Should a diagnosis of cancer impact the anticoagulant therapy in patients with recurrent thromboembolic disease?

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ABSTRACT

Venous thromboembolism often coexists with cancer, deteriorating patient prognosis. The diagnosis of cancer in patients who suffer from venous thromboembolism may lead to changes in the anticoagulant therapy administered. We present a case report involving a 72-year-old patient with recurrent venous thromboembolism and chronic thromboembolic pulmonary hypertension in whom the diagnosis of colorectal cancer resulted in the need for modification of the anticoagulant therapy. Oral anticoagulant was replaced with low molecular weight heparin and an inferior vena cava filter was implanted due to active bleeding from the anus, high perioperative risk of bleeding, which caused the need for a temporary interruption of anticoagulant therapy.

KEY WORDS: venous thromboembolism, cancer, anticoagulation, vena cava filter implantation

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INTRODUCTION

The association between venous thromboembolism (VTE) and cancer is a well-researched one. The risk of VTE is 4-fold higher in cancer patients than in the general population [1], and it is the highest in patients suffering from brain, pancreas, stomach, ovarian, colorectal, prostate, lung, and kidney cancers [2]. In the case of a previously diagnosed VTE, the presence of neoplastic disease renders patient prognosis poorer, increasing nosocomial mortality and long--term mortality alike [3]. Oncological patients have a higher risk of VTE recurrence as well as a higher risk of bleeding during anticoagulation [4]. Below, we present a clinical case of a patient with recurrent VTE and thromboembolic pulmonary hypertension in whom the diagnosis of colorectal cancer resulted in the need for modification of the anticoagulant therapy and implantation of an inferior vena cava filter.

CASE PRESENTATION

A 72-year-old female with recurrent pulmonary embolism, chronic thromboembolic pulmonary hypertension, and NYHA functional class III heart failure, receiving chronic oral anticoagulant treatment (warfarin), was admitted to the clinic for exacerbated exertion dyspnoea, general fatigue, lower limb oedema, loss of body weight, and bleeding from the anus, which began one week prior to hospitalization. Additionally, she had a few months' history of diarrhoea and constipation, microcytic iron deficiency anaemia (with the patient on iron supplements), and lumbar spine pain. Within half a year, she lost 5 kilos. Under physical examination, the patient's general condition was average, with RR of 104/70 mmHg, HR of 105/min, normal vesicular breath sounds over the lungs, and only few crepitations at the base of the right lung, while over the heart there was accentuated second heart sound over the pulmonary artery, and quiet systolic murmur in the sixth right intercostal space. There was also doughy oedema in both lower legs. The *per rectum* examination revealed a cauliflower-like tumour on palpation, involving the entire circumference of the rectum, and fresh blood in the stool.

CBC revealed no anaemia, with RBC 5.2 mln/mm^3, MCV 76 fl., HGB 12.4 g%, PLT 285 thousand/mm^3. Arterialized capillary blood gases revealed respiratory alkalosis, hypoxemia, and hypocapnia. The patient's INR was 5.7, APTT was 74 s, CRP was 0.94 mg/ml, and ESR was 3 mm/h, while the NT-proBNP was 2270 pg/ml. Kidney and liver functions were within normal limits.

Transthoracic echocardiogram revealed enlarged right atrium and right ventricle, right ventricular hypertrophy and its abnormal systolic function, signs of pulmonary hypertension with tricuspid valve pressure gradient (TVPG) of 79 mmHg, and dilated inferior vena cava with no collapsibility. The estimated right ventricular systolic pressure (RVSP) was 94 mmHg. The 6-item lower limb vein examination did not demonstrate any thromboembolic lesions in the proximal segment of the deep vein system. ECG revealed tachycardia, dextrogram, total right bundle branch block, sign of hypertrophy and overload of the right ventricle. Spiral chest CT revealed thromboembolic lesions in the distal segments of pulmonary arteries, dilated pulmonary artery trunk, enlarged right ventricle, and an abnormal > 1 right ventricle to left ventricle ratio. CT of the small pelvis revealed a rectal tumour, narrowing rectal lumen along a 71-mm-long segment, enlarged numerous lymph nodes of the small pelvis, and Th12 compression fracture, indicative of a metastatic lesion.

Warfarin was discontinued. Oxygen therapy and symptomatic treatment of the right ventricular heart failure (furosemide, spironolactone, oxygen therapy) were initiated. Due to the chronic thromboembolic pulmonary hypertension, with distal thromboembolic lesions, the patient received riociguat dosed at 3 × 2.5 mg. Once her INR went back to normal, subcutaneous enoxaparin dosed at 1 × 90 mg was included (the patient weight was 89 kg).

