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A Case Of Sarcomatoid Hepatocellular Carcinoma With Prominent PD-L1 Expression

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Abstract

We report a case of sarcomatoid hepatocellular carcinoma with characteristic immune microenvironment. A 76-year-old man with a previous medical history of diabetes, dyslipidemia, and cerebral infarction was referred to our hospital for a liver mass found by abdominal ultrasonography. Contrast-enhanced computed tomography and gadoxetate magnetic resonance imaging showed a hepatocellular carcinoma in segment 5. The patient underwent laparoscopic partial liver resection and was discharged uneventfully on postoperative day 5. Three months later, the patient developed recurrence of intrahepatic metastasis, peritoneal dissemination, pulmonary metastasis, and pleural dissemination. The patient opted to receive palliative care and died 18 months after surgery. The histopathological findings of the resected tumor revealed an ordinary HCC with sarcomatoid features, demonstrating cytological pleomorphism with round cells, giant cells, and spindle cells on hematoxylin and eosin staining. Immunohistological expression of CAM5.2 and hepatocyte paraffin 1 was observed both in ordinary hepatocellular carcinoma and sarcomatoid cells. Furthermore, marked vimentin and programmed death-ligand 1 were specifically observed in the sarcomatoid component. Together with the histology showing prominent lymphocytes in the sarcomatoid component, sarcomatoid hepatocellular carcinoma could have a characteristic immune microenvironment and should be further investigated as a candidate for anti-programmed death-1 / programmed death-ligand 1 pathway inhibitor.

INTRODUCTION

Sarcomatoid hepatocellular carcinoma (HCC) is observed in 0.79% of histologically proven HCC, in 1.8% of surgically resected cases of primary HCC ,and in 3.9-9.4% of autopsy cases (1-5).Sarcomatoid HCC has several synonyms, including "spindle cell HCC", "pseudosarcomatous HCC", and "sarcomatous HCC". More difficulty in the preoperative diagnosis of sarcomatoid HCC, larger tumor size, and more aggressive clinical behavior with poorer clinical outcome compared with ordinary HCC have been reported previously(4). However, because of its rarity, the immunological character of sarcomatoid HCC has not been elucidated. In the present report, we describe a case of sarcomatoid HCC with characteristic immune microenvironment (IME).

CASE REPORT

A 76-year-old male who had been treated for diabetes, dyslipidemia, and previous cerebral infarction was referred to our hospital with a liver mass found on abdominal ultrasonographic examination (AUS). He had no past history of alcohol abuse and had abstained from drinking since his thirties. On admission, the patient reported no symptoms. On physical examination, he appeared to be in good general condition, and his abdomen was soft and flat without tenderness.

The initial laboratory findings were within normal range except for low hemoglobin and high protein induced by vitamin K antagonist II. Viral markers, including hepatitis B surface antigen and hepatitis C virus antibody, were negative (Table1).

Table 1

Laboratory data at first visit

WBC	6100	/μL	AMY	68	U/L	CEA	2.6	ng/mL
Hb	12.8	g/dL	BUN	14.6	mg/dL	CA19-9	11	U/mL
Plt	21.5	×10^4/μL	Cr	0.72	mg/dL	AFP	2.0	ng/mL
AST	36	U/L	Na	142	mEq/L	PIVKA-II	257	mAU/mL
ALT	32	U/L	K	4.2	mEq/L			
ALP	172	U/L	TP	7.5	g/dL	HBs-Ag	(-)	
γ-GTP	47	U/L	Alb	4.1	g/dL	HBs-Ab	(-)	
ChE	393	U/L	PT%	116	%	HCV-Ab	(-)	
LDH	179	U/L	PT-INR	0.93		ICGR15	12	%
T-Bil	0.32	mg/dL	APTT	23.8	sec	HbA1c	7.0	%
D-Bil	0.09	mg/dL	CRP	0.24	mg/dL			

AUS showed a lobulated, partially poorly circumscribed, hypoechoic mass with a diameter of 38 millimeters in segment 5 of the liver (Fig. 1). The tumor showed inhomogeneous echogenicity, and Doppler ultrasonography displayed partial flow.

