Case Report

Warfarin-Induced Skin Necrosis

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ABSTRACT

Background: Warfarin is a frequently used oral anticoagulant in the treatment and prevention of various medical conditions. One uncommon adverse effect that can occur following the initiation of therapy is warfarin-induced skin necrosis. Because it is a rare effect with an undetermined pathophysiology of disease, the treatment is not well established.

Case: A 52-year-old female was prescribed warfarin and enoxaparin for a newly diagnosed deep vein thrombosis (DVT) in the left lower extremity. On day 4 of therapy, the patient had a supratherapeutic international normalized ratio (INR), prompting the discontinuation of enoxaparin and a decrease in the warfarin dose. The patient returned to the emergency department on day 7 of treatment with a purple, cold, and extremely painful right foot with punctate areas of necrosis and petechiae proximal to the discoloration. The patient's INR was found to be 10.64. Following the diagnosis of warfarin-induced skin necrosis, the patient was administered vitamin K intravenously and fresh frozen plasma (FFP) to reverse the effects of warfarin and promote protein C and S synthesis. Once the patient's INR was no longer supratherapeutic, subcutaneous enoxaparin was re-started as treatment for the known recent DVT. The patient's necrotic foot began to improve and she was discharged home with an anticipated full recovery.

Conclusions: Based on the proposed pathophysiology of disease, adequate bridge therapy may decrease the likelihood of developing this life-threatening condition. Early recognition and treatment with intravenous vitamin K, FFP or 4-factor prothrombin complex concentrate, and continued wound care are essential to prevent further complications.

Key Words—protein C deficiency, purple toe syndrome, warfarin, warfarin adverse effects, warfarin effects, warfarin-induced skin necrosis

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Warfarin is a frequently used oral anticoagulant that is approved by the US Food and Drug Administration (FDA) for the treatment and prevention of various medical conditions. Warfarin inhibits the activation of vitamin K-dependent clotting factors II, VII, IX, and X and the anticoagulant proteins C and S.¹⁻³ Warfarin-induced skin necrosis is a rare (0.01%-0.1%) but serious complication that usually occurs within the first several days following warfarin initiation, although case reports have described this phenomenon later in therapy as well.²⁻⁵ This adverse drug reaction appears

to be associated with larger doses of warfarin without the use of bridge therapy.³ The pathophysiology is not well understood, however it is theorized that this complication is due to the initial procoagulant state that warfarin causes, leading to the formation of fibrin clots within the microvasculature. These blood clots cause interruption in blood supply to the skin, resulting in necrosis. The general progression of warfarin-induced skin necrosis is as follows: pain and erythema; petechial hemorrhages; red, purple, blue, or black discoloration; necrosis; and hemorrhagic blisters and/or bullae. Early recognition of symptoms

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and treatment are vital to preventing substantial morbidity associated with warfarin-induced skin necrosis; however, due to its rare occurrence, appropriate treatment has not been well established.²

CASE REPORT

A 52-year-old Caucasian female presented to the emergency department (ED) with a 2-day history of left lower extremity edema and pain. Duplex ultrasound revealed a nonocclusive thrombus in the left distal superficial femoral and popliteal veins. The patient was initiated this day (day 1 of treatment) on treatment for the deep vein thrombosis (DVT) with warfarin 5 mg by mouth once daily and enoxaparin 60 mg (1 mg/kg; patient's total body weight 57 kg; serum creatinine 1.1 mg/dL) subcutaneously twice daily and then was subsequently discharged. As instructed, the patient returned to the ED on day 4 of treatment to have her international normalized ratio (INR) checked as she was unable to follow-up with her primary care physician in the given time frame. Due to a supratherapeutic INR of 3.63, the patient was instructed to hold one dose of warfarin and discontinue enoxaparin, then resume on day 5 of treatment with warfarin 2.5 mg by mouth daily. On day 6, the patient reported going to bed with her right foot "ice cold," but denied pain or discoloration. When she awoke on day 7 of treatment, her foot was purple, cold, and extremely painful, which prompted

