CASE REPORT

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Primary hepatic carcinosarcoma with multimodal treatment

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ABSTRACT

Hepatic carcinosarcoma (HCS) generally presents in advanced stages, demonstrates aggressive behavior, and has a poor prognosis. Other than curative primary resection, no effective treatment options exist. We present a case of resected HCS with four repeat resections for solitary lymph node recurrence followed by chemoradiotherapy with doxorubicin and ifosfamide. A 67-year-old Japanese man was admitted to our hospital for evaluation of an asymptomatic hepatic tumor. The patient underwent right hepatectomy with a presumptive preoperative diagnosis of atypical hepatocellular carcinoma. Based on histopathological and immunohistochemical findings, the tumor was diagnosed as HCS containing osteosarcoma and chondrosarcoma components. After the initial surgery, the patient underwent four additional resections for solitary lymph node HCS recurrence, and then underwent chemoradiotherapy with doxorubicin and ifosfamide for an unresectable lymph node recurrence. Chemotherapy was stopped after two cycles because of severe adverse events, although chemoradiotherapy markedly reduced the size of the lymph node recurrence and provided a progression-free survival of 12 months. Thirty-seven months after the initial surgery, the patient died of cardiac invasion of multiple mediastinal lymph node metastases. The clinical course outlined in this case report suggests that chemoradiotherapy with doxorubicin and ifosfamide for metastatic HCS may prolong survival in patients with unresectable lesions.

Keywords: hepatic carcinosarcoma, chemoradiotherapy, doxorubicin, ifosfamide

INTRODUCTION

Hepatic carcinosarcoma (HCS) is defined as a tumor containing a mixture of carcinomatous and sarcomatous elements. HCS patients have a high recurrence rate and a poor prognosis1). Other than curative primary resection, no effective treatments exist. Here, we present a case of resected HCS with four repeat resections for solitary lymph node recurrence followed by chemoradiotherapy with doxorubicin and ifosfamide.

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CASE PRESENTATION

A 67-year-old Japanese man was admitted to our hospital for evaluation of an asymptomatic hepatic tumor. Laboratory data, including liver function tests and tumor markers, were normal except for an elevated level of protein induced by vitamin K absence or antagonist-2 (PIVKA-2) of 32,700 mAU/mL. Viral markers for hepatitis B and C were negative. Dynamic computed tomography (CT) revealed a heterogenous low-density tumor in the posterior hepatic segments with rim enhancement during the portal phase (Fig. 1A). The tumor was accompanied by an arterio-portal shunt and tumor thrombus in the right posterior portal vein (Fig. 1B), and appeared to invade the right diaphragm. There were no swollen lymph nodes or distant metastases. Based on these findings, the patient was diagnosed with atypical hepatocellular carcinoma (HCC). At laparotomy, the tumor was located in the posterior hepatic segments with a firm adhesion to the right diaphragm. Thus, a right hepatectomy with partial resection of the right diaphragm was performed. Regional lymphadenectomy was not performed. The operation time was 294 min and blood loss was 1340 mL.

The resected liver specimen contained a yellowish-gray solid tumor without a capsule, measuring 7.8 × 7.5 × 5.5 cm, and included a central necrotic area (Fig. 2A). Microscopically, the tumor was composed of sarcomatous and carcinomatous components (Fig. 2B). The majority of the tumor was sarcomatous, composed of spindle-shaped sarcoma and small foci of osteosarcoma and chondrosarcoma components with bone and cartilage formation (Fig. 3A, B, C). The carcinomatous components included small foci of moderately differentiated clear cell HCC and poorly differentiated adenocarcinoma, which could not be classified as either HCC or cholangiocellular carcinoma (Fig. 3D, E). There was a limited transitional zone composed of atypical epithelial cells between the carcinomatous and sarcomatous components (Fig. 3F). Resection margins of the tumor were negative, and the tumor penetrated to the serosa without invasion of the diaphragm. The surrounding liver showed non-cirrhotic changes. The results of immunohistochemistry were summarized in Table 1. The clear cell HCC was positive for CK18, glypican-3, and CD10. The adenocarcinoma was positive for EMA, CAM5.2, CK7, and CA19-9. The spindle-shaped sarcoma was positive for vimentin, glypican-3, and CD10. The osteosarcoma and chondrosarcoma were positive for S-100 protein. The transitional zone was positive for vimentin, EMA, CK18, and CD10. Thus, the tumor was diagnosed as HCS, T3bN0M0 according to the UICC 7th edition. The patient had an uneventful recovery.

