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Case report

Lower-extremity deep vein thrombosis induced by oxaliplatin and capecitabine chemotherapy: A case report

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ABSTRACT

Oxaliplatin and capecitabine are instrumental in the adjunctive and palliative systemic management of colorectal cancer. The concurrent administration of these chemotherapeutic agents often results in adverse effects, such as nausea, vomiting, diarrhea, leukopenia, and hand-foot syndrome. However, reports of deep vein thrombosis (DVT) caused by oxaliplatin and capecitabine are scarce. In this case study, we report a rare occurrence of lower-extremity DVT triggered by synergistic oxaliplatin and capecitabine chemotherapy in a patient diagnosed with malignant colon cancer. During the initial cycle of chemotherapy, the patient demonstrated DVT within the intermuscular veins of the right calf and abnormalities in markers of coagulation function. Enlargement of the intermuscular venous thrombosis and an increase in coagulation markers were observed subsequent to the second chemotherapy cycle. From our experience of this case, we suggest that DVT is induced by oxaliplatin and capecitabine warrants vigilant attention. Risk assessment for DVT prior to chemotherapy, coupled with early detection and intervention, is crucial for DVT prevention. Furthermore, enhancing the awareness of health care professionals and patients about the potential of chemotherapy-induced DVT is of paramount importance. Consequently, this case carries significant clinical implications.

Introduction

Colorectal cancer (CRC) is a prevalent gastrointestinal malignancy, and its incidence shows a global upward trend. In February 2024, the World Health Organization's International Agency for Research on Cancer published the latest estimates of the global burden of cancer in 2022. The estimates highlight that CRC ranks third in incidence and second in mortality among all cancers worldwide, and it accounted for 1.9 million new cases of cancer (9.6% of total new cases) and 900,000 deaths from cancer (9.3% of total cancer deaths) in 2022.[1] Currently, treatment for CRC primarily involves surgery, chemotherapy, radiotherapy, molecular-targeted therapy, and immunotherapy, with chemotherapy remaining a crucial modality.[2] Oxaliplatin and capecitabine are essential chemotherapeutic agents used in the adjuvant and palliative treatment of CRC.[3] The common adverse reactions during combined chemotherapy includes nausea, vomiting, diarrhea, leukopenia, and hand-foot syndrome, while deep vein thrombosis (DVT) is a rare complication. This article reports a case of lower-extremity DVT induced by chemotherapy with oxaliplatin and capecitabine, aiming to provide a basis for clinical practice, enhance the awareness of health care professionals with regard to chemotherapy-induced lower-extremity DVT, and promote safe and rational medication use.

Case presentation

A 64-year-old male patient (height, 178 cm; weight, 76 kg) was clinically diagnosed with colon cancer. Subsequent chest computed tomography (CT) and positron emission tomography/CT unveiled secondary malignancies manifesting in the lungs, bones, and lymph nodes. Elevated tumor markers were noted, with the carcinoembryonic antigen (CEA) concentration reaching 49.03 ng/mL (standard reference $\leq$ 5.00 ng/mL) and the cytokeratin 19 fragment concentration reaching 21.89 ng/mL (standard reference $\leq$ 3.30 ng/mL). Coagulation function indicators, including prothrombin time (PT), prothrombin activity (PTA), international normalized ratio (INR), fibrinogen, thrombin time, D-dimer (DD), fibrin degradation products (FDP), and antithrombin III activity, as well as activated partial thromboplastin time (APTT), were all within normal limits. Histopathological analysis confirmed a moderately differentiated adenocarcinoma located in the sigmoid colon.

