Successful direct oral anticoagulant management of asymptomatic superior mesenteric vein thrombosis after adjuvant chemotherapy for colorectal cancer patient: A case report

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Abstract. Owing to advances in cancer treatment and the diversification of treatment methods, cancer-associated thrombosis is increasing. Cancer can cause blood clots by activating the blood clotting system, increasing clotting factors through inflammation, reducing blood flow due to immobilization and damaging blood vessels through treatments such as chemotherapy. In clinical practice, superior mesenteric vein (SMV) thrombosis is occasionally observed in patients with cancer; however, certain cases of asymptomatic thrombosis can be serious. In the present case, a 71-year-old woman underwent laparoscopic high anterior resection for colorectal cancer. The patient received capecitabine as postoperative adjuvant chemotherapy for 6 months. Contrast-enhanced CT after the completion of chemotherapy revealed a sizable thrombus in the SMV. The thrombus occupied the SMV lumen without evident intestinal ischemia. D-dimer levels were elevated. Since the patient remained asymptomatic, edoxaban (30 mg/day) was administered in an outpatient setting. Six months later, contrast-enhanced CT confirmed thrombus resolution. No hemorrhagic events were observed during edoxaban treatment. In conclusion, cancer and chemotherapy are risk factors for thrombosis, indicating that regular D-dimer measurements may be necessary during cancer treatment. In addition, edoxaban may be an effective therapeutic tool for SMV thrombosis during chemotherapy for cancer.

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Abbreviations: SMV, superior mesenteric vein; VTE, venous thromboembolism; SFMC, soluble fibrin monomer complex

Key words: chemotherapy, cancer, asymptomatic, superior mesenteric vein thrombosis, direct oral anticoagulant, edoxaban

Introduction

Thrombosis is known to develop due to various risk factors classified as blood flow stagnation, vascular endothelial dysfunction and hypercoagulability. In patients with cancer, hypercoagulability due to the cancer and other factors that may present during cancer treatment, such as excessive bed rest, surgery, central venous catheter placement, medication and infection, are risk factors for thromboembolism development. Thus, since patients with cancer may have several of these risk factors, they are considered to be at high risk for thrombosis development. With the increase in the number of patients with cancer and the development of chemotherapy, cancer- and chemotherapy-related thromboses are being increasingly observed (1). This increase is in proportion to an increase in the number of patients with cancer globally (2-4), which is attributable to a broadening array of treatment modalities (5) and improvements in the accuracy of diagnosis, such as CT imaging examinations (6). To the best of our knowledge, no studies have discussed superior mesenteric vein (SMV) thrombosis that was discovered incidentally during postoperative chemotherapy. In the present case, a patient with asymptomatic SMV thrombosis noted on contrast-enhanced CT after postoperative chemotherapy for colorectal cancer was treated with direct-acting oral anticoagulants (DOACs). In addition, the literature was reviewed, with a focus on the risk of SMV thrombosis during the perioperative period and cancer chemotherapy. Treatment strategies, depending on the presence or absence of symptoms, and methods for the early detection of asymptomatic venous thromboembolism were also discussed.

Case report

In May 2020, a 71-year-old woman was diagnosed with occult blood in their stool during a health check. A mass was also detected in the rectum during a colonoscopy, following which the patient was referred to Gifu University Hospital (Gifu Japan) that same month. The patient had a history of arrhythmia and had been taking pilsicainide orally at a dosage of 150 mg three times a day since the previous year. After multiple examinations using computed tomography (CT)

scans, endoscopy and fluoroscopy, among others, the patient was diagnosed with colorectal cancer and underwent a laparoscopic high anterior resection that same month (May 2020). In the resected specimen, the tumor was centrally depressed, and the border of the peritumor was clearly defined. (Fig. 1). The postoperative course was uneventful, and the patient was discharged on postoperative day 12. The pathological findings were T3, N0, M0, and Stage IIA according to the Union for International Cancer Control 8th edition classification (7). The patient subsequently underwent postoperative adjuvant chemotherapy with capecitabine. Capecitabine (3,600 mg/day) was administered for 2 weeks, followed by a 1-week break. This was counted as 1 course, and a total of 8 courses were administered, but suffered from Grade 1 diarrhea and Grade 2 anorexia during the regimen of capecitabine (grades according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (8).

