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Hepatocellular Carcinoma With Extensive Cancer-associated Thrombosis Successfully Treated With Liver Resection and Direct Oral Anticoagulant: A Case Report

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Abstract. *Aim: To assess the utility of the perioperative use of direct oral anticoagulants for patients with hepatocellular carcinoma (HCC) with cancer-associated thrombosis. Case Report: An 83-year-old woman was admitted with a solitary HCC (10-cm diameter), as well as with multiple sites of venous thromboembolism and macroscopic portal vein tumor thrombosis. She had appropriate liver function without viral hepatitis, triple-positive tumor markers, and secondary polycythemia. Edoxaban at 30 mg was initiated 10 days before surgery to remove HCC. Complete remission of the pulmonary embolism and stability of the deep vein thrombosis and massive superior mesenteric vein thrombosis were recognized preoperatively. An extended left hepatectomy was successfully performed. To avoid hemorrhage complications, we used intravenous administration of nafamostat mesylate for 2 days, thereafter we restarted edoxaban. Superior mesenteric vein thrombosis resolved 5 months after surgery. Conclusion: Perioperative oral administration of edoxaban was useful in multidisciplinary treatment for a patient with advanced HCC with cancer-associated thrombosis.*

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Cancer frequently develops venous thromboembolism (VTE), possibly due to increased platelet activation by tumor-derived pro-coagulant proteins, overexpression of tissue factors, and overproduction of inflammatory cytokines (1). So-called cancer-associated thrombosis (CAT) confers a three-fold higher risk of recurrent VTE, a poorer prognosis, and carries with it a significant morbidity and mortality burden when compared to patients without malignancy (2-4). Patients with hepatocellular carcinoma (HCC) have an increased risk of developing VTE. The portal vein is the most frequent site, with a reported incidence of 20-40% (5). Both HCC and background liver cirrhosis are associated with an increased risk of developing not only portal vein thrombosis (PVT), but also non-splanchnic VTE (6).

Patients with HCC were occasionally also found to have macroscopic portal vein tumor thrombosis (PVTT), which is an exclusion criterion for liver transplant, liver resection, ablation therapy, and chemoembolization (7, 8). In order to distinguish PVT from PVTT, the following criteria can be used: i) Continuity of HCC and PVT, PVTT is present continuously to HCC; ii) enlargement of portal vein diameter >23 mm; iii) hypervascularity of the thrombus in the arterial phase of contrast-enhanced computed tomography (CT) or Doppler ultrasound (9, 10).

Direct oral anticoagulants (DOACs), which are direct inhibitors of activated factor X, have been shown to be noninferior to warfarin and vitamin K antagonists (VKA) for VTE treatment by major phase III trials with pooled-analysis (11). For patients with CAT, DOACs have independently demonstrated similar efficacy to low-molecular-weight heparin (LMWH) plus warfarin, often while exhibiting less associated major bleeding (2-4, 12). Edoxaban (Lixiana,

Daiichi-Sankyo, Tokyo, Japan) is increasingly being investigated as a viable option for many unmet needs in the treatment of CAT (12-14).

We herein present a patient with advanced HCC with accompanying pulmonary embolism (PE), deep vein thrombosis (DVT) and massive superior mesenteric vein (SMV) thrombosis, as well as PVTT at the time of initial diagnosis. Perioperative administration of edoxaban enabled the patient to undergo a curative and safe liver resection.

