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【 CASE REPORT 】

Portal Vein Thrombosis in Metastatic Colorectal Cancer During FOLFIRI-bevacizumab Chemotherapy Successfully Treated with Apixaban

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Abstract:
Portal vein thrombosis (PVT) while using an angiogenesis inhibitor is relatively rare. A 70-year-old Asian man was diagnosed with PVT two months after initiating 5-fluorouracil/leucovorin, irinotecan, and bevacizumab therapy for rectal cancer with liver metastases. Because the metastases were small and shrinking, we suspected that the thrombosis might have been caused by bevacizumab-containing chemotherapy. We stopped bevacizumab and started apixaban, a direct oral anticoagulant (DOAC). Eight months later, the complete dissolution of the thrombus and recanalization of the portal vein were attained. Our case suggests that PVT can occur during bevacizumab-containing chemotherapy, and DOAC therapy might be beneficial for treating PVT in patients with cancer.

Key words: bevacizumab, chemotherapy, portal vein thrombosis, colorectal cancer, DOAC

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Introduction

Angiogenesis plays an important role in tumor growth and metastasis, and angiogenesis inhibitors, such as bevacizumab, ramucirumab, and aflibercept, are now frequently used for a variety of cancer types (1). The mechanism by which these agents act involves blocking vascular endothelial growth factor (VEGF) or VEGF receptor, interrupting the angiogenesis process, and blocking tumor cell growth. In addition, these agents are also reported to inhibit the immunosuppressive effect in the tumor microenvironment, suggesting the possibility of having synergetic effects when used with immune checkpoint inhibitors (2, 3). Thus, the application of these agents is expected to steadily increase.

However, venous thromboembolism (VTE) has been frequently documented during the use of angiogenesis inhibitors in advanced-stage cancer patients. In particular, deep vein thrombosis (DVT) and pulmonary embolism (PE) are the main thrombotic events caused by these agents (4). Although treatment guidelines for cancer-VTE have been gradually established, no strategy for treating portal vein thrombosis (PVT) in patients with cancer has yet been developed well due to a lack of sufficient evidence.

We herein report a case of metastatic rectal cancer complicated with PVT formed soon after the initiation of 5-fluorouracil/leucovorin, irinotecan (FOLFIRI) plus bevacizumab therapy. Bevacizumab was suspended, and apixaban, a direct oral anticoagulant (DOAC), was initiated. The thrombus dissolved successfully with this intervention, and the patient has been receiving FOLFIRI therapy, maintaining a partial response to metastatic rectal cancer.

Case Report

A 70-year-old man with chronic kidney disease, type 2 diabetes mellitus, fatty liver, and hypertension came to our hospital with a diagnosis of stage IV, RAS-wild, BRAF-wild, microsatellite instability (MSI)-negative rectal adenocarcinoma with small liver metastases and was referred to our department after resection of the primary tumor. Computed tomography (CT) showed two small liver metastases and no thrombus (Fig. 1A, B). FOLFIRI and bevacizumab treatment was started because the patient declined surgery

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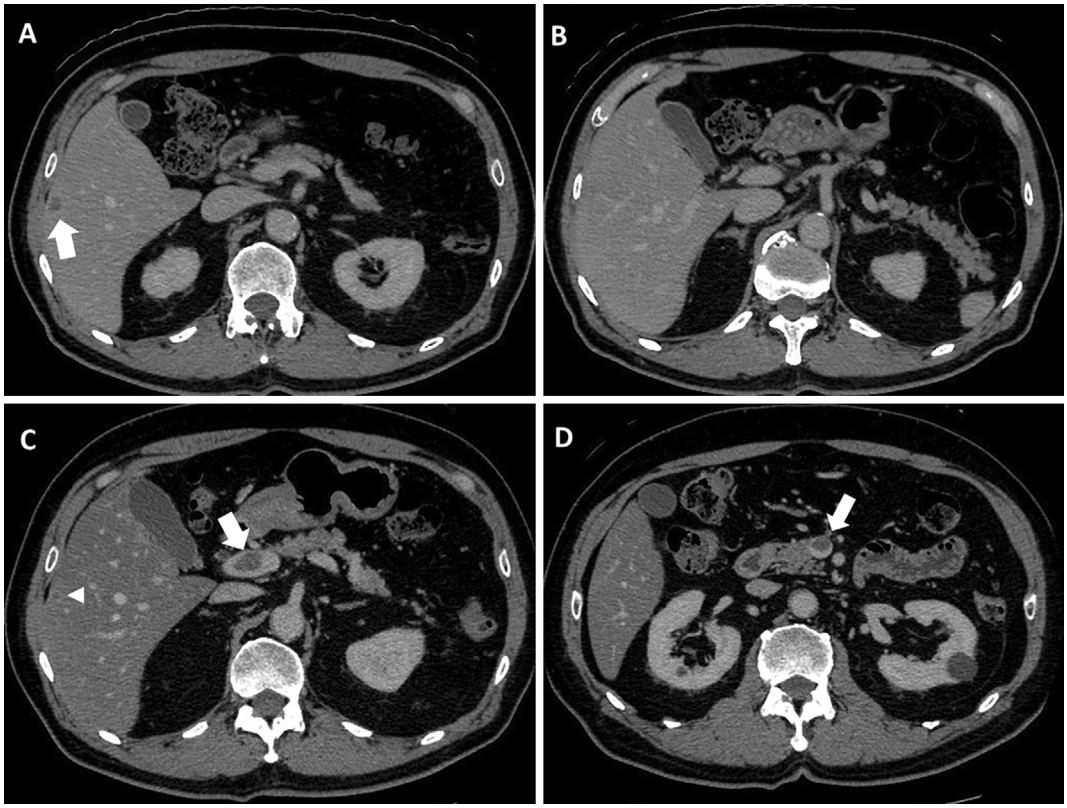

