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ABOUT COVER

Peer Reviewer of *World Journal of Clinical Cases*, Luca Mezzetto, MD, Surgeon, Department of Vascular Surgery, University Hospital of Verona, Verona 37126, Italy. luca.mezzetto@aovr.veneto.it

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CASE REPORT

Challenging anticoagulation therapy for multiple primary malignant tumors combined with thrombosis: A case report and review of literature

Jia-Xin Chen, Ling-Ling Xu, Jing-Ping Cheng, Xun-Hua Xu

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Abstract

BACKGROUND

Venous thromboembolism significantly contributes to patient deterioration and mortality. Management of its etiology and anticoagulation treatment is intricate, necessitating a comprehensive consideration of various factors, including the bleeding risk, dosage, specific anticoagulant medications, and duration of therapy. Herein, a case of lower extremity thrombosis with multiple primary malignant tumors and high risk of bleeding was reviewed to summarize the shortcomings of treatment and prudent anticoagulation experience.

CASE SUMMARY

An 83-year-old female patient was admitted to the hospital due to a 2-wk history of left lower extremity edema that had worsened over 2 d. Considering her medical history and relevant post-admission investigations, it was determined that the development of left lower extremity venous thrombosis and pulmonary embolism in this case could be attributed to a combination of factors, including multiple primary malignant tumors, iliac venous compression syndrome, previous novel coronavirus infection, and inadequate treatment for prior thrombotic events. However, the selection of appropriate anticoagulant medications, determination of optimal drug dosages, and establishment of an appropriate duration

of anticoagulation therapy were important because of concurrent thrombocytopenia, decreased quantitative fibrinogen levels, and renal insufficiency.

CONCLUSION
Anticoagulant prophylaxis should be promptly initiated in cases of high-risk thrombosis. Individualized anticoagulation therapy is required for complex thrombosis.

Key Words: Venous thromboembolism; Cancer-associated thrombosis; Anticoagulation therapy; iliac vein compression syndrome; COVID-19; Thrombocytopenia; Case report

Core Tip: Lung cancer and pancreatic cancer form a rare combination of multiple primary malignant tumors. This patient had a rare lower extremity venous thrombosis complicated by pulmonary embolism. Its causes included a history of various malignant tumors, recent novel coronavirus infection, insufficient anticoagulant therapy for previous lower extremity thrombosis, and iliac vein compression syndrome. Anticoagulant therapy poses challenges to patients with active cancer and reduced fibrinogen levels; abnormally elevated D-dimer levels; and decreased platelet counts. This article provides a comprehensive overview of the therapeutic options for anticoagulation.

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INTRODUCTION

Venous thromboembolism is a leading cause of patient deterioration and mortality. The management of anticoagulant therapy for this condition is inherently complex, requiring careful consideration of various factors including bleeding risk, dosage and type of anticoagulants, and duration of treatment. Patients at high risk of thrombosis should receive prompt anticoagulation prophylaxis.

We present a case of venous thrombosis in the lower extremities and pulmonary embolism caused by an active tumor, iliac vein compression syndrome, history of novel coronavirus infection, and previous thrombosis that was inadequately treated. This case poses challenges for anticoagulation treatment, and we have provided a review of the relevant literature.

CASE PRESENTATION

Chief complaints

An 83-year-old female patient complained of edema in her left lower extremity for the 2 wk, which had worsened over the last 2 d.

History of present illness

A 2-wk history of swelling in the left lower extremity, which worsened in the last 2 d without dyspnea or chest pain.

History of past illness

The patient had a history of novel coronavirus infection 6 months prior and venous thrombosis in the right lower extremity (administered oral edoxaban tablets for 2 months but discontinued on her own). No blood clots were observed on ultrasound examination of either lower limb after treatment discontinuation. Two months prior, she was diagnosed with non-small cell lung cancer, pancreatic ductal adenocarcinoma, and metastasis to the liver and right inguinal lymph node. Her current treatments included oral tegafur, gimeracil, and oteracil potassium + almonertinib mesilate tablets. Routine blood tests, liver function tests, renal function tests, and coagulation results were normal.