Figure 1

Abdominal ultrasonographic examination. Ultrasonography demonstrated the presence of a 38-millimeter lobulated hypoechoic lesion with partially poor demarcation in segment 5 of the liver.
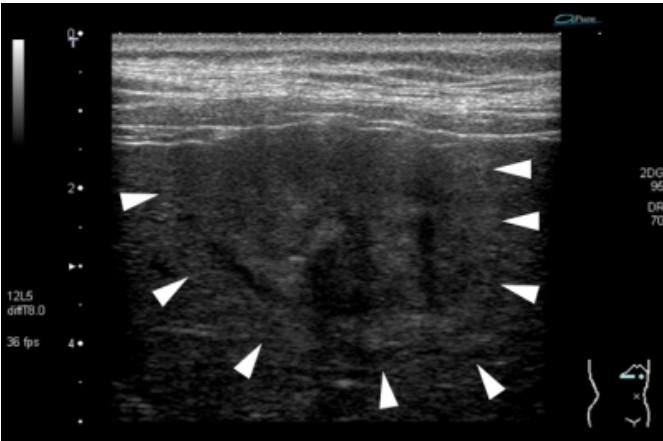
Contrast-enhanced computed tomography (CT) demonstrated an irregularly shaped, hypodense tumor located in segment 5 of the liver. In the early phase, the tumor showed patchy hyperenhancement, and in the late phase, it showed partial washout and a rim-like enhancement (Fig. 2a and b).

Figure 2

Contrast-enhanced computed tomography (CT). a: early phase at first visit, b: late phase at first visit, c: early phase 1 month later, d: late phase 1 month later, e: early phase 3 months later, f: late phase 3 months later Contrast-enhanced computed tomography showed a mixture of areas with early enhancement and late washout and areas with continuous hypodensity (a, b). Tumor growth and enlargement of the hypodense area were observed (c, d, e, f).
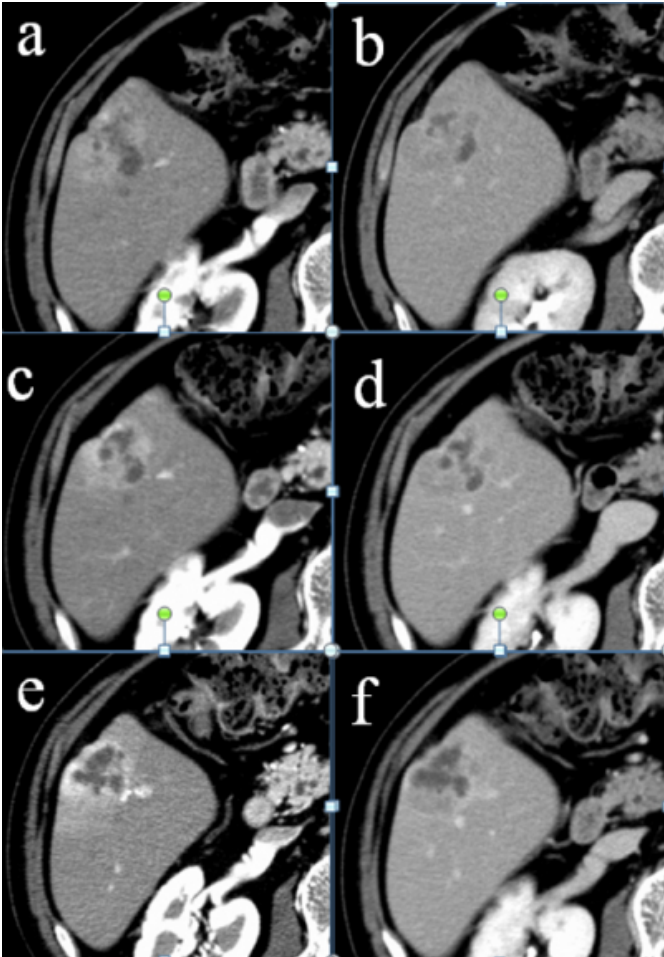
Gadoxetic acid-ethoxybenzyl diethylenetriamine-enhanced magnetic resonance imaging (Gd-EOB-MRI) showed a lesion with hypointensity on T1-weighted imaging (T1WI), slight hyperintensity on T2-weighted imaging (T2WI), and hypointensity on hepatobiliary phase (Fig. 3).