her return to the ED. She denied any chest pain, shortness of breath, fevers, chills, nausea, vomiting, or bleeding. The patient's past medical history is extensive and significant for a chronic left elbow ulcer (stage 3), chronic hip and back pain, and opioid dependency. Her surgical history is significant for right hip arthroplasty with several (8+) revisions and chronic infections, and amputation of the second toe of the right foot. On last culture, she was found to be growing *Candida tropicalis* in the hip joint and was taking fluconazole 200 mg by mouth daily for long-term treatment. She also reported a 10 pack-year smoking history. Her home medications at the time of admission were extensive; however she noted no changes in her medication regimen except for the addition of anticoagulants. On physical exam, the right foot was noted to have purple skin discoloration, mild edema, and was cold to the touch. Proximal to the discoloration were punctate areas of necrosis and petechiae. A duplex ultrasound was negative for DVT in the right lower extremity. A urine drug screen was positive for opiates and tetrahydrocannabinol. The patient's INR was found to be 10.64 (hemoglobin 10.5 g/dL, hematocrit 33.1%, platelet count 346 K/ μ L) and she was admitted (Figure 1).

Warfarin-induced skin necrosis was immediately suspected based on presentation and time since initiation of warfarin therapy. The patient was administered vitamin K 10 mg intravenously once and 2 units

Figure 1. The patient's foot at the time of admission. [Color image is available in the digital edition and online archive.]

of fresh frozen plasma (FFP) to reverse the effects of warfarin and promote protein C and S synthesis. On the evening of day 7 (1st day of admission), her INR had dropped to 1.73, so enoxaparin was re-started as treatment for the known recent DVT. Hematology and surgery were consulted, however no interventions were needed. Tests for antiphospholipid antibody panel, factor V Leiden mutation, and prothrombin gene mutation were all negative. Throughout the next 11 days, the patient's foot necrosis was stable and did not exceed the borders drawn on admission. The bullae began to rupture and desquamation was noted on the foot. The foot improved in color and temperature and did not require debridement or surgical intervention. Parenteral anticoagulation was transitioned to the oral anticoagulant rivaroxaban in preparation for discharge. Because the DVT was diagnosed only 1 week prior to this hospital admission, the dose of rivaroxaban was that of a newly diagnosed DVT: 15 mg twice daily for 21 days followed by 20 mg once daily. The patient required a substantial pain regimen to control the acute pain in the necrotic foot in addition to her pre-existing chronic hip and back pain. The patient was discharged home with an anticipated full recovery of the foot, as the necrosis had improved tremendously during the hospital course (**Figure 2**).

Twelve days following the patient's discharge from the hospital, the patient was readmitted for a below the knee amputation as her foot had become

black and gangrenous with no sensation below the ankle. Per the patient's report, she had been adherent with her anticoagulation therapy with rivaroxaban prior to admission. Upon re-initiation of rivaroxaban following the amputation, the patient developed a gastrointestinal bleed secondary to a gastric ulcer. She was deemed no longer a candidate for anticoagulation, so an IVC filter was placed. Two months later, she was re-admitted with complaints of a necrotic perineal ulcer in addition to her decubitus, elbow, right leg stump, and right knee necrotic lesions/ulcers. She was found to have a pulmonary embolism in addition to recurrent infections and sepsis. Ultimately, she was transitioned to comfort care and was transferred to hospice.

DISCUSSION

Warfarin-induced skin necrosis, although rare (<0.1%), is a known complication of warfarin therapy.^{4,5} Necrosis occurs more often in females and can occur in the limbs and adipose tissue, including the breast, buttocks, and penis, with an onset usually within several days of initiation of therapy.^{4,7} In addition to the inhibition of the coagulation factors II, VII, IX, and X, warfarin also inhibits the anticoagulant proteins C and S. Due to the different half lives of each of these factors, there is an imbalance that favors coagulation during the first few days of warfarin therapy. It is theorized that warfarin-induced skin

Figure 2. The patient's foot with bullae several days after admission. [Color image is available in the digital edition and online archive.]

necrosis is caused by this transient hypercoagulable state.^{8,9} The American College of Chest Physicians guidelines recommend bridge therapy for at least 5 days and until the INR is stable and therapeutic for at least 24 hours in patients receiving warfarin for treatment of a DVT.¹⁰ For this patient, bridge therapy was discontinued due to concerns for bleeding with a supratherapeutic INR at day 3. She then experienced skin necrosis of the right foot after taking 4 doses of warfarin in the 5 days after diagnosis of a DVT.