Figure 1. **CT images of liver metastasis and portal vein thrombosis before and after chemotherapy. (A) Liver metastasis (arrow) is seen before starting chemotherapy. (B) There is no thrombus in the portal vein before the initiation of chemotherapy. (C) Two months after initiating FOLFIRI+Bevacizumab therapy. Portal vein thrombosis is formed (arrow) with liver metastasis shrinking (arrowhead). (D) Two months after initiating FOLFIRI+Bevacizumab therapy. Thrombus has also developed in the superior mesenteric vein (arrow).**

for liver metastasis, the use of anti-epidermal growth factor receptor (EGFR) monoclonal antibody due to its possible skin toxicities, and the administration of oxaliplatin due to possible peripheral neuropathy. The laboratory data when the chemotherapy was started are shown in Table 1.

After two months, CT showed not only shrunken liver metastases with a partial response (PR) as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) but also thrombosis in the PV and superior mesenteric vein (SMV) (Fig. 1C, D). PE was not detected by this CT scan, and ultrasound of the lower extremities did not reveal any evidence of DVT. At this time, the patient did not have any symptoms related to cancer or thrombosis, such as abdominal pain or diarrhea. His vital signs were within normal limits, and a physical examination showed no abnormal findings. Laboratory data showed an elevated level of D-dimer (1.1 mg/dL). Prothrombin and partial thromboplastin times were within the normal range. The activities of proteins C and S were both normal. Lupus anticoagulant and anti-cardiolipin-β2-glycoprotein I complex antibodies were also negative. The liver function was normal. The patient had chronic kidney disease (Grade 3) with an estimated glomerular filtration rate (eGFR) between 30 and 60 mL/min/1.73 m^2, but it was stable without any changes during chemotherapy. Abdominal ultrasound did not detect evidence of portal hypertension. In addition, there were no collateral vessels on CT or ultrasound, suggesting that this PVT was in the acute phase.

Because the patient had not had thrombosis before starting chemotherapy and the liver metastases were small and far from the PV, we attributed the thrombus formation to the use of bevacizumab. We therefore stopped the use of bevacizumab and started apixaban (10 mg twice a day for seven days followed by 5 mg twice a day) to treat the thrombosis instead of using subcutaneous injection agents, considering the patient's quality of life. Soon after this intervention, the thrombus dissolved gradually (Fig. 2A-C). CT eight months after this treatment showed no thrombus in the PV or SMV (Fig. 2D).

Chronological changes in tumor marker and D-dimer levels during treatment for PVT are shown in Table 2. Upon confirming the complete dissolution of the thrombus, apixaban was finished because the thrombus was thought to have been caused not by the increased tumor burden but mainly by the initiation of bevacizumab-included chemotherapy. After the discontinuation of apixaban, there has been no recurrence of PVT for about a half year. The patient is now receiving FOLFIRI therapy and has been doing well, main-

Table 1. Initial Laboratory Data When Chemotherapy was Started.