Figure 3

Gadoxetic acid-ethoxybenzyl diethylenetriamine-enhanced magnetic resonance imaging. a) T1-weighted image (T1WI) displayed a tumor with hypointensity . b) Fat-suppressed T1WI displayed a tumor with hypointensity. c) T2-weighted image displayed a tumor with hyperintensity. d) T1WI on arterial phase displayed a tumor with patchy enhancement. e) T1WI on hepatobiliary phase displayed a tumor with hypointensity.
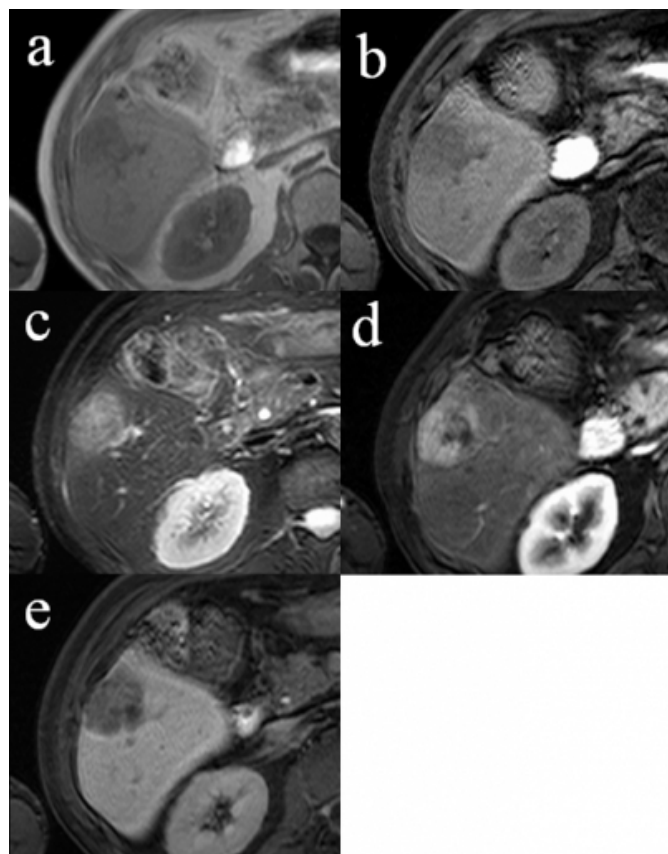
The patient was diagnosed as having HCC and was scheduled to receive surgical resection; however, during the preoperative examination, he was found to have severe stenosis of the coronary arteries and required percutaneous coronary intervention with subsequent anticoagulant therapy for 3 months prior to surgery. Follow-up CT 3 months after initial diagnosis showed tumor growth with enlargement of the internal hypodense area (Fig. 2c-f). There was no obvious distant metastasis on imaging. The patient then underwent laparoscopic partial liver resection.
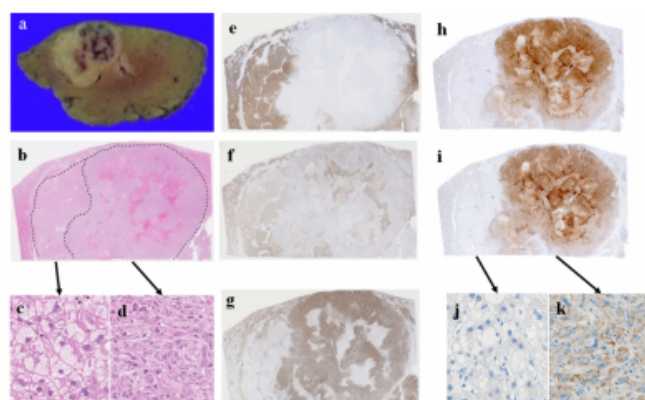
Intraoperatively, the tumor was found to be located in segment 5 of the liver without exposure on the liver surface, and no peritoneal dissemination was observed.

