Case Report

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Rivaroxaban-induced chest wall spontaneous expanding hematoma

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Summary **Rivaroxaban is an oral direct Factor Xa inhibitor approved in the European Union and the United Sates for the single-drug treatment of several thromboembolic diseases in adults. It has been evaluated in large phase III clinical trials and has been found to have similar efficacy and safety with standard therapy. Herein, is described a very rare case of a rivaroxaban-induced spontaneous expanding chest wall hematoma, that required surgical intervention, in a breast cancer patient. Use of the Naranjo adverse drug reaction probability scale indicated a probable relationship (score of 7) between the patient's development of hematoma and treatment with rivaroxaban. Physicians should be cautious when prescribing rivaroxaban in groups of patients associated with increased bleeding risk such as patients with impaired renal or hepatic function, hypertension, coronary heart disease, heart failure, patients with certain types of cancers and patients receiving concomitant medications which may alter the pharmacokinetic or pharmacodymamic parameters of rivaroxaban. Anticoagulant treatment should be tailored to each individual patient weighing the bleeding risk against the risk of recurrent thrombosis.**

Keywords: Rivaroxaban, hematoma, anticoagulation, bleeding, spontaneous

1. Introduction

Rivaroxaban is an oral direct Factor Xa inhibitor that has been approved for the prevention of venous thromboembolism in patients undergoing elective hip or knee replacement surgery, for stroke prevention in patients with nonvalvular atrial fibrilation and for the treatment and secondary prevention of recurrent deep vein thrombosis and pulmonary embolism (*1,2*). Bleeding is the most common complication of anticoagulant therapy (*3*). Patients with cancer have an increased risk of venous thromboembolism compared to patients without cancer and they are at increased risk of bleeding during anticoagulant therapy (*4,5*). Herein is described a case of a rivaroxaban induced spontaneous expanding chest wall hematoma that required surgical intervention, in a breast cancer patient.

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2. Case Report

A 67-year-old Caucasian female presented with a 24-hour history of acute chest wall pain associated with a palpable mass and extensive bruising in a previous left mastectomy site. She had undergone a left modified radical mastectomy five months prior to the current admission for a pT3N3aM0 invasive ductal breast carcinoma, after neoadjuvant chemotherapy. Chemotherapy consisted of four cycles of fluorouracil, epirubicin and cyclophosphamide (FEC) followed by four cycles of docetaxel. One month prior to surgery she developed left lower extremity deep vein thrombosis for which she was treated with rivaroxaban 15 mg twice daily for three weeks, followed by 20 mg daily. Preoperatively a retrievable inferior vena cava filter was inserted. Postoperatively, she received adjuvant radiotherapy and hormonal therapy with letrozole, an aromatase inhibitor.

She was unable to recall any trauma, whereas she did not have any history of bleeding manifestations and there was no family history of bleeding disorders. In adittion, she had no history of any chronic illness and she was not taking any medications apart from letrozole 2.5 mg daily.

Physical examination revealed a left chest wall

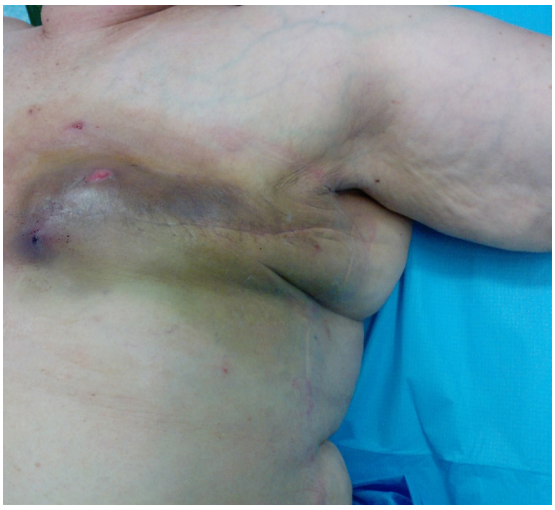

Figure 1. Photo showing signs of chest wall hematoma in a previous left mastectomy site. Signs of skin ischemia are also noted.

