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CASE REPORT

Percutaneous transvenous shunt occlusion for portosystemic encephalopathy due to lenvatinib administration to a patient with hepatocellular carcinoma and portosystemic shunt

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Abstract
We report a 74-year-old male patient with compensated cirrhosis after hepatic C virus eradication. After the patient underwent hepatectomy for hepatocellular carcinoma, multiple lung and lymph node metastases were detected by computed tomography. Computed tomography also revealed a portosystemic shunt from the superior mesenteric vein to the right testicular vein. He was administered lenvatinib (12 mg). Five days after the initiation of lenvatinib, he developed grade 3 hepatic encephalopathy, and his ammonia level increased. Lenvatinib was stopped, with improvement of the encephalopathy and decrease in ammonia level. When lenvatinib was restarted, grade 2 encephalopathy recurred which then improved upon stopping the drug. We thought that the encephalopathy was due to the portosystemic shunt, and occlusion of the shunt was performed. The day after shunt occlusion, lenvatinib (8 mg) was restarted, and the lenvatinib dose was increased to 12 mg at 2 days after shunt occlusion. Subsequently, the ammonia level remained stable and the patient remained alert and conscious. Lenvatinib was continued until the time of this report (40 days after shunt occlusion), and after 1 month of lenvatinib therapy, the computed tomography verified absence of the portosystemic shunt and stable disease of hepatocellular carcinoma.

Keywords Hepatocellular carcinoma · Lenvatinib · Portosystemic shunt · Encephalopathy · Shunt occlusion

Introduction

Lenvatinib is an oral multikinase inhibitor that targets the vascular endothelial cell growth factor (VEGF) receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, RET, and KIT [1–3]. In 2018, lenvatinib was reported to be noninferior to sorafenib in the randomized phase 3 noninferiority trial (REFLECT study). Lenvatinib has become available as a primary treatment for patients with unresectable advanced hepatocellular carcinoma (HCC) who are not suitable for treatments such as surgery, radiofrequency ablation (RFA), transcatheter arterial chemoembolization, and liver transplantation [4, 5].

In the REFLECT study, hepatic encephalopathy was observed in 3.8% of patients receiving lenvatinib [4]. The risk of hepatic encephalopathy is generally thought to increase in patients with portosystemic shunts. Hepatic encephalopathy that develops during administration of lenvatinib is reversible however, and resolves after the drug is stopped. Lenvatinib can then be restarted at a reduced dose.

On the other hand, percutaneous transvenous embolization is effective for treating a portosystemic shunt, which also causes hepatic encephalopathy [6, 7]. Here, we report a patient with HCC, a portosystemic shunt, and repeated encephalopathy after a second attempt at lenvatinib administration with reduced dose, with inability to continue receiving the drug. The patient's encephalopathy was improved after occlusion of the portosystemic shunt, and subsequently he could be treated with a sufficient dose of lenvatinib.

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Case report

The patient was a 74-year-old man who developed chronic hepatitis C virus infection in 2003. Interferon treatment provided a sustained virological response in 2004. He was followed at our hospital regularly until 2011, when he stopped of his own accord. In 2016, the patient was examined at a clinic and found to have a hepatic mass. He returned to our hospital, and hepatocellular carcinoma (HCC) was diagnosed. It was a solitary HCC nodule located in S2/S3, and lateral segmentectomy was performed. Subsequently, in 2017, a single recurrence was noted in the residual left hepatic lobe, and left hepatic lobectomy was performed. In February 2018, a solitary lymph node metastasis of the pancreatic head was discovered, and radiotherapy of the lesion was performed. CT after the radiotherapy revealed a necrosis in the lymph node metastasis and no other recurrence, and he was followed continuously. In July 2018, multiple lung and lymph node metastases were observed, and he was hospitalized to receive lenvatinib for extrahepatic metastases. He had no history of hepatic encephalopathy. Upon admission, the patient was alert and conscious, with a height of 176.6 cm and weight of 68.0 kg. Physical examination did not reveal signs of anemia or jaundice. The abdomen was flat and soft, and the liver and spleen were not palpable. Laboratory testing revealed a mildly elevated ammonia level at 39 mg/dL. The patient was found to have Child–Pugh grade A disease (Table 1). Contrast-enhanced computed tomography (CT) revealed a portosystemic shunt from the superior mesenteric vein (SMV) to the right testicular vein (Fig. 1a). Upper gastrointestinal endoscopy revealed no esophageal and gastric varices. Lenvatinib (12 mg/day p.o.) was administered. After 5 days of lenvatinib, the patient developed grade 3 hepatic encephalopathy. His ammonia level increased 158 μmol/L, and the levels of aspartate aminotransferase [(AST) 24 IU/L] and alanine aminotransferase [(ALT) 16 IU/L] were normal. The level of bilirubin slightly increased [(T.Bil) 1.6 mg/dL)], the level of Albumin [(Alb) 3.4 g/dL] and prothrombin time activity [(PT) 50%] decreased when the patient developed grade3 hepatic encephalopathy after 5 days of lenvatinib. Although branch chain amino acids (BCAAs) and lactulose were administered, the patient's ammonia level and encephalopathy did not improve. Lenvatinib was stopped 8 days after it was begun, with overnight improvement in the patient's encephalopathy. The patient became conscious and alert. He was restarted on lenvatinib (8 mg/day) 4 days later with recurrence of hepatic encephalopathy and elevated ammonia level (145 μmol/L). Lenvatinib was then stopped again. Because we thought that the SMV systemic shunt was responsible for hyperammonemia, shunt occlusion was performed 21 days after the initiation of lenvatinib. A microcatheter was taken from the drainage vein side to the shunt point and coil embolization of the shunt was performed (Fig. 1c, d). Occlusion of the shunt led to a drastic decrease in the ammonia level with no recurrence of encephalopathy. The second day after occlusion of the shunt, oral lenvatinib (8 mg/day) was started and the dose