Complete blood cell			Biochemistry		
WBC	6,700	/μL	TP	7.4	g/dL
Stab+Seg	28	%	Alb	4.6	g/dL
Lymphocyte	59	%	LDH	128	IU/L
Monocyte	9	%	T-Bil	0.4	mg/dL
Eosinophil	3	%	AST	17	U/L
Basophil	1		ALT	13	U/L
RBC	458	10^4/μL	ALP	161	U/L
Hgb	14.3	g/dL	γGTP	29	U/L
MCV	91.9	fL	CK	59	U/L
PLT	272,000	/μL	BUN	28.9	mg/dL
			Cr	1.48	mg/dL
Tumor markers			eGFR	37.3	mL/min/L
CEA	6.4	ng/mL	Na	140	mEq/L
CA19-9	13.9	ng/mL	K	4.8	mEq/L
			Cl	106	mEq/L
Coagulation test			Ca	9.9	mg/dL
PT	12.6	second	CRP	0.1	mg/dL
PT-INR	0.96				
APTT	29.6	second			
Fibrinogen	339	mg/dL			
D-Dimer	0.6	mg/dL			

WBC: white blood cell, RBC: red blood cell, Hgb: hemoglobin, MCV: mean corpuscular volume, PLT: platelet: CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, PT: prothrombin time, PT-INR: prothrombin time international normalized ratio, APTT: activated partial thromboplastin time, TP: total protein, Alb: albumin, LDH: lactate dehydrogenase, T-Bil: Total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γGTP: gamma glutamyl transpeptidase, CK: creatine kinase, BUN: blood urea nitrogen, Cr: creatinine, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein

taining a PR according to the RECIST for more than one year.

Discussion

In this report, we described a case of PV and SMV thrombosis in rectal cancer with small liver metastases under FOLFIRI plus bevacizumab therapy. Generally, thrombotic events are frequently seen in patients using angiogenesis inhibitors such as bevacizumab. Bevacizumab is a monoclonal antibody that binds VEGF-A and inhibits its binding to VEGF receptors. The mechanism underlying thrombosis formation induced by angiogenesis inhibitors is complex, but one of the main causes is endothelial dysfunction. VEGF inhibitors may facilitate an imbalance in vasodilation and vasoconstriction induced by changes in the endothelial environment. This dysfunction induces hemostasis and vascular thrombosis (5). In addition, with the use of bevacizumab, VEGF binds heparin and forms an immune complex, exacerbating aggregation and increasing procoagulant activities in the microvasculature (6). However, thrombosis in the portal system during the treatment of angiogenesis inhibitors is rare. We identified just six cases of PV or portal system thrombosis that occurred in cases receiving bevacizumab-included chemotherapy. The details of the five cases are not available because they are written in other languages (7-10). One report written in English was published by Donadon et al. and described a colon cancer patient with liver metastasis in whom PVT occurred during preoperative FOLFIRI plus bevacizumab chemotherapy. In that case, PVT and partial steatohepatitis occurred simultaneously, and the authors suspected that FOLFIRI plus bevacizumab combination therapy might contribute to chemotherapy-induced liver injury (11).

Generally, the risk factors for PVT include cirrhosis, malignancy, myeloproliferative disorders, medications, thrombophilia, local infection/inflammation, and surgery (12). Our patient had risk factors such as malignancy and steatosis that may facilitate thrombosis. However, no thrombus was seen before the initiation of chemotherapy, and there were no changes in liver function during chemotherapy. Furthermore, the liver metastases were small, and the tumor burden was thought to be low in this case. These facts suggest that the use of bevacizumab-included chemotherapy might have contributed to the formation of PVT.

Although thrombotic events are occasionally seen when using angiogenesis inhibitors, PVT is rarely observed, and the evidence supporting how PVT should be treated among patients with cancer is insufficient. General treatment options for PVT are low-molecular-weight heparin or oral anticoagulants, such as a DOAC or warfarin (13). However, this strategy has been developed to treat PVT mainly in patients with cirrhosis, and whether or not this strategy can be applied to treat PVT in patients with cancer is unclear. Although some case reports have found that the use of an antiplatelet agent or urokinase was partially effective in treating PVT in patients with cancer, cases of PVT treated by a DOAC in patients with cancer have not been well reported (7, 10). Recently, treatment guidelines for venous thromboembolism (VTE) in patients with cancer have been developed, and DOAC administration has become a standard treatment option for VTE, although most cases involve DVT and PE (14). Apixaban, a DOAC, was selected to treat PVT in this case for several reasons. For one, apixaban and rivaroxaban (another DOAC) are known to be useful for treating VTE orally in the acute phase. Therefore, choosing these agents to treat VTE both in the acute and late phases of thrombosis can avoid hospitalization and maintain the quality of life. Furthermore, apixaban is known to carry less risk of bleeding than rivaroxaban (15). The successful treatment course of this patient indicates that DOACs such as apixaban are effective for PVT in patients with cancer undergoing chemotherapy, and the further accumulation of cases is necessary to establish a solid strategy to treat PVT in patients with cancer.

