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Primary Hepatic Carcinosarcoma Composed of Hepatocellular Carcinoma, Cholangiocarcinoma, Osteosarcoma and Rhabdomyosarcoma With Poor Prognosis

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Abstract. *Background: Primary hepatic carcinosarcoma is a rare subtype of liver malignancy, with only a small number of cases described in the English literature. Case Report: We report the case of a 72-year-old man with a history of hepatitis C, who presented with complaints of abdominal pain. The patient's alpha fetoprotein (AFP) level was highly elevated at 7,406 ng/ml. His albumin, total bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels were within normal ranges. Computer tomographic scans discovered a 12×9×8 cm mass in the left lobe of the liver, extending to the anterior gastric wall. A partial hepatectomy of segments 2 and 3 with en bloc distal gastrectomy and omentectomy, a Roux-en-Y gastrojejunostomy, and a cholecystectomy were performed. Pathology revealed the mass to be a hepatic carcinosarcoma composed of collision tumor of four malignant components: hepatocellular carcinoma, cholangiocarcinoma, osteosarcoma and rhabdomyosarcoma. One and half month post-surgery, the patient was found to have a mass confirmed by biopsy as hepatocellular carcinoma in the right lobe, nodules in his lung and bone, and his AFP level elevated to 51,027.6 ng/ml. He died after two months during hospice care. Conclusion: To the best of our knowledge, this is the first documented case of primary hepatic carcinosarcoma with collision tumor of four malignant entities (hepatocellular carcinoma, cholangiocarcinoma, osteosarcoma and rhabdomyosarcoma). The pathogenesis, diagnosis, treatment and prognosis of this disease are discussed.*

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Key Words: Primary hepatic carcinosarcoma, collision tumor, hepatocellular carcinoma, HCC, cholangiocarcinoma, CC, osteosarcoma, and rhabdomyosarcoma.

Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) are the most frequent primary hepatic malignancies (1). Primary liver cancer including HCC and ICC, is the sixth most common cancer and the fourth leading cause of cancer-related death worldwide, with an estimated 841,080 new cases and 781,631 deaths in 2018 (1). Combination of HCC and ICC (cHCC-CC) accounts for 2-5% of all primary liver cancer (2). Risk factors for primary liver cancer include chronic hepatitis, hepatitis B and C (HCV) infection, cirrhosis, steatohepatitis, and exposure to environmental toxins such as aflatoxins. Malignant mesenchymaI tumors including osteosarcoma and rhabdomyosarcoma are rarely reported in the liver. Through a PubMed key words search, as far as we are aware, cases of primary liver malignancy with collision tumor of HCC, cholangiocarcinoma, osteosarcoma and rhabdomyosarcoma have not been reported.

Primary hepatic carcinosarcoma is an exceedingly rare tumor with a poor prognosis, with few cases reported to date (3-5). The tumor is specifically defined by the World Health Organization as "a malignant tumor containing an intimate mixture of carcinomatous (either hepatocellular or cholangiocellular) and sarcomatous elements" (6). We report the case of a patient whose hepatic tumor was morphologically and immunohistochemically analyzed, and found to contain closely intermingled epithelial and sarcomatous components of HCC, intrahepatic cholangiocarcinoma, osteosarcoma and rhabdomyosarcoma. To the best of our knowledge, this is the first documented case of