As the active rectal bleeding persisted in the patient with a chronic indication for anticoagulant therapy, and due to the planned invasive diagnostic procedures, involving withdrawal of the antithrombotic treatment, the Gunther Tullip temporary/permanent filter was implanted in the inferior vena cava. Low molecular weight heparin was administered in the perioperative period, with the treatment discontinued only on the day of harvesting colorectal mucosa specimens during colonoscopy. Based on the histopathology examination, a G2 rectal *adenocarcinoma* was diagnosed, staged as cT3N2M1. Over the following several days, symptoms of intestinal subileus emerged, rectal bleeding persisted, and packed red blood cells had to be transfused. The patient was disqualified from subileus stenting by a multidisciplinary medical team (cardiologist, oncologist, oncology surgeon) because of the location of the lesions. Instead, she was qualified for laparotomy with Paul Mikulicz double-barrelled colostomy, followed by small pelvis and spine radiotherapy. The procedure was performed with no complications. Once haemostasis had been obtained, the low molecular weight

heparin anticoagulant treatment was resumed. Subsequently, the patient underwent radiotherapy, involving the dose of 25 Gy in 5 fractions applied to the pelvic region, and 8 Gy applied to the spine. In the course of the follow-up, the patient remained classified as NYHA functional class III. The rectal bleeding and fatigue receded, and the patient gained 10 kg.

DISCUSSION

Presence of cancer in the case of a previously diagnosed VTE negatively affects patient prognosis, and increases both in-hospital and long-term mortality [3]. Patients suffering from VTE and cancer have a higher risk of VTE recurrence as well as a higher risk of severe bleeding episodes compared to non-oncological patients. In their 12-month-long prospective study of 842 VTE patients, including 181 subjects with concomitant cancer, Prandoni and collaborators demonstrated that oncological patients have a 3-fold higher risk of VTE recurrence than patients without cancer, and a 3-6-fold higher risk of significant bleeding in the course of oral anticoagulant therapy. The highest risk was associated with the first few months of therapy, and it would go up along with the neoplastic stage of advancement, while it was not found to depend on INR changes [4].

In accordance with the currently binding recommendations of the European Society of Cardiology, patients with VTE and cancer, following the acute period of disease, should receive low molecular weight heparin at a dose adjusted to their body mass for the first 3–6 months. Afterwards, anticoagulant therapy should be continued as chronic treatment or until the patient is free from cancer [5]. The recommendations are based on the results of two prospective studies. One of the multi-centre prospective randomised studies involved enoxaparin dosed at 1.5 mg/kg once daily in the acute period, and continued for the consecutive 3 months, with the second arm of the study receiving warfarin after the acute phase, with target INR of 2.0–3.0. Following 3 months of antithrombotic therapy, the warfarin group has experienced the composite endpoint (major bleeding and/or VTE recurrence) significantly more frequently than the group of patients treated with enoxaparin (21.1% vs 10.5% respectively; p = 0.04). There were no statistically significant differences in terms of overall mortality in the two arms [6]. The CLOT study involved dalteparin in the acute phase, dosed at 200 IU per 1 kg of body weight for 5–7 days, followed by acenocoumarol with target INR of 2.5 or dalteparin dosed at 200 IU per 1 kg of body weight once daily for one month, followed by 150 IU per 1 kg of body weight once daily for the subsequent 5 months. Six months into the anticoagulant therapy, the dalteparin group had a significantly lower risk of VTE recurrence than the oral anticoagulant study arm (9% vs 17% respectively; p = 0.002), while there was no statistically significant difference in terms of the bleeding rate (4% in the dalteparin arm, and 6% in the oral anticoagulant arm; p = NS). Similarly, no significant difference with respect to overall mortality was reported [7]. A Cochrane meta-analysis of 7 randomized studies, comparing long-term low molecular weight heparin treatment and oral anticoagulant therapy in VTE and cancer patients, demonstrated that prolonged LMWH treatment reduced the incidence of VTE recurrence (HR = 0.47; 95% CI: 0.32–0.71), without reducing the risk of major bleeding (HR = 1.05; 95% CI: 0.53–2.0) or impacting patient survival (HR = 0.96; 95% CI: 0.81–1.14) [8]. The risk of lower limb deep vein thrombosis is 2-fold higher in oncological patients, and the risk of pulmonary embolism is over 3-fold higher in that group as compared to the risk observed in patients undergoing surgery, in whom there is no concomitant neoplastic disease [9]. According to the current recommendations of ACCP (*American College of Chest Physicians*) and ESMO (*European Society for Medical Oncology*), cancer patients should undergo prophylactic perioperative treatment with low molecular weight heparin or unfractionated heparin [10, 11]. Low molecular weight heparin is equally safe and efficacious as unfractionated heparin [12]. LMWH is more convenient in use, and is less likely to result in thrombocytopenia, which is why it is considered as first-line perioperative treatment [11].

