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Case Report

Acute progressing hepatic angiosarcoma: An autopsy case report ☆

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ABSTRACT

A man in his 50s presented with pitting edema of both lower legs and abdominal distension as his chief complaint. His personal medical history and family history were unremarkable, except that he was a heavy drinker consuming 66 g of alcohol per day and a heavy smoker. Blood tests upon admission showed slight hepatic dysfunction, thrombocytopenia, jaundice, hypoalbuminemia, and decreased coagulability. Tumor marker tests showed elevated levels of CA19-9 and PIVKA-II. Contrast-enhanced computed tomography revealed enhancement of multiple masses predominantly in the right lobe of the liver in the early phase, followed by diffuse enhancement of the entire liver in the delayed phase. Hepatic arteriography demonstrated large hemangioma-like lesions corresponding to the masses revealed by computed tomography. That findings seemed to be cotton wool appearance. On magnetic resonance images, there were multiple mass-like lesions that showed homogeneous or heterogeneous low signal intensity on T1-weighted images, and clearly high signal intensity on T2-weighted images. The findings were atypical and no definite diagnosis could be made. Hepatic failure then rapidly worsened, and the patient died on hospital day 20. Autopsy led to the diagnosis of hepatic angiosarcoma.

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Introduction

Hepatic angiosarcoma is a rare neoplasm, reportedly accounting for 0.5% to 2% of primary liver malignancies [1,2] and its various imaging findings have been described. Almost no published reports have described diffuse hepatic angiosarcoma. The prognosis is very poor, and its various images make diagnosis difficult. This report describes our experience with a rare case of diffuse hepatic angiosarcoma including autopsy results with detailed discussion.

Case report

The patient was a man in his 50s who presented with chief complaints of pitting edema of both lower legs and abdominal distension. His personal medical history and family history were unremarkable, except that he was a heavy drinker consuming 66 g of alcohol per day and a heavy smoker. Physical findings included clear consciousness, yellow bulbar conjunctiva, marked lower leg edema, and abdominal distension with a fluctuant sensation on palpation. He was admitted for further detailed examination.

Blood tests upon admission showed slight hepatic dysfunction, thrombocytopenia, jaundice, hypoalbuminemia, and decreased coagulability: white blood cells, 4800/μL; hemoglobin, 13.6 g/dL; platelets, 8.1 $\times$ 10^4 /μL; albumin, 2.7 g/dL; total bilirubin, 5.8 mg/dL; aspartate aminotransferase, 177 U/L; alanine aminotransferase 80 U/L; alkaline phosphatase, 540 U/L; γ-glutamyl transpeptidase, 405 U/L; prothrombin time % activity, 55 %; C-reactive protein 2.0 mg/dL; activated partial thromboplastin time, 43.5 seconds; alpha-fetoprotein, 10.7 ng/mL; carcinoembryonic antigen, 3.6 ng/mL; carbohydrate antigen 19-9, 62 U/mL; hepatitis B surface antigen, negative; hepatitis B surface antibody, positive; and hepatitis C virus antibody, negative. The patient had Child-Pugh class C liver function. The ascites was transudative.

Pre-contrast CT image showed swelling of the hepatic right lobe and multiple low-density mass-like structures in the liver (Fig. 1A). On dynamic contrast enhanced CT images, these lesions showed multiple nodular enhancement in the early-phase (Fig. 1B), and retained or fill-in pattern enhancement in the delayed phase. The lesions that demonstrated both homogeneous and heterogeneous enhancement coexisted (Fig. 1C).

On magnetic resonance images, there were multiple mass-like lesions that showed homogeneous or heterogeneous low signal intensity on T1-weighted images, and clearly high signal intensity on T2-weighted images. As with CT imaging, gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid (Primovist, Bayer Schering Pharma, Berlin, Germany) -enhanced magnetic resonance images showed multiple nodular enhancement of those lesions in the early phase, and followed by gradual fill-in enhancement in the portal and late phase. Enhanced still retained in the hepatocyte phase (Fig. 2). We considered that the findings were atypical of hepatocellular carcinoma, but it was difficult to make definite diagnosis.