On the resected specimen, the tumor was macroscopically a partially poorly defined, yellow-whitish, solid mass of 3.9 x 3.3 x 3.0 cm with a finding of internal necrosis (Fig. 4a). The

surgical margin was negative at the resected cut edge.
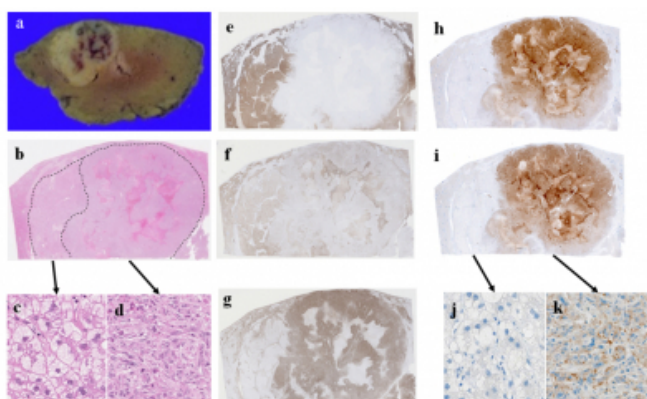
Figure 4

Pathological findings. a) The macroscopic findings showed a 3.9 x 3.3 x 3.0 irregular tumor with necrosis. b) In the loupe image, necrosis was observed in the area with a sarcomatoid component. c) High-power magnification of hematoxylin and eosin (HE) staining showed the presence of an ordinary HCC. d) High-power magnification of HE staining showed cytological pleomorphism. e) In the loupe image, hepatocyte paraffin 1 was focally positive in sarcomatoid neoplastic cells. f) CAM5.2 was focally positive in sarcomatoid neoplastic cells. g) Vimentin was diffusely positive in sarcomatoid neoplastic cells. h) Programmed death-ligand 1(PD-L1) (clone; SP263) was diffusely positive in sarcomatoid neoplastic cells. i) PD-L1 (clone; E1L3N) was diffusely positive in sarcomatoid neoplastic cells j) PD-L1 was negative in ordinary neoplastic cells. k) PD-L1 was membranous or cytoplasmic positive in sarcomatoid neoplastic cells.

Microscopically, the tumor had two components (Fig. 4b). One was an ordinary HCC component featuring eosinophilic cells and clear cells with variably small to large nuclei presenting an obvious trabecular pattern (Fig. 4c). The other component displayed sarcomatoid change with cytological pleomorphism including polygonal cells, spindle-shaped cells, and mono- or multinuclear giant cells arranged in interlacing fascicles (Fig. 4d). Diffuse infiltrating mononuclear lymphocytes and tumor necrosis were observed in the component showing sarcomatoid change. The border between the two components was indistinct, and both ordinary neoplastic hepatocytes and pleomorphic tumor cells were seen in the transitional area. The patient was pathologically diagnosed as sarcomatoid HCC from the above findings.