In the above described case of a patient with indications for chronic anticoagulation therapy for recurrent VTE and severe thromboembolic pulmonary hypertension, with active rectal bleeding and an expected perioperative interruption of the administered antithrombotic treatment, it made sense to consider the implantation of an inferior vena cava filter. Indications for IVC filter implantation in oncological patients are the same as in non-oncological VTE patients. The filter constitutes a mechanical barrier against the thrombus material, blocking its migration to the pulmonary arteries, and providing an additional barrier against pulmonary embolism. Presently, temporary filters are usually implanted, placed in the infrarenal inferior vena cava. The filter remains in the inferior vena cava indefinitely or until there are no indications for anticoagulation any longer, when it can be successfully and safely retrieved from the inferior vena cava [13].

The retrieval takes place a few weeks (ideally up to 12 weeks) following implantation, but cases of successful filter retrieval as late as 16 months following implantation have also been described in literature [14]. According to the currently binding guidelines of the American College of Chest Physicians (ACCP), IVC filter implantation should be considered in patients with acute VTE and absolute contraindications for anticoagulation or haemorrhagic complications in the course of the anticoagulation therapy [10]. These situations may occur, when the patient has:

1. a very high risk of bleeding, and there are absolute contraindications for anticoagulation, including haemorrhagic brain stroke and brain contusion
2. an active and uncontrolled bleeding from the digestive tract, urinary tract, genital tract or the central nervous system
3. a severe and persistent thrombocytopenia < 50 000 IU
4. a large primary tumour or CNS metastases
5. perioperative VTE.

Another clinical situation which may require IVC filter implantation is the recurrence of pulmonary embolism and/or lower limb deep vein thrombosis, regardless of the adequate anticoagulation therapy [10].

Candidates for IVC filter implantation should be carefully selected, taking into consideration patient risks and benefits. Routine IVC filter implantation is not recommended in patients at risk of pulmonary embolism recurrence, if they can undergo antithrombotic treatment. The above described management was evaluated in the *PREPIC* prospective study, involving 400 patients with proximal lower limb deep vein thrombosis at risk of VTE recurrence, treated with low molecular weight heparin or unfractionated heparin. The patients were randomized into two study arms. One study arm had an additional IVC filter implanted, while the other one didn't. In 12-day follow-up, 1.1% of patients with IVC filter, and 4.8% of patients without IVC filter ($p < 0.05$) suffered from symptomatic or asymptomatic pulmonary embolism. 2 years later, 37 (20.8%) IVC filter patients, and 21 (11.6%) patients without IVC filter ($p < 0.05$) experienced a recurrence of deep vein thrombosis. There was no difference with respect to overall mortality. The initial benefits from IVC filter implantation in DVT patients, stemming from a smaller rate of pulmonary embolism, are balanced out by the higher percentage of DVT episodes, with overall prognosis remaining unaffected [15]. Similar results were obtained 8 years into the follow-up period [16]. Hence, IVC filter implantation in VTE and cancer patients is not recommended in the absence of additional indications. In the past, it was suggested that it made sense to take extra precautions in patients with VTE and disseminated cancer, as their risk of VTE recurrence is much higher than in the non-oncological population, but the argument has never been confirmed. A retrospective study looked into the survival of 206 patients with cancer and VTE. The subgroups analysed included 62 patients who received anticoagulant treatment solely, 77 patients who only had an IVC filter implanted for different reasons, and 67 patients who received anticoagulant treatment and additionally underwent IVC filter implantation. Mean survival in the anticoagulant subgroup was 13 months, and it was significantly higher than in the IVC filter only subgroup (2 months) or in subgroup subject to anticoagulant treatment and IVC filter implantation (3.25 months; $p < 0.0002$) [17]. A prospective study examined the fact whether IVC filter implantation in VTE oncological patients treated with fondaparinux brings additional benefits. No additional benefits were reported in terms of treatment safety, recurrence of lower limb deep vein thrombosis, and pulmonary embolism recurrence over the 8 weeks of follow-up. Mean survival in the no-filter group was 493 days, and 266 days in the IVC filter group, but the difference was not statistically significant [18].

CONCLUSION

Patients with recurrent venous thromboembolism have indications for indefinite anticoagulant treatment. Diagnosis of cancer may result in the need for temporary or permanent modification of the anticoagulant treatment. In the perioperative period, treatment modification is necessary, involving low molecular weight heparin or unfractionated heparin. The planned invasive diagnostic procedures and treatment associated with a temporary withdrawal of anticoagulant treatment may require the implantation of an inferior vena cava filter. Clinical decisions regarding an optimum mode of antithrombotic therapy in oncological VTE patients will be impacted by the type of cancer, its location, stage of the disease, oncological treatment, risk of bleeding, and patient preferences. Hence, a multidisciplinary and individual approach to each and every patient is essential.

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