Case Report

An 83-year-old woman visited a primary care physician complaining of upper abdominal pain. CT revealed a large tumor in the left liver, and she was subsequently transferred to our hospital. Upon admission, she had a solitary HCC, 10.4 cm in diameter, with PVTT of the first left portal vein together with PE, DVT and SMV thrombosis (Figure 1). Her laboratory results on admission appear in Table I. Her serum level of D-dimer was elevated to 9.54 μg/ml (normal range ≤1.0 μg/ml), but antithrombin III, and proteins C and S were within normal limits (Table I). She was diagnosed as having CAT. She also showed polycythemia, and her serum erythropoietin level was elevated to 42.9 mIU/ml (normal range=4.2-23.7 mIU/ml). She had neither hepatitis B, hepatitis C, nor liver cirrhosis. Her Child–Pugh grade was classified as A (5 points). She had diabetes mellitus and dyslipidemia; intense insulin therapy was started immediately. She was triple-positive for tumor markers; Alpha-fetoprotein of 70,269 (normal ≤10) ng/ml, protein induced by the absence of vitamin K or antagonist-II (PIVKA-II) of 111,947 (normal ≤40) mAU/ml and an alpha-fetoprotein L3 value of 69% (normal ≤10%). An immediate liver resection was considered to be high risk; therefore, edoxaban (30 mg/day) was initiated prior to surgery. Ten days later, total remission of PE and stability of DVT and SMV thrombosis were observed preoperatively. Furthermore, her D-dimer level gradually reduced to near normal. By intraoperative abdominal ultrasonography, SMV thrombosis was felt to be of a longstanding nature, due to high echogenicity on abdominal ultrasound (Figure 1F) (15). The indocyanine green retention rate at 15 minutes was 12.1%, and the volumetric liver resection rate was estimated at 25%. According to our resection criteria (16), an extended left hepatectomy was conducted and successfully completed. The operative time was 352 min, bleeding amount was 480 g, and no blood transfusion was required.

Macroscopic and microscopic views of the specimen are displayed in Figure 2. Macroscopically, a well-circumscribed whitish-colored tumor nodule with PVTT was shown. Histologically, the main tumor showed moderately differentiated HCC with a pseudoglandular growth pattern, and cancer cell invasion to the portal and hepatic veins was also seen. Severe portal fibrosis with numerous septa (without cirrhosis) was observed in the non-cancerous area. By immunohistochemical

Table I. *Laboratory data on admission.*

Parameter	Value
T-Protein	7.8 g/dl
WBC	4.0×10^3/μl
Albumin	3.8 g/dl
Neutrocytes	60.5%
T-Bilirubin	1.2 mg/dl
RBC	6.41×106/μl
D-Bilirubin	0.4 mg
Hemoglobin	17.2 g/dl
AST	47 U/l
Hematocrit	56.4%
ALT	13 U/l
Platelet	141×103/μl
LDH	261 U/l
PT activity	94.0%
ALP	322 U/l
APTT	25.7%
γ-GTP	180 U/l
Fibrinogen	293 mg/dl
Ch-E	162 U/l
FDP	21.3 μg/ml
BUN	6.7 mg/dl
D-Dimer	9.54 μg/ml
Creatinine	0.53 mg/dl
ATIII	81.8%
T-CholesterоI	337 mg/dl
Protein C	66%
LDL	253 mg/dl
Protein S	79%
HDL	35 mg/dl
HBs-Ag	Negative
TG	224 mg/dl
HBs-Ab	Negative
NH3	56 μg/dl
HCV-Ab	Negative
CRP	0.06 mg/dl
M2BPGi	1.24 C.O.I.
FBS	149 mg/dl
ICG R15	12.1%
Hb A1c	7.8%
EPO	42.6 mIU/ml
AFP	70,269 ng/ml
PIVKA-II	111,947 AU/ml
AFP-L3	69.0%

AFP: Alpha-fetoprotein; ALP: alkaline phosphatase; ALT: alanine transaminase; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; BUN: blood urea nitrogen; Ch-E: choline esterase; C.O.I.: cut-off index; CRP: C-reactive protein; EPO: erythropoietin.; FBS: fasting blood sugar; FDP: fibrin degradation products; Hb: hemoglobin; HBs-Ag: hepatitis B virus surface antigen; HCV-Ab: hepatitis C virus antibody; HDL: high-density lipoprotein cholesterol; γ-GTP: γ-glutamyl transpeptidase; ICGR15: indocyanine green retention rate at 15 min; LDH: lactate dehydrogenase; LDL: low-density lipoprotein cholesterol; M2BPGi: Mac-2-binding protein glycosylation isomer; PIVKA-II: protein induced by vitamin K absence or antagonist-II; PT: prothrombin time; TG: triglycerides.

