Venous thromboembolism recurrence and intracranial hemorrhage in the cancer patient: A fatal course

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ABSTRACT

Objective: Venous thromboembolism (VTE), which encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE), represents a significant source of morbidity and mortality in individuals with malignancies. Thromboprophylaxis is commonly employed in the management of most cancer patients, with the most common side effect being bleeding. It is not uncommon for patients to experience a recurrence of VTE during their treatment, highlighting a notable gap in the available evidence on this issue.

Case: A 67-year-old male patient, actively undergoing chemotherapy for lung adenocarcinoma and initiated on low molecular weight heparin (LMWH) due to the development of PE, presented to the emergency department with DVT as a consequence of irregular use of anticoagulant injections. The patient, after being re-administered heparin, subsequently presented with intracranial hemorrhage on the 5th day post-discharge, ultimately leading to a fatal outcome.

Conclusion: Both cancer patients and the elderly are at a heightened risk of experiencing VTE recurrence. The initiation of anticoagulation treatment elevates the risk of bleeding, particularly within the first ten days. Despite the frequent presentation of VTE recurrence in cancer patients at emergency departments, it remains underreported.

Keywords: cancer; venous thromboembolism; low molecular weight heparin; intracranial hemorrhage

INTRODUCTION

The second most common cause of death after cancer is venous thromboembolism (VTE) (1). It has been observed that one in every four cancer patients requires readmission to the hospital due to the occurrence of venous thromboembolism (VTE) or severe bleeding (2). While surgery, immobilization, and genetic coagulation disorders are considered risk factors that significantly increase the risk of VTE in cancer patients, age, hormonal therapy, and chemotherapy have a synergistic effect (3, 4). The risk of bleeding is exceptionally high in the 5-10 days after heparinization and the first month following the initiation of anticoagulants. Therefore, physicians should closely monitor anticoagulant therapy in the first weeks of treatment in patients with cancer who are at high risk for bleeding (5).

Patients with cancer who have VTE, a condition associated with high mortality, also face an increased risk of bleeding due to anticoagulants. Managing these patients is very challenging due to numerous confounding factors. In this report, we present a case of pulmonary adenocarcinoma in a patient who was receiving low molecular weight heparin (LMWH) for pulmonary embolism (PE) but experienced VTE recurrence after missing a dose of LMWH. Tragically, the patient suffered intracranial hemorrhage and did not survive following re-heparinization.

CASE

A 67-year-old male patient, who received six cycles of carboplatin + paclitaxel treatment because he was diagnosed with lung adenocarcinoma eight months ago and who was treated with dexamethasone and phenytoin one month ago due to brain metastasis, was admitted to the emergency department with the complaint of edema in the right leg that had started the day before. He was hospitalized by the chest diseases service with the diagnosis of thromboembolism and parapneumonic effusion filling the left main pulmonary artery lumen five months ago, and enoxaparin sodium 6000 IU twice a day was prescribed subcutaneously to the patient when he was discharged.
However, he has not used his medicine for the last two days. On physical examination, an increase in diameter and color change was observed in the right leg. On arrival, his vital signs were as follows: blood pressure 100/65 mm Hg, heart rate 84 beats/min, respiratory rate 16 breaths/min, oxygen saturation 96%, body temperature 36.6 °C. In the blood tests of the patient, lymphocyte: 0.76x10^3/mm^3 (reference range, 1-5), platelet: 48x10^3/mm^3 (reference range, 150-500), d-dimer: 3910 ng/mL (reference range, 0-300), C-reactive protein: 6.64 (reference range, 0-0.5), except complete blood count, blood glucose level, liver function tests, renal function tests, including highly sensitive cardiac troponin-I were within normal limits.

The lower extremity diameters were as follows: right thigh 42.1 cm, left thigh 36.6 cm, right knee 40.1 cm, left knee 37 cm, right leg 31.6 cm, left leg 30.2 cm. The patient's score was 5.5, according to the WELLS scoring. Brain CT, pulmonary artery CT angiography, lower extremity arterial and venous Doppler US were ordered due to a previous history of pulmonary embolism and lung cancer with brain metastasis. No acute pathology was detected in CT scans nor arterial lower extremity Doppler US. However, Doppler US revealed that echoic thrombus material did not allow flow in the right external iliac, main femoral, superficial femoral, popliteal, and saphena magna in the venous lower extremity. 0.6 ml of enoxaparin was administered subcutaneously to the patient. The patient has been consulted for cardiovascular surgery and chest diseases. After four days of LMWH initiation in the chest diseases service, the leg's diameter difference regressed. He was discharged with the recommendation of using bemiparin sodium 7500 IU once daily.

The patient revisited the emergency department five days after discharge with complaints of inability to speak for several hours and decreased oral intake. On detailed physical examination, consciousness was in a stupor. Pupillary isochoric, direct, and indirect light reflexes are normal. Eye movements correlated, no nystagmus. There is no facial asymmetry. The gag reflex is intact; the uvula is in the midline. There was no lateralizing deficit in the muscle strength examination. The abnormal values in the laboratory tests of the patient were as follows: lymphocyte 0.51x10^3/mm^3, platelet 36x10^3/mm^3, d-dimer 1754 ng/mL, APTT: 44.7 sec (reference range, 20-28). Brain CT was requested because of the patient's neurological findings. Hemorrhagic metastatic lesions with predominantly hyperdense lesions and surrounding hypodense areas compatible with edema were detected in the bilateral white matter, the largest of which was in the right frontal region, measuring 41x37 mm. The patient was consulted for neurology, neurosurgery, and chest diseases. Dexamethasone 16 mg IV loading, 20% mannitol 300 ml IV bolus followed by 100 ml maintenance treatment four times daily, and the neurology department recommended intensive care follow-up. According to the recommendations of neurosurgery, 500 mg phenytoin IV in 100 ml isotonic solution for 30 minutes after loading, 100 mg maintenance treatment three times a day, and 4 mg IV dexamethasone four times a day maintenance treatment were started. The pulmonologists recommended short-term stopping of enoxaparin because of the continuation of the malignancy in the patient. The patient was transferred to the intensive care unit. After one day of intensive care follow-up, the patient died.