Table 1 Laboratory examinations on admission

CBC			γGTP	23	IU/L	Viral markers	
WBC	2360	/μL	Na	139	mEq/L	HBs antigen	(−)
RBC	3.49×10^4	/μL	K	4.1	mEq/L	HCV antibody	(+)
Hb	12.0	g/dL	Cl	107	mEq/L	HCV-RNA	(-)
Ht	34.9%		TP	6.5	g/dL		
Plt	70×10^3	/μL	Alb	3.7	g/dL	Liver function	
Blood coagulation test			BUN	16.5	mg/dL	ICG-R	22.3%
PT	74%		Cr	0.74	mg/dL	Child–Pugh score	5
PT-INR	1.16		CRP	0.23	mg/dL	Child–Pugh grade	A
Blood chemistry			NH3	39	μmol/L		
T-bil	1.0	mg/dL	HbA1c	4.5%			
AST	21	IU/L	Tumor marker				
ALT	12	IU/L	AFP	54.2	ng/mL		
LDH	256	IU/L	AFP-L3	84.0%			
ALP	208	IU/L	DCP	23	mAU/mL		

AFP a-fetoprotein, *DCP* des-γ-carboxy prothrombin, *Alb* albumin, *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *Cr* creatinine, *CRP* c-reactive protein, *Hb* hemoglobin, *LDH* lactate dehydrogenase, *Plt* platelets, *PT* prothrombin time, *PT-INR* international normalized ratio of prothrombin time, *TBil* total bilirubin, *TC* total cholesterol, *CBC* complete blood cell count, *RBC* red blood cells, *WBC* white blood cells, *ICG* indocyanine green, *HBs antigen* hepatitis B surface antigen, *HCV antibody* hepatitis C virus antibody