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

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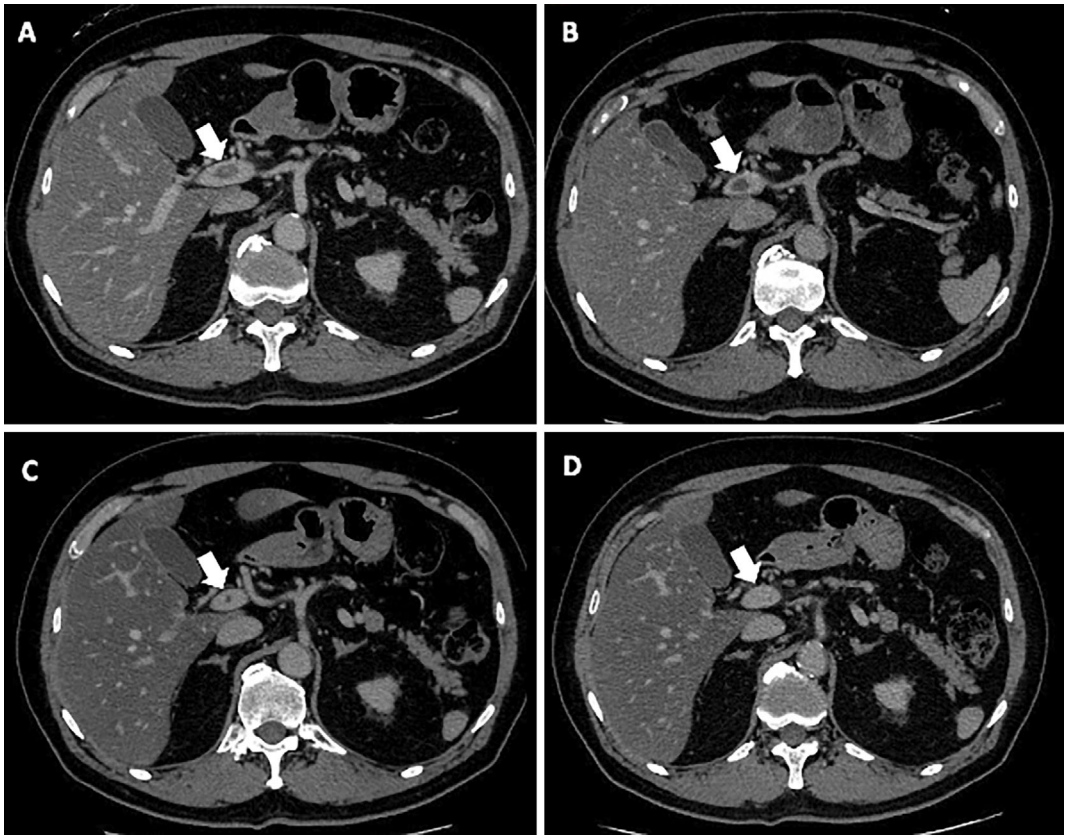

Figure 2. **CT images of portal vein thrombosis after anticoagulant therapy. (A) Thrombus is seen in the PV at the diagnosis (arrow). (B) Two months after anticoagulant therapy, the thrombus is still found in the PV (arrow). (C) Four months after anticoagulant therapy, the thrombus is dissolving gradually (arrow). (D) Eight months after apixaban therapy, the PVT has resolved completely (arrow).**

Table 2. **Time Course of D-Dimer and Tumor Markers during PVT Treatment.**

		-2 M*	0 M**	1 M	2 M	4 M	6 M	8 M***	10 M	12 M
CEA	[ng/mL]	6.4	1.3	1.1	1.2	1.5	1.4	1.7	2.5	2.0
CA19-9	[ng/mL]	13.9	3.6	2.2	2.2	2.7	2.9	3.9	3.2	3.1
D-Dimer	[mg/dL]	0.6	1.1	≤0.5	≤0.5	≤0.5	≤0.5	≤0.5	NA	0.6

* Two months before PVT was formed. Chemotherapy was started at this time.

** The time course is based on PVT diagnosis and treatment. Apixaban treatment was started at this time.

*** Apixaban was finished when CT confirmed the dissolution of thrombosis. Data here was taken after discontinuation of apixaban.

PVT: portal vein thrombosis, M: month(s), CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9

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