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Case Report

An Autopsy Case of Ruptured Hepatic Angiosarcoma Treated by Transcatheter Arterial Embolization

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Hepatic angiosarcoma · Transcatheter arterial embolization · Transcatheter arterial chemoembolization

Abstract
An 80-year-old Japanese man presented to our hospital with intra-abdominal hemorrhage due to a ruptured liver tumor. Transcatheter arterial embolization (TAE) temporarily achieved hemostasis, but he died following re-rupture 4 days later. Based on autopsy findings, the liver tumor was diagnosed as hepatic angiosarcoma. Embolic agents used during embolization were identified within the hepatic small interlobular arteries. However, there were no findings of tumor cell necrosis or ischemic change in the angiosarcoma. In the present case, TAE alone did not induce ischemia-induced tumor necrosis, suggesting that TAE might be unsuitable to treat hepatic angiosarcoma. Treatment optimization for ruptured hepatic angiosarcoma is desired.

Introduction

Angiosarcoma, a malignant tumor originating from vascular endothelial cells, accounts for 2-3% of adult soft tissue sarcomas. The primary site may be skin, breast, liver, spleen, bone, retina, heart, ovary, or small intestine, of which skin and breast are the most common in angiosarcoma [1]. However, hepatic angiosarcoma is extremely rare, accounting for less than 5% of angiosarcoma cases [2]. As for pathogenesis, hepatic angiosarcoma was reported to be caused by occupational exposure to vinyl chloride monomer, and other environmental

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carcinogens such as thorium dioxide and arsenic have been reported [3]. The prognosis of hepatic angiosarcoma is extremely poor with a median overall survival of 6 months and 1- and 2-year survival rates of 30.4% and 17.3%, respectively. Furthermore, the median overall survival of patients with a ruptured tumor was reported to be 3 months [4]. Currently, there is no established effective treatment for hepatic angiosarcoma except for hepatic resection. However, most cases are inoperable, and hepatic resection is possible in only 20% of cases [5]. In most patients, chemotherapy for palliative care is the only option. Although the efficacy of 5-fluorourcil/carboplatin with doxorubicin or ifosfamide has been reported [6], no established chemotherapy regimen exists.

Hepatic angiosarcoma is a hyper-vascularized tumor, and endovascular therapy might be helpful. Transcatheter arterial embolization (TAE) is helpful for acute arterial bleeding due to the rupture of a hepatic angiosarcoma, and transcatheter arterial chemoembolization (TACE) has been reported to improve survival [7]. We report an autopsy case of a ruptured hepatic angiosarcoma treated with TAE for emergent hemostasis. In this case, transient hemostasis was achieved by TAE, but the patient died due to re-rupture. Pathology at autopsy showed embolic material used during embolization within the hepatic small interlobular arteries. However, there were no findings of necrosis of tumor cells around the intralobular artery, and no ischemic changes were identified. The present findings suggest that TAE alone may not have sufficient therapeutic effect on the tumor.

Case Report

An 80-year-old Japanese man was admitted to our hospital for intra-abdominal hemorrhage due to a rupture of a liver tumor. On admission, his vital signs included depressed blood pressure (80/52 mm Hg), tachycardia (111 bpm), and distended abdomen. He had previously been diagnosed with alcoholic cirrhosis. Laboratory examinations showed a hemoglobin (Hb) level of 6.1 g/dL, a platelet count of 94,000/μL. Blood chemistry tests revealed an aspartate aminotransferase level of 42 U/L, an alanine aminotransferase level of 14 U/L, γ-glutamyl transpeptidase level of 266 U/L, an alkaline phosphatase level of 266 U/L, a total bilirubin level of 2.3 mg/dL, an albumin level of 2.0 g/dL, a prothrombin time activity of 36%, and fibrin degradation products of 43.9 μg/mL. He was diagnosed with disseminated intravascular coagulation (DIC). Tests for serum hepatitis B virus surface antigen, hepatitis B virus surface antibody, and hepatitis C virus antibody were all negative. Regarding tumor markers, carcinoembryonic antigen, carbohydrate antigen 19-9, and des-γ-carboxy prothrombin, alpha-fetoprotein were all within normal range. Contrast-enhanced CT scan showed ascites effusion with high density and 40 mm tumors in both lobes of the liver with delayed enhancement from arterial to delayed phases (Fig. 1a, b). We diagnosed intra-abdominal hemorrhage due to rupture of the liver tumor and decided to perform emergent TAE for hemostasis. Angiography showed the tumor with a cotton wool-like staining pattern (Fig. 2a) because a CT scan 6 months earlier revealed no intrahepatic tumor (data not shown), which suggested extremely rapid growth. We diagnosed ruptured hepatic angiosarcoma. Embolization was performed in the tumor lateral and anterior segments using a 300∼500 μm Embosphere™ (Nipponkayaku, Tokyo, Japan), and disappearance of staining was confirmed in the tumor (Fig. 2b). Following treatment, his anemia did not progress and his general condition was stable. However, 4 days after embolization, he became hypotensive again and complained of abdominal pain. A CT scan showed increased dense ascites (Fig. 3a). Although the arterial phase of the tumor area was paler than before (Fig. 3a), the delayed phase was stained dense as in the previous examination, suggesting blood flow to the tumor from the portal vein was not reduced (Fig. 3b). It was assumed to be re-ruptured hepatic angiosarcoma,