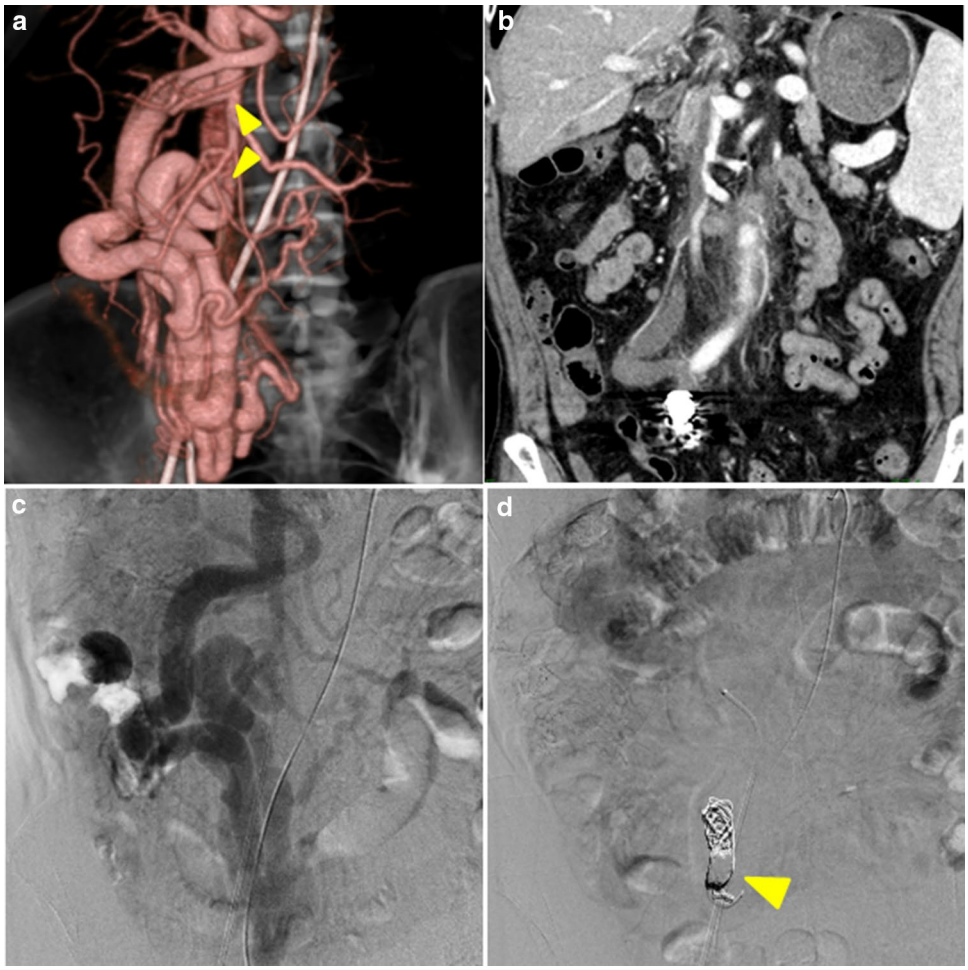

Fig. 1 **a** CT during arterial portography before shunt occlusion, 3D image: a portosystemic shunt is seen from the superior mesenteric vein (SMV) to the right testicular vein; **b** contrast-enhanced CT 1 month after shunt occlusion: the portosystemic shunt is absent; **c** angiography of superior mesenteric artery (SMA) before shunt occlusion: the portosystemic shunt is seen from the SMV to the right testicular vein; **d** angiography of SMA after shunt occlusion: a coil is seen in the shunt, and blood flow in the portosystemic shunt is absent

was increased to 12 mg/day on the third day after shunt occlusion. The patient has continued lenvatinib treatment, and at the time of this writing (40 days after shunt occlusion), his ammonia level has remained stable (Table 2). CT performed 1 month after restarting lenvatinib confirmed absence of the portosystemic shunt (Fig. 1b), and the patient was considered to have stable HCC (Figs. 2, 3).

Discussion

We saw a patient who developed hepatic encephalopathy after starting lenvatinib for HCC with portosystemic shunt. However, occlusion of the shunt improved his encephalopathy, and the patient was able to continue receiving lenvatinib (12 mg) for at least 40 days after shunt occlusion.

There are 2 types of hepatic encephalopathy: portosystemic encephalopathy, and end-stage hepatic encephalopathy in patients with decompensated cirrhosis [8, 9]. Our patient was found to have an SMV-right-testicular-vein shunt, and hepatic encephalopathy had not developed in the patient previous to his receiving lenvatinib. At 5 days after initiation of lenvatinib therapy the patient developed grade 3 hepatic encephalopathy. After lenvatinib was stopped and BCAAs and lactulose were given to the patient, his encephalopathy improved rapidly. However, lenvatinib restarted at a lower dose led to the re-emergence of encephalopathy. Other evidence of liver dysfunction such as elevated AST and ALT levels was not observed. Therefore, we concluded that the portosystemic encephalopathy was triggered by administration of lenvatinib.

Lenvatinib has a VEGF receptor inhibitory activity that is 5–7 times stronger than that of sorafenib [2]. In cirrhotic livers, the dysfunction of liver sinusoidal endothelial cells leads to the decreased production of vasodilator molecules such as nitric oxide (NO) and increased production of vasoconstrictor molecules such as endothelin and thromboxane A2, which leads to contraction of hepatic stellate cells and increased intrahepatic resistance [10, 11]. On the other hand, VEGF stimulates NO production by endothelial NO synthase [12], and administration of a VEGF receptor inhibitor reduces the production of NO. Studies using contrast-enhanced ultrasonography and perfusion CT found that the VEGF inhibitor sorafenib decreased blood flow in the

