

BREAST NECROSIS IN A CHRONIC USER OF WARFARIN

Necrose mamária em usuária crônica de varfarina

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ABSTRACT

Warfarin-induced skin necrosis is a rare event that generally happens within the first days of warfarin use and is due to the initial, and transitory, prothrombotic state caused by unbalanced pro and anticoagulant factors. We describe the first case of breast necrosis in a 50-year-old woman, who uses warfarin chronically, and had its anticoagulant effect enhanced by the concomitant use of diclofenac.

KEYWORDS: necrosis; breast; warfarin.

RESUMO

A necrose cutânea induzida por varfarina é um evento raro, que geralmente ocorre nos primeiros dias de uso dessa medicação, sendo atribuída ao provável efeito inicial pró-trombótico causado pelo desbalanço transitório entre fatores pró e anticoagulantes. É descrito o primeiro caso de necrose mamária em uma mulher de 50 anos usuária crônica de varfarina, a qual teve seu efeito anticoagulante potencializado pelo uso concomitante de diclofenaco sódico.

PALAVRAS-CHAVE: necrose; mama; varfarina.

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INTRODUCTION

The use of warfarin has been associated with skin necrosis since the early 1940s. It is a rare event, with only a few cases described in the literature, occurring more often in the breasts, buttocks, and thighs. Its development is catastrophic, thus requiring early diagnosis and immediate intervention in order to reduce the morbidity and to prevent potential mortality and related complications.

CLINICAL CASE

This study reports a case covered by the Mastology team of the Health Department of the city of Joinville, Santa Catarina, Brazil. The informed consent was signed, and the patient agreed to the exposure of her medical conditions for scientific purposes.

The patient is a 50-year-old woman with body mass index (BMI) of 33.6, with hypertension — using amlodipine 10 mg/day — and pulmonary thromboembolism at age 33 — using warfarin 5 mg twice a week and 7.5 mg on the remaining days. She denied using alcohol, smoking or having allergies. Despite laboratory follow-up of the anticoagulation with the International Normalized Ratio (INR) maintained in the therapeutic range of 2.5–3.0, she presented popliteal venous thrombosis at the age of 44. An extensive thrombophilia research was carried out, which came out negative for protein C deficiency, S factor V Leiden, mutated prothrombin gene, lupus anticoagulant and anticardiolipin antibody. She reported that 10 days before admission, after working out at home, she took some diclofenac for muscle pain. Two days later, she developed a progressive pain in her right breast, with local erythema, without fever or any other associated symptom, and was then hospitalized. When admitted in the hospital, she was in good overall condition, her blood pressure was 130/90 mmHg, heart rate of 80 beats per minute, and she was afebrile. Her right breast had an ecchymotic area with predominant central distribution. Laboratory testing presented: hemoglobin = 12.3; hematocrit = 42; leukocytes = 9,600; platelets = 153,000; and INR = 8.

Warfarin was then discontinued, and frozen fresh plasma was administered. The patient reports that her breast pain continued worsening, evolving with quick hardening and blackening of the skin in the region, hence the diagnosis of extensive right breast necrosis (Figure 1). The patient underwent breast debridement, resulting in total mastectomy; a devitalized mammary tissue with superficial skin necrosis was observed during the intraoperative period. The anatomopathological analysis of the surgical specimen revealed extensive necrosis of coagulation with hemorrhagic areas, congestive vessels and capillaries, releasing a final report of gangrene.

DISCUSSION

Skin necrosis is a rare condition, with incidence of 0.1 to 0.01% of cases in users of oral anticoagulant therapy whose action mechanism is the antagonism of vitamin K¹⁻⁹. Flood et al. described the condition for the first time in 1943¹⁰, but a causal relation between tissue necrosis and use of oral anticoagulants was only established in the late 1950s¹¹. Subsequently, an association between thrombophilia, warfarin use and skin thrombosis was established, which was described in patients with hereditary deficiency of protein C¹²⁻¹⁴, deficiency of protein S¹⁵, antithrombin III¹⁶, V Leiden factor¹⁷, and lupus anticoagulant carriers¹⁸. It was also described in patients requiring high initial doses of oral anticoagulant, higher than 10 mg of warfarin^{2,3}. However, most cases occur without a predisposing risk factor or known cause.

The warfarin-induced skin necrosis usually occurs in areas of excessive subcutaneous cellular tissue, most frequently affecting breasts (10 to 15%)¹⁹⁻²², buttocks, and thighs^{23,24}. It typically occurs in obese middle-aged women, using warfarin due to deep venous thrombosis and/or pulmonary thromboembolism, and it is rare among coumarin users due to cerebrovascular insufficiency and atrial fibrillation¹¹. The first signs appear in the period between the first week and 10 days after the beginning of warfarin use, with visual lesions between the third and sixth days^{4,20}. Late cases developed after 16 days have already been described⁷. The onset of symptoms is characterized by paresthesia, or the sensation of a visceral, poorly located discomfort, which evolves with the appearance of painful, erythematous lesions with poorly defined margins that progress to ecchymotic areas. Edema of the subcutaneous cellular tissue occurs, resulting in an orange peel-like skin in the area²¹, progressing into dry gangrene^{4,21}. The anatomopathological substrate is an occlusive non-vasculitic vasculopathy²⁵.



Figure 1. Right breast necrosis.

The pathophysiology of the condition remains uncertain, but it is believed that in the beginning of oral anticoagulant whose action mechanism is vitamin K antagonism, there might be a transitory deficiency of proteins C and S, predominantly^{26,27}, as well as of factor VII (12-hour shorter half-life), which have faster drop in their concentrations than the other factors involved in pro-coagulation (factors II, IX, X), whose half-life is between 20 and 60 hours. Thus, there is a non-counterbalanced reduction of these proteins, resulting in a prothrombotic period between the first 3 to 6 days, considering the peak of anticoagulant activity is only reached in 72 to 96 hours²⁸. Therefore, the concomitant use of heparin is recommended in the initial phase¹². Some authors also point out that the warfarin has a toxic effect on the pre-capillary and arteriolar junction of the dermis, causing the endothelial lesion¹¹.

The diagnosis is essentially clinical, and the histological aspect is characterized by skin infarcts with hemorrhage areas and rupture of pre-capillary arterioles with fibrin deposit and absence of perivascular inflammation, i.e., an occlusive, non-vasculitic vasculopathy^{4,20,23,25}.

In the case above, the patient was a chronic warfarin user, but who, due to the concomitant and erroneous use of diclofenac,

experienced a potentialized coumarin effect, which was evidenced by larger INR at hospital admission; as a result, there was a transient imbalance between pro- and anticoagulant factors, generating a prothrombotic state that culminated in skin necrosis. It should be noted that the patient had already presented superficial popliteal thrombosis, considering the recurrence of venous thrombosis has also already been described during anticoagulant treatment with warfarin – incidence of up to 3 to 15% of cases²⁸.

The treatment of warfarin-induced breast necrosis, although not interfering with the progression of gangrene, should begin as early as possible in order to avoid related complications, such as secondary infections. It consists in the administration of low-molecular weight heparin doses enough for full anticoagulation, oral anticoagulant suspension, administration of fresh plasma and vitamin K, thus restoring proteins C and S through hepatic production stimulation²⁹. The use of new oral anticoagulants with different action mechanism, such as direct thrombin inhibitors of the Xa factor, is also advocated³⁰. Currently, despite proper treatment, more than half of the patients will require surgical debridement, amputation or total mastectomy^{19-22,24,26,29}.

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