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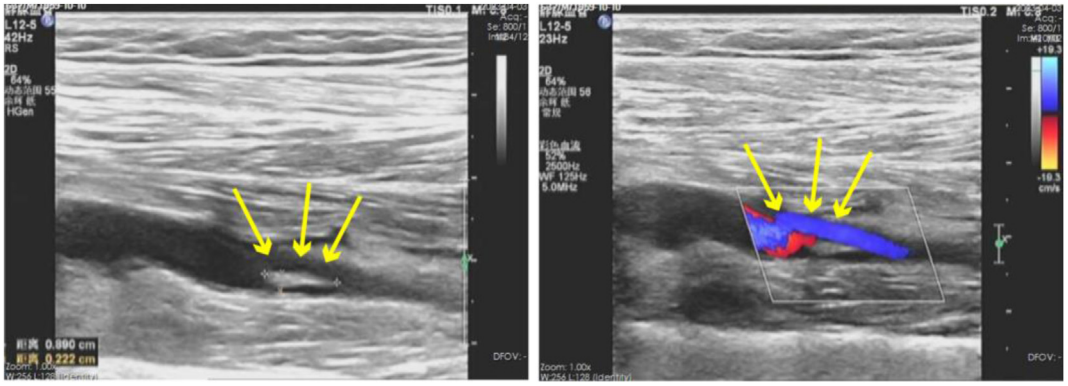

Figure 1. The yellow arrow shows right lower-extremity deep vein thrombosis in a patient with colorectal cancer.

Immunohistochemical staining yielded positive results for creatine kinase, DNA mismatch repair protein Mlh1, PMS2, MSH2, MSH6, and Ki67 exhibited an expression rate near to 80%. Moreover, a mutation within exon 2 of *KRAS* (p.G12S/D) was identified. Following the exclusion of contraindications to chemotherapy, the patient was administered four cycles of oxaliplatin (250 mg intravenous gtt) and capecitabine (2.0 g oral twice a day, days 1–14) on March 15, April 7, May 8, and June 12, 2023. This course of treatment led to a noteworthy decrease in the CEA concentration and partial resolution of pulmonary metastases, confirmed by CT imaging. However, during the initial cycle of chemotherapy, the patient suddenly experienced swelling and pain in the right calf. On April 3, 2023, vascular ultrasound revealed DVT formation in the intermuscular veins of the right calf (measuring approximately 8.9 × 2.2 mm) (Fig. 1). On April 4, 2023, the parameters of coagulation function were as follows: PTA, 71.00% (normal range 80% to 120%); INR, 1.23 (normal range 0.8–1.2); fibrinogen, 4.67 g/L (normal range 2.0–4.0 g/L); DD, 0.70 μg/mL (normal range 0.0–0.5 μg/mL). The patient was initially treated with rivaroxaban 10 mg orally twice a day from April 3 to April 6, 2023, for anticoagulation. Following a consultation with the vascular medicine department, the treatment was switched to sodium enoxaparin injection 4000 IU every 12 hours from April 6 to April 11, 2023. After the anticoagulation therapy, the pain and swelling in the patient's right lower limb decreased. Follow-up vascular ultrasound on April 10, 2023, indicated a reduction in thrombus size to approximately 6.9 × 2.4 mm. Fibrinogen, as an indicator of coagulation function, increased to 5.01 g/L, and the treatment with rivaroxaban 20 mg orally once a day was continued for anticoagulation. During the second chemotherapy cycle on May 4, 2023, vascular ultrasound revealed an increase in the size of the DVT within the intermuscular veins of the right calf, measuring approximately 7.1 × 2.9 mm. Fibrinogen increased to 5.32 g/L, prompting a subsequent round of anticoagulation therapy with sodium enoxaparin injection 4000 IU once a day from May 5 to May 8, 2023. On May 8, the fibrinogen concentration decreased to 4.17 g/L, leading to the administration of rivaroxaban 10 mg orally once a day for ongoing anticoagulation. Subsequent ultrasounds during the third and fourth cycles of chemotherapy showed a decrease in thrombus size, with no further anticoagulation therapy administered. Ultimately, due to the patient's inability to tolerate the gastrointestinal reactions caused by capecitabine and the peripheral neuropathy induced by oxaliplatin, the treatment regimen was modified. The patient is currently under follow-up.