Two months after surgery, a follow-up enhanced CT revealed a swollen lymph node in 16a2 interaorticocaval region, and fluorodeoxyglucose positron emission tomography (FDG-PET) revealed enhanced FDG uptake. No other metastatic lesions were found on either CT or FDG-PET. The patient was given a provisional diagnosis of solitary para-aortic lymph node metastasis of HCS and underwent para-aortic lymphadenectomy from the level of the celiac trunk to the root of the inferior mesenteric artery. Histologically, the tumor was consistent with a spindle-shaped sarcoma lymph node metastasis (Fig. 3G). The patient had an uneventful recovery, and chose not to undergo postoperative chemotherapy.

After the para-aortic lymphadenectomy, the patient underwent 3 additional lymphadenectomies, at 11, 14, and 19 months after the initial hepatectomy, for solitary swollen lymph nodes in the 16b2 retrocaval, 16b2 lateroaortic, and left supraclavicular regions, respectively. In each case, histological tumor characteristics were similar to those of the initial para-aortic lymph node metastasis. Twenty-one months after the initial hepatectomy, CT revealed an irregular-shaped tumor in the left supraclavicular region (Fig. 4A). The tumor appeared to infiltrate the left internal carotid artery, and was felt to be unresectable. Thus, the patient underwent chemotherapy with doxorubicin (60 mg/m^2; 20 mg/m^2 per day, day 1–3) and ifosfamide (10 g/m^2; 2 g/m^2 per day,

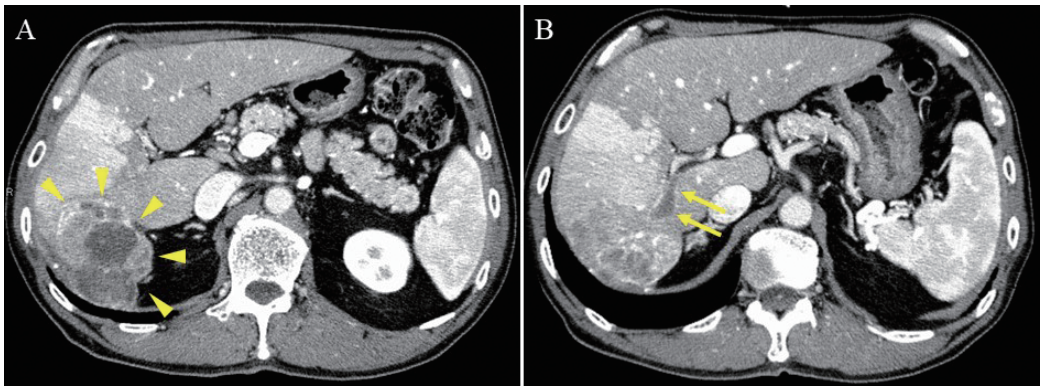

Fig. 1 (A) Dynamic CT revealed a heterogenous low-density tumor in the posterior hepatic segments with rim enhancement during the portal phase (arrowheads). (B) Tumor thrombus in the right posterior portal vein was also observed (arrows).