After completing chemotherapy, contrast-enhanced CT was performed in December 2020 to detect recurrence. Although no recurrence was observed, a thrombus completely occupying the SMV lumen was observed (Fig. 2A-F). Preoperative contrast-enhanced CT showed no thrombi. The patient had no abdominal symptoms after the chemotherapy. Blood tests revealed no liver dysfunction or coagulation abnormalities. D-dimer levels were 6.0 μg/ml, anti-cardiolipin antibody was negative, protein C level was 57% and protein S level was 140%. No abnormalities were evident in anti-cardiolipin antibody or protein C or S activity. Furthermore, no venous thrombus could be detected by lower limb venous ultrasonography, and no pulmonary artery thrombosis was observed on contrast-enhanced CT. Based on these findings, the patient was diagnosed with SMV thrombosis. Since no abdominal symptoms or obvious intestinal ischemia could be detected on CT, conservative treatment with anticoagulants was decided. Treatment with oral edoxaban (30 mg/day) was initiated, following which D-dimer levels normalized after 1 month. Subsequently, 6 months later, a follow-up examination revealed complete resolution of the thrombus and no recurrence of colorectal cancer in June 2021. Therefore, edoxaban treatment was discontinued (Fig. 3). No hemorrhagic events were observed during this treatment period. Subsequent follow-up is presently being conducted in an outpatient clinic to monitor recurrence and thrombus formation, and to date, no thrombus or cancer recurrence has been noted.

Discussion

To the best of our knowledge, the present study is the first to report a cure for asymptomatic SMV thrombosis in an outpatient case of a patient recovering from colorectal cancer after receiving adjuvant chemotherapy using edoxaban.

SMV thrombosis was first reported by Warren and Eberhard (9) in 1935 as a disorder that causes congestive infarction due to impaired blood flow in the mesenteric veins. It is a relatively rare disorder that accounts for 5-15% of all occlusive lesions in mesenteric vessels (10,11). The causative factors can be classified as primary, which occurs idiopathically, and secondary, which is caused by a thrombogenic predisposition or an underlying disease. Secondary factors contributing to thrombosis can include general thrombophilia and inflammatory conditions of the abdomen, such as an abnormal coagulation-fibrinolytic system, liver disease, surgery, malignancy, and chemotherapy (12). In both cases, the underlying cause is damage to the vascular endothelium, impaired blood flow, or thrombus formation due to hypercoagulation caused by inflammation or mechanical stimulation (12). In the present case, no abnormalities were found in coagulability, such as protein C or S deficiency, and no history of liver disease was noted. However, this patient underwent postoperative chemotherapy for a malignant tumor (colorectal cancer) and was considered to be at high risk of SMV thrombosis.

Heit *et al* (13) previously reported on the relationship among patients with cancer, anticancer drugs and thrombosis, stating that the risk of thromboembolism in individuals with cancer is 4 times higher compared with that in those without cancer, which increases further to 6.5 times with chemotherapy. Cancer treatment has been reported to be an independent risk factor for recurrent venous thromboembolism (VTE) (14). In the present case, capecitabine was administered as postoperative chemotherapy for 6 months. Therefore, the possibility that capecitabine is a risk factor for thrombus formation cannot be ruled out. Additionally, the frequency of diarrhea associated with oral capecitabine administration is ~60%, indicating that intravascular dehydration may be a risk factor for thrombosis (15). The present patient had grade 1 diarrhea and grade 2 anorexia during the administration of capecitabine, both of which may have been the causes of SMV thrombosis due to intravascular dehydration.

The onset of SMV thrombosis varies from acute to chronic, as the rate of thrombus formation and extent of occlusion differ with the degree of collateral blood vessel development (16). The acute form is characterized by abdominal pain, hemorrhage, and vomiting, which occurs rapidly due to organ necrosis caused by congestive reflux obstruction resulting from the venous obstruction. By contrast, the chronic form may be asymptomatic without reflux obstruction owing to the development of collateral blood vessels caused by the slower vascular occlusion (16).

Warshauer *et al* (17) previously performed a retrospective study of 43 patients with SMV thrombosis and found that 6 (14%) had no apparent symptoms. Anticoagulation therapy was administered to the 6 asymptomatic patients, all of whom showed favorable progress; however, another systematic review of 604 patients with SMV thrombosis by Acosta and Salim (18) revealed a small bowel resection rate of 43.9% for this disease. Therefore, considering the risk of small bowel necrosis and resection, anticoagulant therapy should be initiated even if the patient is asymptomatic.

Contrast-enhanced CT is the most effective diagnostic method for mesenteric venous thrombosis (successful in 90% of cases) (16). Contrast-enhanced CT images provide an effective means of confirming the site of obstruction, extent of ischemia, and the presence of perforation to make a definitive diagnosis and determine treatment options (19). Notably, treatment guidelines for colorectal cancer recommend a CT scan every 6 months postoperatively. Therefore, CT is not frequently performed (5).

