Warfarin-induced necrosis of the breast: Case report

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ABSTRACT

Warfarin-induced necrosis of the breast is an unusual complication of warfarin therapy. Since its first description in 1943, up to 36 cases have been reported in the English literature. Close association between inherited or functional deficiency of protein C and S and warfarin therapy is frequently reported. A characteristic patient is an obese middle-aged female receiving anticoagulant treatment. The rapidly evolving painful lesion appears suddenly, usually within 3 to 6 days after initiation of warfarin therapy. Prevention may be achieved by identifying the high-risk patients—female gender, middle age, obesity, and avoiding large loading doses of warfarin. Early recognition and treatment are necessary to avoid significant long-term morbidity. Established necrosis necessitates debridement and sometimes mastectomy. A case of warfarin-induced necrosis of the left breast mimicking inflammatory cancer is reported. Current recommendations for the prevention and treatment of this uncommon condition are reviewed.

KEY WORDS: warfarin, necrosis, breast

Necrosis of the skin occurs in 0.1%-1.0% of patients treated with warfarin or its congeners. The reported age range for occurrence is 16 to 93 years with female predominance. Usually, the sites with thick subcutaneous fat are affected. Breasts, buttocks, thighs, arms, hands, digits, legs, feet, face, nose, abdomen, back and penis are the various reported sites. Multiple lesions have been reported in 35% cases and 20% of the lesions are symmetrical. The breast remains the most common site in females followed by the buttocks and thighs. Since its first description by Flood and colleagues, up to 36 cases of warfarin-induced necrosis of the breast (WINB) have been reported in 24 papers in the English literature. To the best of the author’s knowledge this is the first report of WINB from the Kingdom of Saudi Arabia. Knowledge of this uncommon clinical entity allows the clinician to make an early diagnosis. Recognition and adequate treatment are essential to prevent significant morbidity or mortality.

Case History

A 38-year-old obese Saudi female presented to the Al-Iman General Hospital, Riyadh, Saudi Arabia, with 3 days’ history of a progressively increasing painful lump in the left breast. Since the past 2 weeks, she was under treatment in a local hospital for left-sided lobar pneumonia where a subsequent VQ scan had suggested a low probability of pulmonary embolism. She was heparinized employing continuous unfractionated heparin infusion. Three days after commencement of heparin, warfarin (10 mg bolus for 2 days followed by 5 mg daily) was started and heparin was discontinued. On the fifth day after commencement of warfarin, the patient developed a tender mass in the left breast and was referred with a probable diagnosis of inflammatory carcinoma. At presentation she was pale, tachypnoeic, tachycardic and febrile (38°C). Examination revealed symmetrical cauterity scars on both breasts acquired 2 years earlier (local tradition). The left breast demonstrated a warm, moderately tender mass occupying the subareolar region and the entire outer half with a ‘peau d’orange’ appearance. The mass was fixed to the nipple and skin but not to the underlying fascia. Axillary lymph nodes were not palpable. Examination of the chest was suggestive of left basal consolidation. No other similar skin lesions were identified. Her haemoglobin was 7.8 g%, WBC count 9800/mm³; platelets 340,000/mm³ and INR was 2.8. Ultrasound of the left breast demonstrated a complex mass of mixed echogenicity with no evidence of collection and a high likelihood of malignancy. Breast biopsy was planned, treatment with broad-spectrum antibiotics was started and the physician’s advice was obtained. Not convinced with pulmonary embolism, the physician suggested that we continue treatment for pneumonia, discontinue warfarin, and administer vitamin K and fresh frozen plasma (FFP). Neither heparin nor warfarin was re instituted. Estimations of antithrombin III, protein S, Factor V Leiden and lupus anticoagulant were not available. The serum values for clotting factors II, VII, X (112%, 98% and 126% activity of the laboratory control, respectively – ACS, Inc. USA) and protein C (83%, normal 60-140) obtained 2 days after discontinuation of warfarin and before initiation of Vitamin K and FFP were normal. On next day of admission, irregular grayish blue areas of the skin, ecchymosis, and haemorrhagic bullae were noted overlying the previously noticed mass. An urgent surgical debridement revealed extensive necrosis of the skin and breast substance. Tissues were obtained for cultures and histology. The remaining breast was completely necrotic on the following day. Second debridement resulted in total mastectomy. The cultures were negative for bacterial growth. The histology was haemorrhagic necrosis of the breast skin and fat, microvascular thrombosis, fibrin deposition and little inflammation. The features were consistent with WINB. After the second debridement, the patient demonstrated rapid clinical improvement. She was referred to a plastic surgeon and underwent split thickness skin grafting of the mastectomy wound. At six months follow-up, the patient is doing well, with healed grafted area.

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Case Report
Necrosis of the breast is a rare complication of warfarin therapy. Typically, the condition is reported in middle-aged obese women receiving warfarin treatment for pulmonary embolism, deep venous thrombosis, myocardial infarction, or valvular heart surgery. One or both breasts are involved in 15% of the females. In 90% cases, the painful necrotizing lesions appear within 3 to 6 days of initiation of warfarin therapy. The initial manifestation is a well localized indurated erythematous area of skin which may develop a peau d'orange appearance. The lesion rapidly evolves into grayish black ecchymoses. Haemorrhagic infarcts usually follow and progress to dry gangrene. Early histology shows cutaneous infarcts, haemorrhages and breakdown of precapillary arterioles, fibrin deposits in the postcapillary venules and small veins, a distinct lack of arteriolar thrombosis and no evidence of vascular or perivascular inflammation. Thrombosis of larger vessels in the subcutaneous fat results in deep necrotic sloughs and eschar formation. Once gross tissue necrosis or secondary infection ensue, the biopsy becomes non-specific and non-diagnostic. Less severe cases may closely mimic inflammatory carcinoma and an early biopsy helps in excluding the diagnosis. The exact aetiopathogenesis of this condition and the reason for its predilection for adipose tissue remain obscure but may be multifactorial. Local factors, like variation in local temperature, trauma and inadequate local perfusion, have been suggested. Previous exposure to warfarin does not predispose to the development of necrosis and recurrent lesions have been reported even in the absence of further anticoagulation therapy. An inherited or functional deficiency of proteins C and S has been reported by various authors. However, warfarin-necrosis has been reported in patients with normal levels of protein C and S. The necrosis may be prevented by identifying high-risk patients and avoiding large loading doses of warfarin. The initial treatment remains supportive and conservative. Although, discontinuation of warfarin has not been shown to alter the outcome it is generally recommended. Heparin should be started in high doses and vitamin K and FFP should be administered to restore protein C and S levels. With successful treatment, the lesions follow a course of fibrosis, scarring and spontaneous healing. Dose-adjusted subcutaneous heparin therapy is recommended in those patients requiring long-term anticoagulation. With extreme caution, successful recommencement of warfarin therapy has been reported. Allowed to run its natural course, the condition is associated with significant morbidity and deaths have been reported in severe cases. Characteristically, warfarin-induced breast necrosis does not respond to vitamin K therapy and vigorous surgical debridement is usually needed in 50% cases. Mastectomy, unilateral or bilateral, may eventually become necessary. Final closure is usually accomplished by secondary healing, split-thickness skin grafting or flap coverage.

This report describes a typical case of warfarin-induced breast necrosis in a middle-aged obese female observed within one week of initiation of high-dose warfarin therapy. The level of protein C was normal in this case and the disease was resistant to treatment with vitamin K. The traditional cosmetic cautery over the breasts might have contributed as a local predisposing factor.

References