Case Report

Chemotherapy-Related Cerebral Venous Sinus Thrombosis in a Colon Cancer Patient Receiving Adjuvant Chemotherapy: Case Report and Literature Review

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Oxaliplatin-combination treatment has been adopted as a standard adjuvant treatment for high-risk stage II and stage III colorectal cancer. Cerebral venous sinus thrombosis (CVST) is a serious adverse event related to this combination treatment. The benefits of this combination treatment outweigh the risks, yet some physicians are reluctant to resume the treatment after the clot has resolved. The authors reported a case of CVST, and the success in resolving this situation with the use of a secondary prophylaxis, a low-molecular weight heparin.

Keywords: Oxaliplatin; Central venous sinus thrombosis; Chemotherapy-induced VTE

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Cerebral venous sinus thrombosis (CVST) is a lethal thrombosis of the dural sinus or cerebral veins. There is no uniform management for this condition in different circumstances. However, anticoagulation therapy has been accepted as the general concept of treatment to prevent thrombus growth and facilitate recanalization. In the present case, anticoagulant was provided even though there was an obvious evidence of hemorrhagic transformation. There are many risk factors that can cause this deadly disease such as contraceptives, pregnancy, infection, and cancer, with cancer being the most common risk factor associated with this disease in patients older than 50 years-old[(1)]. The authors reported the combination oxaliplatin-based chemotherapy as a risk factor of CVST after excluding predisposed risk for thrombosis. After recognizing that the combination treatment may cause CVST, it is difficult to decide whether to continue administering the treatment that is beneficial in preventing cancer.

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Case Report

The authors reported a case of a 63-year-old woman who developed CVST during chemotherapy treatment for colorectal cancer. She presented with bleeding per rectum for three months. Colonoscopic examination revealed a mass at the rectosigmoid colon, 10 to 15 cm from the anal verge. Initial workups for the disease staging included computerized tomography of the whole abdomen and thoracic regions. There was no metastatic lesion. A low-anterior resection operation was performed with no complication. The pathological report revealed rectal adenocarcinoma with moderate differentiation. There was an early extension of the cancer to the subserosa and the metastatic carcinoma was detected in 5 out of 20 resected lymph nodes. One of the nodes had an invasion in the perinodal soft tissue. After the surgery, the patient had a good physical fitness and normal hepatic and renal functions, so, the authors administered a combination adjuvant chemotherapy composed of Oxaliplatin (Eloxatin®), 5-fluorouracil (5-FU), and folinic acid (FA) as per the standard protocol for the treatment of colon cancer. The FOLFOX4 regimen was administered as intravenous (IV) infusion of Eloxatin® (85 mg/m^2) for two hours on day 1, IV infusion of FA