There is a score known as the 'Khorana score,' which is used to evaluate the risk of VTE in patients with malignant

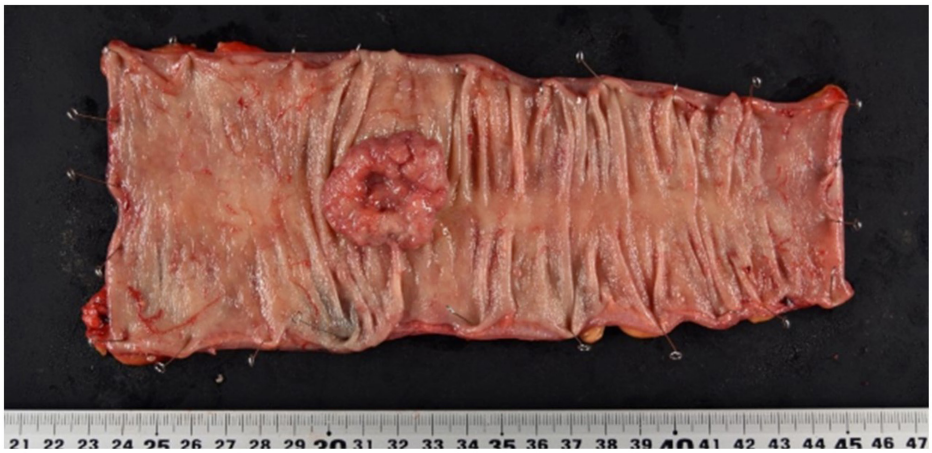

Figure 1. Macroscopic findings of the resected specimen showing a tumor of ulcerative type (Type II).

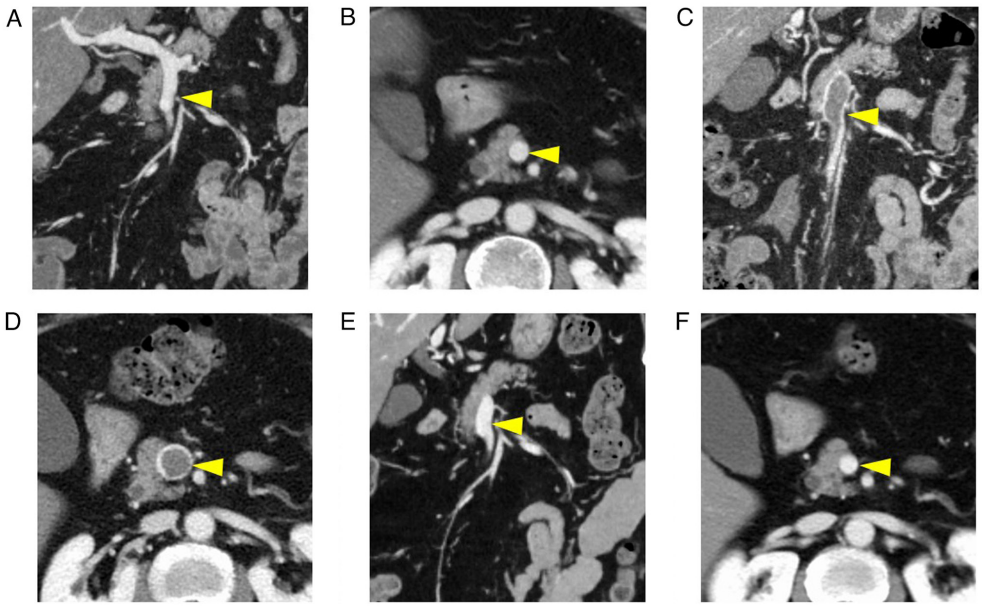

Figure 2. Contrast-enhanced CT images during the clinical course. (A and B) Preoperative CT showing no thrombus in the SMV. (C and D) CT images 6 months postoperatively showing that the lumen of the SMV is occupied by a thrombus. (E and F) The blood clot disappeared 6 months after taking edoxaban. Yellow arrowheads indicate the SMV. SMV, superior mesenteric vein.

