CASE REPORT

A 52-year-old-male patient with metastatic non-small-cell lung cancer and recurrent venous thromboembolism in unusual sites despite anticoagulation

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SUMMARY

The link between cancer and venous thromboembolism is well known, with an annual incidence rate of venous thromboembolism between 0.5% and 20% depending on the primary site and background risk factors. Current guidelines suggest treatment with low-molecular-weight heparin over oral vitamin K antagonists. However, data regarding the management of recurrent venous thromboembolism when the patient is under treatment with anticoagulants are sparse. In this article we present a patient with multiple thromboembolic events in unusual sites despite anticoagulant treatment and we discuss the management options.

BACKGROUND

Patients with cancer are in a hypercoagulable state.^{1 2} The pathophysiology of malignancy-related hypercoagulability is multifactorial: tumour-related factors include the production of tissue factor-bearing microparticles³ and cancer procoagulant from tumour cells,⁴ the primary site and the presence of metastases among others.¹ The patient-related factors include restriction of patients' mobility, advanced age, indwelling central venous catheters and the use of drugs such as erythropoiesis-stimulating agents and certain anti-neoplastic agents such as cisplatin.^{5 6} Here we present the case of a male patient with metastatic lung adenocarcinoma with multiple thromboembolic events in unusual sites despite continuous and adequate treatment with low-molecular-weight heparin (LMWH) and we discuss the management of such patients based on current evidence.

CASE PRESENTATION

A 52-year-old male patient with an unremarkable medical history and a smoking history of 65 pack-years was in his usual state of health until he was admitted to another hospital for further evaluation of left flank pain. A CT scan of the abdomen revealed a haemorrhagic left adrenal mass and additional imaging studies revealed enlarged mediastinal lymph nodes and nodules in the upper lobe of the right lung (figure 1). A biopsy was performed via mediastinoscopy, as endobronchial ultrasound-guided mediastinal biopsy is not available at our institution. The pathological diagnosis was poorly differentiated adenocarcinoma, with sheets of undifferentiated tumour cells with a solid growth

pattern and scant, poorly formed glands. The tumour was immunohistochemically positive for cytokeratin (CK)7 and negative for CK20, thyroid transcription factor-1 and p63, epidermal growth factor receptor wild type. According to the American Joint Committee on Cancer staging 7th edition, the patient was staged as T3N2M1.

One month later he was diagnosed with unilateral distal deep vein thrombosis and therapeutic dose tinzaparin was initiated. He also received chemotherapy, with a cisplatin and docetaxel combination. The next month the patient developed right upper limb and facial oedema and distention of the right chest wall veins. A chest CT scan revealed thrombosis of the right subclavian vein and submassive pulmonary embolism. Testing for anti-Xa activity was within target range. One month later the patient developed worsening left lower limb oedema, which was caused by proximal deep vein thrombosis. Also, imaging studies revealed progressive disease on his right adrenal. As his tumour was tested positive for overexpression of anaplastic lymphoma kinase via immunohistochemistry, treatment with crizotinib was initiated.

Two months later the patient presented with abdominal pain, vomiting and peritoneal signs on physical examination. A CT scan was diagnostic for a superior mesenteric artery and vein obstruction (figure 2). Considering his deteriorating performance status, he was treated with intra-arterial papaverine infusion, leading to significant clinical improvement. Further imaging was indicative of disease progression so the patient was enrolled in a

Figure 1 Chest CT of the patient, initial presentation.

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Figure 2 Abdominal CT: mesenteric artery thrombosis.

clinical trial (Cabazitaxel in Relapsed and Metastatic NSCLC, NCT01852578).

The following month the patient presented with a rapidly growing neck mass, caused by right internal jugular vein thrombosis while still under LMWH treatment (figure 3). Chemotherapy was stopped because of further disease progression, including the development of brain metastases.

INVESTIGATIONS

Owing to the recurrent nature of the thromboembolic events, the patient was screened for inherited thrombophilia. Genetic

Figure 3 Jugular vein thrombosis.

testing via PCR for factor V Leiden, prothrombin G20210A mutation and MTHFR 677C→T variant (methylenetetrahydrofolate reductase) were negative. Also, levels of antithrombin and protein C were normal but protein S levels were low, probably reflecting the acute thromboembolic event at the time of testing. Furthermore, the patient was tested for the presence of antiphospholipid antibodies: IgG and IgM anticardiolipin antibodies were negative and IgG and IgM anti-β₂-glycoprotein-I antibodies were low positive, thus the patient did not fulfill the Sapporo criteria for the diagnosis of antiphospholipid syndrome.