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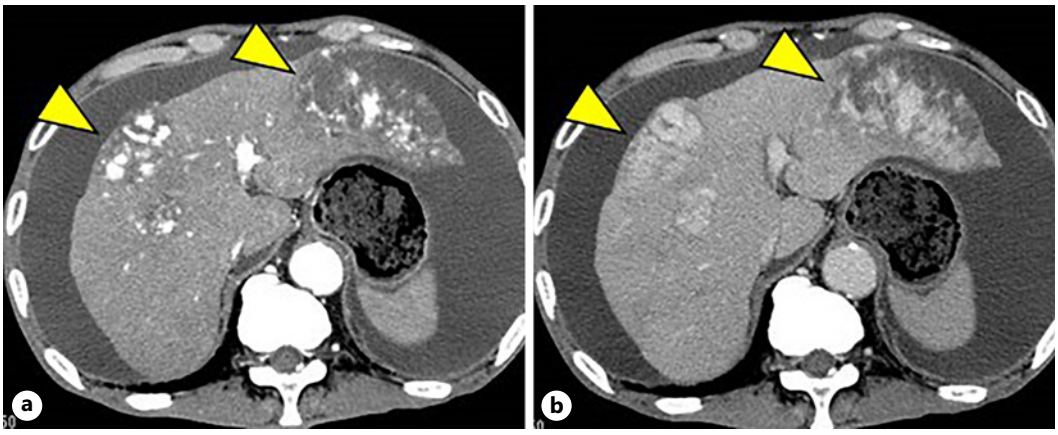

Fig. 1. a Arterial phase contrast-enhanced image showed the presence of a 40-mm tumor in both lobes of the liver. **b** The delayed phase image showed persistent central enhancement.