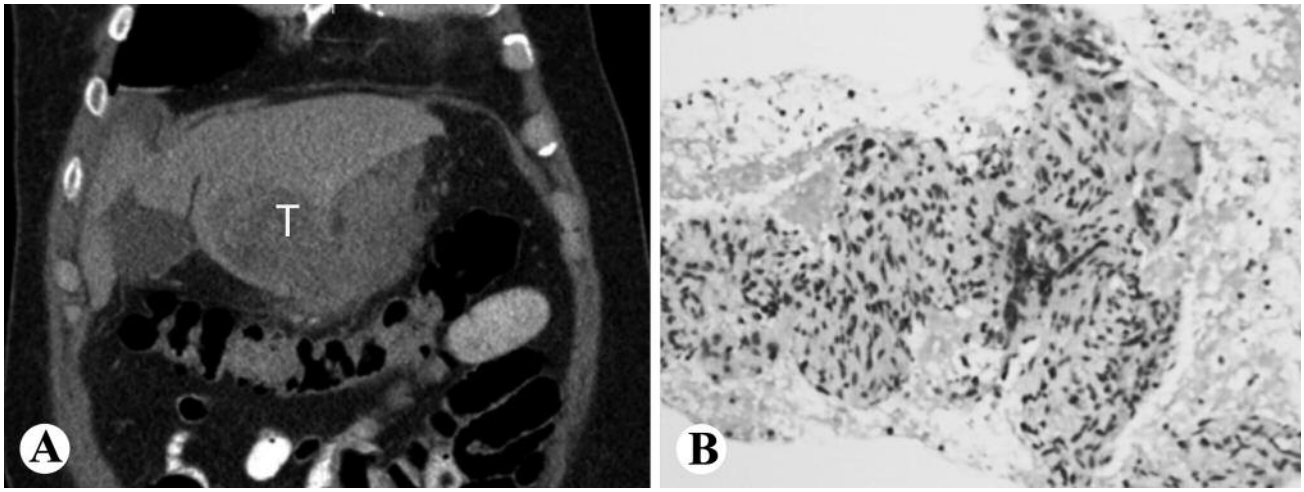

Figure 1. *A: computed tomographic scan (coronal) showing a large hepatic mass (T). B: Endoscopic ultrasound fine-needle biopsy of the tumor showing atypical cells with epithelial and sarcomatous differentiation suggestive of carcinosarcoma. Hematoxylin and eosin stain, ×400.*

primary hepatic carcinosarcoma with collision tumor of these four malignant components. Description of the morphology of the present case may benefit future diagnosis, improve clinical management, and further understanding of tumor progression in similar cases.

Case Report

A 72-year-old African American man with a history of hepatitis C (HCV) genotype 1b infection, with stage 3 fibrosis and successfully treated with ledipasvir/sofosbuvir, presented to another institution due to main complain of abdominal pain. The patient's alpha fetoprotein level was 7,406 ng/ml. His albumin, total bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels were within normal ranges. Total protein was 6.3 g/dl. HCV was not detected in a quantitative polymerase chain reaction. Computed tomographic (CT) scans revealed a 12×9×8 cm hypointense mass involving the left lobe of the liver extending to the anterior gastric wall (Figure 1A). Magnetic resonance imaging of the patient's liver was performed and showed a mass between the liver and stomach. An endoscopic ultrasound fine-needle biopsy was performed. On pathology, fragments of poorly differentiated carcinoma with hepatoid and spindled differentiation were identified with a background of necrosis (Figure 1B). Positron-emission tomography/CT scan showed a large focus of intense 2-^{18}F-fluoro-2-deoxy-D-glucose uptake corresponding to the soft-tissue mass between the left lobe of the liver and stomach but did not show any metastatic disease. A partial hepatectomy of segments 2 and 3 with en bloc distal gastrectomy and omentectomy, a Roux-en-Y gastrojejunostomy, and a cholecystectomy were performed, and the specimen was submitted for pathology evaluation.

On pathology, grossly, a 13×10×10 cm friable mass of the left liver extended into the stomach and there were two hepatic satellite nodules measuring 1.5 cm and 0.5 cm each. The tumor penetrated the visceral peritoneum and invaded the gastric *muscularis propria*. The tumor showed tan-pink soft friable cut surface with areas of hemorrhage and necrosis (10-20%). Microscopically, the tumor was composed predominantly of atypical epithelial component intermingled with 5-10% of a sarcomatous component, with histological features of collision tumor of HCC, cholangiocarcinoma, osteosarcoma and rhabdomyosarcoma (Figure 2A). The epithelial component displayed areas of typical well-differentiated HCC (Figure 2B) with steatosis to solid sheets of poorly or undifferentiated HCC. Unequivocal glandular structures were seen, consistent with moderately differentiated cholangiocarcinoma (Figure 2C and D) with collision with HCC (Figure 2C). The spindled sarcomatous component exhibited heterogenous differentiation morphologically consistent with osteosarcoma with osteoid formation (Figure 3A and 3B) and rhabdomyosarcoma with cytoplasmic rhabdoid features and cross-striations (Figure 3C). The tumor was 2 cm from the closest liver resection margin. The epithelial component invaded into small branch lymphovascular spaces. Twelve lymph nodes were examined, and all were negative for metastatic tumor. On immunostaining, part of the epithelial component was strongly and diffusely positive for cytokeratin CAM5.2, focally positive for arginase-1 and glypican 3, and negative for cytokeratin (CK)20 and CK7 suggestive of HCC, while the other part of the epithelial components with glandular architecture was positive for CK7 and negative for arginase and glypican 3 suggesting cholangiocarcinoma. The tumor was negative for synaptophysin, chromogranin, calretinin and