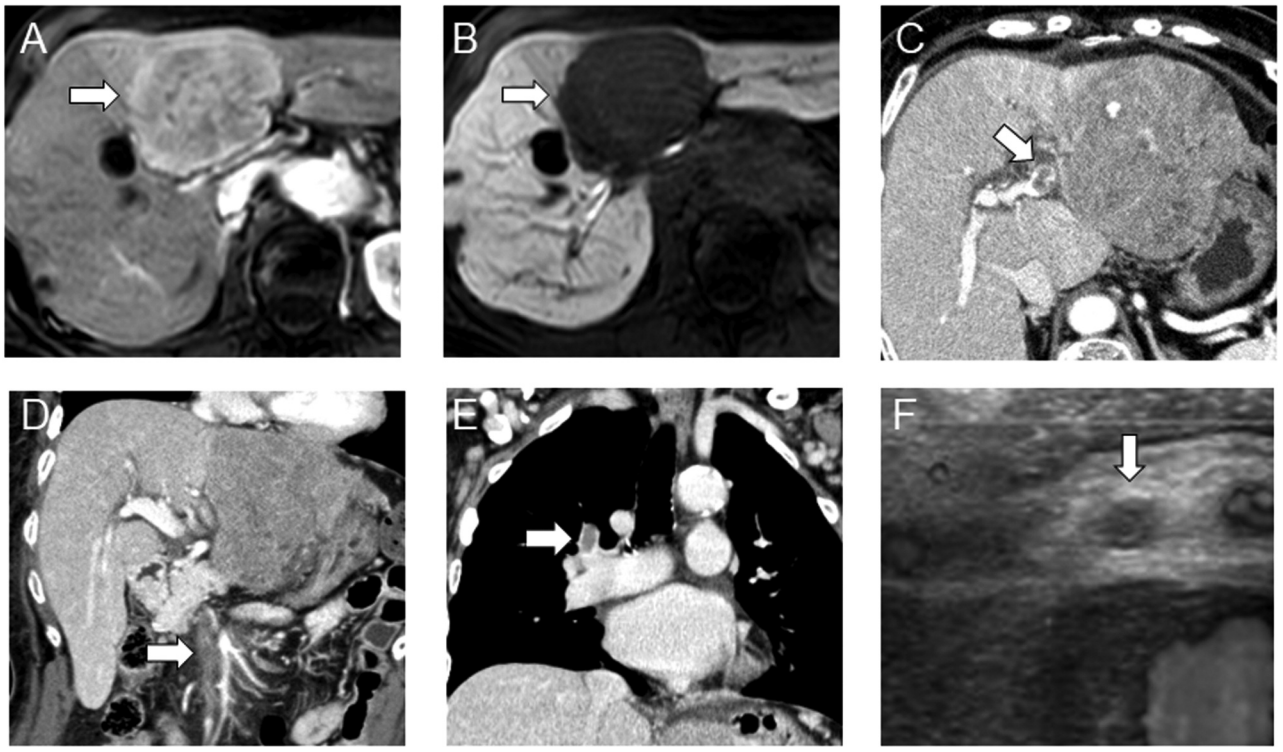

Figure 1. *Diagnostic images on admission and intraoperative ultrasound. A: Contrast-enhanced arterial phase T1-weighted magnetic resonance imaging (MRI) displays a hypervascular tumor (arrow). B: Hepatobiliary phase T1-weighted MRI shows a hypointensity tumor (arrow). C: Axial portal venous phase computed tomographic (CT) image shows a washout appearance, with extension to the left first portal branch of portal vein tumor thrombosis (arrow). D: CT of the portal venous phase image, coronal view, shows massive superior mesenteric vein thrombosis (arrow). E: Coronal equilibrium-phase CT image shows a pulmonary embolus affecting the segmental artery of the right upper lobe (arrow). F: Color Doppler ultrasound showed no blood flow through the superior mesenteric vein (arrow).*

