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Single Case

A Case of Hepatocellular Carcinoma in a Patient with Idiopathic Forearm Arteriovenous Fistula

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Keywords

Idiopathic forearm arteriovenous fistula · Hepatocellular carcinoma · Systemic therapy · Anti-vascular endothelial growth factor receptor inhibitor

Abstract

Introduction: We report an exceedingly rare case of hepatocellular carcinoma (HCC) associated with an idiopathic congenital forearm arteriovenous fistula (AVF). Given the absence of previous reports addressing the treatment of HCC in patients with AVF, we evaluate HCC treatment strategies, including the appropriateness of using angiogenesis inhibitors. ***Case Presentation:*** A 74-year-old man was admitted for the evaluation of liver tumors. His medical history included a chronic, intractable idiopathic right forearm AVF, for which he had undergone multiple surgical interventions. Abdominal EOB-MRI revealed multiple small focal lesions across both liver lobes during the hepatobiliary phase, indicative of multiple HCC, and liver biopsy confirmed early-stage HCC. Considering the potential presence of additional vascular anomalies similar to the forearm AVF, local hepatic artery chemoembolization was performed. Since there is still insufficient discussion about the systemic administration of angiogenesis inhibitors to patients with vascular abnormalities such as AVF, we discuss the treatment options for HCC with AVF, including its strategies in the progressed HCC stage. ***Conclusion:*** As molecularly targeted therapies continue to evolve, recognizing the unique aspects of cases like ours is crucial. Establishing an appropriate treatment strategy for HCC patients with AVF is imperative, highlighting the need for tailored therapeutic approaches based on individual vascular profiles.

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Case Rep Gastroenterol 2025;19:173–183
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Introduction

One of the treatment strategies for hepatocellular carcinoma (HCC) is based on the Barcelona Clinic Liver Cancer (BCLC) staging system [1, 2]. HCCs are staged based on tumor characteristics (tumor number, maximum tumor diameter, presence of vascular invasion, presence of extrahepatic lesions), hepatic reserve (Child-Pugh classification), and Eastern Cooperative Oncology Group performance status (ECOG PS) into five stages [1, 3]: "very early," "early," "intermediate," "advanced," and "terminal." Previously, although transarterial chemoembolization (TACE) was considered the standard treatment of intermediate stage HCC, molecularly targeted drugs are considered the mainstay in recent years. In this report, we describe an extremely rare case of HCC with an idiopathic forearm arteriovenous fistula (AVF). Since there have been no reports of treatment for patients with HCC with AVF in the past, we also discuss the HCC treatment strategies including the appropriateness of usage of angiogenesis inhibitors such as molecularly targeted drugs.

Case Presentation

A 74-year-old Japanese man was admitted to our hospital for evaluation of a hepatic tumor. His medical history included significant alcoholic liver injury, an idiopathic congenital AVF in the right forearm (Fig. 1), and two episodes of cerebral infarction at the ages of 54 and 72. He had undergone repeated surgeries for the AVF from the age of 25 years, including resection of the vascular anomaly, bypass surgery with artificial blood vessels, and removal of the vessel. His right forearm presented the expected changes of long-standing AVF, with a circumference about twice that of the left arm. The skin of the right forearm was fragile, bleeding easily by contact, with several small hematomas on the surface of the skin. Currently, no artificial blood vessel graft was present in the right forearm and the AVF was intractable. Angiography of the arm showed many residual abnormal blood vessels and postoperative changes due to repeated surgeries (Fig. 2). His vascular surgeon determined that there was no other possible effective treatment in his future, and that palliative treatment, such as partial catheter embolization, was the only option in case of progressive thrombus formation. AVF was not detected on brain magnetic resonance angiography.

