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A Case with Sarcomatoid Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) with sarcomatous features is a rare neoplasm which has been found in only 1.8% of surgically resected HCC and has a higher incidence of metastasis than usual HCC. We recently experienced a case of sarcomatoid HCC removed from a 49-year-old man. A surgically resected liver revealed a well-defined grayish-white solid firm mass showing extensive central necrosis and infiltrative growth margin. Microscopically, the entire tumor was composed of pleomorphic spindle cells with prominent nucleoli and frequent mitosis. It showed a sinusoidal infiltrative growth pattern at the tumor-nontumor boundary. The tumor cells reacted positively with AE3 (high molecular cytokeratin) and Vimentin and reacted negatively with AE1 (low molecular cytokeratin), cytokeratin19, carcinoembryonic antigen, alpha-fetoprotein, Factor VIII, CD31 and CD68. The spindle-shaped tumor cells were considered to originate from hepatocyte rather than from bile duct epithelium or mesenchymal elements.

Key Words: Hepatocellular carcinoma, sarcomatoid, liver

Carcinomas with spindle-cell components are unusual neoplasms and such tumors have been referred to using various terms, such as spindle-cell carcinoma, sarcomatoid carcinoma, pseudosarcoma and carcinosarcoma. They have been reported in many organs including the esophagus, upper aerodigestive tract, thyroid, uterus, lung, breast, stomach and gall bladder. In the liver, the incidence of spindle-cell hepatic carcinoma is rare and it has been found in only 1.8% of sugically resected hepatocellular carcinomas (HCCs) and 3.9~9.4% of autopsy cases of HCC (Kakizoe *et al.* 1987; Kojiro *et al.* 1989; Maeda *et al.* 1996). In most sarcomatoid HCC, spindle-cell components represent more than 10% of the viable tumor volume, and most cases have been reported to be accompanied by apparent HCC and more rarely cholangiocarcinoma or combined hepatocellular/cholangiocellular carcinoma, synchronously or heterochronously (Haratoke and Horie 1991; Papott *et al.* 1997). HCC exclusively composed of spindle cells is rare and we report a case diagnosed as having spindle-cell hepatocellular carcinoma, which was entirely composed of spindle cells with a sinusoidal growth pattern.

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CASE REPORT

A 49-year-old man was admitted to the hospital due to epigastric discomfort, weight loss and fever. He had been well until one month before when epigastric discomfort developed. He had drunk 1/3 bottle (100 ml) of 25% alcohol a day for 30 years. Physical examination revealed a palpable liver of two-finger breadth below right costal border. The laboratory data were as follows; hemoglobin 13.1

g/dl, hematocrit 39%, total protein 6.6 g/dl, albumin 4.1 g/dl, total bilirubin 0.6 mg/dl, AST 24 mU/ml, ALT 19 mU/ml, alkaline phosphatase 114 mU/ml and alpha-fetoprotein 8 ng/ml. The viral markers for HBsAg and anti-HBsAb were both negative. A computed tomography revealed a 7×5 cm-sized well-defined ovoid hypodense mass in the 2, 3, and 4 segments of the liver. A percutaneous needle biopsy was taken. The biopsied tissue showed a hypercellular area composed of haphazardly arranged spindle-shaped cells. They also had less cellular area accompanied by hemorrhage and ischemic necrosis. The tumor cells showed marked pleomorphism with frequent mitosis and an extensive sinusoidal infiltrative growth pattern. The tumor cells showed a positive reaction to only cytokeratin (CK) and a negative reaction to Vimentin, Factor VIII, CD31, leukocyte common antigen (LCA), alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA).

Left lobectomy of the liver was performed and the resected specimen (320 g and 13×11×7 cm) revealed an expanded and tense but intact Glisson's capsule. Cut section revealed a 6×4 cm-sized, well-defined, grayish-yellow, solid and expanding type mass without encapsulation. It showed central necorsis and infiltrative margins. The remaining nontumorous liver appeared to be macronodular cirrhosis (Fig. 1).

Microscopically, the entire tumor was composed of nonadhesive spindle-shaped or fusiform cells with oval-to-round pleomorphic nuclei. Frequent mitotic figures and prominent nucleoli were found. Some tumor cells had polygonal and abundant cytoplasms mimicking hepatocytes. However, there was no area

Fig. 1. A gross finding of the tumor. A well-defined expanding type mass (6×4 cm) with central extensive necrosis.