Personal and family history

The patient denied any relevant family history.

Physical examination

Severe swelling in the left lower extremity. A few scattered petechiae were observed in the skin and mucosa.

Laboratory examinations

The patient's platelet count was 75×10^9/L↓, D-dimer (DD) 80.55 mg/LFEU↑, fibrinogen (FIB) 1.86 g/L↓, creatinine 84.9 μmol/L↑, and her liver function was within normal limits.

Imaging examinations

Double lower extremity vascular ultrasound indicated venous thrombosis in the left iliac, femoral, and popliteal veins. The patient underwent inferior vena cava venography, pulmonary arteriography, and lower extremity venography (Figure 1A).

FINAL DIAGNOSIS

Pulmonary artery embolism, left lower extremity venous thrombosis, left iliac vein compression syndrome, thrombocytopenia, renal insufficiency, non-small cell lung cancer, and pancreatic ductal adenocarcinoma.

TREATMENT

The patient discontinued her current treatment (oral tegafur, gimeracil, and oteracil tablets) and underwent percutaneous transcatheter pulmonary artery aspiration thrombectomy, inferior vena cava filter placement, percutaneous transcatheter lower extremity vein aspiration thrombectomy, venous balloon dilation angioplasty of the lower extremity, and stenting of the iliac vein (Figure 1). The patient declined edoxaban tablets due to palpitations and elevated blood pressure. Consequently, she was prescribed apixaban tablets (2.5 mg/dose, Q12h, orally) as anticoagulation therapy following surgery.

OUTCOME AND FOLLOW-UP

Following postoperative re-examination, lower extremity vascular ultrasound revealed venous thrombosis in the distal end of the left femoral and popliteal veins. Additionally, the platelet count was 79×10^9/L, CA199 2.40 U/mL, and DD 8.67 mg/LFEU. The dose of apixaban was adjusted to 5 mg Q12h, and tegafur, gimeracil, and oteracil were continue discontinued. DD and FIB after 4 months were re-examined (Table 1).

DISCUSSION

Coronavirus disease 2019 and venous thrombotic events

Both coronavirus disease 2019 (COVID-19) and long COVID-19 (also known as "acute sequelae of COVID-19") patients are susceptible to thrombotic disease due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis[1-4]. Thromboembolic complications resulting from COVID-19 have been extensively documented as primary contributors to sudden deterioration and mortality[5], highlighting the significance of prevention and early detection of thrombosis. The risk of thrombosis can be assessed by dynamically monitoring DD levels using various thrombus scoring tools, such as Caprini, Padua, and Improve[1,5,6]. Existing guidelines recommend that all COVID-19 patients who are not at a high risk of bleeding should receive anticoagulant prophylaxis[7-11]. The minimum duration of anticoagulant therapy for patients with venous thrombosis is 3 months[12].

In this case, the patient had COVID-19 infection 6 months prior. Anticoagulation prophylaxis was not administered during the infection period, and venous thrombosis of the lower extremities was identified within 1 month of recovery. The patient was prescribed anticoagulant therapy but discontinued after 2 months, which may have contributed to the occurrence of recurrent lower extremity venous thrombosis.

Iliac vein compression syndrome and venous thrombotic event

Iliac vein compression syndrome, also known as May-Thurner syndrome (MTS) or Cockett syndrome, is an anatomical variation resulting from compression of the left common iliac vein (LCIV) between the right common iliac artery and vertebrae[13]. While most cases are asymptomatic, compromised venous return and endothelial injury caused by chronic pulsatile compression of the LCIV by the right common iliac artery can occur, leading to subsequent obstruction and extensive deep vein thrombosis[14,15]. Venography is considered the gold standard for diagnosing MTS. MTS management involves alleviating LCIV compression and restoring normal blood flow through endovascular surgical intervention complemented by anticoagulation therapy[14,16]; this combination has been demonstrated to be an efficacious treatment for MTS[17]. The present patient was treated with this combination therapy.