staining, cancer cells showed positive staining for hepatocyte and glypican-3, and negative for cytokeratin 19; this phenotype is consistent with HCC. Furthermore, HCC cells expressed erythropoietin receptor but did not express tissue factor/coagulation factor III. Administration of edoxaban was discontinued 2 days prior to surgery. In order to avoid microcirculatory failure with micro-thrombosis flowing from the SMV thrombosis, anticoagulant drugs were started immediately following the liver resection. Nafamostat mesylate, a synthetic serine protease inhibitor, was administered for 2 days after surgery, to prevent hemorrhage, and thereafter 30 mg of edoxaban was restarted. Her postoperative course was uneventful. Sonazoid-enhanced ultrasound and enhanced CT were performed within 1 week postoperatively, and confirmed no evidence of extension of the SMV thrombosis. Details of treatment and changes in the plasma D-dimer levels are shown in Figure 3. The D-dimer levels returned to within normal limits due to the cancer treatments and anticoagulant therapy. She had macroscopic vascular invasion, considered to have a high risk of recurrence; therefore, we conducted adjuvant transarterial chemoembolization procedures twice, according to our protocol (17). SMV was completely obstructed by SMV thrombosis until 2 months after surgery, but the SMV thrombosis was no longer visualized on enhanced CT scan 5 months after surgery (Figure 4). The dose of edoxaban was then reduced to 15 mg per day and continued. Unfortunately, 3 months after surgery, she developed massive sternal metastasis, followed by multiple lung metastases, and was treated with radiotherapy and lenvatinib therapy. One year and 2 months after surgery, she is alive and her general condition is stable.

Discussion

At the initial diagnosis of HCC, our patient had PE, DVT, and massive SMV thrombosis; however, she was successfully treated with perioperative anticoagulant, DOACs therapy, and an extended left hepatectomy. Edoxaban was used continuously, except for 2 days each before and after surgery, without any major complications. DVT, including splanchnic DVT, is often observed in patients with HCC with liver cirrhosis (6). In our patient, histopathological findings in the background liver showed pre-cirrhotic fibrosis. The primary HCC was large, and was accompanied by major PVTT; however, the SMV thrombosis

