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Warfarin Induced Necrosis of The Breast: A Case Report

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ABSTRACT

Background: Warfarin induced breast necrosis is a rare complication of oral anticoagulant therapy. Although it can be related to protein C, S, and antithrombin III deficiency; the pathogenesis of necrosis is still unknown.

Case presentation: We report a case of a 38-year-old woman with extensive left breast necrosis after receiving warfarin for treatment of deep vein thrombosis. Simple mastectomy was performed and the wound was closed secondarily with an abdominal advancement flap. Rivaroxaban was prescribed after discontinuation of warfarin.

Conclusion: Although breast necrosis following warfarin usage is uncommon, it should be considered in women presenting with breast symptoms after initiation of warfarin. Early diagnosis and appropriate management are essential to prevent extensive loss of breast tissue.

Introduction

Warfarin is one of the most commonly prescribed oral anticoagulant medications, and it is used for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE); and for thrombo-embolism prophylaxis in patients with valvular heart disease, mechanical heart valves, and atrial fibrillation.[1]

The most common complication of warfarin is bleeding,[1] which can be prevented by adjusting international normalized ratio (INR). Necrosis, osteoporosis, calcification, and purple toe syndrome are other side effects. Skin and subcutaneous tissue necrosis is an extremely rare and serious complication of warfarin with a prevalence of 0.1- 0.01 percent.[2] It was first described by Flood *et al*. in 1943.[3] Since then, there has been more than 300 reported cases in the literature,[2] but less than 40 of the reported cases involved the breast tissue.[4]

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We present a case of warfarin induced necrosis of the breast in a 38-year-old patient, treated with simple mastectomy.

Case presentation

A 38-year-old female presented to the breast clinic of Imam Khomeini Hospital with the complaint of a necrotic ulcer on her left breast for 10 days. She had a history of admission for deep vein thrombosis (DVT) of the left lower limb one month earlier. The deep vein thrombosis occurred following long-term use of oral contraceptive pills (OCP). She received intravenous heparin followed by warfarin. She was discharged from the hospital with a daily dose of 10 mg of warfarin and with an INR of 2.1.

On admission for breast necrosis, no fever was detected but the patient had a foul-smelling necrosis involving most of her left breast (Figure 1). Blood work showed INR, activated thromboplastin time (aPTT), and platelets of 1.32, 38 seconds, and 460,000 per cubic milliliter, respectively. Hematology consultation recommended discontinuation of warfarin and administration of Rivaroxaban.

Considering the extent of breast necrosis (Figure 1), mastectomy was recommended. Before surgery, Rivaroxaban was discontinued, and heparin and