Multiple primary malignant tumors and venous thrombotic event

Individuals with malignant tumors frequently have hypercoagulable blood and are prone to venous thrombotic events (VTEs). The incidence of VTEs varies across different cancers, with notably higher rates observed in pancreatic, gastric,

Table 1 The changes of indexes before and after operation were examined

Date	May 30, 2023, 13:00	May 30, 2023, 23:53	May 31, 2023	Operation	June 1, 2023	June 2, 2023	June 3, 2023	June 5, 2023	June 6, 2023	…	October 27, 2023
D-dimer (mg/L)	80.55	64.91	53.64	Operation	30.89	19.55	13.67	9.02	8.67	…	3.00
Fibrinogen quantification (g/L)	1.86	1.76	2.08	Operation	2.14	1.87	1.92	1.79	1.96	…	2.57

A notable reduction in the patient's postoperative D-dimer level was observed in comparison to the preoperative period.

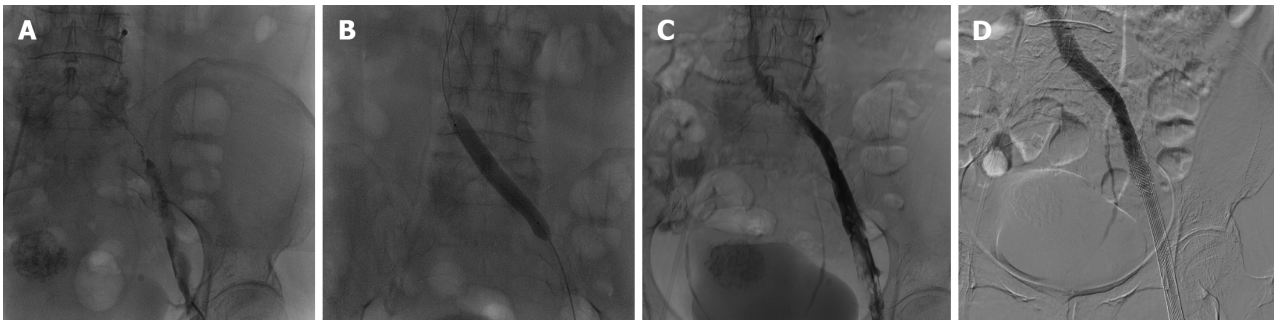

Figure 1 Contrast examination. A: Imaging *via* the left femoral vein. Contrast return into the inferior vena cava is obstructed. A filling defect (thrombus) is seen in the external iliac vein, the common iliac vein is thinned by compression, and the left lumbar ascending vein is visualized; B: Angiography after balloon dilation of the left common iliac vein; C: Post-balloon dilatation angioplasty imaging of the left common iliac vein. The contrast is seen to drain back into the inferior vena cava, but the common iliac vein is still markedly compressed. The external iliac vein and femoral vein are filled with defects (thrombi); D: Imaging after left common iliac vein-femoral vein stenting, with contrast converging into the inferior vena cava patently.

and lung cancers[18]. Furthermore, chemotherapy, radiation, and surgical interventions all elevate the risk of deep vein thrombosis (DVT)[19]. Specifically, the use of systemic chemotherapy has been associated with an 18-19-fold increase in VTE risk[20]. Moreover, cancer patients are at a higher risk of complications, including VTE recurrence and bleeding during VTE treatment, than those without cancer[19,21]. The absolute risk of developing subsequent VTE in patients with cancer with a history of VTE is 6-7-fold higher than that in patients without prior thromboembolic events[18]. The prevalence of DVT accompanied by pulmonary embolism has been documented to be relatively low, ranging from 29 to 78 cases per 100000 individuals annually. This prevalence increases with the presence of active tumors[22,23].