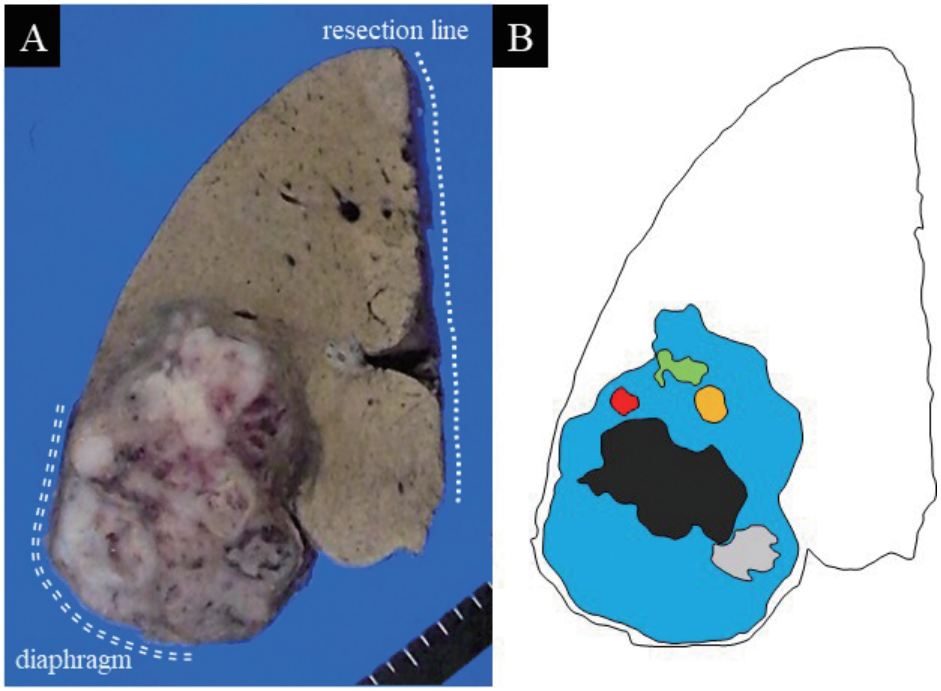

Fig. 2 (A) The cut surface of the resected specimen showed a yellowish-gray solid tumor. (B) The tumor contained elements of HCC (red), adenocarcinoma (orange), spindle-shaped sarcoma (blue), osteosarcoma and chondrosarcoma (gray), transitional zone (green), and necrosis (black).

day 1–5) combined with radiotherapy (51Gy in 17 daily fractions of 3Gy). Chemotherapy was stopped after two cycles because of grade 3 or 4 adverse events including neutropenia, nausea, and vomiting, although treatment had markedly reduced the size of the lymph node recurrence (Fig. 4B). The patient had a progression-free survival of 12 months. However, 34 months after the initial surgery, CT revealed multiple mediastinal lymph node metastases. Thirty-seven months