Table 2 Laboratory examination at restart of lenvatinib and 6 weeks after shunt occlusion

At restart of lenvatinib			At 6 weeks after shunt occlusion		
WBC	2110	/μL	WBC	1660	/μL
Hb	11.4	g/dL	Hb	13.1	g/dL
Plt	44×10^3	/μL	Plt	37×10^3	/μL
PT	53	%	PT	80	%
T-Bil	2	mg/dL	T-Bil	1.2	mg/dL
AST	18	IU/L	AST	27	IU/L
ALT	12	IU/L	ALT	17	IU/L
LDH	156	IU/L	LDH	213	IU/L
ALP	202	IU/L	ALP	241	IU/L
γGTP	14	IU/L	γGTP	48	IU/L
Alb	3	g/dL	Alb	3.9	g/dL
BUN	17.4	mg/dL	BUN	20.8	mg/dL
Cr	0.7	mg/dL	Cr	0.92	mg/dL
NH3	46	μmol/L	NH3	37	μmol/L
AFP	31.7	ng/mL	AFP	21.1	ng/mL

AFP a-fetoprotein, *Alb* albumin, *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *Cr* creatinine, *Hb* hemoglobin, *LDH* lactate dehydrogenase, *Plt* platelets, *PT* prothrombin time, *TBil* total bilirubin, *RBC* red blood cells, *WBC* white blood cells

hepatic artery and parenchyma [13–15]. When lenvatinib was administered to a patient with hepatofugal portosystemic collaterals, the sinusoidal resistance was increased due to decreased production of NO and contraction of hepatic stellate cells. Thereby, blood flow in the hepatofugal portosystemic collaterals was increased and hepatic encephalopathy developed.

Medical treatment such as lactulose, BCAAs or rifaximin is generally performed as first-line treatment of portosystemic encephalopathy. To treat refractory encephalopathy, Hanna et al. [16] reported surgical ligation of portosystemic shunts in 1981 and Potts et al. [17] and Uflacker et al. [18] reported performing shunt occlusion by interventional radiology (IVR) techniques that used coils or balloons. Since surgery is invasive and can be limited when severe liver dysfunction is present, minimally invasive treatment by IVR can be useful. The clinical success rate of percutaneous transvenous embolization has been reported to range from 60 to 100% [6, 19, 20].

In our patient, lenvatinib caused hepatic encephalopathy. Percutaneous transvenous occlusion was performed because encephalopathy was not improved by medical treatment. The patient's encephalopathy subsequently improved, and administration of an adequate dose of lenvatinib became possible.

Portosystemic encephalopathy is caused by splenorenal shunts, gastrorenal shunts, SMV systemic shunts, inferior mesenteric vein systemic shunts, and portal vein-inferior vena cava shunts. Confirming the presence or absence of a portosystemic shunt, change in ammonia level, and history of hepatic encephalopathy is important before deciding to administer lenvatinib. For some cases, the treatment of hyperammonemia, decrease in dose or stoppage of lenvatinib, and confirmation of patient tolerability of lenvatinib and the possibility of continuing lenvatinib treatment must be performed. In addition, if, as in our case, portosystemic encephalopathy is present, occlusion of a portosystemic