Venous thromboembolism ranks as the second leading cause of mortality among individuals with cancer[18,20]. It is advisable to provide thromboprophylaxis to all hospitalized cancer patients and high-risk outpatients, as determined by risk assessment models and computerized tools, in a timely and targeted manner. This approach aims to reduce the incidence of thrombotic events, enhance the prognosis of cancer patients, and ultimately improve survival. A recent article deliberating on the appropriateness of thromboprophylaxis for cancer outpatients suggested that barring a high risk of bleeding, initial thromboprophylaxis is recommended for individuals with pancreatic cancer and lung cancer who may harbor anaplastic lymphoma kinase/ROS proto-oncogene 1, receptor tyrosine kinase translocations. Patients with upper gastrointestinal cancers are at a higher risk of VTE; however, a thorough evaluation of bleeding risk should precede decisions regarding antithrombotic prophylaxis. Notably, for cancer patients with a heightened risk of bleeding, such as those with brain cancer, moderate-to-severe thrombocytopenia, or severe renal impairment, it is not advisable to pursue primary prevention of VTE. In cases where patients present with absolute contraindications for anticoagulation therapy, such as active bleeding or severe long-term thrombocytopenia, inferior vena cava filter implantation may be considered based on specific circumstances[24].

Substantial evidence has accumulated regarding the advantages of anticoagulant therapy in individuals with highly thromboembolic tumors[25,26]. The Prospective Randomized Trial of Enoxaparin and Chemotherapy Concurrently for Pancreatic Cancer was formulated to assess the effectiveness of enoxaparin in patients with locally advanced or metastatic pancreatic cancer undergoing systemic chemotherapy. The findings indicated a reduction in the prevalence of VTEs from 87.1% to 25.3% at 9 months, and from 13.5% to 12% at 15 months[25]. The administration of anticoagulant intervention in patients with pancreatic cancer resulted in a significant reduction in the incidence of VTE, from 23% to 3.4%[26].

A review of multiple clinical guidelines from American society of clinical oncology (ASCO), European society for medical oncology (ESMO), and national comprehensive cancer network (NCCN) states that low molecular weight heparin (LMWH) or normal heparin is the recommended standard of care for the prevention and treatment of cancer-associated thrombosis (CAT)[19,27-29]. LMWH is the preferred choice due to its lower risk of heparin-induced thrombocytopenia and convenient administration[27,30,31]. However, patients may experience an injection burden after hospital discharge, and direct oral anticoagulants are approved as alternatives to LMWH for the treatment of CAT[21,29]. According to the 2023 ASCO guidelines, apixaban is effective in reducing the risk of recurrent VTE and has a lower risk of

Table 2 Anticoagulation regimens in different situations

	Mode of administration	Initial therapeutic dose	Maintenance of therapeutic dose	Extended treatment dose
Unfractionated heparin	Intravenous	Maintain APTT 1.5 times the upper limit of normal	/	/
Low molecular heparin	Subcutaneous	200 IU/kg/d for 1 month	150 IU/kg	/
Rivaroxaban	Oral	15 mg each time, twice a day for 3 wk	20 mg each time, once a day	20 mg each time, once a day
Apixaban	Oral	10 mg each time, twice a day for 1 wk	5 mg each time, twice a day	2.5 mg each time Twice a day
Eldosaban	Oral	At least 5 d of heparin introduction is required, with dose reduction after LMWH introduction, *i.e.* 30 mg each time, once a day	60 mg each time, once a day	60 mg each time, once a day

LMWH: Low molecular weight heparin; APTT: Activated partial thromboplastin time.

major bleeding. Additionally, a panel of experts agreed that apixaban could be recommended as an alternative treatment for CAT[19]. However, the CHEST guidelines update article published in 2021 indicated that oral Xa inhibitors (apixaban, edoxaban, and rivaroxaban) are more strongly recommended than LMWH for treatment initiation in patients with acute VTE and cancer-associated thrombosis (strong recommendation, moderate quality evidence)[32].

However, an article published in 2016 in *Lancet* suggested that direct oral anticoagulants should not be the first choice for VTE in patients with active cancer, although there are no contraindications[33]. The use of LMWH or oral anticoagulants in the acute phase remains controversial; further large-scale clinical trials are needed. In this case, an oral anticoagulant was used immediately after interventional therapy. However, the dose of anticoagulant was insufficient; the therapeutic effect on CAT could not achieve the ideal effect in theory.

