, the serum AFP level was slightly elevated. Immunohistochemical staining revealed AFP production in some tumor cells of the HCC of common type, but not in the fibrolamellar one. The diminished expression of AFP, an oncofetal antigen, in this tumor supports the concept of fibrolamellar HCC being a well-differentiated tumor.[13,16] Further study of additional cases is necessary to better clarify this issue.

Liver cirrhosis carries a high risk of subsequent HCC. Today patients with either chronic hepatitis or liver cirrhosis are being followed closely by the use of imaging techniques, in addition to the measurement of serum AFP.[14,15] In the present case, we also detected small HCC lesions. Therefore, our experience indicates that we should pay close attention to the possible occurrence of rare HCC-like fibrolamellar lesions in patients with chronic liver disease, even in Japan.

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