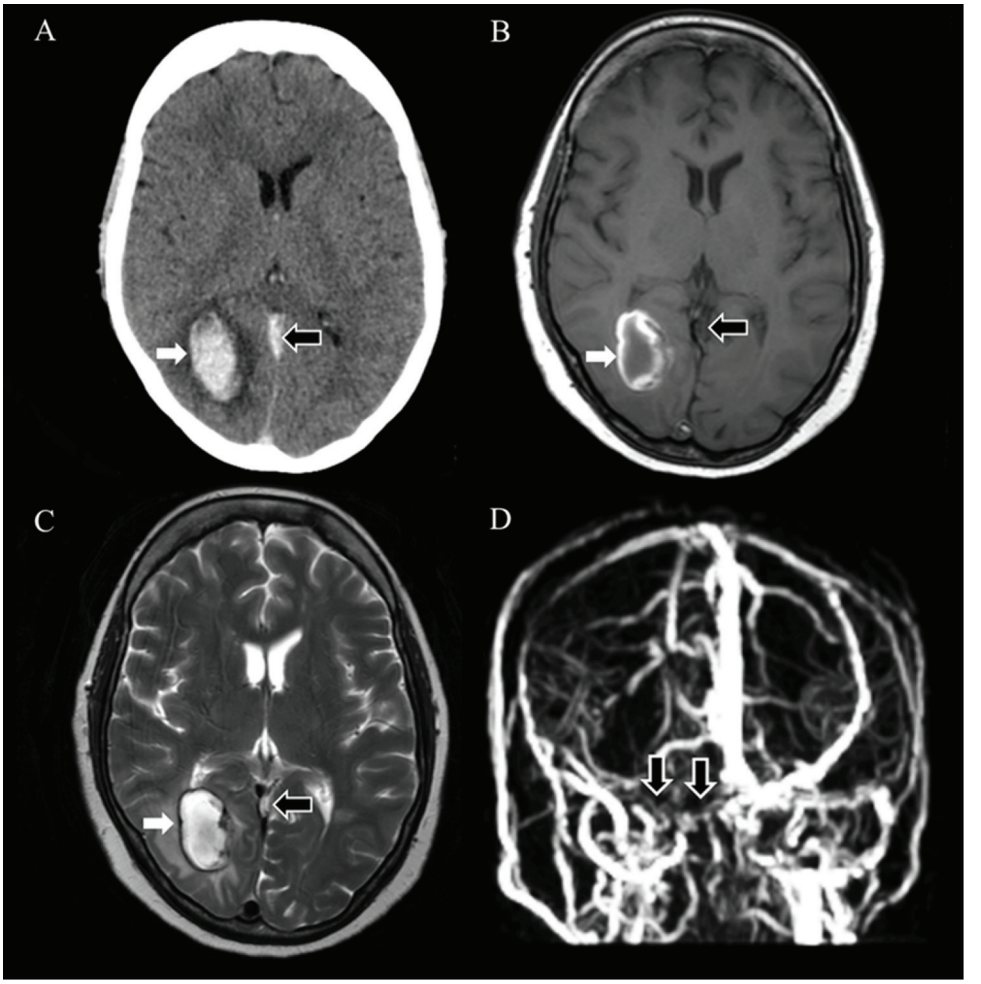

Figure 1. Axial unenhanced CT image (A) at the initial presentation showed an acute thrombus in the straight sinus (black arrow) and an acute hematoma in the right occipital lobe (white arrow). Axial T1-weighted MR image (B) and axial T2-weighted MR image (C) 1-month later showed a thrombus in the straight sinus (black arrow) and a subacute hematoma in the right occipital lobe (white arrow). Coronal reformatted image from contrast-enhanced MR venography (D) showed a filling defect in the right transverse sinus (black arrow) which is consistent with findings of thrombosis.

(200 mg/m²) for two hours on days 1 and 2, short infusion of 5-FU (400 mg/m²) on days 1 and 2, and continuous IV of 5-FU (600 mg/m²) for 22 hours on days 1 and 2. The patients did not report any acute chemotherapy-related complication after the first three cycles of the treatment. Four days after the third cycle of treatment, she suddenly developed an alteration of consciousness. Initial CT brain revealed an acute thrombus along the posterior half of the superior and inferior sagittal sinus extending to the straight sinus, right transverse, and right sigmoid sinuses. She also had an acute hematoma in the right occipital lobe, compatible with extensive dural venous sinus thrombosis and hemorrhagic venous infarction (Figure 1A). The authors started a bolus and continuous drip of heparin. Her symptoms recovered rapidly, and there were minimal residual neurological deficits. Heparin was then switched to subcutaneous low-molecular weight heparin (LMWHs) twice a day, the dose was adjusted by body weight. At 1-month follow-up, the magnetic resonance (MR) imaging brain (Figure 1B, C) and MR venography (Figure 1D) revealed the radiographic improvement with interval recanalization of the venous sinus thrombosis. After recovery from CVST, the plan was to continue the adjuvant chemotherapy for colorectal cancer, but the results of other thrombotic risk factors were still pending. The authors considered the possibility of chemotherapy-related deep vein thrombosis from Eloxatin®. After weighing the benefits of

combination adjuvant therapy and risk of recurrent thrombosis, the authors continuously administered LMWHs (Enoxaparin) once a day after four weeks of treatment was completed. The authors then decided to continue the triple therapy of Eloxatin®, 5-FU/FA for eight cycles with concurrent chemoradiotherapy and bolus 5FU/FA between the fourth and fifth cycles. Twenty-four weeks after the onset of CVST, the results of protein C, protein S level, factor V leiden, prothrombin gene mutation, and antiphospholipid syndrome were all negative. Secondary prophylaxis for CVST using LMWHs was discontinued after the completion of chemotherapy. After a follow-up period of six years, there was no evidence of recurrent venous thromboembolism (VTE) or relapse of the disease. The authors had demonstrated the safety of continuing LMWHs as the secondary prophylaxis for chemotherapy-related CVST.