He had no significant family or allergy history, no blood transfusions history. Although he was previously a heavy drinker, he now habitually consumes approximately 40 g of alcohol per day. A physical examination revealed palmar erythema and vascular spider on the anterior chest wall. In terms of his current medical history, a 10 mm large tumor was observed in the S7 segment of the liver on plain abdominal CT scan. Blood tests showed liver dysfunction and mild elevation of γ-GTP (81 U/L) caused by alcohol intake, and elevation of the tumor marker, des-gamma-carboxy pro-thrombin (DCP; 41 U/mL) (Table 1).

Abdominal ultrasonography (US) showed several hypoechoic regions with a diameter of 3–5 mm in both lobes of the liver, while contrast-enhanced US showed no stained area in the vascular phase, no visible defect lesions in the late phase, and no findings of apparent HCC. Therefore, careful follow-up examination was performed, observing for the presence of abnormal intrahepatic blood circulation similar to the brachial AVF. Abdominal contrast-enhanced CT showed that some of the nodules in both lobes of the liver were stained in the early contrast-enhanced phase and washed out in the portal vein phase, suggesting HCC or alcoholic hyperplastic hepatic nodules (Fig. 3). Abdominal gadolinium ethoxybenzyl-diethylenetriamine penta-acetic acid-enhanced MRI (EOB-MRI) showed staining of the 10 mm diameter nodule in the S7 liver segment in the early contrast-enhanced phase, with wash out in the late phase, which was also depicted as a deficiency area in the hepatobiliary

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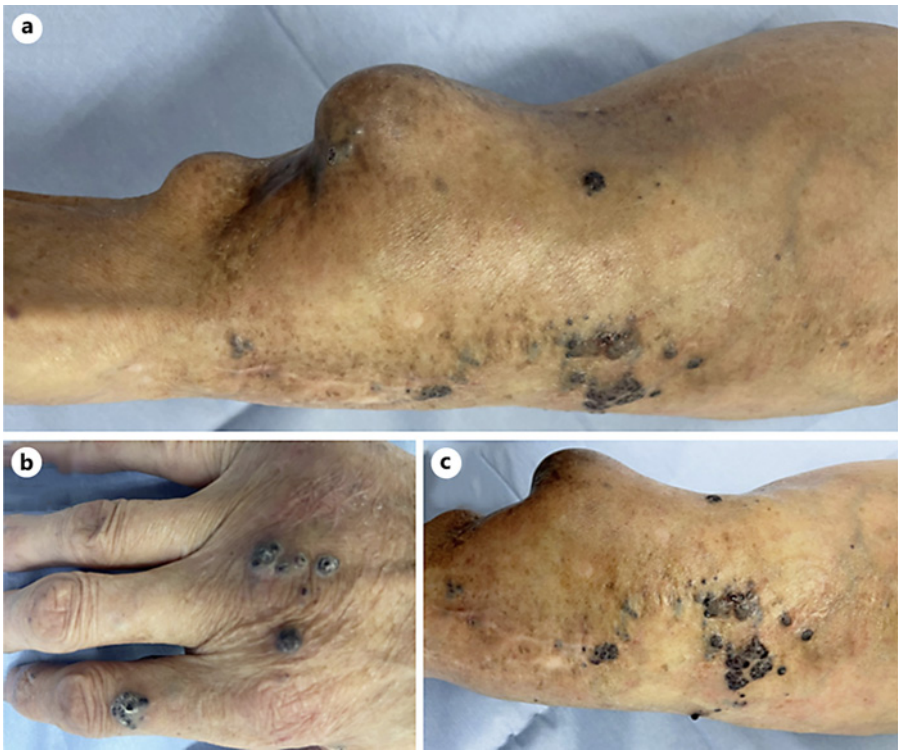

Fig. 1. Appearance of the AVF. **a** The right forearm was enlarged and swollen because of the AVF and about twice the size of the left arm. **b**, **c** The arteriovenous lesions on the skin bled easily on contact, and several small hematomas were observed on the surface of the skin. AVF, arteriovenous fistula.

phase, consistent with HCC (Fig. 4). Hence, liver biopsy was performed. Subsequent pathological evaluation showed fibrous enlargement of the portal area, distortion of the lobular structure, and fatty degeneration of the background liver tissue. Therefore, we diagnosed his condition as alcoholic steatosis, F2A1. Biopsy of the 10-mm tumor in the S7 segment of the liver showed miniaturization of the hepatocytes, increase in cell density to more than twice that of the background liver, and disturbance of the hepatocyte architecture, suggesting early-stage HCC (Fig. 5).