**DISCUSSION**

Cancer-associated VTE accounts for approximately 20% of the total VTE disease burden (6). While cancer can cause VTE, it is frequently seen that cancer is diagnosed after VTE or simultaneously with the diagnosis of VTE. In addition, cancer patients risk of recurrent VTE and anticoagulant-related bleeding and have high mortality (7, 8). Patients with lung, stomach, or pancreatic cancer will likely develop distant metastases within one year after a VTE attack (8). In our case, PE was detected after diagnosing Lung CA, and distant metastases developed within a few months. The close relationship between cancer and thrombosis, known for over a century, suggests that advanced cancer screening may be reasonable in patients with VTE. On the other hand, although thromboprophylaxis is generally recommended in hospitalized cancer patients, there is, unfortunately, no evidence to strongly support this recommendation (6, 9).

In addition to chronic medical comorbidities and major surgeries, the following prothrombotic mechanisms are responsible for the development of cancer-associated thrombosis: disruption of the fibrinolytic system, abnormal blood flow, vascular endothelial dysfunction, systemic hypercoagulability, thrombophilia, neutrophil extracellular traps, cell-surface proteases, inflammatory mediators such as IL6 (6, 10, 11). Many systemic antineoplastic treatments can also cause VTE (10).

As a result of the improvements in health care and technology, the human lifespan has been prolonged, leading to an increase in comorbid diseases. Individuals over the age of 65 have a high risk for both cancer and VTE (8). A recent study of cancer-associated VTE patients in Spain reported that direct oral anticoagulant use was more cost-effective than LMWH, and there was no difference between them regarding bleeding and providing a lower incidence of VTE (12). In a recent meta-analysis, the following conclusions were reached for appropriate anticoagulant therapy in VTE patients with cancer: direct oral anticoagulants have lower VTE recurrence and bleeding outcomes compared to vitamin K antagonists; They provide a lower risk of VTE recurrence with a higher risk of bleeding compared to LMWH. LMWH, on the other hand, has a similar bleeding rate, although it provides a lower VTE recurrence rate than vitamin K antagonists (13). At this point, many confusing issues about what the most appropriate treatment should be have been going on for years. The International Initiative on Thrombosis and Cancer 2022 update offers the following grade 1A or 1B recommendations for the treatment of cancer patients with VTE: LMWH use for the first ten days; In patients with low risk for gastrointestinal/ genitourinary bleeding and without strong drug-drug interactions, initiating direct oral anticoagulants and continuing for at least six months; 4 weeks of prolonged LMWH prophylaxis in patients at low risk of bleeding to avoid postoperative VTE after major abdominopelvic surgery; LMWH or direct oral anticoagulant (rivaroxaban/apixaban) for primary prevention in outpatients with locally advanced cancer or low bleeding risk metastatic pancreatic cancer under anticancer treatment (14). Ultimately, the currently recommended best treatment option to prevent
VTE recurrence in patients with cancer and VTE is as follows: unless there is severe renal failure, starting the first 5-10 days of treatment with LMWH is preferable to unfractionated heparin. LMWH and direct oral anticoagulants are preferred to vitamin K antagonists for long-term anticoagulation for at least six months (15).

Anticoagulation is the mainstay of treatment for VTE, which aims to prevent recurrence and mortality. The treatment should be individualized, considering patient compliance and risks. When the decision to treat LMWH is taken, a single dose of bemiparin may be preferred unless it is necessary to use enoxaparin twice a day (16). In the case we presented, it was observed that the daily administration of LMWH injections caused the patient to become bored with the treatment and delay it. The patient was using enoxaparin twice a day with the diagnosis of PE. DVT developed this time in the patient who did not receive his treatment regularly and was switched to a single dose of LMWH.

Treatment of cancer patients has many difficulties and complications. Although he is followed up in other departments and his treatment is arranged, cancer patients are admitted to the emergency department when their general condition deteriorates or they have acute problems. Therefore, the emergency physician should be familiarized with the complications of oncological diseases. VTE treatment in cancer patients is like a double-edged sword, a risk factor for bleeding by itself. All cancer patients under treatment should be examined in detail regarding bleeding and recurrence since they are more likely to have a mortal course.

CONCLUSION

Although VTE recurrence in cancer patients is frequently encountered in the emergency department, it is under-reported. However, its clinical importance and difficulties in treatment persist; an emergency physician should be qualified to recognize and manage the complications of oncological patients. Anticoagulant use and continuity should be questioned in cancer patients with a history of VTE. In addition, it should be well known that cancer patients have a high risk of both VTE and severe bleeding potential due to using anticoagulants, which may result in mortality.

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Ethical approval: The present study was conducted in strict accordance with the principles outlined in the Declaration of Helsinki. Ethical approval for the study was obtained from the appropriate ethics committee, and all participants provided informed consent before participating in the study.

REFERENCES