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Case Report

Rivaroxaban-induced breast spontaneous hematoma: a case report

Ming-Yang Li[1*], Xiao-Ping Li[2*], Hai-Xian Ren[3*], Shi-Hui Tang[1], Sathwik Booreddy[4], Can-Can Zhang[1], Zhi-Jun Tan[5]

[1]First Central Clinical College of Tianjin Medical University, Tianjin, China; [2]Department of Thoracic Surgery, Tianjin First Center Hospital, Tianjin 300192, China; [3]Department of Pharmacy, Tianjin First Center Hospital, Tianjin, China; [4]Department of Pediatrics, UC San Diego School of Medicine, San Diego, California, United State; [5]Department of General Surgery, Tianjin First Center Hospital, Tianjin 300192, China. [*]Equal contributors and co-first authors.

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Abstract: Rivaroxaban is a highly selective Xa factor inhibitor, and oral administration of rivaroxaban has a diminished risk of major bleeding when compared to the risk of bleeding in patients receiving the standard anticoagulation treatment. Here, we report the case of a 71-year-old female who developed a spontaneous hematoma after receiving rivaroxaban, the patient taken rivaroxaban due to veins cava filter implantation in a lower extremity, at a dosage of 10 mg per day. During the hospital stay, the patient had a blood test and cytologic examination, no obvious coagulopathy and malignant cells found, ultrasonography showed a hypoechoic mass measuring 3.8 × 4.7 cm with areas of cystic degeneration. The patient accepted the puncture drainage treatment for the hematoma. Physical condition of her is good for 1 year since the onset of the disease. The risk of hemorrhage when taking new oral anticoagulants like rivaroxaban is lower than when taking traditional anticoagulants, but clinicians should be aware of the potential for serious complications such as local hematoma. We supply some measures to analyze and treat novel oral anticoagulant induced bleeding that may be helpful for clinicians.

Keywords: NOAC, rivaroxaban, anticoagulant, breast, hematoma, bleed

Introduction

Rivaroxaban, a novel orally administered non-vitamin K-dependent Xa inhibitor, is mainly used for the prevention of embolic stroke in non-valvular atrial fibrillation as well as the prevention of and treatment for venous thromboembolism. The risk of major bleeding involving novel oral non-vitamin K antagonist anticoagulants ranges from 1.4% to 3.6% per year in randomized clinical trials and the risk of life-threatening or critical bleeding is between 0.3% and 1.45% per year [1] These risks are lower than the risk when using the standard anticoagulation treatments [2].

Rivaroxaban-induced breast hematoma is very rare. In this study, we report a case of spontaneous breast hematoma in an elderly patient after taking rivaroxaban.

Case report

A 71-year-old female was admitted due to the discovery of a right breast mass 2 months prior to the examination. There were no special complaints, and no history of right breast trauma. The growth of the mass was slow and the time of formation was unknown. Physical examination showed that a 4 * 5 cm mass had been found in the lower inner quadrant of right breast, appearance of local skin was dark red, and there were no bruises or scars. The surrounding skin around the mass was fine, and there were no orange peel-like changes or skin retraction (**Figure 1A**). The mass was soft, smooth, flexible, tender, and had clear boundaries. Palpation of axillary lymph nodes yielded negative results. Physical condition of the patient was good and body temperature was normal. The patient suffers from Alzheimer's and has an indifferent consciousness, as well

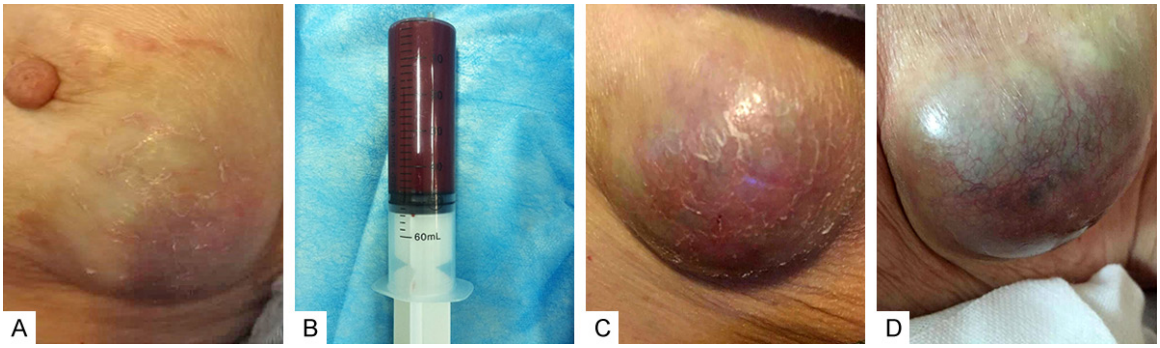

Figure 1. (A) Breast photograph showing the time of onset for the patient, a 4 * 5 cm hematoma exists in the lower inner quadrant of the right breast. (B) Photograph showing the patient's first puncture drainage, the hematocele released about 48 ml of fluid (C) Breast photograph showing the condition of the patient 2 months after onset, hematoma is more pronounced than before. (D) Breast photograph showing the condition of the patient during the last physical examination, hematoma is 6 * 7 cm and local skin vascular engorgement is present.