Clinical Course

Since there were many defects in the EOB-MRI hepatobiliary phase, we considered the possibility of multiple early-stage HCCs. Although systemic molecularly targeted drugs are currently recommended as first line treatment for multiple HCCs, in this case, due to the presence of the congenital intractable AVF in the right forearm, we considered that the use of angiogenesis inhibitors might cause unexpected adverse events. In addition, as the first treatment option, we chose angiography with TACE instead of radiofrequency ablation (RFA) because of the diagnosis whether there are other hypervascular nodules and abnormal blood circulation. He was unable to quit drinking, and did not meet the criteria for liver transplantation.

Therefore, TACE was performed instead of systemic therapy (Fig. 6a). AVF was not detected on hepatic angiography. HCC was treated by super selective TACE with epirubicin, lipiodol and gelatin sponge. Following the TACE procedure, lipiodol-CT demonstrated uptake only in the S7 nodule, with no other accumulation areas observed, indicating no residual tumor. As a result, at this stage, it was confirmed that the treated HCC was limited to a single

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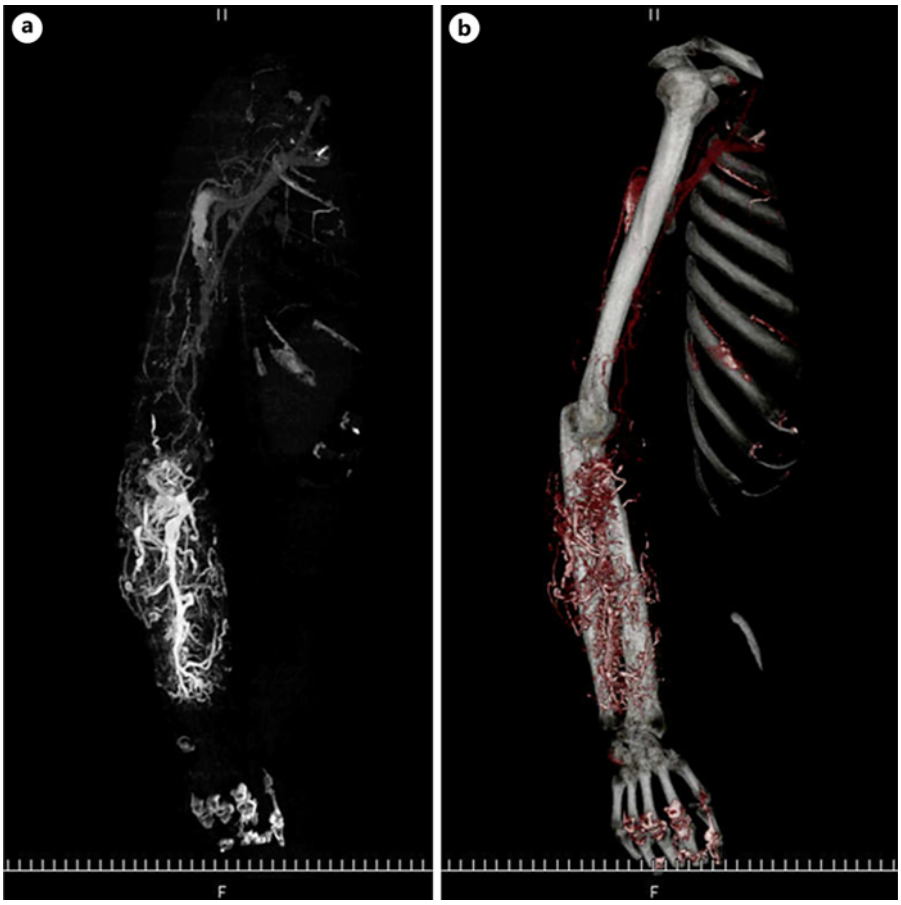

