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Typical Fibrolamellar Hepatocellular Carcinoma in Japanese Patients: Report of Two Cases

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Abstract: We report herein the cases of two Japanese patients with typical fibrolamellar hepatocellular carcinoma treated at our institute. The first patient was a 19-year-old man with no hepatitis B or C viral infection and a normal, noncirrhotic liver in the nontumorous area. The second was a 36-year-old woman with no viral infection and a noncirrhotic liver in the nontumorous area. The clinicopathology, imaging appearances, and histology of both cases were similar to reports from the United States.

Key Words: fibrolamellar hepatocellular carcinoma, clinicopathology, histology, preoperative diagnosis

Introduction

Primary hepatocellular carcinoma (HCC) is one of the most prevalent malignancies in Japan. Nearly 80% of cases are associated with liver cirrhosis as a direct result of hepatitis B or C viral infection[1] and the prognosis is generally poor. In contrast, fibrolamellar hepatocellular carcinoma (FLHC), considered to be a clinicopathologic variant of HCC, has a relatively favorable prognosis with good long-term survival.[2,3] As such, it has been suggested that FLHC may constitute a distinct disease entity.[4] Fibrolamellar hepatocellular carcinomas are very rare in Japan, and almost all the reported cases have been from the United States or other Western countries. To date, there has been only one report in English of fibrolamellar hepatocellular carcinoma in the Oriental population, although this report noted considerable differences in the clinicopathologic profile of FLHC between Western and Oriental countries, including variability in such factors as cirrhosis and the associated incidence of positive hepatitis B surface antigen (HBsAg), and old age.[5] This paper describes two typical cases of resected fibrolamellar hepatocellular carcinoma from patients treated at our institute in Japan.

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Case Reports

Case 1

A 19-year-old Japanese man presented to a local hospital with abdominal pain and a fever of up to 39°C following acute alcoholism. A laparotomy was subsequently performed under the provisional diagnosis of an acute abdomen. A tumor in the left caudate lobe was detected, without any evidence of acute abdominal involvement. A biopsy was performed and fibrolamellar carcinoma diagnosed by a pathologist. Following recovery from the laparotomy, the patient was referred to our University Hospital for curative resection of the tumor. Initial laboratory tests upon admission yielded the following results: WCC, 5,000/mm^3; Hb, 14.3 g/dl; Hct, 42.2%; GOT, 14 U/l; GPT, 12 U/l; LDH, 290 U/l; T-Bil, 0.8 mg/dl; prothrombin time, 12.7 sec; CEA, 1.0 ng/ml; AFP: 5.1 ng/ml; CA 19–9: 12 U/ml; CA12–5: 16 U/ml; PIVKA-ll: 1.0 ng/ml; HBsAg, negative; HBsAb, negative; and HCV-Ab, negative. As indicated by these results, there was no evidence of liver dysfunction, no elevation of the tumor markers, and no viral hepatitic infection. The preoperative diagnosis was evaluated by computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography, and selective angiography. The CT images revealed a low-density area with punctate calcification encompassing an area of even lower density in the plain CT, which was suspected to be scar tissue at the center of the lesion. An even clearer low density area was observed at the center by the enhanced CT image. MR images revealed

a heterogeneous lesion of isointensity at the periphery and a low intensity area at the center under a short TR/TE sequence (600/20) condition. Under a long TR/TE (2000/60) condition, a high intensity area at the periphery and a low intensity area at the center were observed. Both CT and MRI findings indicated that the tumor originated in the caudate lobe and involved the inferior vena cava. The selective angiographic appearance was compatible with a diagnosis of ordinary hepatocellular carcinoma, showing both hypervascularity and tumor staining. Ultrasonograms revealed an iso- and hypoechoic mass.