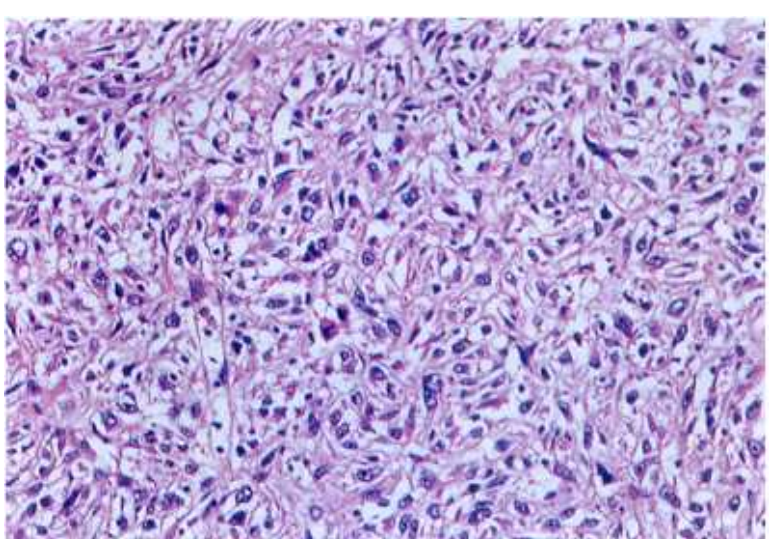

Fig. 2. A microscopic finding of the same tumor, which was composed of nonadhesive spindle-shaped or fusiform cells with oval-to-round pleomorphic nuclei, prominent nucleoli and frequent mitoses (H&E, ×200).

showing a typical trabecular or adenoid pattern of HCC, despite thorough sampling of the specimen (Fig. 2). No area of cholangiocarcinoma was present. The periphery of the tumor showed extensive sinusoidal growth of spindle-shaped tumor cells (Fig. 3). There were several entrapped bile ducts in the peripheral portion of the tumor, some of which showed deformed features with reactive atypia. There was extensive necrosis in the center of the specimen. There was neither intracellular nor extracellular mucin on Periodic acid-Schiff or Alcian blue stains. The tumor cells reacted positively with AE3 (high molecular cytokeratin) and Vimentin (Fig. 4). They showed a negative reaction to the

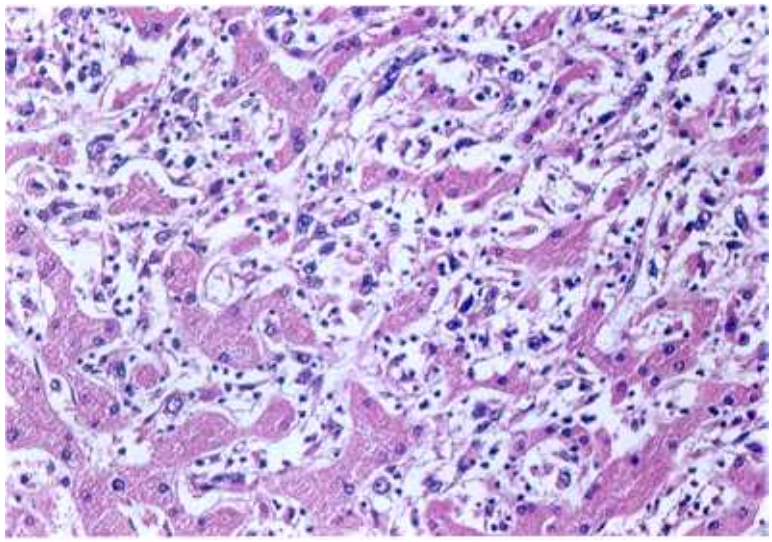

Fig. 3. A microscopic finding at the periphery of the tumor showing sinusoidal growth (H&E, ×200)

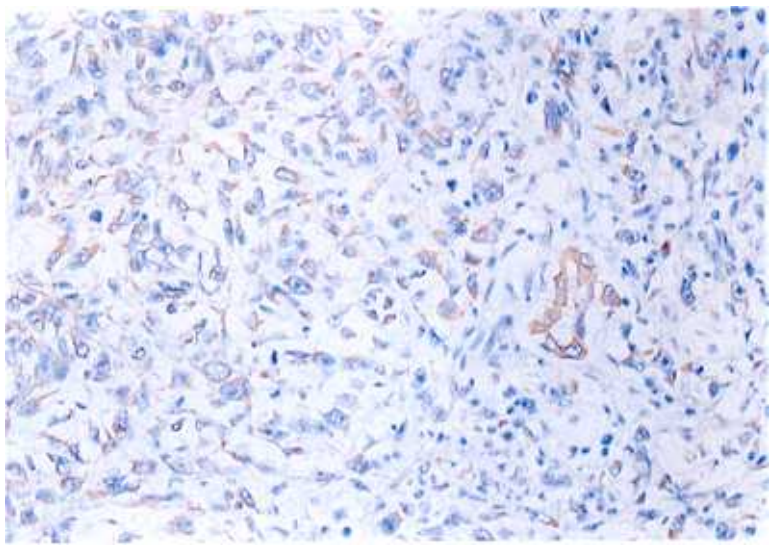

Fig. 4. Immunohistochemical stain for high molecular cytokeratin (AE3) showing a positive reaction in tumor cells (LSAB, ×200)