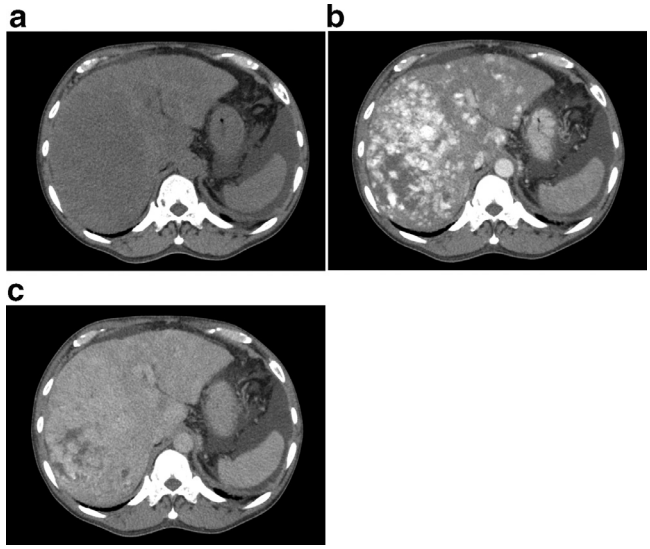

Fig. 1 – Contrast-enhanced computed tomography (CT). (A) Precontrast (B) Early phase (C) Delayed phase Precontrast CT image showed swelling of the hepatic right lobe and multiple low-density mass-like structures in the liver (Fig. 1A). On dynamic contrast enhanced CT images, these lesions showed multiple nodular enhancement in the early-phase (Fig. 1B), and retained or fill-in pattern enhancement in the delayed phase. The lesions that demonstrated both homogeneous and heterogeneous enhancement coexisted (Fig. 1C).

We performed hepatic arteriography to investigate the hemodynamic characteristics. Hepatic arteriography showed multiple foci of dense and nodular contrast opacification that are so called “cotton-wool appearance” (Fig. 3). CT during hepatic arteriography showed multiple nodular enhancement in the early phase and followed by retained or fill-in pattern enhancement in the delayed phase as well as dynamic contrast enhanced CT images. CT during arterial portography showed heterogenous contrast-enhancement that suggested blood supply from the portal vein into the masses (Fig. 3).

Differential diagnoses based on these findings included cavernous hemangiomatosis, diffuse hepatocellular carcinoma, and hepatic angiosarcoma. Because of the poor general condition of the patient, no biopsy could be performed, and thus no definite diagnosis could be made. Treatment was started with intravenous furosemide 40 mg, oral tolvaptan 7.5 mg, and albumin in combination. However, hepatic failure rapidly worsened, and the patient died on hospital day 20. An autopsy was performed after informed consent was obtained from the patient’s family.

Autopsy findings are shown in Fig. 4. The liver was swollen. On the cut surface of the liver, there were multiple, cystic areas of varying sizes that contained blood, along with some areas of hemorrhage and necrosis. Hematoxylin-Eosin staining showed proliferation of spindle cells surrounded by hepatocytes. At high magnification, these cells showed nuclear enlargement and karyokinesis including heterotypic division. Immunohistochemical staining showed negative results for