Discussion

In the present case, the patient was treated with a combination of oxaliplatin (250 mg intravenous gtt) and capecitabine (2.0 g oral twice a day, days 1–14). Following the initial administration of this regimen, the patient developed swelling and pain in the right lower limb. Vascular ultrasound revealed DVT formation occurs in the intermuscular veins of the right lower limb, with blood tests indicating abnormal coagulation function markers. After treatment with anticoagulant medication, the swelling and pain in the right lower limb subsided, and ultrasound showed a reduction in DVT size within the intermuscular veins, with an improvement in coagulation function markers. This incident was considered an adverse effect of oxaliplatin and capecitabine. Upon admission, the patient's coagulation function markers were normal. After the first cycle of chemotherapy, there was a significant reduction in the tumor marker CEA, and CT showed an alleviation of pulmonary metastases, indicating the efficacy of the oxaliplatin and capecitabine treatment regimen with no progression, excluding tumor progression as a cause of DVT. Based on the Naranjo Adverse Drug Reaction Probability Scale,[4] the patient scored 6 points (Table 1), suggesting that the adverse reaction was “Probable,” not excluding the possibility of DVT-induced by combined treatment with oxaliplatin and capecitabine.

Venous thromboembolism (VTE) is a common complication in patients with malignant tumor, and it is one of the leading causes of death among patients with cancer, typically manifesting as DVT or pulmonary embolism (PE).[5,6] The formation of cancer-associated VTE is a complex

Table 1
Naranjo Adverse Drug Reaction Probability Scale of adverse reaction.

Questions	Yes	No	Do not know	Patient
1. Are there previous conclusive reports on this reaction?	+1	0	0	1
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0	2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	1
4. Did the adverse event reappear when the drug was re-administered?	+2	−1	0	2
5. Are there alternative causes (other than the drug) that could affect their own have caused the reaction?	−1	+2	0	0
6. Did the reaction reappear when a placebo was given?	−1	+1	0	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	0
Total score				6

process that is closely linked to a variety of mechanisms and influenced by numerous factors. Etiologically, VTE involves hypercoagulability, vascular wall damage, and blood flow stasis due to tumor compression.[7,8] The presence of additional risk factors, such as patient-, tumor-, and treatment-related elements, further increases the likelihood of VTE occurrence.[9] Although the risk associated with cancer-related VTE varies significantly among different types of cancer, patients with CRC are considered to be at a high risk of concurrent VTE.[10] In a retrospective study involving 436 patients with cancer with VTE, 94 patients (21.6%) had CRC.[11] Research on the risk factors for VTE in Chinese patients hospitalized with CRC revealed differences between the non-VTE and VTE groups in terms of demographic factors, comorbidities, and hematological indicators. Age, body temperature, volume of blood loss, the use of a peripherally inserted central catheter, chemotherapy, anemia, INR, and carbohydrate antigen 199 were identified as independent risk factors for VTE development.[12] Additionally, another study[13] compared patients with CRC with a healthy control group, and patients with CRC exhibited elevated thrombin–antithrombin complex, plasmin–α2 antiplasmin complex, tissue plasminogen activator–plasminogen activator inhibitor-1 complex, FDP, fibrinogen, and DD concentrations, along with lower antithrombin, APTT, and PT values. This profile suggests an increased predisposition toward coagulopathy and thrombosis development among patients with CRC.