Fig. 2. Angiographic image of the AVF. **a** The main trunk of the right brachial artery was dilated and partially interrupted. **b** Branching blood vessels developed as collateral circulation, and tortuous arterioles were present from the elbow to the proximal forearm. AVF, arteriovenous fistula.

nodule (Fig. 6d). However, further appropriate follow-up and treatment were deemed necessary for multiple deficiency nodules observed during the hepatobiliary phase of the EOB-MRI. Regular post-treatment follow-up imaging was conducted, and no definitive evidence of recurrence was observed up to 20 months later.

Discussion

AVF is an abnormal connection between arteries and veins without an intermediate capillary network. Although it is a rare condition, it can develop in various parts of the body, such as the brain, lungs, liver, spleen and extremities [3]. Upper limb AVF is even rarer and is usually traumatic or iatrogenic in nature. It is caused by abnormal differentiation of vascular tissue due to impaired growth of the vascular primordia into arteries and veins, and it may indicate the presence of connective tissue diseases such as Marfan syndrome and Ehlers-Danlos syndrome [4].

Symptoms of limb AVFs become apparent with growth and are often noticed at an early age. They might also become apparent during increased tissue activity such as due to trauma, pregnancy, or physical labor [4]. Its symptoms range variously from completely asymptomatic to discomfort, hot to the touch, spontaneous pain due to pulsatile swelling in the affected area,

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Table 1. Laboratory data on admission

Peripheral blood	
WBC	6,700/mL
RBC	509 × 10^4/mL
Hb	17.2 g/dL
Plt	17.1 × 10^4/mL
Blood chemistry	
TP	7.1 g/dL
Alb	4.3 g/dL
BUN	12.7 mg/dL
Cre	0.84 mg/dL
T-Bi	0.6 mg/dL
AST	24 U/L
ALT	18 U/L
LDH	185 U/L
ALP	93 U/L
GTP	81 U/L
Na	140 mEq/L
K	3.9 mEq/L
Cl	101 mEq/L
CRP	0.07 mg/dL
Coagulation tests	
PT	100%
APTT	30.0 s
Hepatitis viral markers	
HBs-Ag	(−)
HBc Ab	(−)
HCV-Ab	(−)
Tumor markers	
DCP	41 U/mL
AFP	6.7 ng/mL

WBC, white blood cell count; RBC, red blood cell count; Hb, hemoglobin; Plt, platelet count; TP, total protein; Alb, albumin; BUN, blood urea nitrogen; Cr, creatinine; T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γ-GT, γ-glutamyl transferase; CRP,C reactive protein; PT, prothrombin time; APTT, activated partial thromboplastin time; HBs-Ag, hepatitis B surface antigen; HBc-Ab, hepatitis B core antibody; HCV-Ab, hepatitis C antibody; DCP, des-gamma-carboxy pro-thrombin; AFP, alfa-fetoprotein.