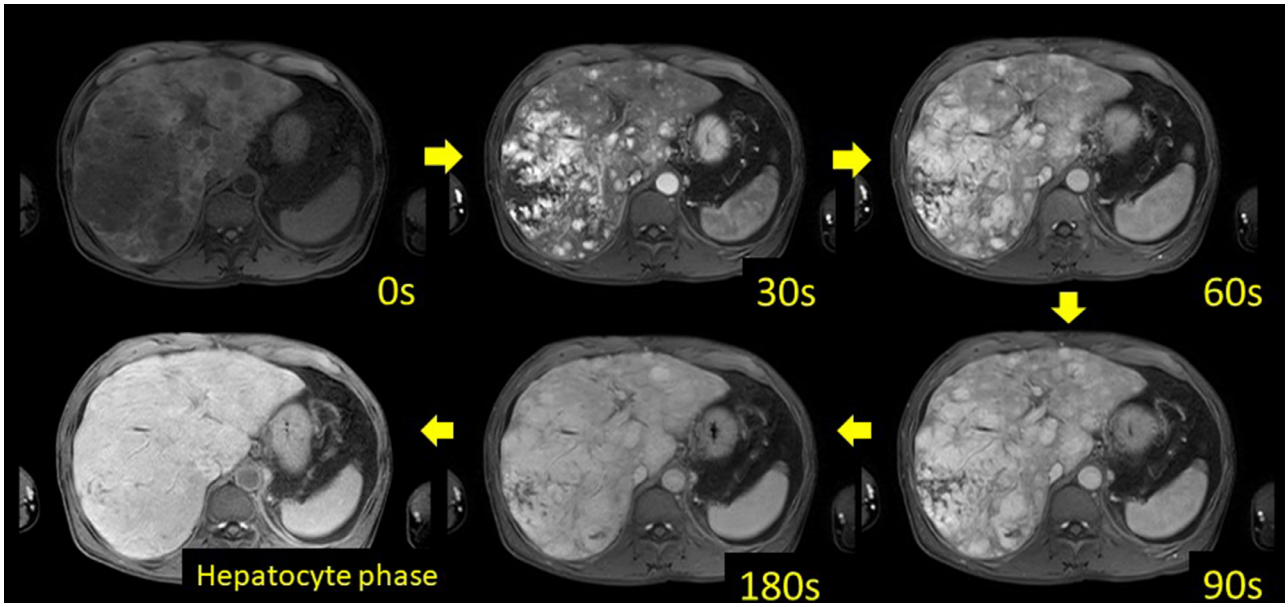

Fig. 2 – Contrast-enhanced MRI.
Gd-EOB-DTPA-enhanced MR images showed multiple nodular enhancement of those lesions in the early phase, and followed by gradual fill-in enhancement in the portal and late phase. Enhanced still retained in the hepatocyte phase. Gd-EOB-DTPA, gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid.

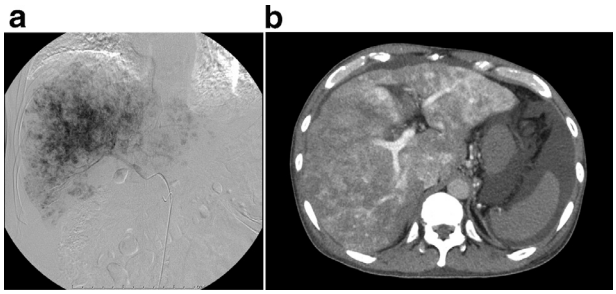

Fig. 3 – (A) Hepatic arteriography Hepatic arteriography showed multiple foci of dense and nodular contrast opacification that are so called "cotton-wool appearance". (B) CT during arterial portography (CTAP). CTAP showed heterogenous contrast-enhancement that suggested blood supply from the portal vein into the masses.

epithelial markers AE1/AE3 and CAM5.2; positive result for a mesenchymal marker of vimentin; and positive results for vascular markers CD31, CD34, and Factor VIII. Although p53 was negative, the MIB-1 index was as high as 20–30%. Since these findings were compatible with malignancy, a diagnosis of hepatic angiosarcoma was made.

Discussion

Hepatic angiosarcoma is a malignancy that arises from vascular endothelial cells, and is a rare occurrence accounting for 0.5 to 2% of primary liver malignancies [1,2]. The disease typically affects men in their 60s or 70s. Onset of hepatic angiosarcoma is associated with exposure to vinyl chloride, Thorotrast, arsenic, and androgens, as well as systemic diseases such as hemochromatosis and von Recklinghausen's disease [3–5]. In many cases, however, the cause is unknown, as in the present case. The prognosis is extremely poor, with reported mean survival times of 6 months or less [4].