TREATMENT

The patient was initially treated with tinzaparin 18 000 anti-Xa IU/day, a therapeutic dose of approximately 175 IU/kg. After the first recurrence of venous thromboembolism (VTE) at the subclavian vein, he was tested for anti-Xa activity which was found to be 1.0 IU/mL, within the target range, and the dose remained the same. Following the next recurrences (lower extremity, mesenteric vessels, jugular vein) the dose was kept at 18 000 IU/day, corresponding to an increase of 120–150% due to weight loss. The patient was encouraged to wear graduated compression stockings and glove but his compliance was poor. Also, placement of a vena cava filter was deemed not to be beneficial due to the sites of VTE so it was not performed.

OUTCOME AND FOLLOW-UP

A few days after the diagnosis of the jugular vein thrombosis, marked thrombocytopenia was noted without anaemia or leukopenia, with a hypercellular marrow, normal clotting times and no clinical or laboratory clues indicating disseminated intravascular coagulation or thrombotic thrombocytopenic purpura. Also, the time of onset of the thrombocytopenia (months after the initiation of LMWH), the degree of the thrombocytopenia (platelet level <10 000/μL) and the accompanying bleeding rather than new thrombotic events pointed away from heparin-induced thrombocytopenia. Prednisone at a dose of 1 mg/kg was initiated and LMWH was discontinued but 3 days later he developed profound haematochezia. Despite supportive measures, refractory hypovolaemic shock developed and the patient died the next day, 8 months after the initial diagnosis of metastatic lung adenocarcinoma.

DISCUSSION

Treatment with LMWH has been shown to decrease the risk of recurrence of VTE and improve survival among non-metastatic patients compared to warfarin, with a recurrence rate despite treatment with LMWH of 9% over a period of 6 months.⁷ Tinzaparin, which was used to treat our patient, is currently under evaluation in a prospective trial (Long-Term Innohep Treatment vs a Vitamin K Antagonist for the Treatment of Venous Thromboembolism in Cancer, NCT01130025). Since patients with cancer are a heterogeneous group, a clinical prediction rule to determine the risk of VTE recurrence has been developed.⁸ If a patient with cancer presents with recurrent VTE despite anticoagulation, he should be assessed for malignancy-related venous compression, poor compliance or the development of heparin-induced thrombocytopenia if he is receiving LMWH.²

Data regarding the treatment of patients with cancer with recurrent VTE are sparse. The optimal therapeutic approach of these patients has not been evaluated in prospective randomised trials. In a retrospective study, patients with recurring VTE despite treatment with therapeutic dose LMWH were treated

with dose escalation to 120% of the therapeutic dose, a reasonable approach that resulted in only 8.6% of the patients recurring for a second time, without an increase in bleeding risk.⁹ In the recent update of the American Society of Clinical Oncology guidelines the treatment options include an alternate anticoagulation regimen if the patient was receiving vitamin K antagonists, increased LMWH doses and the addition of a vena cava filter.² Switching from LMWH to vitamin K antagonists or to another LMWH is not supported by current evidence. Furthermore, there are no data concerning the management of further recurrence of VTE.² Our patient was treated with a LMWH dose of 120–150% of the therapeutic dose after his second recurrence and experienced multiple episodes of recurrent VTE despite achieving optimal antifactor Xa activity.¹⁰ The role of newer anticoagulants in the treatment of VTE in patients with cancer is yet to be clarified.²

In conclusion, we presented a case of a patient with metastatic lung adenocarcinoma who exhibited recurrent VTE despite treatment with LMWH and briefly reviewed available data concerning the management of such patients. The scarcity of such data underscores the clearly unmet need of further randomised trials which establish the optimal treatment options for this patient subgroup.

Learning points

- ▶ Venous thromboembolism is a common complication among patients with cancer.
- ▶ The treatment of choice for malignancy-related thromboembolic events is low-molecular-weight heparin; heparin-induced thrombocytopenia remains a concern.
- ▶ Nine per cent of patients under therapeutic doses of low-molecular-weight heparin had recurrent thromboembolism in one trial.
- ▶ Treatment options for recurrent thromboembolism despite adequate anticoagulation are not based on prospective randomised trials.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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