as mildly poor cognitive and expressive abilities. A veins cava filter was implanted in a lower extremity 2 years ago due to formation of deep vein thrombosis. Following this procedure, the patient was prescribed rivaroxaban for long-term anticoagulation, at a dosage of 10 mg per day. Any other disease or medication history does not exist, and this information was supplied by the patient and family members. This study does not involve any ethical issues or a breach of patient privacy; therefore, no ethics approval or informed consent is necessary.

During the hospital stay, the patient had a blood test. Serum tumor marker tests returned the following results: AFP 1.9 IU/ml, CEA 1.1 ug/L, CA153 13.7 U/ml, CA199 24.9 U/ml, CA125 6.3 U/ml. Coagulation function tests: PT 11s, APTT 39 s, PT-INR 0.99, TT 17 s. Routine blood tests: Hb 130 g/L, PLT 196 * 10^9/L. All of the above values were within normal range except for APTT, which was prolonged by 3 s. Mammography was not conducted in the acute setting because it would have been quite painful for the patient. The patient underwent a puncture drainage procedure under ultrasound guidance, and the ultrasonography showed a hypoechoic mass measuring 3.8 × 4.7 cm with areas of cystic degeneration. No other positive signs were found. The hematocele released about 48 ml (**Figure 1B**) of fluid, and hemostasis was conducted by compression with a bandage. Cytologic examination of the displaced fluid did not reveal any malignant cells. The patient was discharged after consultation with vascular surgeons regarding breast hematoma, and the doctors did not recommend a cessation of rivaroxaban. The patient took rivaroxaban daily after being released from hospital. As of this report, and since the first admission 1 year ago, the patient presented the symptoms of a hematoma in the same place several times. We have chosen to show one photograph of a hematoma which occurred 2 months after onset (**Figure 1C**). The hematoma was 6 * 7 cm and although there was greater local skin vascular engorgement than there was in the last physical examination, there were no significant changes in the rest of clinical signs (**Figure 1D**). The patient accepted the puncture drainage treatment for the hematoma. Vascular surgeons were not consulted regarding whether or not the rivaroxaban treatment should be continued. No examinations were made related to rivaroxaban during the hospital visit, and its use was continued by the patient after discharge.

Discussion

Tumor markers tests, cytologic examination of the displacing liquid and physical examination for signs of breast cancer all returned negative results, and the patient has been in good physical condition for 1 year since the onset of the disease. It is unlikely that the hematoma was caused by breast cancer. The possibility of a cystic breast tumor induced vascular malformation has not been ruled out, but is considered highly unlikely. There is no history of the use of any other medications that would predispose the patient to hemorrhage. This is a case of breast hematoma caused by rivaroxaban, as inferred by a clinical pharmacist. In 2015, the

Australian scholar Kyra L. Sierakowski reported a case of rivaroxaban-associated spontaneous periprosthetic hematoma [3]. The characteristics of that case were as follows: the elderly female presented a right breast huge hematoma suddenly. The patient has background of right latissimus dorsi breast reconstruction with an implant insertion due to mastectomy for breast cancer. She was noted to be taking rivaroxaban for deep vein thrombosis and atrial fibrillation. After surgery and extraction of 650 ml hematocele, the elderly female was discharged. Differences between that case and ours are that this patient had a sudden onset of symptoms and had underwent breast augmentation surgery. There are a number of literatures reporting breast hematoma after augmentation mammoplasty, although the mechanism by which the hematoma occurs remains unclear [4, 5]. In our report, we analyzed a patient with slow onset of symptoms, and no basic breast disease history. The correlation between rivaroxaban use and breast hematoma is clearer in our case.

Rivaroxaban is an orally administered, highly selective Xa factor inhibitor with a rapid effect, short half-life, and lower cross drug interactions. In addition, the pharmacokinetics of the drug are accurately known and monitoring the international normalized ratio is unnecessary. It is a cost-effective option for patients unwilling or unable to administer subcutaneous injections for venous thromboembolism prophylaxis after surgery, and for patients with nonvalvular atrial fibrillation who are unable to see a medical care provider for routine coagulation monitoring [6]. On the other hand, warfarin, the current widely used anticoagulant, may lead to fatal bleeding, has complex pharmacokinetics and pharmacodynamics, a narrow therapeutic range, multiple drug and dietary interactions, and demands frequent monitoring to maintain the desired therapeutic range [7]. Heparin is an injectable drug that can only be used for inpatients or as a short-term prophylaxis for intravenous thrombosis [8]. Compared with enoxaparin, rivaroxaban preforms equally as well or even better for the prevention of deep vein thrombosis and major cardiovascular disease. The risk of bleeding is not increased by rivaroxaban based on completed clinical trials. Common adverse events due to rivaroxaban use include nausea, vomiting, and constipation [9]. Severe adverse events such as hematomas are rare. There has been literature reporting spontaneous rectus sheath hematomas [10] and spontaneous epidural hematomas [11] that were caused by rivaroxaban.