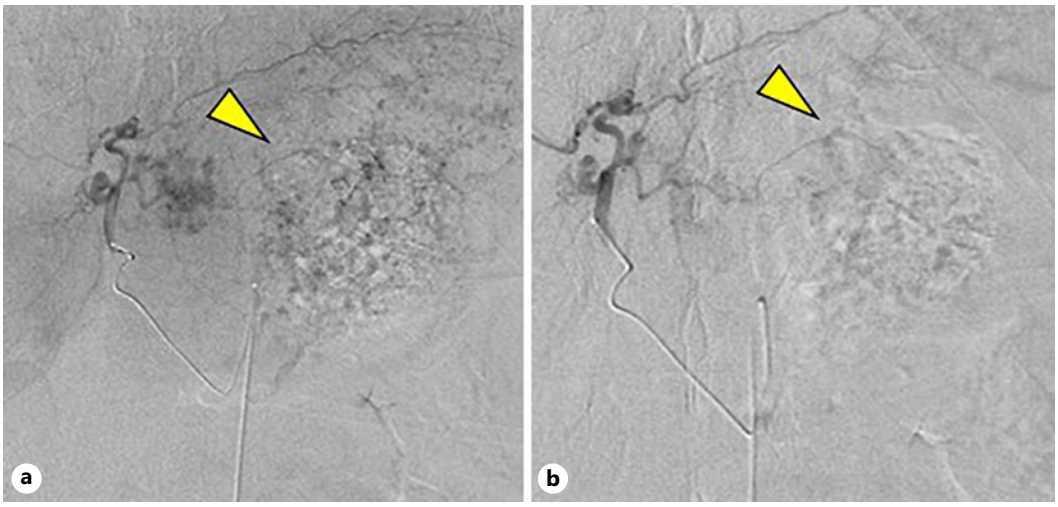

Fig. 2. a Abdominal angiography revealed pooling of the contrast medium called a cotton wool appearance. **b** Dense staining disappeared after embolization.

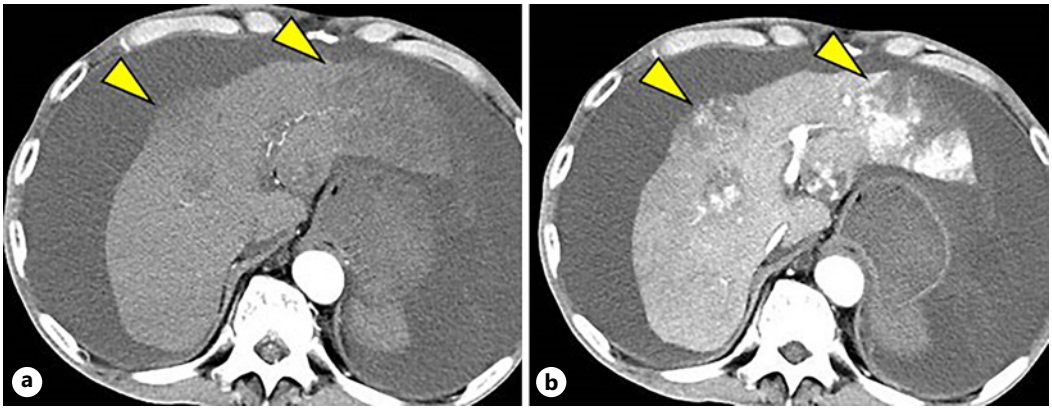

Fig. 3. Arterial phase contrast-enhanced image showed the tumor area was paler than before (**a**), and the delayed phase image showed persistent enhancement (**b**).