Thrombocytopenia frequently leads to the discontinuation of anticoagulation therapy in cancer patients. Therefore, the guidelines recommend that patients with platelet counts ≥ 50×10^9/L receive full-dose anticoagulation (whether with using LMWH or an oral anticoagulant) without concomitant platelet transfusions[34-36]. CAT therapy typically consists of three phases: acute (occurring 5-10 d after diagnosis), maintenance (lasting 3-6 months), and extended phase (lasting > 6 months). In patients with active cancer undergoing cancer therapy, where the risk of recurrence outweighs bleeding complications, an extension of anticoagulation therapy for > 6 months may be considered. The recommended anticoagulation therapies for each period are presented in Table 2 Unfractionated heparin is recommended for patients with severe renal insufficiency (CrCl < 30 mL/min) because of the elevated risk of hemorrhage and recurrent venous thrombosis associated with anticoagulant therapy[29].

In conclusion, the patient was in the acute stage of thrombosis at present. However, considering advanced age; thrombocytopenia; renal insufficiency; presence of a few scattered petechial dots on the skin and mucosa; and the slightly higher risk of anticoagulant bleeding in this patient, interventional therapy and apixaban (2.5 mg twice a day) were initially administered. After observation, petechiae in the skin and mucosa did not progress; the DD was 13.67 mg/L; and there was still thrombus on the reexamination using color Doppler ultrasound. The effect of anticoagulant therapy was considered to be unsatisfactory. Therefore, the dose of apixaban tablets was adjusted to 5 mg twice a day. The deficiencies in the treatment of the low-risk thrombocytopenia in this patient include: Receiving no anticoagulant prophylaxis. In addition, the dose of anticoagulant therapy was slightly lower than the recommended dose according to the guidelines. After follow-up, DD in the patient was significantly decreased. Furthermore, no more serious bleeding events occurred, which also indicated that the combined treatment scheme in this case was feasible; anticoagulant therapy was safe and effective.

Paradoxical manifestation of DD and FIB

FIB plays a crucial role as a reactive substrate in thrombosis and is implicated in critical stages[37]. DD, a small protein fragment resulting from fibrin breakdown, has been the subject of research as a predictive biomarker for VTE in cancer [18,38]. Elevated DD and FIB levels are commonly observed in patients with COVID-19 and those with malignancy[5]. The decrease in FIB is common in patients with primary and secondary hyperfibrinolysis, such as DIC. Additionally, impairment in liver cell function leads to the decrease in liver synthesis, snake venom therapy, and thrombolytic therapy. In conjunction with the present case, the patient in question had a tumor and experienced VTEs. In such cases, DD and FIB should be theoretically elevated; however, this patient exhibited abnormally elevated DD, low FIB levels, and a decreased platelet count. When considering the patient's history of a normal coagulation phase, it is reasonable to suspect the presence of DIC and a reduction in FIB due to the substantial consumption of FIB within the body.

CONCLUSION

In summary, patients with active cancer, chemotherapy, novel coronavirus infection, and iliac vein compression syndrome should be on high alert for venous thrombosis. This requires dynamic assessment of anticoagulation and bleeding risks; comprehensive management; reduction in thrombotic events; preventing bleeding complications and recurrence; and improvement in prognosis.

FOOTNOTES

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Co-corresponding authors: Jing-Ping Cheng and Xun-Hua Xu.

Author contributions: Chen JX and Xu LL contributed to manuscript writing and editing, and data collection; Cheng JP and Xu XH were responsible for conceptualization, supervision and communication contacts. All authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. The reasons for designating Cheng JP and Xu XH as co-corresponding authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-corresponding authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, the overall research team encompassed authors with a variety of expertise and skills from different fields, and the designation of co-corresponding authors best reflects this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, Cheng JP and Xu XH contributed efforts of equal substance throughout the research process. The choice of these researchers as co-corresponding authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Cheng JP and Xu XH as co-corresponding authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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