biliary epithelial markers of AE1 (low molecular cytokeratin) and CK19. The immunohistochemical stains for AFP, CEA, Factor VIII, CD31 and CD68 were also negative. Electronmicroscopic study showed that the neoplasm was composed of spindle cells with pleomorphic nuclei. Most of the intracytoplasmic organelles were washed out due to previous formalin fixation, but there were abundant perinuclear intermediate filaments in some cells. There was no intracellular mucin. There were occasional intermediate intercellular junctions. According to the above features, the tumor was diagnosed as sarcomatoid hepatocellular carcinoma. The nontumorous liver tissue showed macro and micronodular cirrhosis, alcoholic, and there was confluent ductular proliferation in the areas adjacent to the tumor. Five months after discharge, a follow-up computed tomography scan of the abdomen revealed a 5×4 cm-sized ill-defined hypodense mass around the resection margin of the liver and it was suggested to be a recurrence. However, the patient was lost for follow-up without further treatment.

DISCUSSION

Clinically, HCCs with sarcomatous appearance do not differ from ordinary HCC in incidence with regard to age and sex distribution. Abdominal pain and fever may be the most frequent symptoms, and they are characterized by negative or low serum AFP levels (Kakizoe *et al.* 1987). In this case, the patient had low serum levels of AFP and the tumor cells showed a negative reaction to AFP.

The basic growth pattern of well-differentiated HCC is a replacing pattern, and the sinusoidal growth pattern is common in poorly-differentiated HCC, in which extrahepatic metastasis is reported to be more frequent. Sarcomatoid HCCs show sinusoidal infiltrative growth at the tumor-nontumor boundary (Nakashima *et al.* 1982) and this may be a reason for the high incidence of extrahepatic metastasis in HCCs with sarcomatous appearance (Kakizoe *et al.* 1987). The presenting case also showed an extensive sinusoidal growth pattern.

The differential diagnosis could include angiosarcoma or hemangioendothelioma due to a sinusoidal growth pattern and spindle-shaped tumor cells, especially in the examination of small-sized biopsied tissue. Immunohistochemical stain for CD31 and factor VIII can be helpful and this case showed a negative reaction to them.

The pathogenesis of the sarcomatoid appearance of hepatic carcinoma has not been thoroughly clarified. The following evidence suggests that spindle-cell HCC represents a sarcomatous differentiation from epithelial malignancy rather than a combination of HCC and sarcoma: (1) the presence of transitional features from ordinary HCC to spindle-cell components, (2) the extremely low incidence of primary sarcoma of the liver, and (3) the high incidence of Vimentin expression in the spindle cell component, in which cytokeratin or AFP was positive (Kakizoe *et al.* 1987; Maeda *et al.* 1996). Kinjo *et al.* suggested that Vimentin increased when an epithelial tumor exerted a sarcomatous change in an experimental model (Kinjo *et al. 1984).*

The presenting case was predominantly composed of spindle-cells with some polygonal-cells and there was no glandular formation or trabecular pattern. Most of the pleomorphic spindle-shaped cells expressed both AE3 and Vimentin. It is suggested that this tumor was epithelial in origin and transformed to sarcomatous. This tumor did not express biliary epithelial markers such as AE1, cytokeratin 19 and CEA and we would suggest that it originated from hepatocytes rather than bile duct epithelium.

Degeneration, necrosis and regeneration of carcinoma cells due to anticancer drugs or transarterial chemoembolization may be possible triggers, however no preoperative therapy was performed. In this case, therefore, treatment was not considered to be responsible for the sarcomatoid transformation (Kojiro *et al.* 1989).

A previous report suggests that the prognosis for sarcomatoid HCC is less favorable than that of ordinary HCC (Maeda *et al.* 1996). The poor prognosis could be attributed to aggressive intrahepatic spreading and frequent metastasis of sarcomatous cells. Radical surgery and careful follow-up would be necessary for patients of HCC with sarcomatous change.

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