One method for estimating the probability of an adverse drug reaction is with the Naranjo score.¹¹ This scoring system stratifies the likelihood that the clinical event does indeed correlate with the drug in question into the following categories: definite (score 9-10), probable (score 5-8), possible (score 1-4), or doubtful (score 0). Based on the Naranjo scoring system, it is "probable" that the patient in question suffered from warfarin-induced skin necrosis (score 7).

Literature describing appropriate treatment of warfarin-induced skin necrosis is lacking due to its very low incidence. Current treatment options are based on previously published case reports and include the following, depending on the extent of the necrosis: immediate discontinuation of warfarin to prevent further necrosis, reversal of warfarin effects with the administration of vitamin K, possible administration of FFP and protein C concentrate to replace coagulation and anticoagulation factors, respectively, and wound care with possible amputation.¹⁻⁷ Anticoagulation should be continued with a parenteral agent once appropriate. These case reports do not specify the dose and/or route of administration of vitamin K or how they correlate with INR. Also lacking is information in determining the appropriateness and dosages of FFP and protein C concentrate.

Based on American College of Chest Physicians guideline recommendations, this patient was a candidate for oral vitamin K therapy due to an INR greater than 10 without evidence of active bleeding.¹⁰ The decision was made to administer 10 mg intravenous vitamin K for this patient in order to promote protein C and S synthesis rapidly as the patient was experiencing an acute adverse effect. Oral vitamin K may require up to 48 hours for the INR to return to a normal range, whereas the intravenous formulation may only take 12 to 14 hours.^{10,12} By emergently reversing warfarin to a therapeutic or subtherapeutic INR, the patient may safely receive a parenteral anticoagulant to treat the current DVT and prevent any further complications.

FFP contains the coagulation factors II, VII, IX, and X and protein C and S and is therefore recommended to replace proteins C and S.^{10,13} Historically, FFP has been used in the treatment of patients with a major bleeding event in the setting of anticoagulant therapy. The dosage recommendation for patients who are actively bleeding is approximately 10 mL/kg body weight (one unit FFP = ~200 mL).¹³ As most patients with warfarin-induced skin necrosis are not actively bleeding, this dose may be slightly higher than necessary. Taking this information into consideration, the administration of 2 units of FFP for this patient appears appropriate.

There are drawbacks to the use of FFP, including the storage at specific temperatures, high volumes of infusion, and the potential transfer of infection.¹⁰ A new option is 4-factor prothrombin complex concentrate (PCC). This product contains the coagulation factors II, VII, IX, and X and proteins C and S, similarly to FFP.¹⁴ Although there are no reports of its use in patients with warfarin-induced skin necrosis, it has been proven favorable in patients with an acute warfarin-related bleed. When compared to FFP, 4-factor PCC reduces INR and increases the concentration of proteins C and S faster and more effectively with a lower volume of infusion.¹⁴⁻¹⁶ Four-factor PCC may be considered in patients with warfarin-induced skin necrosis.

Protein C concentrate is often recommended, however it is rarely used in patients with warfarin-induced skin necrosis, likely due to a lack of evidence for its use for this indication, its high cost, and its lack of availability at the majority of hospitals.^{1-7,17} Clinicians may consider the use of protein C concentrate, particularly in patients with an underlying deficiency.

Although ultimately this patient did not have a good outcome, the inpatient treatment of her warfarin-induced skin necrosis proved to be appropriate and beneficial. During her 11 day hospital stay, the necrotic foot was improving tremendously without the need for surgical intervention or debridement. Upon discharge, the color of the foot had begun to return to normal and she had intact pulses with normal arterial duplex. Unfortunately, self-care over the next 12 days led to a clinical deterioration.

Prescribers of warfarin should be aware of induction of skin necrosis as a rare, but known, adverse effect of the medication. Adequate bridge therapy may decrease the likelihood of the development of this life-threatening condition. Early recognition and treatment with intravenous vitamin K, FFP or 4-factor PCC, and continued wound care are essential to prevent further complications.

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