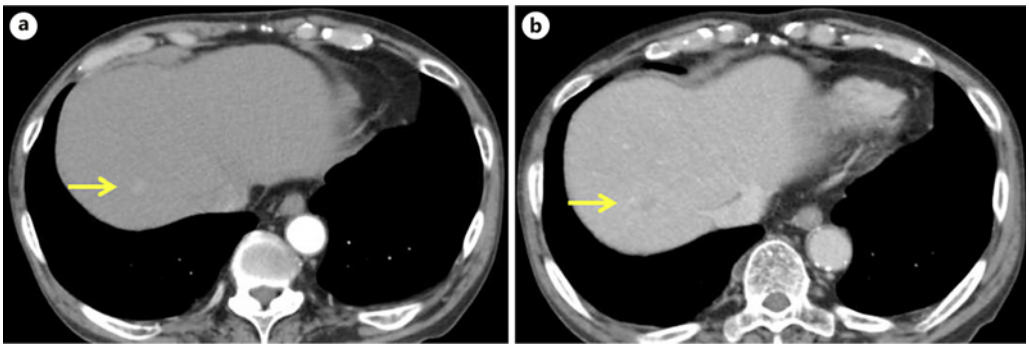

Fig. 3. Abdominal contrast-enhanced CT. The tumor (arrow) was stained in the early phase of contrast-enhanced CT (**a**) and washed out in the portal vein phase (**b**), suggesting HCC or alcoholic hepatic hyperplastic nodule.

heart failure, and ischemia of the affected limb due to high shunt flow from infancy [3, 5]. Several cases have been reported in which ischemia led to pigmentation and edema, followed by the formation of intractable ulcers that required amputation of the forearm [3]. These symptoms generally appear unilaterally, and there are reports of excessive tissue growth in the affected limb with AVF, resulting in excessive hair growth and sweating [4].

In this case, pulsatile swelling and tortuosity of the local vein were observed in the right upper limb at a young age, for which surgical treatment was performed. Although arteriography was previously used for the diagnosis of AVF, recent advances in diagnostic imaging technology have made it possible to diagnose AVF using minimally invasive techniques such as CT, Doppler US, and MRI [3]. As for the treatment, surgical treatment to reconstruct the blood circulation in regions of arteriovenous anomalies, and ligation and cutting of the major shunts are the main methods, although palliative treatment with elastic bandages and vascular embolization [3] have also been reported. On the other hand, there are cases of recurrence or exacerbation after surgical treatment [4]. In our case as well, although surgical treatment was performed to achieve a cure, the treatment itself caused the formation of new arteriovenous veins and AVF, intractably resulting in a large forearm.

The BCLC staging system divides HCC into five stages: “very early,” “early,” “intermediate,” “advanced,” and “terminal” [1, 2], and in our case, four or more multiple lesions with no vascular invasion and no extrahepatic lesions. Therefore, our case was diagnosed as an intermediate stage HCC with Child-Pugh class A hepatic reserve and ECOG PS of 0. The treatment of intermediate stage HCC is based on TACE, which is the standard option, although sorafenib [6, 7], regorafenib [8], lenvatinib [9], ramucirumab, [10], and cancer immunotherapies, including atezolizumab plus bevacizumab [11] and cabozantinib [12] are also widely used in Japan.

However, one of the main mechanisms of action of these molecularly targeted drugs is inhibition of the vascular endothelial growth factor receptor (VEGFR) and tumor angiogenesis [13, 14]. This inhibition might influence abnormal blood vessels as well as tumor vessels. At present, however, there is little evidence related to their systemic administration in patients with comorbid arteriovenous malformations; additionally, chemotherapy with bevacizumab for colorectal cancer has been reported to form inferior mesenteric AVF, suggesting the need for its careful administration [15]. In addition, due to their inhibitory effect on VEGF, these drugs inhibit VEGF production by podocytes constituting the renal glomerular filtration membrane and the interaction of VEGF with VEGFR-2 in glomerular