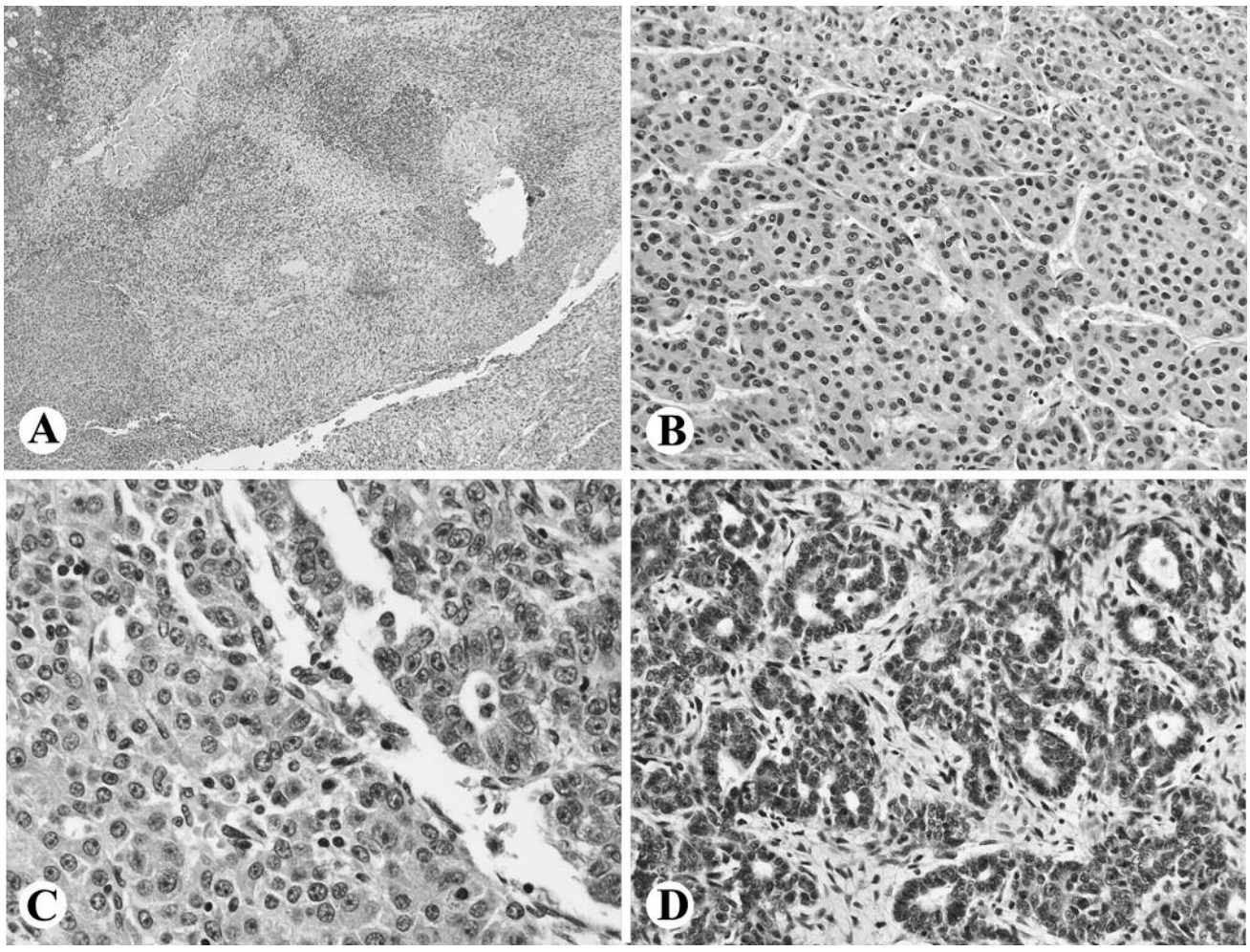

Figure 2. *Resection of the hepatic tumor showing collision tumor of the carcinoma and sarcoma components (A), well-differentiated hepatocellular carcinoma (B), hepatocellular carcinoma (C left) with collision of cholangiocarcinoma (C, right and D) (hematoxylin and eosin stain, A: ×40; B: ×200; C: ×400; and D: ×200).*

