WARFARIN-INDUCED SKIN NECROSIS AND SUCCESSFUL RE-ANTICOAGULATION: CASE REPORT AND REVIEW OF THE LITERATURE

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CUTANEOUS COMPLICATIONS of warfarin include ecchymosis and purpura, especially in patients who are elderly, patients on long-term corticosteroid therapy, or patients who have maculopapular, vesicular, or urticarial eruptions; purple toe syndrome; or warfarin skin necrosis. Although warfarin skin necrosis was initially described in 1943,2 it was only in 1954 that reports related to warfarin were first published.3 Since then, several reports have appeared in the literature.4

We describe a 30-year-old female who developed warfarin skin necrosis at the lateral aspect of the right thigh after she was initially started on warfarin. The patient was restarted on warfarin successfully under therapeutic doses of intravenous heparin. The skin necrosis healed without complications.

Case Report

A 30-year-old female presented with swelling and pain of the left leg. A venogram showed evidence of venous thrombosis involving the left external iliac vein. She was started on intravenous (IV) heparin 24,000 to 28,000 U/24 h. On the fifth day, she was started on warfarin 10 mg daily for 3 days, followed by a 7.5 mg daily dosage. Heparin was discontinued on the fourth day after starting warfarin. On the fifth day, she developed pain, erythema, and swelling at the lateral aspect of the mid-right thigh. Petechiae appeared which later developed into a large well-demarcated ecchymotic area at the lateral aspect, approximately 9 x 6 cm in size. Almost 7 days after onset of symptoms, an eschar formed which later sloughed (Figure 1). She was treated with normal saline and sofra-tulle dressing. She developed fever which responded to antibiotics. No organisms could be cultured and the lesion healed within 5 weeks.

When her symptoms first appeared, the patient's prothrombin time (PT) was 18/13 s with an INR of 1.8 (Diaplastin, DIAMED AG) and the activated partial thromboplastin time (APTT) was 37/29 s (Cephalite, bioMerieux). After the appearance of the large ecchymotic area, warfarin was discontinued and IV heparin was restarted at 24,000 to 30,000 U/24 h. Her APTT was kept at 50 to 55/29 s. While the patient was in the hospital, warfarin was restarted at 2 mg for 2 days, then 3 mg for 4 days; it later increased to 4 mg and 5 mg per day. Heparin was discontinued on the ninth day and no new lesion appeared. Protein C and protein S (Assera-plate proteins C and S, Diagnostica Stago [quantitative]) were measured before restarting warfarin and found to be normal (protein C = 113%, protein S = 120%).

Figure 1. Warfarin-induced skin necrosis, lateral aspect of the right thigh with black eschar (10 days after onset of symptoms).
Discussion

Warfarin skin necrosis is a rare nonhemorrhagic complication of warfarin therapy. It affects 0.01% to 0.1% of patients receiving warfarin and usually occurs within 3 to 5 days (range, 4 hours to 17 months) after starting warfarin. Typically, warfarin necrosis begins with pain or a burning sensation, followed by the appearance of a well-demarcated ecchymotic area which may develop into a hemorrhagic bulla and then changes into necrosis. Later, there is a black eschar which sloughs and the lesion may heal on its own, heal by granulation tissue and scarring, or may require grafting or even amputation. Our patient had almost typical presentation and the lesion healed with no need for grafting.

Most lesions occur in the lower half of the body (70% to 80%), at sites containing abundant subcutaneous fat content such as the buttocks, thighs, and breasts. Other areas such as the foot, upper extremity, face, and genitalia may also be affected. Warfarin necrosis develop mainly in middle-aged women.

Histologic findings include thrombosis of the dermal capillaries and small venules with interstitial hemorrhage. The vessel walls and perivascular tissues are unremarkable. The arterioles are usually spared, except in a few cases where arteritis is suspected as the underlying cause. Another theory is hypersensitivity reaction, but these lesions may not recur with subsequent challenge. They may occur with the use of various coumarin compounds as in the case of a patient who had decreased vitamin K-dependent coagulation factors secondary to cholestasis without being on anticoagulants.

When warfarin skin necrosis developed in a patient with protein-C deficiency, it was postulated that an exaggerated imbalance between protein-C activity and the level of procoagulant factors II, IX, and X during the beginning of warfarin therapy provided the necessary thrombogenic mechanism. Protein C is a vitamin K-dependent protein (a blood-coagulation inhibitor). The thrombin-thrombomodulin complex converts protein C to activated protein C. To be fully active, activated protein C requires a cofactor = protein S, another vitamin K-dependent protein. Activated protein C inactivates factors Va and VIIIa. Both protein-C and protein-S deficiencies are considered as hypercoagulable states and are associated with thrombosis. Because of the short half-life of protein C (about 6 hours) compared to factors IX, (about 24 hours), X (about 40 hours) and II (about 60 hours), warfarin skin necrosis was postulated to result from a transient hypercoagulable state secondary to loss of regulation of coagulation cascade that occurs after the initiation of warfarin therapy. When necrosis occurs during long-term therapy, the transient hypercoagulable state is attributed to the relative protein-C deficiency in relation to the other factors.

Warfarin skin necrosis has been reported more frequently in patients with inherited protein-C deficiency, accounting for one third of patients. However, other cases have been reported in patients with acquired protein-C deficiency, with inherited and acquired protein S, and without a known deficiency. Since proteins C and S were measured quantitatively, the possibility of functional abnormality of these two proteins has not been ruled out.

Treatment

Since a sudden drop of protein C may be a factor in warfarin skin necrosis, avoiding large initial doses of warfarin as well as having 4 to 5 days overlap with heparin may prevent this complication. However, by taking some precaution, successful restarting warfarin could be done through several approaches which include (1) using a slow, progressive anticoagulation and a low-dose regimen during the crossover periods, almost similar to what was done with our patient; (2) administering subcutaneous heparin in therapeutic doses; and (3) infusing fresh frozen plasma during the crossover period in patients with protein-C deficiency.

Although it has been reported that continuation of the drug after the appearance of the lesion did not result in exacerbation of the disease or the development of new lesions, treating the patient immediately with heparin or vitamin K or both with fresh frozen plasma may prevent the progression to necrosis. This report emphasizes that warfarin skin necrosis, though rare but a serious complication, may be prevented by starting with a low-dose warfarin and having an adequate overlap before discontinuing heparin.
References