Differential diagnoses include cavernous hemangioma, epithelioid endothelioma, and diffuse hepatocellular carcinoma. All of these appear as hypervascular neoplastic lesions, and distinguishing hepatic angiosarcoma from these conditions is difficult before progression of the disease [6].

In hepatic angiosarcoma, similar to cavernous hemangioma, rim enhancement may be seen in the early phase of post-contrast imaging, followed by gradual centripetal filling-in of the enhancement [7–9]. However, imaging findings can vary, reflecting various histopathological findings with a varied extent of hemorrhage and necrosis in the lesions. Non-contast enhanced CT images usually show homogeneous low density, however, they may contain high density components reflecting the presence of hemorrhage and/or calcifications caused by necrosis. Contrast-enhanced CT images also can various enhancement pattern reflecting the extent of blood flow or hemorrhage inside the lesions. Discontinuous enhancement in the early phase (so called spotty, globular, or bright dot enhancement) and prolonged or progressive centripetal fill-in enhancement in the delayed phases are typically shown, which are also specific findings for benign hepatic cavernous hemangiomas. Therefore, the findings reflecting the presence of hemorrhage, necrosis and/or calcifications might be helpful for differential diagnosis.

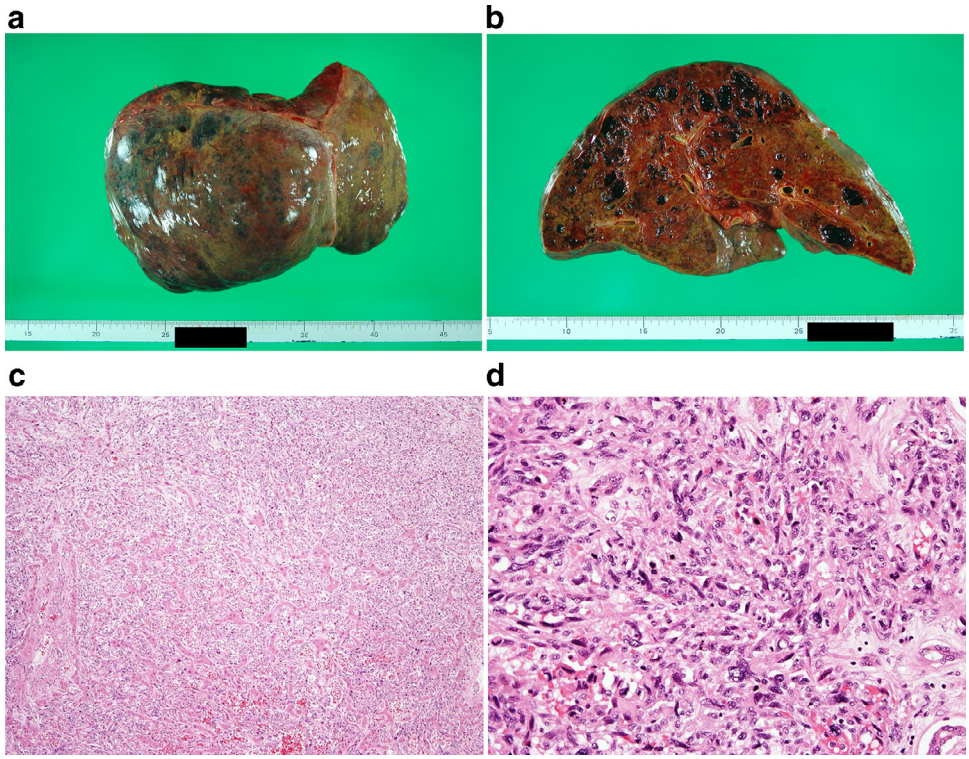

Fig. 4 – Autopsy specimens. (A) Entire liver (B) Cut surface of the liver (C) H&E stained liver section at low magnification (D) H&E stained liver section at high magnification.
The liver was swollen. On the cut surface of the liver, there were multiple, cystic areas of varying sizes that contained blood, along with some areas of hemorrhage and necrosis. Hematoxylin-Eosin (HE) staining showed proliferation of spindle cells surrounded by hepatocytes.