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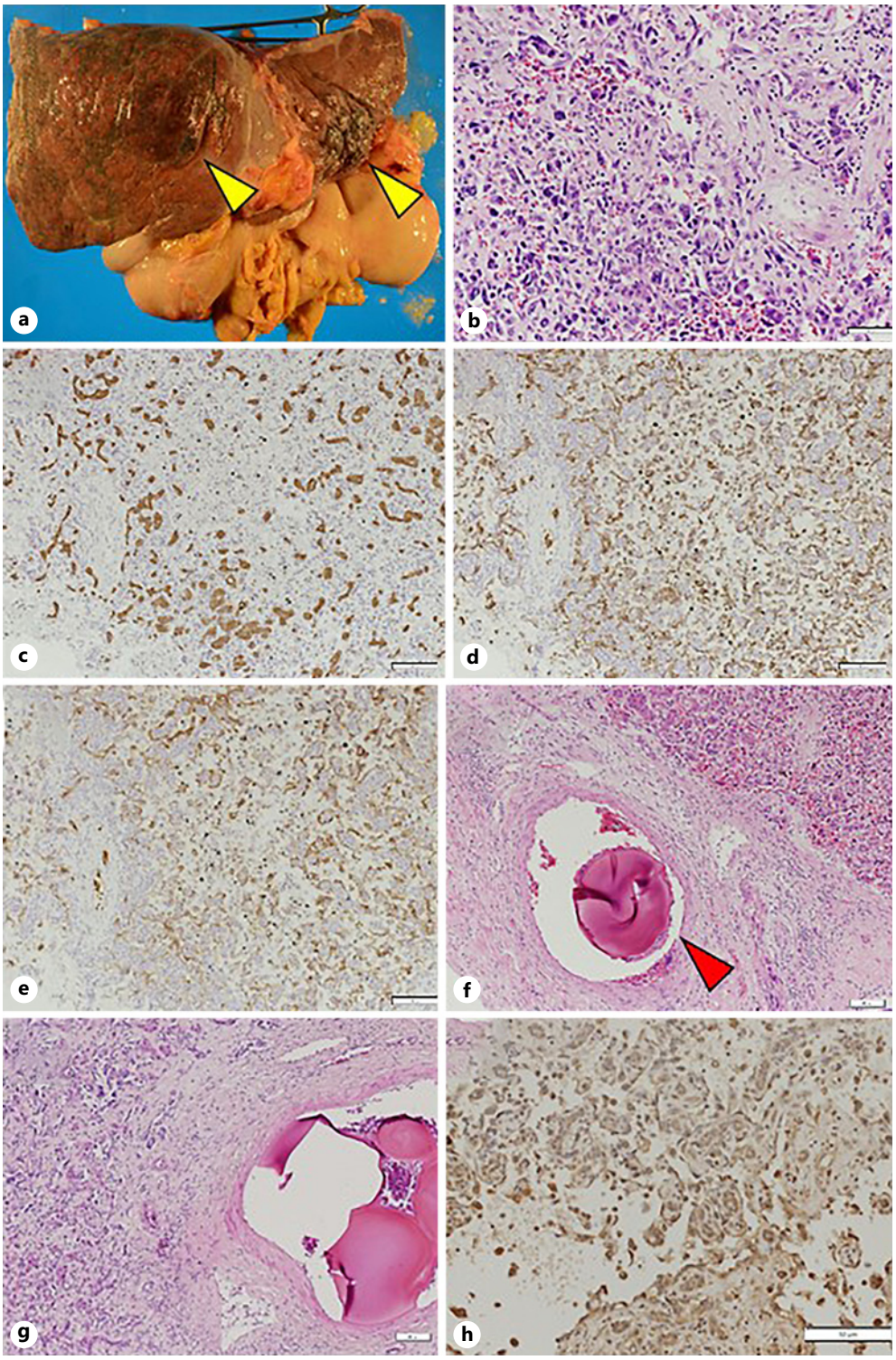

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but he and his family declined further treatment, and he passed away. An autopsy revealed 40 mm tumors in both lobes of the liver with partial disruption of the tumor membrane in the left lobe (Fig. 4a). The pathology showed proliferation of spindle-shaped tumor cells and red blood cells filling spaces between tumor cells (Fig. 4b). Cytokeratin AE1/AE3 was negative in

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tumor cells (Fig. 4c), and CD31 and CD34 were positive, consistent with hepatic angiosarcoma (Fig. 4d, e). Embosphere™ used during embolization was identified within the hepatic small intralobular artery. However, inflammatory changes were scarce in surrounding tissues, and there was no evidence of tumor cell necrosis or ischemic tissue change in proximity to the same arteries (Fig. 4f, g).

Discussion

In the present case, TAE was performed for hemostasis of a ruptured hepatic angiosarcoma, but a re-rupture resulted in death. Tumor rupture in hepatic angiosarcoma with intra-abdominal bleeding has been reported to occur in 15–27% of cases [8, 9]. The survival time of patients without tumor rupture was 7.4 months, whereas that of patients with ruptured tumors was 3 months, indicating a poor prognosis for patients with ruptured hepatic angiosarcoma [4]. TAE is usually the first choice for hemostasis of intra-abdominal bleeding due to the rupture of a hepatic angiosarcoma [9, 10]. A case in which surgical resection was successfully performed 2 weeks after TAE for a ruptured hepatic angiosarcoma was reported [11].

The pathological findings of an autopsy after TAE treatment in the present case informed us about the therapeutic effect of TAE for hepatic angiosarcoma. Despite the presence of embolic materials in the hepatic interlobular artery, there was no evidence of necrosis due to ischemia in the tumor cells neighboring the arteries where the embolic materials were present. It has been reported that TAE induces extensive tumor necrosis in a dominant region of the embolized hepatic artery in hepatocellular carcinoma (HCC) [12, 13] and that TAE reduces the size of hepatic hemangiomas and facilitates surgical treatment [14]. Although TAE induced ischemia tumor necrosis in HCC and hepatic hemangioma, there were no such findings in hepatic angiosarcoma in the present case. Although the embolic procedure of TAE was inadequate in the present case, hemostasis was transiently obtained and arterial enhancement was remarkably attenuated 4 days after TAE. Lack of evidence of any embolic effect on pathology suggests hepatic angiosarcomas may have mechanisms to avoid necrosis due to ischemia and to differentiate from other tumors.