A laparotomy was performed through a thoracoabdominal incision to enable direct viewing of the inferior vena cava. An extended left lobectomy encompassing the caudate lobe was performed, in addition to a partial resection of the inferior vena cava with reconstruction using a reinforced vascular graft (Goretex: EPTFE). Figure 1 shows the resected specimen, demonstrating the typical central stellate scar formation, a multinodular but sharply circumscribed pale yellow-green mass that was partially encapsulated, and normal noncancerous liver tissue. Histological examination of the tumor, shown in Fig. 2, revealed that nodules of

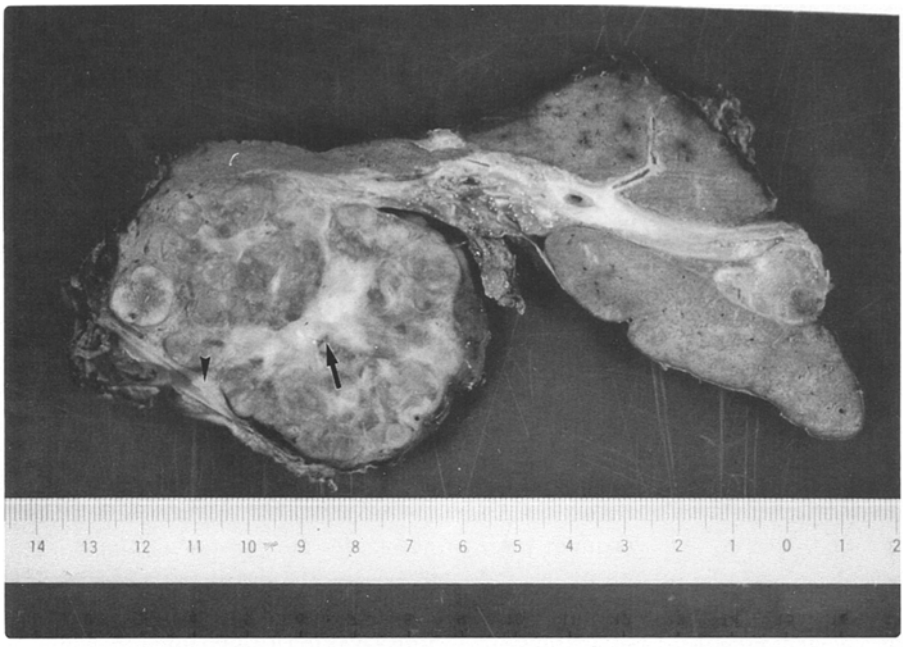

Fig. 1. The resected specimen from case 1 shows the apparent formation of a central scar (*long arrow*) and the resected inferior vena cava wall (*small arrow*).

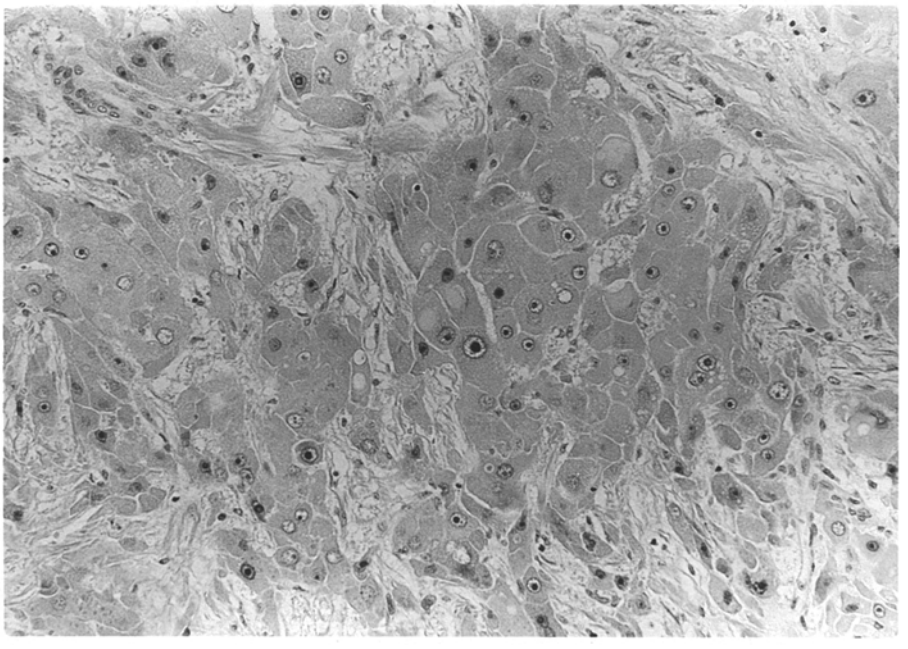

Fig. 2. Histologic examination of case 1 revealed nodules of polygonal cells surrounded by parallel lamellar bundles of fibrous tissue. (H & E, ×166)

polygonal cells, with fine granular eosinophilic cytoplasma, were surrounded by parallel lamellar bundles of fibrous stroma. The patient is alive without recurrence 3 years after the operation.

