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

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 synergistic 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 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 5-fluorouracil/leucovorin, irinotecan (FOLFIRI) therapy, maintaining a partial response to metastatic rectal cancer.

Case Presentation
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. 2A, B). FOLFIRI and bevacizumab treatment was started because the patient declined surgery...
for liver metastasis, the use of anti-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. 2C, 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 m², 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-
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vironment. This dysfunction induces hemostasis and vascular
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hitors may facilitate an imbalance in vasodilation and
one of the main causes is endothelial dysfunction. VEGF in-
mation induced by angiogenesis inhibitors is complex, but
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antibody that binds VEGF-A and inhibits its binding to
thrombosis in rectal cancer with small liver metastases under
FOLFIRI plus bevacizumab therapy. Generally, thrombotic
events are frequently seen in patients using angiogenesis in-
	Table 1. Initial Laboratory Data When Chemotherapy
was Started.

| Biochemistry | Complete blood cell | Stab+Seg | Lymphocyte | Monocyte | Eosinophil | Basophil | RBC | Hgb | MCV | PLT | PT | APTT | Fibrinogen | D-Dimer |
|--------------|---------------------|----------|------------|----------|------------|----------|-----|-----|-----|-----|----|------|-----------|---------|
| TP           | 7.4 g/dL            | 6,700 μL | 28 %       | 59 %     | 9 %        | 3 %      | 458 | 14.3 | 91.9| 272,000 | 12.6 | 29.6 | 339 | 0.6 |
| Alb          | 4.6 g/dL            |          |            |          |            |          |      |      |      |      |     |      |          |         |
| LDH          | 128 IU/L            |          |            |          |            |          |      |      |      |      |     |      |          |         |
| T-Bil        | 0.4 mg/dL           |          |            |          |            |          |      |      |      |      |     |      |          |         |
| AST          | 17 U/L              |          |            |          |            |          |      |      |      |      |     |      |          |         |
| T-Bil        | 13 U/L              |          |            |          |            |          |      |      |      |      |     |      |          |         |
| ALP          | 161 U/L             |          |            |          |            |          |      |      |      |      |     |      |          |         |
| γ-GTP        | 29 U/L              |          |            |          |            |          |      |      |      |      |     |      |          |         |
| ALT          | 59 U/L              |          |            |          |            |          |      |      |      |      |     |      |          |         |
| BUN          | 28.9 mg/dL          |          |            |          |            |          |      |      |      |      |     |      |          |         |
| Cr           | 1.48 mg/dL          |          |            |          |            |          |      |      |      |      |     |      |          |         |
| eGFR         | 37.3 mL/min/L       |          |            |          |            |          |      |      |      |      |     |      |          |         |
| Na           | 140 mEq/L           |          |            |          |            |          |      |      |      |      |     |      |          |         |
| K            | 4.8 mEq/L           |          |            |          |            |          |      |      |      |      |     |      |          |         |
| Cl           | 106 mEq/L           |          |            |          |            |          |      |      |      |      |     |      |          |         |
| Ca           | 9.9 mg/dL           |          |            |          |            |          |      |      |      |      |     |      |          |         |
| CRP          | 0.1 mg/dL           |          |            |          |            |          |      |      |      |      |     |      |          |         |
| Cr           | 1.48 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: pro-
thrombin time international normalized ratio, APTT: activated partial
thromboplastin time, TP: total protein, Alb: albumin, LDH: lactate dehydro-

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 in-
hibitors such as bevacizumab. Bevacizumab is a monoclonal
antibody that binds VEGF-A and inhibits its binding to
VEGF receptors. The mechanism underlying thrombosis for-
mation induced by angiogenesis inhibitors is complex, but
one of the main causes is endothelial dysfunction. VEGF in-
hibitors may facilitate an imbalance in vasodilation and
vasoconstriction induced by changes in the endothelial envi-
rnment. This dysfunction induces hemostasis and vascular
thrombosis (5). In addition, with the use of bevacizumab,
VEGF binds heparin and forms an immune complex, exac-
terating aggregation and increasing procoagulant activities
in the microvasculature (6). However, thrombosis in the por-
tal 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-
cluded 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 sus-
pected that FOLFIRI plus bevacizumab combination therapy
might contribute to chemotherapy-induced liver injury (11).

Generally, the risk factors for PVT include cirrhosis, ma-
lagnignancy, myeloproliferative disorders, medications, throm-
bophilia, 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 con-
tributed 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 op-
tions for PVT are low-molecular-weight heparin or oral anti-
coagulants, 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 ap-
tiled to treat PVT in patients with cancer is unclear. Al-
though some case reports have found that the use of an anti-
platelet 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 re-
ported (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 rivar-
oxaban (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 qual-
ity 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 apix-
aban are effective for PVT in patients with cancer undergo-
ing chemotherapy, and the further accumulation of cases is
necessary to establish a solid strategy to treat PVT in pa-
patients with cancer.

Personal financial interests
The authors declare that they have no conflicts of interest.
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

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

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