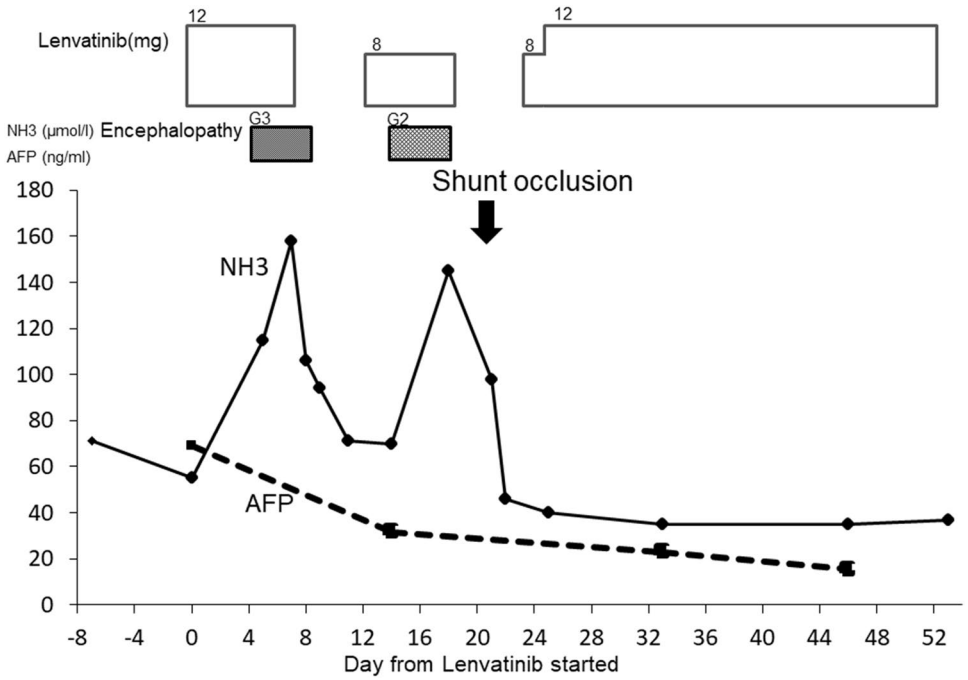

Fig. 2 Clinical course. AFP: a-fetoprotein. G3 and G2: the grade of hepatic encephalopathy

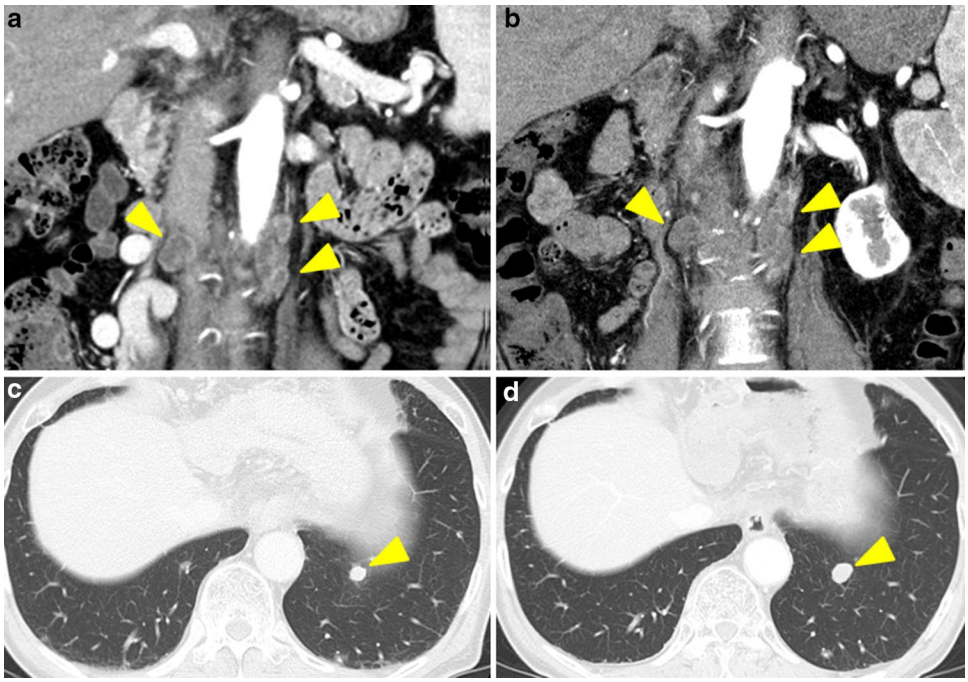

Fig. 3 Contrast-enhanced CT findings: **a** para-aortic lymph node metastases before administration of lenvatinib; **b** para-aortic lymph node metastases 1 month after initiation of lenvatinib; **c** lung metastasis before administration of lenvatinib; **d** lung metastasis 1 month after starting lenvatinib

shunt might be an effective option for enabling the continuation of lenvatinib treatment.

Compliance with ethical standards

Conflict of interest Kazuaki Chayama has received honorarium from MSD, Bristol-Myers Squibb, AbbVie, Ajinomoto Pharma, Abbott, Astellas Pharma, Chugai, Dainippon Sumitomo Pharma, Gilead Sciences, Mitsubishi Tanabe. Kazuaki Chayama has received research funding from Janssen, Mitsubishi Tanabe, Dainippon Sumitomo, Toray. Kazuo Awai has research funding from Canon Medical Systems, Hitachi, Rrserch. Kazuaki Chayama has received educational grants from AbbVie, Dainippon Sumitomo, Ajinomoto Pharma, MSD, Eisai, Toray, Otsuka, Mitsubishi Tanabe, Chugai, Daiichi Sankyo, Takeda, Nippon Kayaku, Bristol-Myers Squibb, Roche.

Human rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all patients for being included in the study.

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