

[CASE REPORT]

Hepatocellular Carcinoma in a Patient with Hereditary Hemorrhagic Telangiectasia

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Abstract:

A 76-year-old woman with hereditary hemorrhagic telangiectasia (HHT) showed elevated serum hepatobiliary enzyme levels, and abdominal imaging studies revealed a hepatic tumor. Her serum alpha-fetoprotein level was 759.5 ng/mL. A pathological examination after hepatectomy confirmed a diagnosis of hepatocellular carcinoma (HCC). An examination of the surrounding liver revealed dilated vessels and thickened endothelial cells without inflammations. HHT patients without other risk factors (like this patient) reportedly have a lower incidence of common cancers, including HCC, in comparison to the unaffected population. One intriguing hypothesis that might explain the hepatocarcinogenesis in this situation is the ischemic liver cirrhosis theory, which suggests that chronic ischemia may cause parenchymal strain and promote inappropriate hepatocyte proliferation.

Key words: hepatocellular carcinoma, hereditary hemorrhagic telangiectasia, vascular malformation, focal nodular hyperplasia, ischemic liver cirrhosis theory

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Introduction

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant genetic disease with a prevalence of approximately 1 case per 5,000 population (1). HHT is related to mutations in two genes, *endoglin* or *ALK1*, which encode the type III and type I transforming growth factor- β receptors, respectively. Both are exclusively expressed on vascular endothelial cells (2). A wide range of vascular malformations (VMs) develop in patients with HHT. Hepatic VMs include telangiectasias, dilated tortuous vessels, aneurysms, various vascular shunts, and transient hepatic attenuation differences (3). They are observed in 41-84% of HHT patients, and are more commonly associated with *ALK1* mutation (HHT-2 phenotype) (4). These VMs can cause hepatic parenchymal hypo-perfusion or hyper-perfusion depending on their location, which may induce regenerative responses including nodular transformation, focal nodular hyperplasia (FNH), and nodular regenerative hyperplasia (3, 5, 6). Im-

portantly, these hepatic nodules are benign conditions in nature, and HHT patients with no other risk factors have been reported to rarely develop hepatocellular carcinoma (HCC) (7), or to develop HCC less frequently than the general population (8). We herein present a very rare case of HCC in a HHT patient without any other predisposing factors and discuss the possible associations between the hepatocarcinogenesis and hepatic VMs in HHT patients. This case highlights the importance of considering HCC as a potential diagnosis when HHT patients present with hepatic nodular lesions.

Case Report

A 76-year-old woman was referred to our department for the evaluation of elevated liver enzyme levels, which were detected when gastric bleeding from angiodysplasia was treated with endoscopic hemostasis clips (Fig. 1). Her significant medical history included HHT, which had been diagnosed based on the Curaçao criteria (4). The patient re-

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ported no abdominal pain or weight loss, nor did she report drinking alcohol, smoking cigarettes, or taking any medications. Conjunctival anemia, small telangiectasia on her lips and tongue, and cardiac enlargement with systolic murmur were noted during a physical examination. The liver span was 5 cm below the right costal margin, with no tenderness to palpation. Laboratory test results revealed the following: hemoglobin, 10.5 g/dL; International Normalized Ratio, 1.05; total bilirubin, 1.0 mg/dL; albumin, 3.7 g/dL; and alanine aminotransferase, 9 U/L. The other laboratory test results are shown in Table. Abdominal contrast-enhanced computed tomography imaging of the late arterial phase re-