In recent years, the emergence of novel oral anticoagulants (NOAC) has made it possible to replace warfarin due to their convenient use and reliable efficacy [12]. However, clinicians should be aware of the possibility of serious complications, such as major bleeding and hemorrhage of vital organs. As of now, there are no listed reverse agents for NOAC available. The following methods are being tried to use against NOAC according to current literatures. (a) Specific reversal agents. Idarucizumab, the first novel antidote against direct thrombin inhibitor dabigatran was approved by US FDA in October 2015. A phase III trial on idarucizumab showed complete reversal of the anticoagulant effect of dabigatran. In preclinical studies, idarucizumab showed rapid reversal effects against dabigatran via various animal models, and meanwhile showed no evidence to support thrombus formation [13]. Andexanet alfa, a specific reversal agent against factor Xa inhibitors, showed a complete reversal of the anticoagulant effect against apixaban and rivaroxaban within minutes after administration. Severe adverse effects do not exist, according to recently completed parallel phase III trials ANNEXA-A and ANNEXA-R. It is currently being studied in phase IV trials. (b) Activated charcoal has been used in the setting of apixaban and rivaroxaban overdose [14]. In a small pharmacokinetic study (n = 18), charcoal administration up to 6 h after apixaban ingestion reduced apixaban exposure and facilitated the elimination of apixaban [15]. Activated charcoal might be reasonable to administer in the setting of acute overdose with NOAC. (c) Prothrombin complex concentrates (PCC) consist of several hemostatic factors. The European Heart Rhythm Association recommends using hemostatic factors, such as PCC, activated PCC, and recombinant activated factor VII (rFVIIa) to reverse anticoagulation. [16] There is some evidence from pre-clinical in vitro, ex vivo, and in vivo animal studies that hemostatic factors could reverse NOAC-induced anticoagulation, but the data to support such recommendations are limited. PCC should only be given after careful consideration because of the associated increased risk of thromboembolic complications [17]. (d) Limited data support

that hemodialysis can also be considered for the reversal of dabigatran-induced anticoagulation. In addition, a recent study demonstrated that hemodialysis was not an effective mechanism for removing the medication from blood [18]. Apixaban and rivaroxaban are highly bound to proteins (87-95 %) and thus cannot be removed with hemodialysis [19]. (e) Fresh frozen plasma and vitamin K can reverse warfarin-induced bleeding, but neither fresh frozen plasma nor vitamin K have proven to be effective in reversing the effects of NOAC [20]. Owing to the short-half lives of NOAC compared with the VKA, discontinuation of treatment normally allows for normalization of coagulation parameters within one day in patients with normal renal function. The measures for patients with urgent life-threaten bleeding who receiving NOAC are as follows: (1) Detection of coagulation function. Some NOACs affect INR, but INR is not used for monitoring anticoagulation. A novel fluidic universal coagulation test using surface acoustic waves has been reported to be able to detect anticoagulation levels, as well as rivaroxaban and dabigatran levels [21]. Dilute thrombin time is a viable method for monitoring coagulation status in patients who are receiving dabigatran therapy. Clinicians could employ it in some urgent situations, but it lacks FDA approval [22]. (2) Taking antidote against NOAC. Idarucizumab can specifically bind to dabigatran, and andexanet alfa can be used against factor Xa inhibitors, like apixaban and rivaroxaban. Activated charcoal could absorb dabigatran in blood and could also be helpful in treating an adverse reaction caused by apixaban or rivaroxaban. PCC and rFVIIa could reverse NOAC-induced anticoagulation. (3) It is important to avoid the risk of bleeding complications by employing careful consideration and responsible use of the NOAC, such as taking precautions when prescribing the medication to high-risk patient populations.

We hope the case we shared and the measures we provided to inhibit NOAC-induced bleeding may helpful to clinicians.

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Disclosure of conflict of interest

None.

Address correspondence to: Zhi-Jun Tan, Department of General Surgery, Tianjin First Center Hospital, No. 24 Fukang Road, Nankai District, Tianjin 300192, China. Tel: 86-13821270709; E-mail: zhijuntan2017@163.com; Xiao-Ping Li, Department of Thoracic Surgery, Tianjin First Center Hospital, No. 24 Fukang Road, Nankai District, Tianjin 300192, China. Tel: 86-02223627068; E-mail: eonelxp@163.com

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