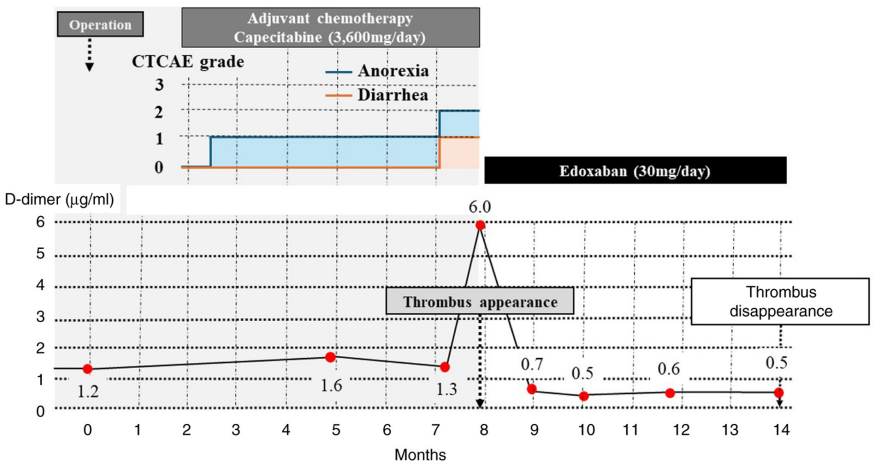

Figure 3. Clinical course of the patient, including CTCAE grades of adverse events. One month after taking edoxaban, D-dimer levels normalized. Additionally, contrast-enhanced CT performed 6 months later revealed the complete disappearance of the thrombus. CTCAE, Common Terminology Criteria for Adverse Events, version 5.0.

tumors (20). During chemotherapy, no abnormalities in blood cells were observed, and the retrospective Khorana score in the present study was 0 points. Furthermore, D-dimer has been reported to be a useful indicator of thrombus development. The American Society of Clinical Oncology guidelines recommend measuring D-dimer levels at the beginning of a new chemotherapy regimen (21). A previous large cohort study assessing a list of risk factors for symptomatic VTE revealed that abnormal D-dimer values were a significant risk factor (14).

Given that SMV thrombosis occurred either in the perioperative period or during adjuvant chemotherapy in the present case, D-dimer measurement could have detected clots earlier. Treatment guidelines for colorectal cancer recommend measuring tumor markers, such as CA19-9 and CEA, every 3 months. Therefore, D-dimer levels should be measured simultaneously. Tanaka *et al* (22) reported that in addition to D-dimer, soluble fibrin monomer complex (SFMC) may also be a beneficial biomarker for thrombosis in patients with esophageal cancer, where measuring both D-dimer and SFMC levels is believed to enhance the reliability of thrombus detection.

In terms of anticoagulant therapy, vitamin K antagonists or low-molecular-weight heparin sodium are frequently used (23,24). Cytochrome P450 (CYP) is a key enzyme in the metabolic pathway of a variety of chemotherapeutic drugs (25), including capecitabine. Capecitabine inhibits the DNA synthesis of CYP2C9, resulting in the reduction of vitamin K antagonist-metabolizing enzyme levels to enhance the effects of vitamin K antagonists (26). Therefore, edoxaban, which exerts its antithrombotic effects by selectively but reversibly inhibiting activated blood coagulation factor Xa (23), is metabolized by CYP3A4 at <10% of the dose, meaning it may be safer for patients using capecitabine (27). Additionally, edoxaban requires no volume adjustment according to clotting factor values, reaches maximum blood concentration quickly, and its effects diminish relatively quickly after drug withdrawal (28). For these reasons, although no reports exist on the treatment of asymptomatic SMV thrombosis with DOAC to the best of our knowledge, edoxaban was selected in the present case. Although a previous HOKUSAI Cancer VTE study demonstrated non-inferiority of the efficacy of edoxaban to dalteparin, caution was needed for cases of major bleeding (23). In addition, there is an antagonist against DOACs. In the event of uncontrolled bleeding, andexanet α, a DOAC antagonist, has been designed to reverse the anticoagulant effects of DOAC (29). Even when performing conservative treatments for SMV thrombosis, as in the present case, there is always a risk of bleeding due to mechanical stimulation from the insertion of a gastric or ileus tube and bloody stool due to poor intestinal blood flow. Therefore, the use of edoxaban, an antagonist available on standby, would be highly beneficial.

In conclusion, the present case documents a patient with asymptomatic SMV thrombosis that developed during anticancer treatment for rectal cancer and was treated safely with edoxaban. Cancer and chemotherapy are risk factors for thrombosis; therefore, regular D-dimer measurements may be necessary during cancer treatment. In addition, edoxaban may be considered an effective therapeutic tool for SMV thrombosis, even in seemingly severe cases.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

TH and YT contributed to the design of the case report. YS, KY, SK, and NM analyzed the data. MF, IY, RA and JYT performed data collection. SK and NM confirm the authenticity of the raw data. RA and JYT designed the study and prepared the manuscript. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the publication of the manuscript, including any identifying images or data.

Competing interests

The authors declare that they have no competing interests.

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