Case 2

A 36-year-old woman, previously in good health, was admitted to the gynecology department of our hospital following menstrual disturbances. A liver tumor was subsequently detected during an ultrasonographic study and the following laboratory data were obtained: WCC, 5,600/mm^3; Hb, 12.3 g/dl; GOT, 34 U/l; GPT, 31 U/l; LDH, 287 U/l; T-Bil, 0.4 mg/dl; AFP, 5.6 ng/ml; CEA, 1.0 ng/ml; CA 19-9, 12 ng/ml; DUPAN-2, 374 U/ml the normal being below 150 U/ml; HBsAg, negative; HBsAb, negative; and HCV-Ab, negative. The liver function test results were almost within the normal range, and the tumor markers were similarly all within normal range with the exception of a slightly elevated DUPAN-2 value. Ultrasonograms showed a hypoechoic mass. CT revealed a massive low-density area in the right lobe, with a central area of even lower density. The very high density spots on the CT image were due to the accumulated lipiodol infused during a selective angiographic study. MRI also showed a high-intensity mass, both at short (TR/TE: 600/20) and long (TR/TE: 2000/20) sequences. Selective angiography revealed the hypervascularity and tumor staining characteristic of common HCC in Japan. The patient underwent a right trisegmentectomy through a thoracoabdominal incision. The resected specimen, shown in Fig. 3, had a typical stellate central scar formation with a grayish-green macroscopic appearance. The boundary between the tumor and nontumorous liver tissue was also well circumscribed, with partial encapsulation. Histological examination of the resected tissue revealed cells similar in appearance to those found in the first case. The patient is alive without recurrence 1 year after the operation.

Discussion

FLHC was first reported by Edmondson[6] in 1956, and later expanded upon in 1980 by Berman et al.[7] To date, approximately 150 cases have been reported, primarily in the United States and other Western countries.[2,3] FLHC represents about 1%–2% of all HCCs according to a large autopsy series, but accounts for 43% of all HCCs in patients younger than 35 years of age.[8] Although HCC is one of the most common malignancies in Japan, to our knowledge, there have only been two case reports of FLHC in Japan; one in English and one in Japanese.[5,9] FLHC was first reported in an Asian in 1988,[5] and that patient was reported to be HBsAg-positive, cirrhotic, and 56 years old. This description is notably atypical of the FLHC cases previously reported in the United States. According to the literature,[3] FLHC has a higher frequency in younger patients, ranging from 5–65 years with a mean of 23 years, and equal sex distribution. Cirrhosis is rare, elevation of α-fetoprotein (AFP) is uncommon, and calcification is frequent in most patients with FLHC. The tumor is typically slow-growing, and the prognosis is usually good.[2,3] These features are completely con-