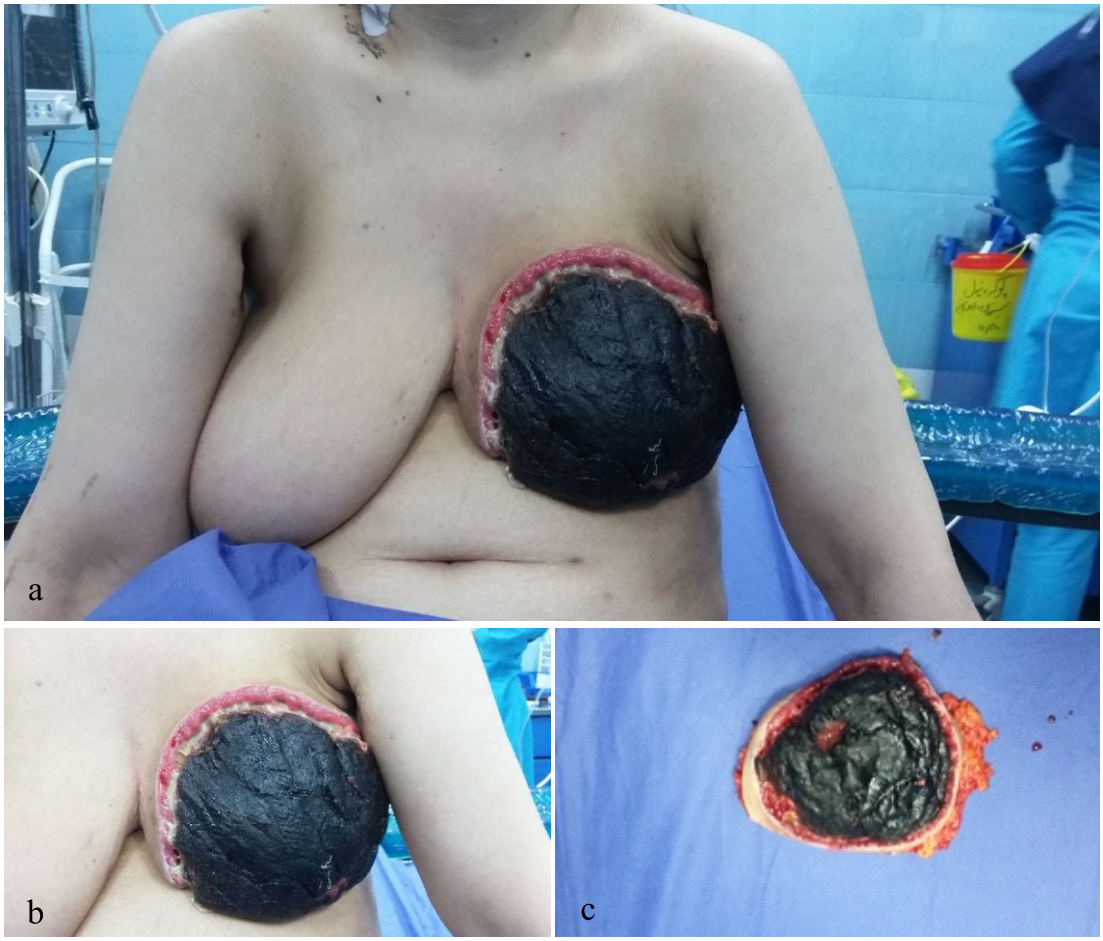

Figure 1. A, B: Left breast necrosis, C: Removed specimen

broad-spectrum antibiotics were started. The patient underwent left mastectomy. There were purulent secretions under the necrotic tissue and the wound was left open. Intravenous antibiotics were continued for 7 days. The wound irrigation and dressing were performed daily. The patient was discharged from the hospital with Rivaroxaban 7.5 mg/ twice a day for 21 days, then 20 mg/ day, and daily irrigation of the wound was arranged at a local clinic. Healing of the wound was monitored by the surgeon on a weekly basis. After one month, the wound was closed with abdominal advancement flap. Anticoagulation was continued for 6 months.

Further hematologic evaluation showed protein C deficiency. Pathology report confirmed breast parenchyma with diffuse and extensive necrosis and acute inflammation.

Discussion

Skin and subcutaneous tissue necrosis is a rare complication of warfarin, occurring in 0.1-0.01% of patients receiving oral anticoagulation.[2] Women are more commonly affected with a female to male ratio of 3:1.[5] The areas with increased subcutaneous fat (abdomen, thighs, buttocks, legs, and breasts) are more susceptible to necrosis.[6-9] Breast is affected in about 10-15% of the patients.[4] It usually affects one breast, but bilateral breast necrosis is also reported.[4,10]

The symptoms start 1 to10 days after initiation of warfarin, and the majority of cases occur within 3 to 6 days.[4,6] However, there are reports of late-onset symptoms several years after commencement of therapy.[11-13] The initial manifestations of breast necrosis are paresthesia, pressure, and discomfort in the affected area. Later, erythematous or hemorrhagic skin lesions appear and will develop in to blisters and bullae, leading to skin necrosis and scar formation.[4,8]

It is important to consider other conditions that can mimic warfarin necrosis in differential diagnosis, such as micro-embolization (septic emboli, cholesterol emboli), heparin-induced skin necrosis as a result of the thrombocytopenia and thrombosis syndrome, disseminated intravascular coagulation, purpura fulminans, necrotizing fasciitis, cryoglobulinemia, inflammatory breast cancer, decubitus ulcers, snake venom induced skin necrosis, cellulitis, venous gangrene, necrotizing fasciitis, calciphylaxis, and hematoma.[1,14]

The exact pathogenesis of necrosis following warfarin usage is still unclear, however protein C deficiency, hypersensitivity, and direct toxic effect of warfarin are possible mechanisms of necrosis.[1,6] The most popular pathogenesis is acute protein C deficiency. Warfarin blocks vitamin K epoxide reductase enzyme and inhibits synthesis of clotting factors II, VII, IX, and X. It also inhibits synthesis of

anticoagulant protein C and protein S. Protein C and protein S have shorter half-life than vitamin K dependent clotting factors. Consequently, the patient develops a transient hypercoagulable state at the beginning of warfarin therapy and needs another form of anticoagulation, such as heparin, for 48-72 hours to prevent clot formation.[1,7,8,15]

Management of breast necrosis following oral anticoagulation therapy with warfarin, starts with discontinuation of warfarin. However, withdrawing warfarin will not affect the course of the established skin lesions.[4, 5, 16] Vitamin K and fresh-frozen plasma are administered to replenish protein C levels,[8] and anticoagulation should be continued by administering intravenous heparin or the non-vitamin K antagonist oral anticoagulants (NOACs) such as Dabigatran or Rivaroxaban.[17] The necrotic lesions should be managed surgically with debridement and appropriate wound care.

In conclusion, fulminant painful purpura and erythematous skin lesions in patients receiving warfarin should be suspected as warfarin induced necrosis. Immediate discontinuation of warfarin, administration of vitamin K, and fresh-frozen plasma is recommended. The skin lesion should be managed with appropriate surgical debridement and wound care.

Ethical Consideration

The patient announced her consent for using her data for this case report.

Conflict of Interest

The authors have no conflict of interest to disclose.

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