Figure 4

Pathological findings. a) The macroscopic findings showed a 3.9 x 3.3 x 3.0 irregular tumor with necrosis. b) In the loupe image, necrosis was observed in the area with a sarcomatoid component. c) High-power magnification of hematoxylin and eosin (HE) staining showed the presence of an ordinary HCC. d) High-power magnification of HE staining showed cytological pleomorphism. e) In the loupe image, hepatocyte paraffin 1 was focally positive in sarcomatoid neoplastic cells. f) CAM5.2 was focally positive in sarcomatoid neoplastic cells. g) Vimentin was diffusely positive in sarcomatoid neoplastic cells. h) Programmed death-ligand 1(PD-L1) (clone; SP263) was diffusely positive in sarcomatoid neoplastic cells. i) PD-L1 (clone; E1L3N) was diffusely positive in sarcomatoid neoplastic cells j) PD-L1 was negative in ordinary neoplastic cells. k) PD-L1 was membranous or cytoplasmic positive in sarcomatoid neoplastic cells.

On immunohistochemistry, ordinary HCC cells showed positive expression of CAM5.2 and hepatocyte paraffin 1 (HepPar 1) but were negative for vimentin (Fig. 4e-g). In contrast, sarcomatoid tumor cells showed only focal expression of HepPar 1and CAM5.2 (Fig. 4e, 4f) and marked expression of vimentin and programmed death-ligand 1 (PD-L1; SP263 and E1L3N) (Fig. 4g-k). The percentage of tumor cells with membranous staining for PD-L1 was 75%. The microsatellite instability status of the tumor was reviewed by immunohistochemistry, and we could not observe loss of nuclear staining of MLH1, MSH2, MSH6, or PMS2 (Fig.5). The tumor did not display smooth muscle alpha-actin, CD34, desmin, or S-100 protein expression.

Figure 5

Immunohistochemical stain of mismatch repair proteins. The immunohistochemistry displayed nuclear staining of MLH1, MSH2, MSH6, and PMS2.
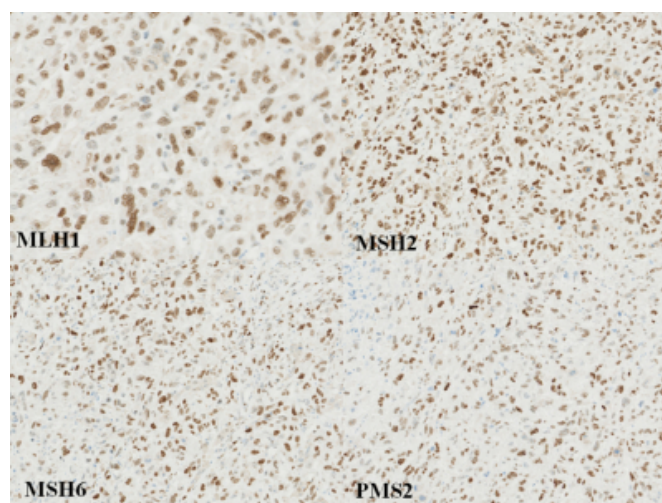
The postoperative course was uneventful, and the patient was discharged on postoperative day 5. Three months after resection, he developed multiple metastatic lesions in the liver, abdominal cavity, lung, and thoracic cavity. The patient opted to receive palliative care and died 18 months after surgery.

DISCUSSION

HCC generally exhibits histological heterogeneity. Among the histopathological manifestations observed, a part of the tumor (or its entirety) typically shows cytological pleomorphism, including the presence of giant cells or spindle cells (5). When such sarcomatoid features are prominent, the tumor is classified as sarcomatoid HCC (5).

Sarcomatoid HCC tends to be more frequent in HCC that occurs after repeated transcatheter arterial chemoembolization, radiofrequency ablation, and percutaneous ethanol injection(3-5). However, in recent years, cases of sarcomatoid HCC have increasingly been reported in patients who have not received previous anticancer therapies, as in the present case (6).