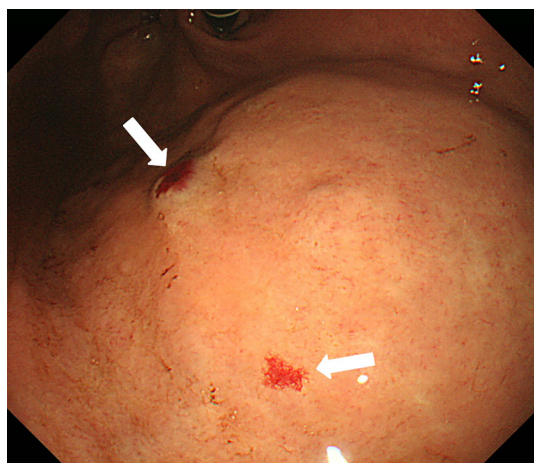


Figure 1. Esophagogastroduodenoscopy revealed multiple gastric angiodysplasias (arrows). Bleeding from one of these lesions was treated with endoscopic hemostasis clips.

vealed an encapsulated protruding tumor measuring 8 cm in diameter in the right lobe of the liver (Fig. 2). Diffuse hepatic parenchymal telangiectasias, a dilated tortuous hepatic artery, and early opacification of the hepatic veins were observed. Although arterial enhancement of the nodule was scarcely appreciable on CT, subsequent magnetic resonance imaging depicted a slight arterial enhancement and late-phase washout (Fig. 3). The serum alpha-fetoprotein level was 759.5 ng/mL. Viral studies for hepatitis B and C were negative. There were no biochemical or imaging findings suggestive of diabetes, fatty liver disease, or iron-overload. The imaging findings combined with the elevated serum alpha-fetoprotein suggested a diagnosis of HCC. Hepatic angiography showed few large VMs near the boundary between the HCC and the hepatic right lobe (Fig. 4). Despite the risk of perioperative bleeding due to HHT, a decision was made to perform partial hepatectomy, based on the absence of both clinically significant portal hypertension and large VMs near the HCC. The postoperative course was uneventful.

The cut surface of the resected tumor showed an encapsulated, well-circumscribed lobulated solid lesion measuring 85×70×50 mm, with intratumoral hemorrhage (Fig. 5, left). The microscopic examination of the tumor confirmed the diagnosis of moderately differentiated HCC (Fig. 5, right upper). The surrounding hepatic parenchyma was noncirrhotic and showed abnormally dilated vessels, thickened endothelial cells, dilated sinusoids, and intervening fibrosis with no inflammatory changes or iron deposits (Fig. 5, right lower). Unfortunately, a recurrent hepatic tumor developed 8 months postoperatively, and grew to occupy the entire liver, metastas-

Table. Laboratory Test Results on Initial Evaluations.

Variables	Reference Ranges	This Patient	Variables	Reference Ranges	This Patient
Hemoglobin, g/dL	10.7-15	10.5	Triglycerides, mg/dL	50-150	120
Hematocrit, %	34.4-44	32.9	Iron, µg/dL	50-150	36
Red-cell count, 10 ³ /mm ³	3,700-4,900	3,150	Iron-binding capacity, µg/dL	253-365	332
White-cell count, /mm ³	3,300-8,600	3,700	Ferritin, ng/mL	13-277	13
Platelet count, 10 ³ /mm ³	140-360	221	Copper, µg/dL	68-128	86
International normalized ratio		1.05	Ceruloplasmin, mg/dL	21-37	25
Activated partial-thromboplastin time, sec	23-40	32	Ammonia, µmol/L	12-66	54
Fibrinogen, mg/dL	170-400	335	C-reactive protein, mg/L	0-3.0	2.8
Total protein, g/dL	6.7-8.3	6.8	Immunoglobulin G, mg/dL	870-1,700	1,596
Albumin, g/dL	4.1-5.1	3.7	Antinuclear antibodies		negative
Total bilirubin, mg/dL	0.4-1.5	1.0	Antimitochondrial antibody		negative
Aspartate aminotransferase, U/L	13-33	22.0	Alpha-fetoprotein, ng/mL	0-10	759.5
Alanine aminotransferase, U/L	6-42	9	Des-γ-carboxy prothrombin, mAU/mL	<40	2,068
Lactate dehydrogenase, U/L	119-229	206	Carcinoembryonic antigen, mg/mL	0-5	1.5
Alkaline phosphatase, U/L	115-359	490	Carbohydrate antigen 19-9, U/mL	0-37	10.2
Gamma-glutamyl transpeptidase, U/L	10-47	94	Hepatitis B virus surface antigen		negative
Urea nitrogen, mg/dL	8-20	20.4	Hepatitis B virus DNA		negative
Creatinine, mg/dL	0.2-0.8	1.1	anti-Hepatitis B virus surface antigen		negative
Glucose, mg/dL	70-110	94	anti-Hepatitis B virus core antigen		negative
Hemoglobin A1c, %	4.3-5.8	4.1	anti-Hepatitis C virus		negative
Total cholesterol, mg/dL	130-220	164	Hepatitis C virus RNA		negative