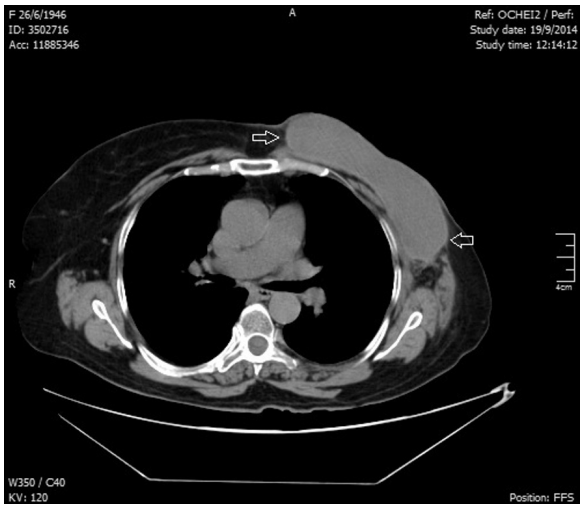

Figure 2. Contrast enhanced CT scan of the chest demonstrating a large left chest wall hematoma measuring 17 × 8 × 5 cm (arrows).

painful swelling associated with extensive ecchymosis (Figure 1). A complete blood count revealed a hematocrit of 32.4%, a white blood cell count of 5.600 × 10^3 mL, a hemoglobin level of 10.5 × 10^3 dL, and a platelet count of 200 × 10^3 mL. Coagulation studies revealed: international normalized ratio (INR): 0.95 (range 0.85-1.15) and activated partial thromboplastin time (APTT): 28.2s (range 26-38). Liver function tests and renal function tests were within normal limits. Blood Urea: 38.7 mg/dl (range 20.0-50.0) and serum creatinine: 1.00 mg/dl (range 0.20-1.50).

A contrast enhanced computed tomography (CT) scan of the chest revealed a large cutaneous hematoma measuring 17 × 8 × 5 cm in the previous left mastectomy site (Figure 2). There were no signs of local or regional recurrence of breast cancer. Rivaroxaban was discontinued and a local compression of the hematoma was applied. Despite compression, the hematoma continued to expand and signs of skin ischemia were noted and we therefore decided to proceed with hematoma evacuation and exploration. During surgery a large amount of blood clots was evacuated and a thorough irrigation of the large cavity was performed. A thorough inspection ruled out local recurrence from breast cancer. No bleeding vessel was found but a diffuse oozing was noted. The incision was closed after a drain was placed and compression was applied. The patient had an uncomplicated postoperative course without any signs of recurrent bleeding. During hospital stay a thorough investigation for haemorrhagic disorder was negative. She was discharged three days later after her anticoagulant therapy was modified. She is well without any signs of recurrent bleeding 23 months after the hematoma formation.

3. Discussion

Rivaroxaban has gained approval for the treatment and prevention of venous thromboembolism in adults. It has been evaluated in large phase III trials and has demonstrated non inferior or superior efficacy with a similar safety profile to current treatment standards (*2,3,6*). It has certain advantages over traditional agents.

Rivaroxaban has predictable pharmacokinetic and pharmacodynamic parameters thus allowing a fixed dose without the need of routine coagulation monitoring. It additionally has low potential for drug and food interactions. It has a rapid onset of action, reaches maximal plasma concentration 2-4 hours after administration and has high bioavailability (*2,6*). After administration, two thirds of the drug is metabolized to inactive metabolites in liver *via* cytochrome P450 (CYP) 3A4/A5 and CYP2J2, half of which is excreted through the kidneys and other half is excreted *via* the fecal route. The other one-third is excreted unchanged by the kidneys (*1*). Rivaroxaban, however, is contraindicated in patients with severe renal impairment and in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (*1*).

The acute deep vein thrombosis (DVT) randomized study enrolled 3449 patients and compared the efficacy and safety of rivaroxaban with standard treatment with enoxaparin and a vitamin K antagonist in patients with acute symptomatic DVT (*6*). The authors suggested that oral rivaroxaban at 15 mg twice daily for three weeks followed by 20 mg daily may provide an effective single drug approach to the initial and continued treatment of venous thrombosis (*6*). The proportion however, of patients with active cancer at the time of enrolment was 7% for both groups thus indicating that more data are needed in this subgroup (*6*).

A prespecified pooled analysis of the EINSTEIN DVT and EINSTEIN pulmonary embolism (PE) studies involving 8,252 patients suggested that simple drug therapy with rivaroxaban resulted in similar efficacy to standard therapy and was associated with a significantly

lower rate of major bleeding (*3*). The reduction was mainly seen in fatal and non fatal critical site bleeding such as intracranial and retroperitoneal bleeding. In fragile patients the incidence of major bleeding was reduced from 4.5% with standard treatment to 1.3% with rivaroxaban therapy, while in cancer patients the incidence of both bleeding and recurrent DVT tended to be lower in the rivaroxaban group (*3*).