The pathogenesis of sarcomatoid HCC has not been clarified; however, given the coexpression of epithelial and mesenchymal markers by sarcomatoid neoplastic cells and the presence of transitional areas between ordinary and sarcomatoid HCC, it is hypothesized that sarcomatoid change may occur as a result of dedifferentiation or anaplasia in HCC(3, 4).

The radiological characteristics of sarcomatoid HCC are

reported to be peripheral enhancement with central hypodensity on CT and hypointensity on hepatobiliary phase and hyperintensity on T2WI of gadoxetic acid-ethoxybenzyl diethylenetriamine-enhanced magnetic resonance imaging (Gd-EOB-MRI) (7, 8). On CT of the present case, a part of the tumor showed a classical HCC pattern enhancement (early enhancement and late washout), whereas the other part of the tumor remained hypodense. In Gd-EOB-MRI, the tumor demonstrated slight hyperintensity on T2WI and hypointensity on hepatobiliary phase. Interestingly, the hypodense component that increased in size during the 3-month period following the initial imaging corresponded to the pathological sarcomatoid component; accordingly, the rapid growth of the tumor appeared to result from the proliferation of the sarcomatoid tumor cells. Regarding radiological diagnosis, although the main differential diagnosis for such an aggressive tumor could be combined HCC-cholangiocarcinoma, the rapid increase in tumor size and the presence of an internal hypodense area might suggest sarcomatoid HCC (9).

The histopathological finding that a portion of the sarcomatoid tumor cells expressed both epithelial and mesenchymal markers leads to the speculation that the tumor described in the present case originally had the character of HCC.

The primary treatment for sarcomatoid HCC is surgical resection. However, the median overall survival time after surgery is 12.7 months; disease-free survival time is 3-6 months, and most cases show extrahepatic metastases as initial recurrence sites (10, 11). The present case developed multiple extrahepatic metastases shortly (3 months) after surgery.

Regarding systemic chemotherapy for sarcomatoid HCC, a few reports have shown a survival benefit in patients treated with sorafenib. Further study is necessary to verify the effectiveness of molecular targeted drugs in cases of sarcomatoid HCC (6, 12).

In recent years, the effectiveness of immune checkpoint inhibitors, including anti-programmed death-1 (PD-1)/PD-L1 antibodies, against solid cancers of many organs has been recognized (13, 14). PD-L1 expression in cancer cells could be a therapeutic predictor for the use of anti-PD-1/PD-L1 antibody inhibitors (15). A favorable response of immune checkpoint inhibitors for sarcomatoid HCC has not yet been reported, but several reports showed the effectiveness of immune checkpoint inhibitors in any other sarcomatoid

carcinomas. For example, it was reported that 60% of overall response rate (ORR) in patients with PD-L1-positive metastatic renal cell carcinoma with sarcomatoid features treated with atezolizumab and bevacizumab, while 19% of ORR in PD-L1-negative patients(16). Sarcomatoid carcinomas in the kidney or lung often show high expression of PD-L1; such expression has not yet been reported in the sarcomatoid carcinoma of the liver (17, 18). Regarding PD-L1 expression of HCC, 1% or more of PD-L1 expression on tumor cells was observed in 17-20% HCCs and the percentage of tumor cells with membranous staining for PD-L1 was reportedly 1-30% with a mean of 5% (19, 20).

The results described above suggest that histological findings of prominent lymphocytes, necrosis and marked PD-L1 expression in tumor cells with sarcomatoid changes might reflect a characteristic tumor IME. Further investigation must be needed to confirm whether sarcomatoid change is associated with immune tolerance for tumors or not. Common gene alterations have also been reported to occur in tumors with sarcomatoid features (21). Therefore, the characteristic features of tumor IME in the present case can serve as a basis for further understanding of tumors with sarcomatoid features that may occur in a variety of organs. Further investigation is necessary because clarifying the IME of sarcomatoid HCC might make it possible to develop an adequate treatment for this tumor involving anti-PD-1/PD-L1 antibody inhibitors.

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