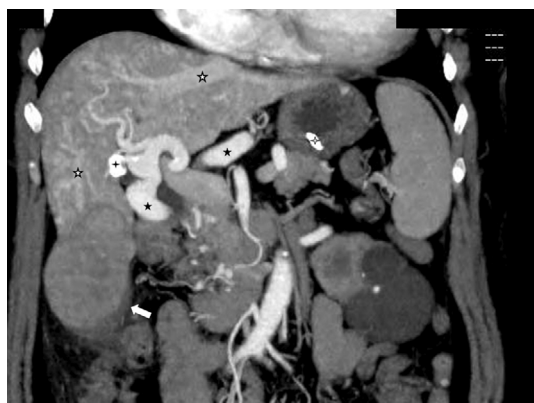


Figure 2. Coronal abdominal contrast-enhanced computed tomography in the late arterial phase revealed an encapsulated protruding hepatocellular carcinoma (HCC, arrow) measuring 8 cm in diameter in the right lobe of the liver. Diffuse hepatic parenchymal telangiectasias, dilated tortuous hepatic artery (closed asterisk), and early opacification of the hepatic veins (open asterisk) were observed. Arterial enhancement of the nodule was scarcely appreciable in comparison to the hepatic parenchyma. The two high-density materials were hemostasis clips in the stomach and gallstones (open and closed cruciform, respectively).



Figure 4. Right hepatic angiography showed a dilated tortuous hepatic artery, diffuse hepatic parenchymal telangiectasias, and early opacification of the hepatic veins. Arterial enhancement of the HCC was scarce (arrows). Note the fact that there were no large VMs near the boundary of the HCC.

sizing to the lungs. The patient could not tolerate anti-cancer treatments because of her rapidly worsening general condition, and died of massive hematemesis at 13 months after surgery.

Discussion

Patients with HHT often develop multiple vascular abnormalities including pulmonary, cerebral, spinal, and hepatic VMs. The mortality rate of HHT patients of <60 years of age is higher in comparison to the age-adjusted unaffected

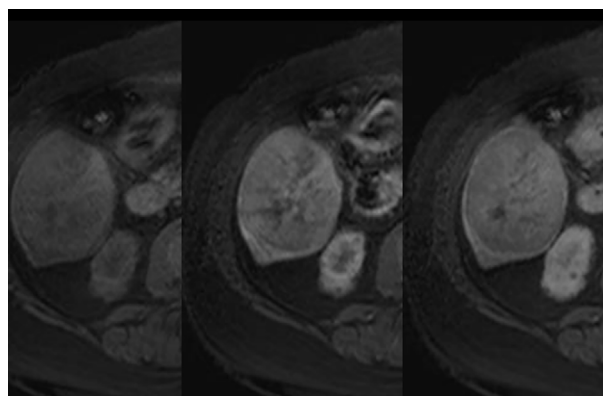


Figure 3. T1-weighted magnetic resonance imaging after the administration of intravenous gadolinium depicted slight arterial enhancement and late-phase washout of the HCC. These figures represent pre-contrast, arterial phase, and venous phase images in order from left to right.

