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Case Report

Eptifibatide induced profound thrombocytopenia in a patient with pelvic malignancy: A case report

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Background

Uterine carcinosarcoma is a rare gynecologic neoplasm with an overall poor prognosis (Arrastia et al., 1997). The care of women with uterine carcinosarcoma and other gynecologic cancers is often complicated by medical co-morbidities. However given the aggressive nature of this malignancy, the physician frequently cannot delay surgical and/or medical interventions and must balance treatment of the underlying malignancy and management of these co-morbidities.

We describe a case of a woman with a recent history of acute coronary syndrome (ACS) requiring coronary artery drug eluting stent placement that presents for surgical treatment of a uterine carcinosarcoma. During her post-operative management she develops eptifibatide induced thrombocytopenia. Eptifibatide is a synthetic cyclic heptapeptide which acts with a high affinity at the platelet GPIIb/IIIa receptor. It mitigates the pro-thrombotic cascade by competitively inhibiting the interaction between fibrinogen and the platelet fibrinogen receptor, resulting in inhibition of platelet aggregation and intracoronary thrombus formation during ACS and percutaneous coronary intervention (PCI).

The medication has also grown to be more widely used in the perioperative period for anticoagulation due to its short half life (2.5 h) and the rapidity with which platelet aggregation returns to normal (4 h) (Hodivala-Dilke et al., 1999). The typical regimen of administration is a 180 mcg/kg bolus with a 2 mcg/kg/min IV infusion (The PURSUIT Trial Investigators, 1998). With the growing use of the glycoprotein (GP) IIb/IIIa inhibitors and the major incidence of serious medical co-morbidities in gynecologic oncologic patients, we present our experience, which we believe to be the first occurrence of eptifibatide induced thrombocytopenia in a patient with active malignancy and only the second case of potential thrombosis associated with eptifibatide use, to raise awareness of these rare but serious adverse drug reactions (The PURSUIT Trial Investigators, 1998).

Case presentation

A 65 year-old G0 Caucasian female was in her usual state of health until she presented to an outside hospital with ACS. Her past medical history was significant for Type II diabetes mellitus, hypertension, arthritis and a remote ovarian cystectomy for benign disease. She had no known exposure to anticoagulant medications and no family history of thrombosis. She subsequently underwent extraction of a right coronary artery plaque and placement of two drug eluting stents, during which she received aspirin, heparin, clopidogrel and eptifibatide. While hospitalized, she complained of abdominal pain. A computed tomographic (CT) scan of the abdomen/pelvis demonstrated a complex adnexal mass ($14.3 \times 10.3 \times 7.9$ cm) with associated hydroureter and periaortic lymphadenopathy but no ascites. Biopsy of an enlarged lymph node demonstrated a poorly differentiated neoplasm suggestive of Mullerian origin. Given her recent myocardial infarction requiring clopidogrel, neoadjuvant chemotherapy with taxotere and carboplatinum was initiated as an outpatient, but the patient tolerated one dose poorly secondary to hypotension from an acute reaction to chemotherapy administration and recalcitrant nausea and fatigue.

The patient sought a second opinion at our institution, and an endometrial biopsy was obtained which established the diagnosis of uterine carcinosarcoma. Since surgery was thought to be the preferred treatment with the new diagnosis of carcinosarcoma and her impending colonic obstruction, she was referred for pre-operative cardiology evaluation, which included a review of her outside hospital echocardiogram, catheterization films, and electrocardiogram as well as an outpatient cardiology work-up with and scheduled for surgery. Lower extremity venous dopplers one week prior to surgery did not demonstrate evidence of thrombosis. Given her recent stent placement, clopidogrel was discontinued five days prior to surgery, and she was admitted for an eptifibatide infusion (180 mcg/kg bolus with a 2 mcg/kg/min IV infusion). Pre-eptifibatide infusion blood counts included a platelet count of 373,000 per mm^3(Fig. 1 for the platelet trend). Six hours after eptifibatide infusion discontinuation,