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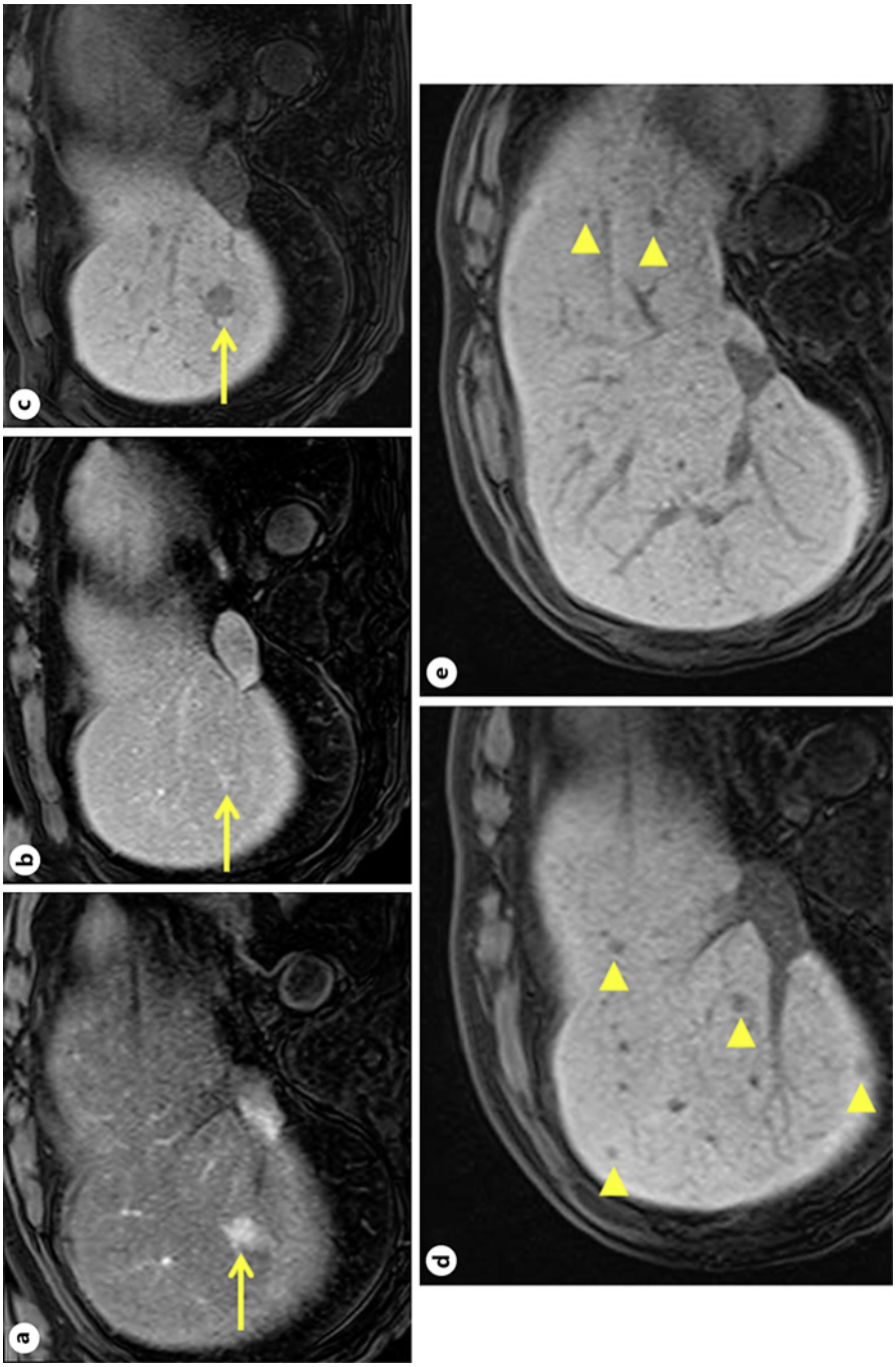

Fig. 4. Abdominal EOB-MRI. The 10 mm diameter nodule in the S7 segment of the liver (arrow) was stained in the early phase of contrast-enhanced MRI (**a**), washed out in the late phase (**b**), and was also depicted as a deficiency area in the hepatobiliary phase (**c**), which are the classical findings of HCC. In addition, multiple areas of contrast deficiency (arrow heads) were observed in the hepatobiliary phase (**d**, **e**).