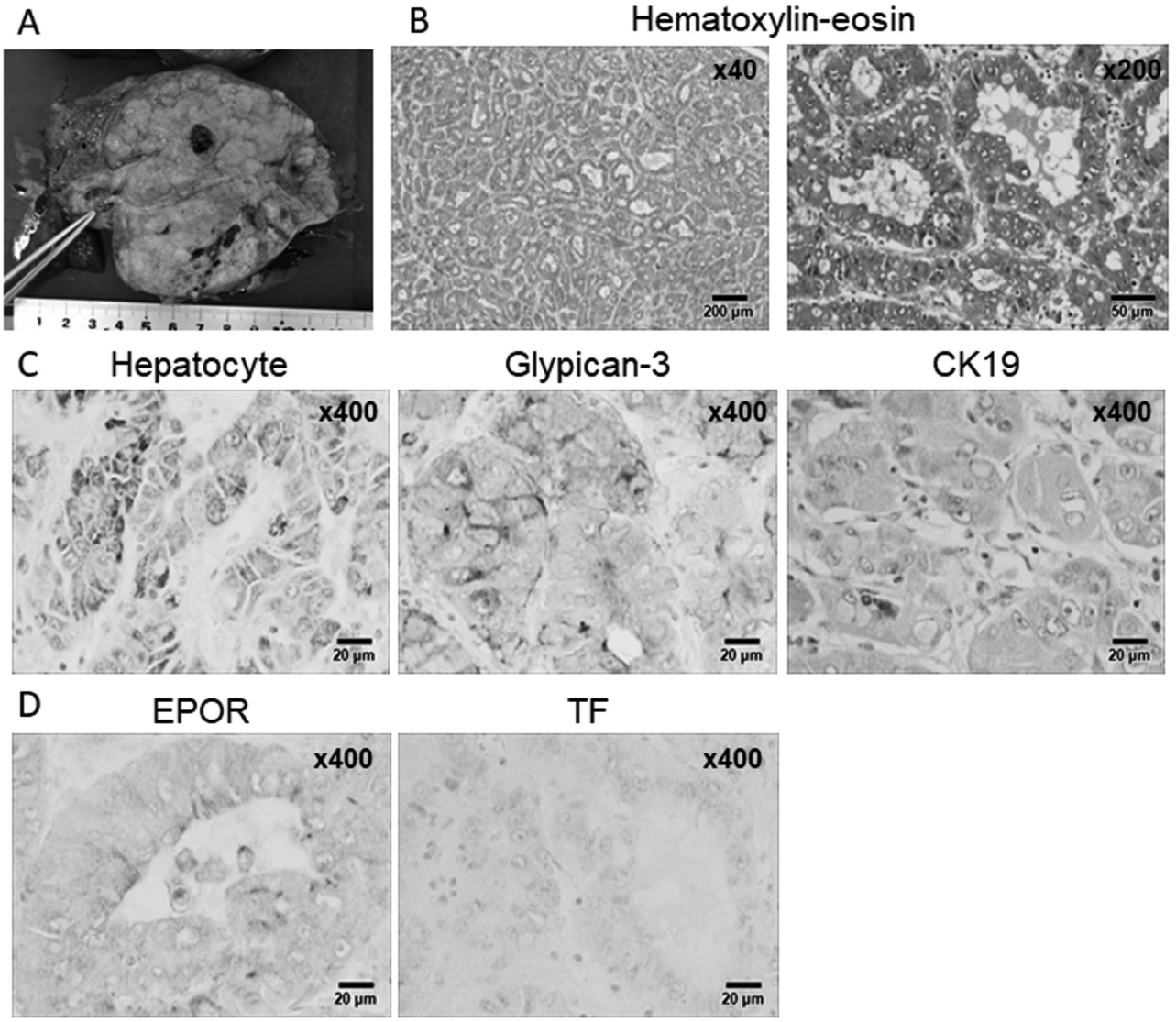

Figure 2. *Macroscopic and microscopic findings. A: The cut surface of the fresh resected liver showed the whitish, well-circumscribed main tumor and connecting portal vein tumor thrombosis. B: Microscopic figure of hematoxylin-eosin section indicated moderately differentiated hepatocellular carcinoma with a pseudoglandular growth pattern. C: Tumor cells were positive for hepatocyte (clone OCH1E5; DAKO, Glostrup, Denmark) and glypican-3 (clone 1G12; Nichirei, Tokyo, Japan) and negative for cytokeratin (CK19) (clone RCK108; DAKO), and this phenotype is consistent with hepatocellular carcinoma. D: Tumor cells expressed erythropoietin receptor (EPOR) (clone BCO-3H2; Merck Millipore, Burlington, MA, USA), but not tissue factor/coagulation factor III (TF) (#GTX100808; GeneTex, GeneTex, Irvine, CA, USA).*

was clearly separated from the PVTT. She demonstrated high levels of D-dimer and fibrin degradation product without any other coagulation factors. In consideration of all of these observations, VTE in this patient was identified as CAT. A Khorana Score of ≥3 points is a well-known predictor of CAT risk (18), but unfortunately is not useful for patients with HCC (19). In fact, our patient showed only a Khorana Score of 1 point but developed excessive VTE. The reasons for CAT development are not fully understood but tissue factor/coagulation factor (TF) is one of the key factors leading to CAT (4). TF was also known to be associated with tumor angiogenesis and invasiveness of HCC (20). In our patient, TF expression of HCC cells was unclear using immunohistochemical staining of the resected specimen. It had been reported that cancer diagnosis synchronous with or within 1 year after an episode of VTE had a close correlation with an advanced stage of cancer, and a poor long-term outcome (2). For patients with HCC, development of VTE is an independent poor prognostic factor (hazard ratio=5.37, 95% confidence interval=1.84-15.6, $p<0.01$) (21).