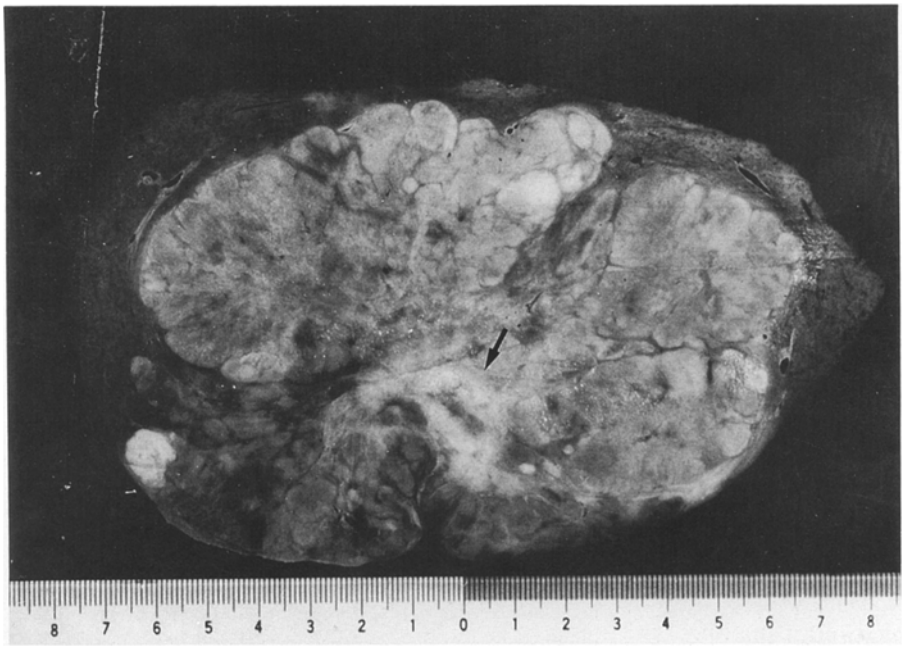

Fig. 3. The resected specimen from case 2 shows the typical stellate central scar formation (*arrow*) with partial encapsulation

sistent with the two Japanese patients presented in this report.

Patients with FLHC commonly present with abdominal pain, as our first patient did, or a palpable mass, as our second patient did.[3] Additional symptoms such as obstructive jaundice[10] or gynecomastia[11] have also been reported. Serologically, no meaningful tumor markers, with the exception of unsaturated vitamin B12-binding capacity and neurotensin, have been reported.[12,13] Although we did not measure these markers, no notable elevation of any of the other tumor markers, except for DUPAN-2 in the second patient, was observed, and to our knowledge, this is the first report of an elevated DUPAN-2 level in a patient with FLHC.

Recent developments in imaging modalities have revealed considerable new information regarding FLHC. In general, it is difficult to differentiate FLHC from ordinary HCC by selective angiograms, which reveal that both HCC and FLHC are hypervascular, or ultrasonograms, which reveal both as hypoechoic lesions. Accurate preoperative diagnoses of our two patients were not even made by the CT and MRI images. The CT image reveals punctate calcification with signs of a central stellate scar, which is characteristic of FLHC[14,15] as noted in our patients. Furthermore, Bedi et al.[16] reported similar dynamic CT findings to those seen in our second patient, using an initial enhancement followed by a gradual washout of the contrast medium from the center to the periphery, until the tumor becomes hypodense. On MRI, a low-intensity region surrounded by a heterogeneous region of higher signal intensity is consistent with the presence of central scar tissue.[17] This central scar tissue, the most typical macroscopic finding of FLHC, was evident in both our patients. The frequent association of a central stellate scar with FLHC has led to the suggestion that FLHC may constitute a malignant variant, or a malignant degeneration, of focal nodular hyperplasia, which is typically characterized by a central scar.[4] In this context, the reported association between FLHC and the use of oral contraceptives is probably coincidental.[4] No etiologic association was found in our two patients between FLHC and an abnormal sex steroid milieu. On the other hand, hepatobiliary carcinoma is a well-described complication of both ulcerative colitis and sclerosing cholangitis. In fact, Snook et al.[18] reported a case of FLHC complicating ulcerative colitis with primary sclerosing cholangitis.

Generally, FLHC is noninvasive and well-circumscribed, although in our first patient, the FLHC was tightly adherent to the inferior vena cava and required a combined resection of the vena cava. Similar invasive characteristics were reported in a case of obstructive jaundice due to tumor invasion of the bile ducts;[10] however, such invasive characteristics appear to be rare. Nevertheless, lymph node involvement is not uncommon according to the literature.[3,18]

Histologically, the lamellar formation of fibrous tissue around the tumor cells is characteristic of FLHC,[3,4] as noted in both our patients. With respect to this fibrous formation, Altmann[19] proposed that the progressing fibrosis has considerable influence on cell shape, since the surrounding cell complexes are immured, and their blood supply and transport mechanisms become progressively impaired. The typical histologic features of FLHC are polygonal, deep eosinophilic-staining tumor cells with intracytoplasmic hyaline globules, pale-colored bodies, and pleiomorphic nuclei.[3,4] All of these characteristics, as well as a typical lamellar formation of fibrous tissue surrounding the tumor cells, were observed in the two cases presented herein. This excessive fiber formation may explain the slower growth rate and consequently, more favorable prognosis of this type of tumor.[19] This, in turn, could evoke a compensatory increase in the mitochondria such that in advanced cases, these cells may be mistaken for genuine oncocytes, even when an oncocytic tumor has not been confirmed.[4,19]

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