The first is due to the feeding arteries. The hepatic artery is the main supply artery for HCC and hepatic hemangioma, and embolization of this artery is expected to have ischemic effects. Hepatic angiosarcoma is a malignant mesenchymal tumor composed of spindle-shaped cells derived from vascular endothelial cells, characterized by the diffuse spread of angiosarcoma cells within sinusoids and forming blood vessels and growing into open spaces such as sinusoids and small veins [15]. It is possible that not only the hepatic artery but the portal vein became a feeding vessel with hypertrophy of the blood vessels and formation of atypical vessels. It might be why embolization of the hepatic artery alone did not induce ischemic necrosis. The second is the effect of abnormalities in the coagulation-fibrinolytic system due to DIC. In DIC, intra-tumor hemorrhage, which consumes platelets and fibrinogen and is associated with a bleeding tendency, is known as Kasabach-Merritt syndrome,

Fig. 4. The pathological findings of the liver at autopsy. **a** The liver showed 40 mm-sized tumors in both lobes, with partial membrane disruption in the left lobe lesion. **b** Hematoxylin-eosin (H&E) staining (×200) showing spindle-shaped tumor cells. **c** Cytokeratin AE1/AE3 staining (×200). **d** CD 31 staining (×200). **e** CD34 staining (×200). **f**, **g** H&E staining (×40) showing Embosphere used during embolization was also identified within the hepatic lobar artery. Inflammatory changes were absent around embolized arteries and surrounding tissue and ischemic changes and necrotic changes were also absent in the surrounding tissue. **h** VEGF in the vicinity of tumor cells was negative (×200).

sometimes found in vascular-originated tumors [16]. Although thrombus was not evident in intrahepatic arteries, a background coagulation-fibrinolytic abnormality might have made it difficult to induce ischemic changes in tumor cells around the embolized arteries. A third mechanism we suspect was that growth of neovascular vessels around the tumor occurred to maintain a tumor-feeding blood flow. Immunostaining for vascular endothelial growth factor expression around the tumor was examined, but no significant upregulation of vascular endothelial growth factor was confirmed and neovascular growth was not found in the present case (Fig. 4h). Fourth, tumor necrosis might not have been induced because TAE was done instead of TACE. In a review of histological changes in TACE for HCC, no significant histological change was observed 8 h after TACE, but necrosis was present around 37% of vessels at 9–14 days and 40% at 32–36 days [17]. It is thought that tumor necrosis is induced mainly by the pharmacological effects of anti-cancer agents whereas ischemia might be caused by embolic substances. In contrast, anti-tumor effects have been shown even with TAE alone in HCC [18]. Hepatic angiosarcoma is suspected of having characteristics different from HCC, and it may be difficult to induce ischemia-induced tumor necrosis with TAE alone. Previous reports have indicated that TACE may be effective in hepatic angiosarcoma with a few intrahepatic metastases or large tumors [7]. In the present case, treatment with TACE instead of TAE might have improved the clinical course after the intervention. Further accumulation of findings from cases with ruptured hepatic angiosarcoma is needed to determine the efficacy of TACE and optimum choice of anti-cancer agents.

In conclusion, we experienced a case of ruptured hepatic angiosarcoma treated with TAE. Although TAE contributed to temporary hemostasis, TAE alone did not induce ischemia-induced tumor necrosis, suggesting that hepatic angiosarcoma has mechanisms that prevent ischemic necrosis from arterial embolization. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material at https://doi.org/10.1159/000533552.

Statement of Ethics

Ethical approval is not required for this study in accordance with national guidelines. Written informed consent for publication was obtained from the patient's wife for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

E.T. and T.K. wrote this paper. E.T., K.T., M.A., M.N., and H.Y. contributed to the patient's medical treatment. N.A. performed pathological evaluation. Y.I. supervised this work.

Data Availability Statement

All data generated during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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