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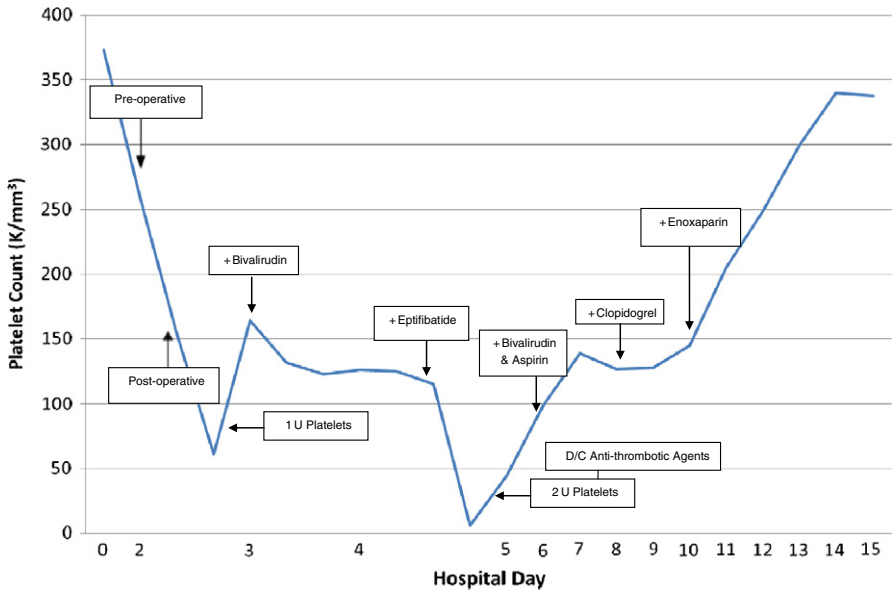

Fig. 1. Trend in platelet levels during hospital stay. Various interventions are documented along with change in platelet levels in the figure.

the patient underwent an exploratory laparotomy, radical tumor debulking, total abdominal hysterectomy, bilateral salpingo-oophorectomy, rectosigmoid resection with end colostomy, small bowel resection and re-anastomosis, bilateral ureterolysis, partial cystectomy, and appendectomy. Bilateral intermittent pneumatic compression devices were used for intra-operative venous thromboembolism (VTE) prophylaxis. Estimated blood loss was 5 l secondary to the patient's recent anti-coagulation, extensive underlying tumor burden, and the radical dissection required to debulk the majority of the disease. During the operation she received crystalloid, colloid, 9 U of packed red blood cells and 3 U of fresh frozen plasma. No platelets were transfused intra-operatively, and her immediate post-operative platelet count was 155,000 per mm^3. One unit of single donor platelets was transfused after her platelets nadired to 61,000 per mm^3 in the post-operative period.

Within 2 h of her tenure in the post-operative unit, the patient's left lower extremity was noted to be swollen with marked poikilothermia and pallor. Lower extremity venous dopplers demonstrated diffuse VTE involving the right popliteal, gastrocnemius and soleal veins and the left common femoral, femoral, popliteal, posterior tibial and peroneal veins (Supplementary Figs. 1 and 2). Given the patient's operative blood loss and increased risk of bleeding in the immediate postoperative period, targeted tissue plasminogen activator therapy and mechanical thrombectomy were not initiated. The patient instead underwent inferior vena cava filter placement and initiation of a bivalirudin (direct thrombin inhibitor, which is utilized as an effective anti-platelet therapy in the setting of PCI with a decreased bleeding risk) infusion per vascular surgery (Palmerini et al., 2011). Given her drug eluting stents, she was restarted on an eptifibatide infusion (2 mcg/kg/min) approximately 36 h after the diagnosis of the thrombus.

Within 6 h of eptifibatide re-initiation, she developed a profound thrombocytopenia to 6000 per mm^3 from previous platelet count of 130,000 per mm^3. Both the bivalirudin and eptifibatide infusions were immediately discontinued. Work-up for disseminated intravascular coagulopathy revealed a normal lactate dehydrogenase and slightly elevated haptoglobin; peripheral smear was notable only for profound thrombocytopenia, making pseudo-thrombocytopenia unlikely. An anti-heparin platelet factor 4 (PF4) panel was negative. An inherited thrombophilia work-up was also unremarkable. Over the course of the next two days the patient received 2 U of platelets, increasing her platelet to 28,000 per mm^3. Secondary to her extensive VTE, she was cautiously restarted on the bivalirudin infusion on post-operative day #6

She was eventually initiated on clopidogrel on post-operative day #8 (a thienopyridine, which blocks the interaction of ADP with a platelet receptor thereby preventing platelet aggregation and is employed as an agent in dual anti-platelet therapy after PCI to prevent stent re-thrombosis) and therapeutic enoxaparin for long term anticoagulation (Park et al., 2008). The use of prophylactic anti-coagulation, including low molecular weight heparin (LMWH) and enoxaparin, was delayed in this case secondary to the patient's initial profound thrombocytopenia and blood loss. In addition the patient's thromboembolic disease developed on the day of surgery, which was prior to post-operative day #1, the typical date of anti-coagulation initiation. Her platelet count continued to increase back to her baseline of 340,000 per mm^3 on post-operative day #14 when she was discharged after meeting her post-operative milestones.

The patient initially did well following discharge to a rehabilitation facility with improvements in mobility and functional status. She received one cycle of adjuvant taxotere and carboplatinum four weeks post-operatively. Two weeks later a CT scan showed diffuse metastatic disease, specifically to her ostomy site, with associated symptomatic hemorrhage. Two months post-operatively the patient was admitted to an outside hospital with acute mental status changes and hypercalcemia and was placed on palliative care with her eventual death during that hospitalization.