MR images reportedly shows typically low signal intensity on T1-weighted image and high signal intensity on T2-weighted image [8], but some cases may show heterogenous lesions containing both high and low signal intensity reflecting hemorrhage and necrosis as well as CT images [10].

Angiography has been described to be the most important modality for distinguishing hepatic angiosarcoma from other diseases. Angiographic features of hepatic angiosarcoma include: (1) compression or stretching of a hepatic artery; (2) cotton-wool appearance from the arterial phase to the late venous phase; (3) central hypovascular portion in the tumor; and (4) tumor enhancement at a peripheral hepatic artery [11,12]. In the present case, angiography showed early enhancement of multiple nodular lesions, followed by gradual centripetal enhancement progression and a prolonged contrast-enhanced effect, and these findings were consistent with the diagnosis of hepatic angiosarcoma. However, these findings also can be depicted in the benign hemangiomas. The hyperintensity areas on T1-weighted MRI seemed to have reflected necrosis and hemorrhage in the tumors. On the hepatocyte phase image of gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid-enhancement, the lesions showed not low signal but isointense to surrounding normal liver parenchyma and this finding was atypical for malignant lesions. However, autopsy findings showed very little normal residual hepatocytes in this patient. Therefore, the images of the hepatocyte phase could not be attributed to accurate diagnosis due to hepatic failure. Koyama et al. reported imaging findings in 13 cases of hepatic angiosarcoma, including only 1 case of diffuse hepatic angiosarcoma. This finding might be caused by the same condition as that of the present case. Kojiro et al. described sinusoidal and solid patterns of tumor growth in hepatic angiosarcoma [7]. In the present case, the sinusoids were filled with tumor cells, indicating a sinusoidal growth pattern. In a published case by Hoshi et al., the portal vein area was surrounded by tumor cells but remained undamaged, based on which the authors speculated that the relatively slow tumor cell infiltration into the portal vein areas coupled with the rapid sinusoidal tumor cell infiltration had led to additively increased blood supply to the tumor by both hepatic artery and portal vein [13]. Tumor fed by hepatic artery and portal vein is a remarkable finding. Thus, a CT or CT during arterial portography finding of portal venous blood supply to tumors, as seen in the present case, can be a sign of hepatic angiosarcoma.

The potential usefulness of ^{18}F-FDG PET in the differential diagnosis has not been established [14,15].

For treatment of hepatic angiosarcoma, surgical resection may be chosen if the diagnosis is made early. According to a report in Germany, complete resection was performed in 18 of 22 patients between 1985 and 2006 and, although local recurrence or distant metastasis to the lung occurred during the

follow-up, the 5-year survival was 65% and as high as 41% of the patients lived 10 years or more [16].

For unresectable tumors in patients with preserved hepatic function, transarterial chemoembolization (TACE) may be beneficial. Given that the prognosis is related to the number of intrahepatic metastases and tumor rupture, and 15% of the patients suffer fatal intra-abdominal hemorrhage as a result of tumor rupture or other problems, TACE is useful for hemostatic purposes [17]. Along with TACE, radiofrequency ablation should also be considered depending on the tumor size and location [18].

No standard systemic chemotherapy regimens are available for hepatic angiosarcoma. A median survival of 14 months was reported with adriamycin, cyclophosphamide, and methotrexate [11,19]. As for liver transplantation, a report from the United Network for Organ Sharing database described a mean survival of 262 days in 7 recipients. A report from the European Liver Transplant Registry described a mean survival of 7 months in 17 recipients. Based on these data, liver transplantation is not recommendable at present [20].

Conclusion

Hepatic angiosarcoma should be included in the differential diagnosis if imaging shows not only cotton-wool appearance and prolonged contrast material retention that are characteristic findings of cavernous hemangioma, but also variable findings compatible with intratumor hemorrhage and necrosis. Since hepatic angiosarcoma has a very poor prognosis, prompt diagnosis and treatment are necessary.

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