population, due to cerebral VM bleeds and pregnancy-related death (9-11). However, HHT patients of >60 years of age have surprisingly good survival rates (12). In this older population, HHT-related mortality may be offset by a reduction in deaths from common life-threatening diseases, including cancers. Clinical observational studies indicated that HHT patients showed lower rates of specific types of cancer-including lung and liver cancer-in comparison to controls (8). Actually, there are few reports of the development of HCC in HHT patients who have no other risk factors (7). Another large retrospective cohort study suggested that HHT patients had improved survival outcomes in multiple cancers (13).

The consequences of the mutation of *endoglin* or *ALK1* are complex and may depend on the location of its expression, such as in cancer cells, stroma, or vascular compartments (14-16). Laboratory and animal studies have shown that endoglin and ALK1 apparently have opposing effects on the carcinogenic signaling pathway. For example, a study using human prostate cancer cell line models demonstrated that the overexpression of endoglin inhibited tumor cell invasion and metastasis (anti-metastatic) (17). On the other hand, a study using mouse model of prostate cancer indicated that endoglin was required for tumor vascularization and metastatic spread by cancer-associated myofibroblasts (pro-metastatic) (18). In any case, clinical observational studies indicate that mutations of *endoglin* or *ALK1* do not usually increase the specific cancer incidence in real world cohorts (5, 6, 8).

FNHs and nodular regenerative hyperplasia are sometimes encountered in patients with HHT (3, 5, 6). Some authors have hypothesized that FNH and nodular regenerative hyperplasia may transform into, or be associated with HCC (19, 20). Others have reported that HCC had different origins from FNH based on a clonal analysis (21, 22). In the present case, neither FNHs nor nodular regenerative hyperplasias were observed; thus, it was unlikely that the patient's