Bleeding complications are frequent in patients treated with rivaroxaban but mainly consist of minor bleeding events (*7*). In the large prospective noninterventional oral anticoagulation registry of daily care patients (Dresden NOAC registry) with 1,775 rivaroxaban patients enrolled, major bleeding represented only 6% of the bleeding events. Sixty per cent of these cases managed conservatively with tamponade compression and red blood cell transfusions, while in the remaining 40% of major bleeding events a surgical or interventional treatment and rarely procoagulant treatment with prothrombin complex concentrates was required (*7*).

In a pharmacovigilance study of 27,467 patients taking rivaroxaban 496 major bleeding events occurred indicating an incidence of 2.86 per 100 person years (*8*). Major bleeding affected more frequently elder patients with hypertension, coronary heart disease, heart failure and renal disease. The most common site of bleeding was the gastrointestinal tract (88.5%) followed by intracranial bleeding (7.5%). Fourteen patients died indicating a fatal bleeding incidence of 0.08 per 100 person years (*8*).

The treatment of choice for cancer associated venous thromboembolism (VTE) is generally accepted to be at least 6 months of low molecular weight heparin (LMWH) (*4,9*). The effectiveness and safety of rivaroxaban is similar for venous thromboembolism patients with and without active malignancy, although borderline higher rates of major bleeding and non major clinically relevant bleeding have been reported in patients with cancer (*10*). In a retrospective review of 237 active cancer patients treated with rivaroxaban the authors reported that the recurrence and major bleeding events were low despite the fact that a half of the patients had metastatic disease (*9*).

Currently, there are no specific reversal agents for rivaroxaban. In addition, no prospective randomized clinical trials for patients presenting with acute bleeding have been conducted (*1*).

Discontinuation of rivaroxaban 20-30 hours before an elective surgery is sufficient to minimize the bleeding risk. In cases of severe bleeding discountinuation of rivaroxaban along with compression or appropriate surgical or interventional treatment are necesseary, while for life threatening bleeding the use of prothrombin complex concetrate is needed (*1*). In a recent study andexanet alfa, a recombinant modified human factor Xa decoy protein, reduced the anti-factor Xa activity by 92% in a series of 27 healthy older rivaroxaban treated participants within minutes after administration, without any side effects. The authors however, did not present any data on the efficacy and safety of andexanet in patients requiring urgent reversal of factor Xa inhibitor due to a bleeding or emergency surgery (*11*).

Patients with cancer receiving anticoagulant therapy have a higher bleeding risk than patients without cancer (*5,12,13*). Overall, 241 (5.1%) out of 4,709 patients with active cancer enrolled in the RIETE multicenter prospective registry, developed a major bleeding event which in most cases occurred during the first three months after the initiation of the anticoagulant therapy. The most common sites of bleeding were the gastrointestinal tract (49%), genitourinary tract (18%), and the brain (11%). One third of the patients who developed major bleeding died (*12*).

The bleeding in a cancer patient may present either as a localized bleeding diathesis as a result of tumor invasion or as a generalized hemorrhagic tendency (*13*). Apart from the known bleeding risk factors such as age and impaired renal function, cancer patients, particularly those under anticoagulation, may have specific risk factors that further influence bleeding. These factors include certain types of solid tumors such as gastric, neck or lung cancer, thrombocytopenia, platelet dysfunction, prior surgeries, metastatic disease, myelosuppressive chemotherapy and use of vascular endothelial growth factor (VEGF) receptor tyrosine-kinase inhibitors (*13*). Since there is no reported score assessing the risk of bleeding, an individual approach to assess the bleeding risk is essential when anticoagulant treatment is initiated especially in certain cancer patients, those with renal impairment, hypertension, coronary heart disease, heart failure and the very elderly (*8,12,13*).

Our patient had no history of any chronic disease and was not receiving any medication other than letrozole 2.5 mg daily. She had completed chemotherapy and radiotherapy seven and five months ago respectively. All laboratory values were within the normal range. There is no reported interaction between rivaroxaban and aromatase inhibitors. The use of rivaroxaban is however recent and all potential drug interactions may have not yet been reported. Based on the adverse drug reaction probability scale described by Naranjo *et al*. (*14*), a score of 7 indicated that the treatment with rivaroxaban was the probable cause for the development of the spontaneous chest wall hematoma in our patient.

In conclusion, physicians should be cautious when prescribing rivaroxaban in certain groups of patients associated with increased bleeding risk, such as patients with renal or hepatic impairment, hypertension, coronary heart disease, heart failure, patients with certain types of cancer and patients receiving concomitant medications which may alter the pharmacokinetic and pharmacodynamic parameters of rivaroxaban. Anticoagulant treatment should be tailored to each

individual patient weighing the bleeding risk against the risk of recurrent thrombosis.

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