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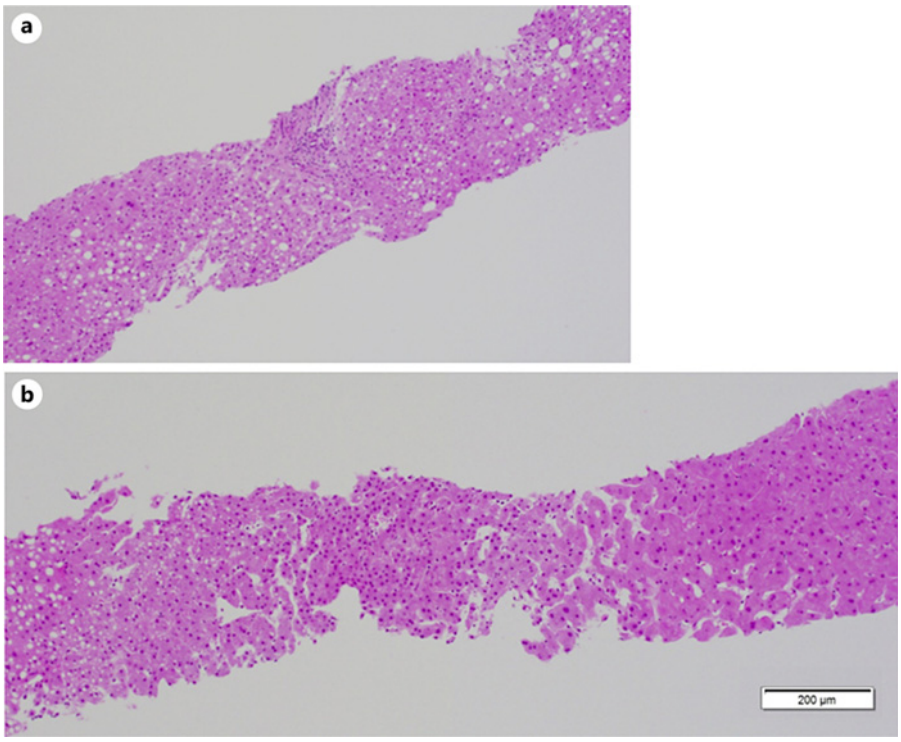

Fig. 5. Pathological findings of the liver biopsy specimen. **a** The background liver tissue was characterized by fibrous enlargement of the portal area, distortion of the lobular structure, and fatty degeneration. **b** The tumor cells consisted of miniaturized hepatocytes with a density more than twice that of the background hepatocytes, leading to a diagnosis of early HCC.

endomembrane cells, and disrupt the glomerular structure and filtration function, causing proteinuria.

The concept of TACE refractory and TACE inappropriate tumors has been proposed in the treatment of intermediate stage HCC using TACE [14]. In this case, although local TACE treatment was selected at present, in the future, when his HCC transitions to TACE refractory or inappropriate, molecularly targeted drugs or cancer immunotherapy might be considered as one of the options for its treatment. The usage of molecularly targeted drugs that inhibit angiogenesis in patients with congenital vascular abnormalities requires careful consideration of the indications. In addition, the treatment option of molecularly targeted drugs and systemic cancer immunotherapy when cancer of other organs except liver occurs in AVF cases is also uncertain.

Recently, atezolizumab/bevacizumab (Atez/Bev) and durvalumab/tremelimumab (Dur/Tre) treatments have shown positive results in intermediate stage HCC [11, 16]. In our patient, when liver cancer became more multiple and hypervascular hereafter, Dur/Tre treatment could be a potential option [11, 16]. Although, the criteria for choosing between Atez/Bev and Dur/Tre treatments as first-line therapy have not yet been determined, one of the key points is to decide whether anti-VEGF therapy is acceptable and tolerable. In our case, Dur/Tre treatment might be a better option as first-line therapy because of adverse events associated with anti-VEGF inhibitors, such as hypertension, bleeding, and thromboembolism. Additionally, since Dur/Tre does not contain anti-VEGF inhibitors, it might be preferred in patients such as ours. Immunotherapy, especially immune checkpoint inhibitors (ICIs) such as Dur/Tre, holds potential for the treatment of HCC. However, specific case reports addressing