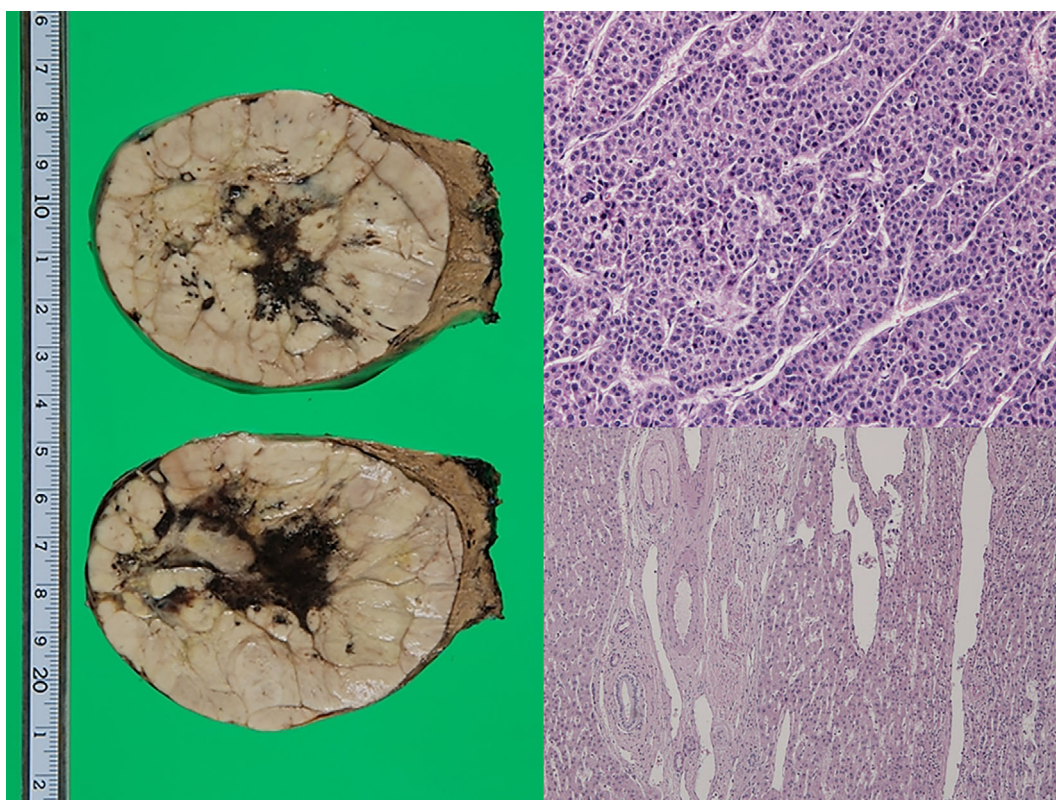


Figure 5. The pathological examinations of the resected specimen. (Left) The cut surface of the resected tumor showed an encapsulated, well-circumscribed lobulated solid lesion measuring 85×70×50 mm, with intratumoral hemorrhage. (Top right) Microscopically, the tumor was composed of proliferating abnormal hepatocytes with swollen nuclei in thick trabecular structures, which confirmed the diagnosis of moderately differentiated HCC [Hematoxylin and Eosin (H&E) staining]. (Bottom right) The surrounding hepatic parenchyma was non-cirrhotic and showed abnormally dilated vessels, thickened endothelial cells, dilated sinusoids, and intervening fibrosis with no inflammatory changes or iron deposits (H&E staining).

HCC emerged from such hyperplastic lesions.

Then, what is a plausible explanation for the occurrence of HCC in this patient? An alternate, intriguing hypothesis is “the ischemic liver cirrhosis theory” (23). It is widely recognized that hepatocarcinogenesis is driven by both the altered intracellular signaling pathways and the hepatic microenvironment. HCCs often develop in a background of cirrhosis which is accompanied by decreased oxygen delivery to the liver cells (24). In this patient, hepatic microvascular and perfusion abnormalities may have caused endothelial damage, sinusoidal thrombosis, and chronic regional hypoxia, leading to hepatic parenchymal strain and extinction with the promotion of fibrosis. This hypoxic microenvironment could also induce a key transcription factor, hypoxia-inducible factor-1 α , which influences signaling pathways involved in angiogenesis, cell growth and survival, and apoptosis, resulting in the transactivation of a plethora of genes to evoke genetic instability and inappropriate hepatocyte proliferation (25, 26). The tipping of the balance of these pathways might have been critical for the hypoxia-induced carcinogenic processes.

There are few reports of hepatectomy in patients with HHT, with the exception of hepatectomy for liver transplan-

tation (27). Widespread hepatic VMs may lead to portal hypertension, hepatic parenchymal and/or biliary ischemia, and high-output cardiac failure. All of these are associated with the risk of peri-operative bleeding and hepatic functional compromise. We decided to perform hepatectomy based on the absence of both distinct VMs near the surgical margins and clinically significant portal hypertension. Our experience has shown that major hepatectomy can be safely performed in carefully selected HHT patients.

The administration of bevacizumab, a vascular endothelial growth factor (VEGF) antibody, reportedly led to a regression of hepatic VMs, portal hypertension, and high-output cardiac failure in patients with HHT (28, 29). If the patient’s condition had been eligible for anti-cancer treatment at the time of postoperative recurrence, the antagonism of VEGF might have been a beneficial treatment approach for both HCC and HHT.

In conclusion, we reported a case of HCC and HHT. Benign hepatic nodules, such as FNH and nodular regenerative hyperplasia sometimes develop in patients with HHT; however, HCC seldom occurs in this situation. One intriguing hypothesis that might explain the hepatocarcinogenesis in this situation is the ischemic liver cirrhosis theory. Our ex-

perience showed that major hepatectomy can be safely performed in carefully selected patients with HHT. Anti-VEGF therapy may be applicable for both HCC and HHT in this rare situation.

The authors state that they have no Conflict of Interest (COI).

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