thyroid transcription factor (TTF1). The sarcomatous component was positive for vimentin. Areas with morphological features of rhabdomyosarcoma were positive for desmin (Figure 3D). The background liver showed focal mild lymphocytic inflammation and lymphoid aggregate in portal triads, consistent with history of chronic HCV-associated hepatitis, with no significant activity. Trichrome stain highlighted mainly portal fibrosis with areas of bridging fibrosis. No cirrhosis was identified. Iron stain was negative for hemosiderosis, and periodic acid Schiff with diastase stain was negative for alpha 1 antitrypsin deficiency-like intracytoplasmic globules. The final pathology diagnosis was hepatic carcinosarcoma (T4N0M0 stage IIIB) with mixed and collision tumor of HCC, cholangiocarcinoma, osteosarcoma and rhabdomyosarcoma.

The patient had a relatively uncomplicated postoperative course but was found to have an abscess in the surgical resection bed, which was managed with a drain. The culture from the abdominal drain showed *Enterobacter* alpha strep viridans and *Prevotella* species, and the patient was treated with antibiotics. One and a half months after surgical resection, the patient was found to have masses in his right liver and a liver biopsy showed only epithelioid component of HCC and the AFP level was elevated to 51,027.6 ng/ml. Positron-emission tomography–CT showed hypermetabolic bony lesion and *porta hepatis* mass, with pulmonary nodules. The patient received hospice care and died 2 months later.

Discussion

Primary hepatic carcinosarcoma is a very rare subtype of hepatic neoplasm, comprising less than 1% HCCs (7), with only a small number of cases reported in literature to date (3-5). The characteristics of this tumor are poorly