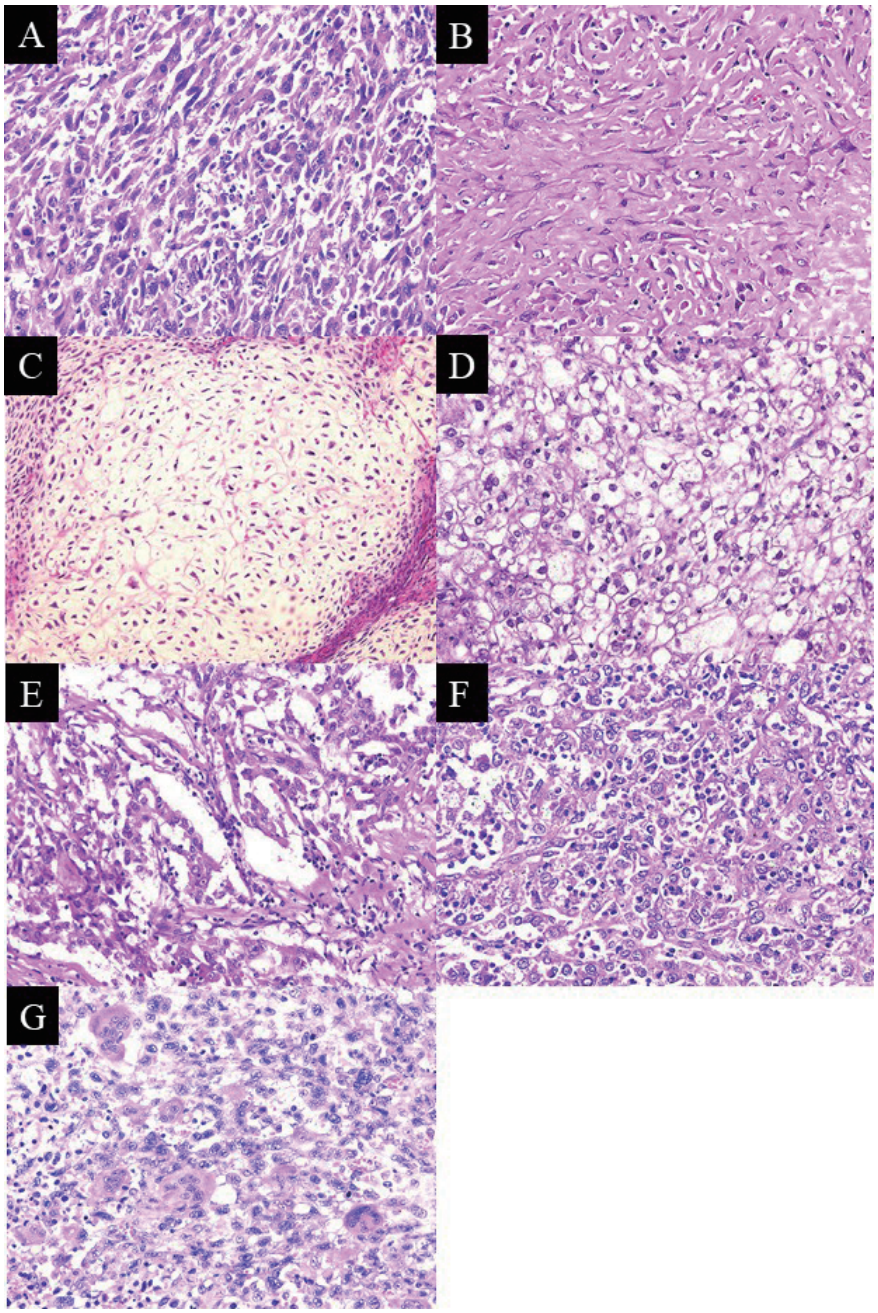

Fig. 3 Hematoxylin-eosin stain (× 20) of the tumor showed the following: (A) spindle-shaped sarcoma; (B) osteosarcoma; (C) chondrosarcoma; (D) moderately differentiated clear cell HCC; (E) poorly differentiated adenocarcinoma; (F) transitional zone composed of atypical epithelial and sarcomatous cells; (G) lymph node metastasis composed of spindle-shaped sarcoma.

Table 1 Results of immunohistochemistry

Marker	HCC	adenocarcinoma	sarcoma	transitional zone
EMA	−	+	−	+
CAM5.2	−	+	−	−
CK7	−	+	−	−
CK18	+	−	−	+
CA19-9	−	+	−	−
Glypican-3	+	−	+	−
CD10	+	−	+	+
Vimentin	−	−	+	+
S-100	−	−	+	−

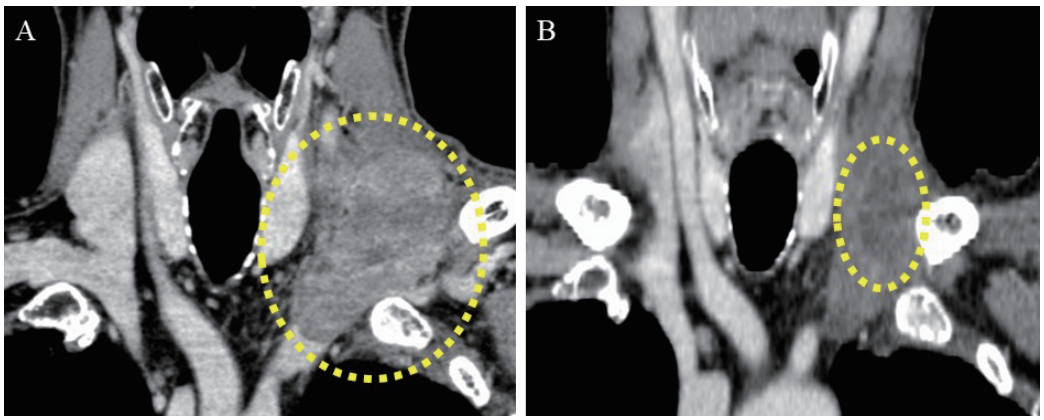

Fig. 4 (A) CT revealed an irregular-shaped tumor in the left supraclavicular region with infiltration of the internal carotid artery. (B) Chemoradiotherapy markedly reduced the size of the lymph node recurrence.

after the initial surgery, the patient died of cardiac invasion of the lymph node metastases. Autopsy was not permitted.