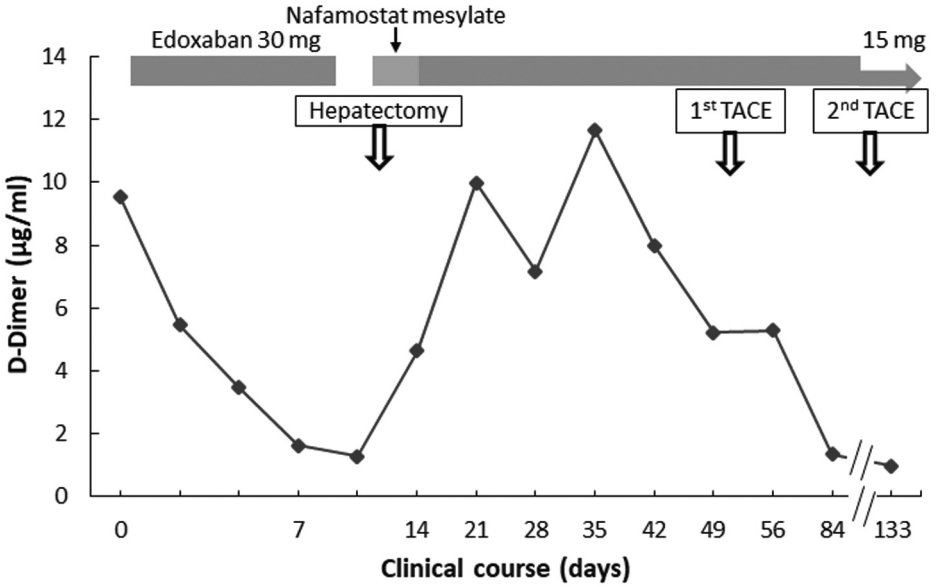

Figure 3. *Detail of treatments and changes in the D-dimer levels. TACE: Transarterial chemoembolization.*

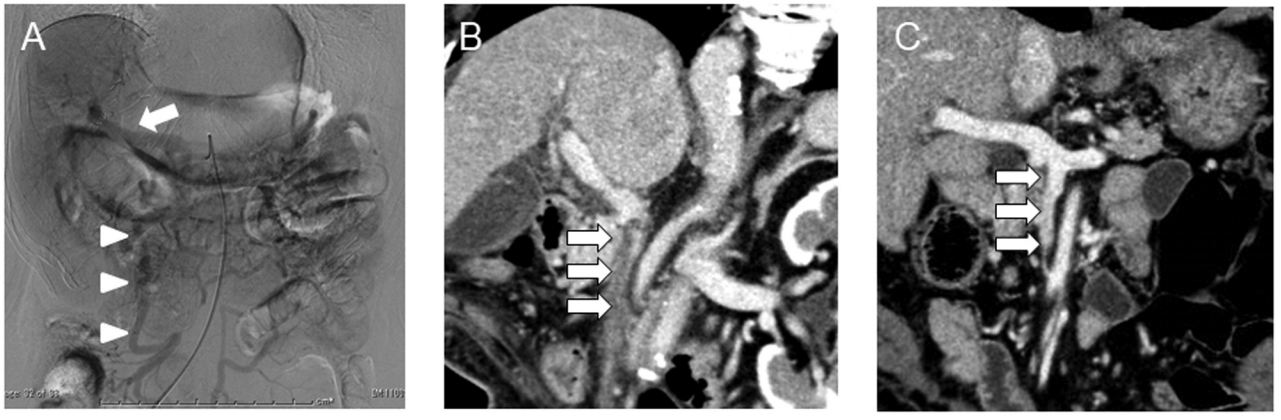

Figure 4. *Images of superior mesenteric vein thrombosis. A: Portal venous phase of the superior mesenteric artery angiogram 2 months after surgery. The main portal vein is patent (arrow) with collateral veins (arrow heads) and the superior mesenteric vein is absent. B: Coronal reformatted contrast-enhanced computed tomographic (CT) image before surgery, depicting superior mesenteric vein thrombosis (arrows). C: CT image 5 months after surgery, showing complete recanalization of the superior mesenteric vein (arrows).*