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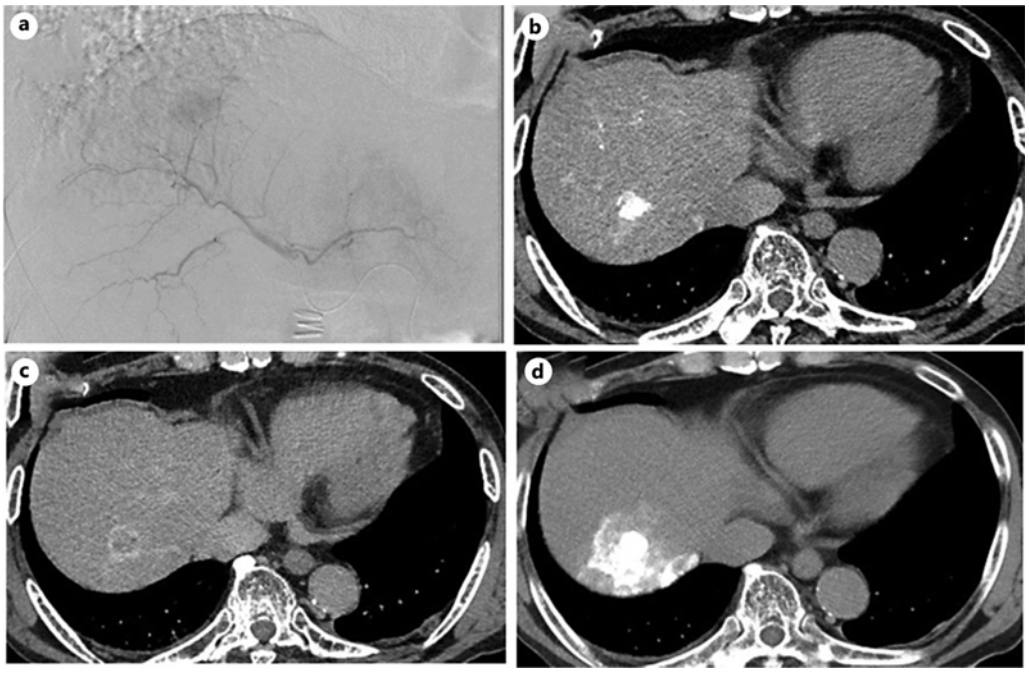

Fig. 6. The tumor was treated with transcatheter arterial chemoembolization (TACE) using epirubicin, lipiodol, and gelatin sponges. **a** The tumor was stained and observed by transcatheter arterial imaging with DSA. **b** The tumor was stained in the early phase. **c** Corona-like staining was observed in the late phase. **d** Plain CT showed the tumor with lipiodol deposition after the TACE procedure.

AVF in the forearm remain scarce. In cases where hemodynamic abnormalities are induced by AVF, the local distribution and effectiveness of therapeutic agents may be compromised. Therefore, the administration of such therapies should be approached with caution, taking into account the severity of the individual AVF. Further investigation and case accumulation are required to clarify this.

Conclusion

We experienced a case of HCC associated with idiopathic congenital forearm AVF. Since molecularly targeted therapies continue to advance, it is very important to be aware of the existence of such as our case, and the appropriate treatment strategy for HCC patients with AV malformations should be determined in the future.

Statement of Ethics

This study was reviewed and the need for approval was waived by IRB of Hanwa memorial hospital. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration. The CARE checklist has been completed by the authors of this case report and is attached as an online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000544101).

Conflict of Interest Statement

No conflicts of interest to declare.

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Author Contributions

S.T. and Y.Y. contributed to the study conceptualization. S.T., Y.Y., S.I., A.J., A.Y., and H.H. contributed to the data curation. S.T., Y.Y., H.I., Y.I., T.K., S.I., A.J., A.Y., H.H. and N.K. reviewed and revised the manuscript.

Data Availability Statement

All the data used to support the findings of this case series are available as part of the article and references. Further inquiries can be directed to the corresponding author.

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