Thrombogenesis could potentially manifest as an adverse effect of oxaliplatin and capecitabine therapy. However, despite conducting an extensive literature review, reports on cases of DVT induced by the combined use of oxaliplatin and capecitabine are scant. Research utilizing the Health Insurance Review and Assessment Service database in Korea, spanning from 2013 to 2020 indicated that of 6494 patients with CRC treated with oxaliplatin combined with 5-fluorouracil or capecitabine, 140 individuals (2.16%) developed VTE. Within this subset, 95 patients (1.46%) exhibited PE or a combination of PE and DVT, while 45 patients (0.69%) experienced DVT only.[14] Capecitabine, a fluoropyrimidine nucleoside analog is metabolized into 5-fluorouracil to exert its antitumor effect. In a retrospective study of 206 patients with cancer, 7.3% were confirmed to have developed VTE either during chemotherapy or within 3 months after treatment. Specifically, in patients with CRC treated with a combination of fluorouracil and leucovorin, the incidence of VTE was notably high, affecting 6 of 39 patients (15%).[15] In one case report, a patient treated with 5-fluorouracil for CRC developed DVT.[16] However, no previous studies have reported VTE caused by oxaliplatin alone. In phase II monotherapy study of oxaliplatin for the treatment of CRC involving 134 patients, there were no reports of VTE events.[17] The literature suggests that chemotherapy may increase VTE risk in patients with cancer.[18] The augmented risk is multifactorial. Chemotherapeutic agents can compromise the vascular endothelium, culminating in hindered blood flow and intravascular thrombus formation.[19] Concurrently, these medications can interfere with the body's anticoagulant framework, diminishing the efficacy of protein C and antithrombin III, thus escalating the propensity for VTE.[20] Additionally, the use of intravenous catheters may inflict damage on the vascular intima, decelerate the venous circulation and induce blood stasis, consequently amplifying the vulnerability to VTE. To conclude, DVT development in the present case can likely be ascribed to the synergistic impact of various contributory elements.

Implementing an exhaustive VTE risk assessment prior to chemotherapy initiation is essential, and the Khorana scoring system can be utilized to ascertain VTE risk among patients with cancer treated with chemotherapy.[21] This evaluation encompasses the cancer type, therapeutic regimen, and individual risk factors, including age, body mass, and VTE history. Established clinical practice guidelines delineate the management of cancer-associated VTE, advocating for prophylactic anticoagulation in individuals who are identified as high risk.[22,23] In instances where symptoms indicative of DVT emerge, such as edema, discomfort, or erythema in the limbs, an immediate clinical and diagnostic imaging review is imperative for diagnosis, which should be promptly succeeded by anticoagulation treatment, excluding contraindications. Individualized therapeutic strategies are requisite for patients who are at an increased risk of bleeding or those with unique clinical scenarios, potentially involving the selection of alternative anticoagulants or dose adjustments. The course of anticoagulation therapy demands regular surveillance of coagulation profiles, hepatic and renal function, and hemorrhage risk, necessitating adjustments that are contingent upon the therapeutic response and adverse effects. Importantly, educating patients about DVT prophylaxis and management is vital, accentuating the recognition of preliminary symptoms and the urgency of implementing immediate actions. The adept management of DVT in patients undergoing chemotherapy mandates a collaborative effort from a multidisciplinary health care team, including oncologists, vascular medicine specialists, clinical pharmacologists, and nursing professionals, to ensure a holistic approach to treatment and support.

Conclusions

In conclusion, this analysis underscores the importance of raising awareness among medical practitioners regarding lower limb DVT induced by chemotherapeutic agents. Emphasizing prompt identification, immediate intervention, and sustained prophylaxis is crucial. Implementing this comprehensive management approach aims to significantly reduce DVT prevalence and improve therapeutic outcomes and patients' quality of life.

Ethics statement

The patient has given his written informed consent for this case report to be published.

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CRediT authorship contribution statement

Yinghui Ju and **Yue Zhu** (Co-first authors): Conceptualization, Methodology, Case Investigation, Writing – Original Draft Preparation, Writing – Review & Editing. **Gaochao Zhu** and **Menglin Wang**: Visualization, Writing – Review & Editing. **Rui Wu** (Corresponding author): Supervision, Project Administration, Writing – Review & Editing, Final Responsibility for Submission. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of competing interest

The authors declare no conflict of interest.

Declaration of generative AI and AI-assisted technologies in the writing process

No AI tools/services were used during the preparation of this work.

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