The patient showed secondary polycythemia which might have been caused by erythropoietin production from HCC cells. We also tried to carry out immunostaining of erythropoietin; however, we were unable to obtain the satisfactory antibody available for paraffin sections. The plasma erythropoietin level was elevated before surgery, and returned to the normal range immediately after surgery. Additionally, high expression of erythropoietin receptor was confirmed with immunohistochemical staining of the tumor. It has been reported that both high erythropoietin production and high expression of erythropoietin receptor are highly associated with vasculogenic mimicry and poor prognosis in patients with HCC (22). In fact, early in the postoperative period, our patient developed an aggressive sternal metastasis and multiple lung metastases. Furthermore, D-dimer levels tended to increase when the massive recurrence occurred in the postoperative period.

Abdominal ultrasound is a convenient diagnostic modality for patients with CAT. In our patient, SMV thrombosis was felt to be an old one due to the high echogenicity on abdominal ultrasound (15). Intraoperative Doppler US is frequently used to evaluate the hepatic blood flow. To avoid any micro-thrombus flowing from the SMV thrombosis, we enforced gentle intraoperative handling of the digestive tract.

Sonazoid-enhanced US and enhanced CT were performed within 1 week postoperatively, and confirmed no evidence of SMV thrombosis extension.

LMWH was a standard treatment regimen for CAT (23, 24); however, recent randomized control trials suggested that oral DOAC administration was noninferior to subcutaneous LMWH with respect to the composite outcome of recurrent VTE or major bleeding (12, 14). More recently, a unique network meta-analysis of randomized control trials of LMWH, VKAs, and DOACs for treatment of CAT demonstrated that the effectiveness and safety of DOACs were noninferior to VKAs, and possibly comparable with LMWH (25). International Society on Thrombosis and Haemostasis Scientific Standardization Committee 2018 guidance suggests edoxaban or rivaroxaban for cancer patients with an acute diagnosis of VTE, low risk of bleeding, and no drug–drug interactions with current systemic therapy (26). Recently, a unique study was published investigating the effects of edoxaban on VTE between cancer and non-cancer patients (27). It clearly demonstrated that the frequencies of recurrence of VTE and clinically relevant bleeding of edoxaban were equivalent for the treatment of VTE between patients with and without cancer. Unfortunately, these studies included patients with cancer mainly with DVT or PE; therefore, the therapeutic effect for splanchnic DVT including SMV thrombosis is still unclear. Furthermore, in order to prevent recurrent VTE in patients with CAT, anticoagulant therapy with DOACs may be more effective than traditional anticoagulants with equal safety as compared with that of traditional anticoagulants (28).

There were several studies that reported an excellent anticoagulant effect of DOAC for atypical thrombosis, including PVT (29). We deem the SMV thrombosis in the current patient to have been caused by a cancer-associated hypercoagulable state and cancer-induced PVTT. The former promoted thrombosis formation and the latter resulted in portal vein congestion. SMV thrombosis was progressing throughout SMV but intestinal blood flow was maintained by collateral veins caused by total obstruction of an original SMV. After a 5-month administration of DOAC, SMV thrombosis had almost completely disappeared. Even the old portal thrombosis in the area of impaired blood supply might dissolve via long-term administration of DOAC (30). Interestingly, some published data suggested that other than their anticoagulant effects, DOACs have potential anticancer effects for patients with cancer (31).

In conclusion, perioperative oral administration of edoxaban was useful in the multidisciplinary treatment for an advanced HCC patient with CAT. Insurance coverage for DOAC for splanchnic DVT is expected to expand all over the world.

Conflicts of Interest

The Authors have no conflicts of interest.

Authors' Contributions

KY and TB identified the concept and wrote the draft of the article. All Authors treated the patient and collected data. YK investigated pathological findings. All Authors have read and approve the final version of the article.

Compliance With Ethical Standards

Informed consent was obtained from the patient for use of her data.

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