Discussion

Eloxatin® is a second-generation platinum-based drug. It is used in combination with infusion of 5-FU and FA (FOLFOX4). This adjuvant therapy has been approved to treat stage II/III colorectal cancer because of its efficacy has been shown to be superior to LV5FU2 regimen in the MOSAIC study [infusion of LV (200 mg/m²) for two hours followed by bolus 5-FU (400 mg/m²), and infusion of 5-FU (600 mg/m²) for 22 hours for two consecutive days every two weeks][2]. Eloxatin® blocks the DNA synthesis by causing intra strand cross-links in the DNA, which is its major cytotoxicity property. Among several side effects of Eloxatin®, VTE in the setting of adjuvant colorectal cancer was rarely reported. VTE had been reported in 9% of advanced colorectal patients on FOLFOX4 and 4% of advanced colorectal patients on LV5FU2. For the present case, besides the chemotherapy and colon cancer, the authors had excluded other hereditary and secondary thrombotic risks. The incidence of CVST in colon cancer is unknown, but it is extremely rare. The event that occurred after a short period of adjuvant chemotherapy was consistent with VTE-related chemotherapy[3]. The authors then concluded that, FOLFOX4 was the most possible risk factor correlated with this fatal thrombosis.

VTE in various cancer types have been reported in several studies[4-8]. The VTE risk increases in concomitant advanced stage of disease and is augmented by additional risk of treatment procedure such as surgery or chemotherapy. The hypercoagulable stage and presence of intracranial metastasis were proposed as the pathogenesis of VTE in active solid cancer[9]. The life expectancy of cancer patients with VTE is relatively short, due to death from recurrent VTE or the cancer itself. The balance of treatment to overcome both conditions in the present case was conflicting among the treating clinicians. LMWHs were recommended because it is more effective in preventing VTE and had less bleeding complication compared to oral vitamin K antagonists[10]. In a randomized control study of pediatric CVST, a novel anticoagulant, rivaroxaban, had an efficacy of 78% in recanalizing the sinus compared to the standard anticoagulant (74%)[11]. The duration of the secondary prophylaxis for VTE in cancer patients is controversial, for at least six months, and the evidence is mainly limited to deep vein thrombosis or pulmonary embolism. The lack of supporting evidence for secondary prophylaxis in this rare fatal thrombosis is not the only issue for clinicians but also the possibility of continuing the suspicious agents. In the present case, Eloxatin®, 5-FU and LV were the mainstay of adjuvant stage III colorectal cancer treatment. The authors reviewed the management of cancer treatment-related CVST in PubMed database and Google Scholar. This condition is a classic complication of the L-asparaginase therapy, where the prevalence was 3.1%, via the inhibitory effect of L-asparagine-dependent hemostatic protein, particularly plasma anti-thrombin level. The management of chemotherapy-related CVST includes interruption of treatment and maintenance of anticoagulation for at least six months[12]. CVST has been sporadically reported with various chemotherapeutic agents such as tamoxifen[13], cisplatin-based combination chemotherapy[14-17], combination Irinotecan/5-FU/LV, and bevacizumab[18]. In these reports, the clinical manifestation was similar to CVST developed from other risk factors[1]. Some clinicians declared to withhold the suspected hormone or chemotherapy, while others did not. However, there have been case reports of continuing the suspected drugs administered concurrently with anticoagulant, which showed good efficacy as a secondary prophylaxis[19].

Conclusion

Secondary prophylaxis of low-molecular weight heparin is sufficient to prevent a recurrence of oxaliplatin-associated CVST.

What is already known on this topic?

Combination oxaliplatin-based chemotherapy

had been reported as a risk factor of venous thrombosis such as deep vein thrombosis, and pulmonary embolism. The strategy to continue the treatment concurrent with anti-coagulation has been widely accepted in general practice but is still equivocal for lethal central venous thrombosis.

What this study adds?

The efficacy of low-molecular weight heparin can be used to prevent secondary venous sinus thrombosis from oxaliplatin-based chemotherapy so that the physician can administer concurrent therapy. This combination treatment has been shown to be the most beneficial adjuvant treatment for colorectal cancer.

Ethical approval and consent to participate

The informed consent was obtained from the patient.

Conflicts of interest

The authors declare no competing financial interests.

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