

WARFARIN INDUCED MASSIVE AND BILATERAL SKIN NECROSIS OF THE BREASTS: A CASE REPORT AND REVIEW OF THE LITERATURES

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Abstract- Warfarin induced skin necrosis is a rare complication associated with the use of oral anticoagulants. Most patients develop this complication at the initiation of therapy. The complication is usually associated with an underlying thrombophilia. We described a case of 75 year old patient who developed skin necrosis in her both breasts during warfarin treatment for a deep vein thrombosis. Thrombophilia screen demonstrated the presence of protein S and antithrombin III deficiency. The necrotic lesion was excised and defects eventually covered with skin flaps.

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INTRODUCTION

Warfarin is used extensively for the treatment and prophylaxis of thromboembolism. Warfarin-induced skin necrosis (WISN) is a rare complication of anticoagulant therapy, occurring in 0.01-0.1% of warfarin treated patients, which was first described in 1943 (1, 2). It usually appears 3-6 days after initiating warfarin treatment and almost always between days 1 and 10, but a case of late-onset (16 days after initiation of therapy) has also been reported in the literature (3). These lesions first appear as painful localized areas of erythema. Petechiae, ecchymoses and hemorrhagic bullae develop soon. The affected skin undergoes hemorrhagic infarction and a dark eschar develops over the necrotic area. The necrotic lesions progress to full thickness skin loss with variable necrosis of the subcutaneous layers. Typical patient is an obese middle aged woman around 50 years old. The affected areas are usually the buttocks,

thighs and breasts where heavy subcutaneous fat layers exist (4). Severity of skin lesions may have no relationship with stop or continuation of anticoagulant therapy with warfarin (1).

Hypercoagulability state which is mainly due to a low level or absence of protein C and also to a lesser extent a low level or absence of protein S has been demonstrated in these patients (5). Since protein C and protein S are vitamin K-dependent anticoagulant factors, these lesions could also occur without anticoagulant therapy with warfarin, just as a result of vitamin K deficiency (6).

Differential diagnoses of WISN are purpura fulminans, necrotizing fasciitis, microembolization, breast cancer, and pressure sores. The associated mortality and morbidity rates are high and failure of early diagnosis and treatment may result in death (7,8).

CASE DESCRIPTION

A 75-year-old woman admitted to hospital due to pain and swelling of her left leg. Her left lower limb was cyanotic and cold. Left leg circumference was 6 centimeters more than the right one. Thrombosis in

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popliteal, superficial, deep and common femoral and external iliac veins was shown by color Doppler ultrasound of lower limb vessels. Parenteral heparin and oral warfarin have been started and coagulation tests have done daily. On day six, international normalized ratio (INR) was in normal range and parenteral heparin was discontinued.

Nine days after initiation of warfarin therapy, the patient developed pain in her breasts. Petechiae and mild erythema were seen in physical examination. Two days later two extensive well defined non-raised ecchymoses with an erythematous halo developed on both breasts. Then hemorrhagic bullae developed and after their rupture full-thickness necrosis occurred (Fig. 1-3). Biopsy was done which showed necrosis, hemorrhage, epithelial degeneration, damage to precapillary arterioles, dermal and subcutaneous vessels thrombosis, and tissue edema which confirmed WISN. Thus diagnosis of warfarin-induced skin necrosis was made.

Warfarin was discontinued and IV heparin was started. Vitamin K and fresh frozen plasma were also administered. Tests for factor V Leiden, lupus anticoagulant, anticardiolipin and antiphospholipid antibodies were negative. Functional protein C level was normal (69%), but both functional protein S (29%), and antithrombin III level (78%) were decreased.

Surgical debridement of the wounds and the necrotic area was performed and then skin flaps applied through a surgical operation (Fig. 4,5). Eventually the patient was discharged with good general condition on Enoxaparin.



Fig. 1. Extensive bilateral skin necrosis of the breasts



Fig. 2. Close up view of left breast skin necrosis



Fig. 3. Right breast necrosed areas which include nipple and areola



Fig. 4. Right breast after operation and reconstruction with skin flap .



Fig. 5. Left breast after operation and reconstruction with skin flap

DISCUSSION

Warfarin-induced skin necrosis usually appears 3-6 days after initiating warfarin treatment. (3) Biopsy of the skin shows fibrin and platelet thrombi in small dermal vessels with no evidence of inflammatory infiltration, a finding characteristic of WISN. Hemorrhagic necrosis and subepidermal bullae may also occur (9). Protein C is a vitamin K dependent protein that, in association with protein S, inactivates activated factors V and VIII, down regulating thrombin formation and coagulation. They also promote fibrinolysis through TPA inactivation. The pathogenesis of WISN is believed to be secondary to a more rapid initial reduction in blood levels of vitamin K dependent anticoagulants (proteins C and S) than the procoagulants (factors II, IX & X) during the warfarin anticoagulation. The lowering of protein C level occurs much earlier, as the half-life of protein C is much shorter compared with most of the procoagulant factors (protein C, 6-8 hours vs. factor VII, 6 hours; factor IX, 24 hours; factor X, 40 hours; factor II 60 hours). This would paradoxically render a temporary hypercoagulable state in the patient. In those patients already deficient in the natural anticoagulants, i.e. protein C, protein S and antithrombin III, this hypercoagulable state is further amplified resulting in the development of thrombi in the microvasculature of the skin. This results in the clinical picture of warfarin induced skin necrosis.

Although protein C deficiency has been implicated in less than 50% of cases, the association of protein S and antithrombin III deficiency has been reported (2, 5). Lupus anticoagulant has also been associated with skin necrosis (10). WISN usually occurs after warfarin therapy with large loading doses (i.e. > 10 mg). Low dose heparin administration for few days to gain a good anticoagulation (PTT = 60-80) and then giving low dose oral warfarin in WISN patients is possible (8). Warkentin and coworker (s) showed the probability of thrombosis in protein C deficient patients in spite of high INR levels which are usually associated with substantial increased thrombin-antithrombin complex level (11).

This case report documents protein S deficiency which itself is a risk factor for both thromboembolic events and skin necrosis due to warfarin. Also this

study shows routine tests for thrombotic factor levels (aPTT and PTT) measurement are not good markers for evaluating coagulation system.

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