DISCUSSION

Carcinosarcoma is more frequent in the uterus, ovary, and urinary bladder.[1)] Including the current report, 37 cases of surgical resection for HCS have been reported in the English literature. Among reported HCS cases, the median tumor diameter was 9.2 cm (range: 2.6–19 cm), and portal/hepatic vein tumor thrombus, intrahepatic metastasis, and abdominal dissemination were found in 9 (24%), 9 (24%), and 3 (8.1%) patients, respectively. Adjacent organ extension was found in 11 cases (30%), which is 3 times more frequent than that found in HCC (10%).[2)] Moreover, regional lymphadenectomy was performed in only 4 cases (11%). Lymph node metastasis was found in all 4 cases, suggesting that the actual incidence of lymph node metastasis in HCS is probably much higher. It has also been reported that lymphadenectomy is the standard approach for uterine, ovarian, and urinary bladder carcinosarcoma.[3-5)] Together, the available data suggest

that HCS should be part of the differential diagnosis of large hepatic tumors extending to adjacent organs. Furthermore, in HCS cases, lymphadenectomy may result in an improved prognosis.

Previous studies have reported curative primary resection as the only treatment for HCS.[6] Even with surgery, however, most patients died within a year, with a median survival time of only 6 months (range: 1–37 months). Although 8 patients survived without recurrence after curative primary resection, most patients, including those with early-stage HCS, showed early recurrence and a poor outcome. The mean time to recurrence was 4.9 months (range: 1–15 months). The most common site of recurrence was the peritoneum, followed by the liver, lung, and para-aortic lymph node. In terms of the treatment of HCC, sorafenib is effective for unresectable HCC with or without extra-hepatic metastasis,[7] although few data predictive of its effectiveness for HCS are available. Furthermore, several cases had improved outcome following resection of a solitary lymph node recurrence of HCC.[8,9] Given the lack of recommended treatment options for HCS, we performed four repeat resections for solitary lymph node recurrence after proper counselling and informed consent. However, each recurrence occurred soon after the previous surgery. Histologically, all of the metastatic lesions consisted of sarcomatous elements. Yamamoto *et al.* reported that 93% of metastatic HCS lesions contained mostly sarcomatous elements.[10] Because HCS is characterized by aggressive dissemination due to the sarcomatous element, physicians needed to consider not only surgical resection but also systemic treatment.

To our knowledge, this is the first reported case of HCS treated with doxorubicin and ifosfamide, which are considered key agents in the treatment of advanced soft-tissue sarcoma.[11,12] We used doxorubicin and ifosfamide for the following reasons: First, it has been reported that chemotherapy including sorafenib, imatinib, tegafur/gimeracil/oteracil (S-1), cisplatin, carboplatin, epirubicin, etoposide, and mitomycin, which are commonly used for HCC, has no survival benefit in HCS. Second, the resected recurrent lesions consisted of sarcomatous elements only, suggesting that chemotherapy for soft-tissue sarcoma might be effective. Furthermore, previous studies reported that ifosfamide-based combination chemotherapy was effective for other advanced carcinosarcomas, especially in the field of gynecology.[13,14] In addition, a satisfactory outcome of radiotherapy alone for soft-tissue sarcoma is not usually expected. However, Eckert *et al.* suggested a better outcome with chemoradiotherapy including ifosfamide compared to radiotherapy alone for unresectable locally advanced soft-tissue sarcoma.[15] In our patient, each recurrence occurred soon after the previous surgery, but chemoradiotherapy with doxorubicin and ifosfamide markedly reduced the size of the lymph node recurrence and provided a progression-free survival of 12 months, suggesting that chemoradiotherapy might be more effective than surgery alone in the treatment of metastatic HCS. However, the risk of toxicity associated with combination chemotherapy (doxorubicin and ifosfamide) is generally high.[16] In our patient, chemotherapy was stopped after two cycles because of severe adverse events. Thus, the risks and benefits combination chemotherapy should be carefully considered, including the patient's age and general condition.

CONCLUSIONS

The clinical course outlined in this case report suggests that chemoradiotherapy with doxorubicin and ifosfamide for metastatic HCS may prolong survival in selected patients, such as those with unresectable lesions. However, the risk of severe adverse events due to this chemotherapeutic option must be carefully considered. Future reports will help determine the most appropriate treatment of HCS.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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