Discussion

Due to the growing use of drug eluting stents, the use of eptifibatide is becoming more widespread. The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Trial demonstrated an increased incidence of profound thrombocytopenia (platelets<20,000 per mm^3) in 0.2% of the population receiving eptifibatide compared to <0.1% of the control population (RR 5.0; 95% CI 1.3 to 32.4) (Russell et al., 2009). A few case reports have described a similar degree of thrombocytopenia within 2 to 24 h of eptifibatide exposure (Bougie et al., 2002; The PURSUIT Trial Investigators, 1998). Research has shown that pre-existing drug-dependent antibodies bind platelets in the presence of the GPIIb/IIIa inhibitor and cause profound thrombocytopenia by platelet and megakaryocyte destruction (Greinacher et al., 2009). In addition

similar to HIT with thrombosis (HITT), a recent study suggests that eptifibatide is also associated with an increased incidence of thrombosis. In the presence of these pre-existing drug-dependent antibodies, like heparin, eptifibatide can cause platelet secretion and aggregation mediated through interaction of the antibody Fc region with the platelet FcγRIIa receptor (Gao et al., 2009).

Our patient experienced an acute decrease in platelets within 6 h of her third exposure to eptifibatide indicating that eptifibatide was the most likely cause of her thrombocytopenia. She maintained her platelet levels on re-exposure to bivalirudin, clopidogrel, aspirin and enoxaparin. Although the combination of thrombocytopenia and thrombosis was very concerning for HITT, an anti-heparin PF4 panel was negative. Her clinical picture and labs did not support disseminated intravascular coagulopathy or thrombotic thrombocytopenic purpura. Although her tremendous clot burden could have consumed a significant amount of platelets, her platelet count was stable immediately before eptifibatide initiation and greater than 36 h after the incidence of clot. Consistent with prior cases, upon discontinuation of eptifibatide and initiation of supportive therapy with platelet transfusion as necessary, she recovered to a normal platelet count prior to discharge without adverse events.

Patients with a gynecologic malignancy are at increased risk for VTE given their often advanced age, need for long extensive abdominal and pelvic surgeries and the inherent hypercoaguability of their malignancy. However the rapid development of our patient's clot and the extensive nature of her thromboembolic burden are not consistent with the standard presentation of gynecologic malignancy associated VTE. Despite an extensive clinical work-up our patient had no identifiable etiology for a pro-thrombotic state except her underlying cancer. Data regarding thrombosis associated with eptifibatide is limited. None of the major clinical trials evaluating the use of the drug in the setting of ACS or PCI reported the incidence of thrombosis. Only one other case report describes the development of thrombosis secondary to eptifibatide use (The PURSUIT Trial Investigators, 1998). Despite this limited data, given that our patient had an abnormal presentation of VTE for a gynecologic malignancy and negative thrombophilia work-up, we believe the clinical presentation is highly suggestive of eptifibatide induced thrombosis.

We present a case of both thrombocytopenia and thrombosis associated with eptifibatide use to add to the growing literature regarding this phenomenon. Most data about this GP IIb/IIIa inhibitor is extrapolated from its use as an anti-platelet therapy in the setting of ACS. We believe our case is the first to describe the phenomenon in a patient undergoing treatment for active malignancy requiring prophylaxis against stent re-thrombosis. In addition it is one of a few studies to describe the phenomenon on second re-exposure; most cases are either on initial exposure or first re-exposure. Finally this is only the second case to describe potential thrombosis associated with eptifibatide use. Although our patient had a number of etiologies for her extensive lower extremity thrombosis including underlying malignancy and prolonged immobility intra-operatively during pelvic surgery and the incidence of eptifibatide induced thrombosis appears to be rare, this case highlights the need for caution when using eptifibatide in those with an increased pre-disposition to hypercoaguability. A recent *in vitro* study which included cell cultures of thrombin, platelets and HeLa cells with and without the addition of eptifibatide demonstrated that the GPIIb/IIIa inhibitor effectively blocked platelet GPIIb/IIIa integrin and subsequently decreased HeLa cell transmembrane translocation and migration. This data suggests that eptifibatide may have a role in decreasing metastatic spread of disease by inhibiting the aggregation of thrombin activated platelets with cancer cells (Liu et al., 2009). As the various forms of GPIIb/IIIa inhibitors become employed in more broad clinical settings, such as a preventative intervention against metastatic disease, we hope that in adding this case to the literature we can raise awareness of this rare but potentially devastating side effect of eptifibatide use.

Consent

Written informed consent was obtained from the power of attorney of the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflict of interest statement
None.

Authors' contributions

PT and SG both conceived the idea for the case report and were integrally involved in both the drafting and revision of the manuscript. KS collected the necessary data and was involved in both the drafting and revision of the manuscript. All authors read and approved the final manuscript.

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