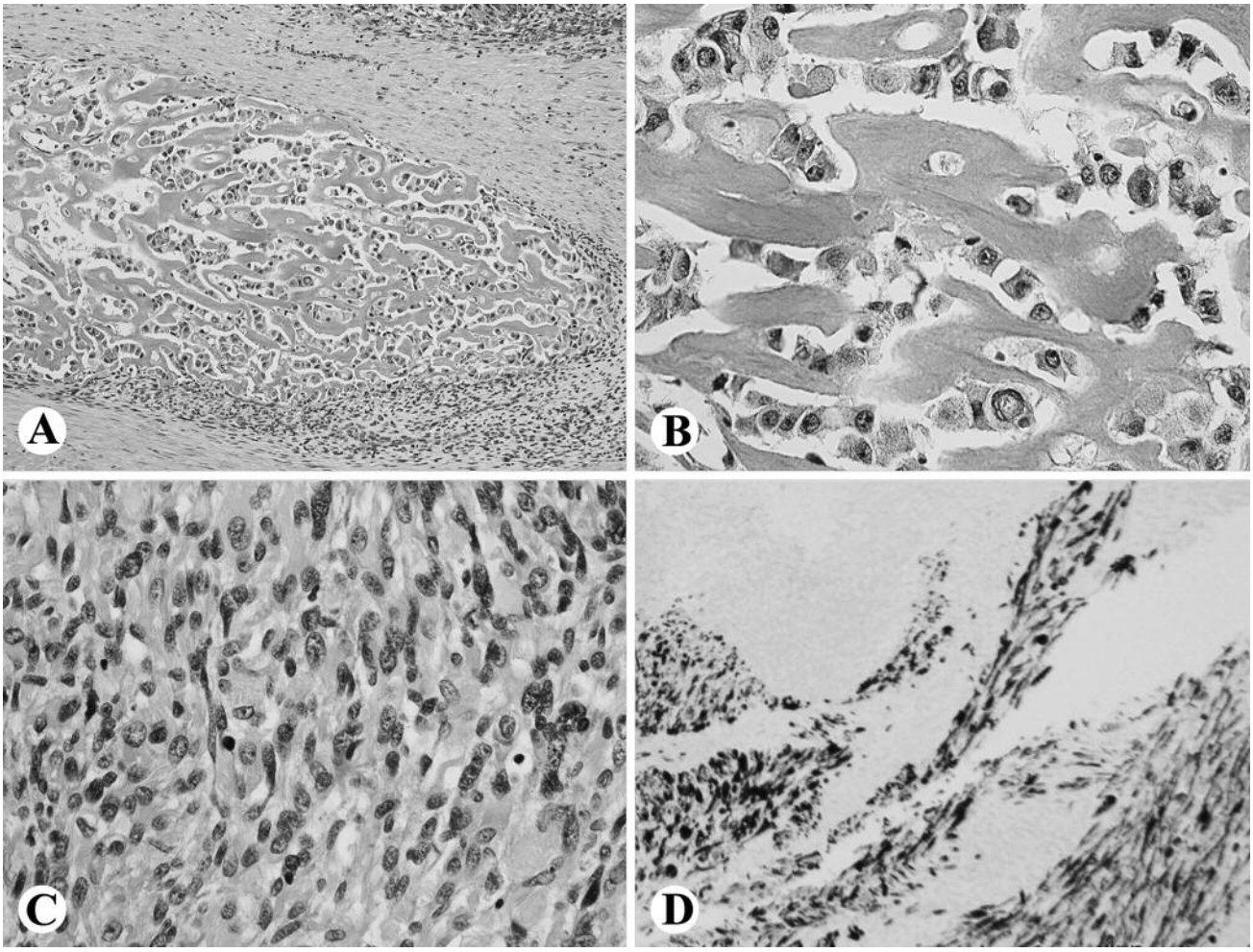

Figure 3. *High magnification of the sarcomatous components in Figure 2A, showing osteosarcoma (A and B) and rhabdomyosarcoma (C and D). Hematoxylin and eosin stain, A: ×100; B and C: ×400. Immunostain of desmin, D: ×100.*

understood, and awareness of hepatocellular carcinosarcoma is further muddled by confusion with other terms such as sarcomatoid HCC, spindle-cell HCC, sarcomatous carcinoma, and adult hepatoblastoma (7). Therefore, it is important to report the type of tumor morphology for this relatively unknown malignancy. Through the presentation of our case, we hope to benefit future diagnosis, improve clinical management, and further the understanding of tumor progression in similar cases.

The case presented here is especially uncommon due to the combination and tumor collision of both mixed HCC and cholangiocarcinoma in the epithelial part of the tumor and the mixture of rhabdomyosarcoma and osteosarcoma in the sarcomatous part of the tumor. In general, hepatic carcinosarcoma has a worse prognosis than conventional HCC, which is primarily attributable to the aggressive sarcomatous elements (5). The sarcomatous elements can differentiate widely, which was demonstrated by the heterogeneous differentiation seen in the present case. Specifically, our case was distinguished from sarcomatoid HCC through the differentiation of the sarcomatous component to specific mesenchymal lineages (7). Tumor morphology identified by histological analysis is important for the evaluation of patient prognosis. The tumor in the present case was predominantly composed of carcinomatous elements, with only 5-10% of sarcomatous element seen in the tumor. Both hepatic satellite nodules were of epithelial composition, and lymphovascular invasion was seen only with the epithelial elements. This is an unusual case with four such malignant components; we found nothing comparable reported in the English literature through a PubMed search using relevant key words.

The tumor in the present case was treated through surgical resection. However, only 48 days after the surgical resection, an early recurrence or intrahepatic metastasis of the tumor was detected in the right lobe of the liver through a CT scan, and confirmed by liver biopsy. Early recurrence/intrahepatic metastasis and poor prognosis after surgical resection were common in previously reported cases of hepatic carcinosarcoma (8). Curative surgical resection is usually limited by metastatic lesions, which are primarily composed of sarcomatous elements, as described in a study of 21 cases of primary hepatic carcinosarcoma (9). The epithelioid nature of the recurrent tumor in the present case reflected the predominance of epithelial elements in the original tumor. Prior lymphovascular invasion of carcinomatous elements of the original tumor made surgical resection unlikely to succeed in the present case. However, surgical resection remains the primary method of treating hepatic carcinosarcoma (8).

In summary, we report an unusual case of primary hepatic carcinosarcoma composed of collision tumor of HCC, cholangiocarcinoma, osteosarcoma and rhabdomyosarcoma in a patient with history of chronic HCV infection. Surgical resection is the cornerstone treatment for hepatic carcinosarcoma if it is resectable. Our patient had a poor prognosis due to the intrahepatic metastasis of the HCC components and distant metastasis of the tumor. More case reports are needed to further characterize the disease.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in regard to this case

Authors' Contributions

LL made the diagnosis, collected the data and wrote the article; EA wrote the article; KS made the diagnosis; KC performed the surgery; and JL analyzed the data, wrote and finalized the article. Authors have approved this article.

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