

Warfarin-Induced Skin Necrosis

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Oral anticoagulation therapy with warfarin may cause injury to the skin. Cutaneous injury from warfarin begins as localized paresthesias with an erythematous flush, progresses to petechiae and hemorrhagic bullae, and may eventually result in full-thickness skin necrosis. Patients typically experience pain in affected areas. The onset of disease is usually between the third and sixth day of therapy. Early recognition and treatment are important to avoid substantial morbidity. This article describes the clinical course of a patient who developed warfarin-induced skin necrosis (WISN) and discusses the clinical manifestations, diagnosis, treatment, and prevention of this condition.

CASE PRESENTATION

Emergency Department Evaluation

A 73-year-old woman with a history of hypertension, glaucoma, and heavy tobacco abuse was brought to the emergency department after being found lying on the floor semiconscious at home. Chest radiography revealed right middle/lower lobe pneumonia. Further evaluation revealed atrial fibrillation with a rapid ventricular response, temperature of 40.2°C (104.3°F), leukocyte count of $28.4 \times 10^3/\text{mm}^3$, mild respiratory distress, and altered mental status. These findings were subsequently attributed to pneumococcal meningitis after culture of cerebrospinal fluid. She was treated with oxygen, intravenous hydration therapy, antibiotic drugs, and heparin, and she was admitted to the hospital for further evaluation and treatment.

Hospital Course

Because of decreasing PaO_2 , despite the administration of 100% oxygen, the patient was urgently intubated for ventilatory support during her first day in the hospital. The neurology department was consulted for assistance with the management of her meningitis after she began to experience seizures and left-sided flaccidity.

Diagnostic studies. An electroencephalogram revealed generalized slowing, secondary to nonspecific encephalopathy, but no seizure activity. An echocardiogram showed moderate-to-severe aortic regurgitation

with an ejection fraction of approximately 58% and no vegetations. Results of an upper-extremity ultrasonographic examination were normal, and a Doppler examination of the carotid arteries showed only minimal changes, bilaterally. A venous duplex ultrasonographic examination of both lower extremities revealed acute right sural and peroneal vein thromboses (ie, deep venous thromboses [DVTs]), which supported the decision to administer heparin to the patient.

Heparin therapy. Heparin was administered by using our institution's protocol of 5000 U administered via intravenous bolus, followed immediately by maintenance therapy involving the continuous intravenous infusion of heparin at an initial rate of 1000 U/h. According to the protocol, adjustments to the infusion rate are to be made every 6 hours, until the partial thromboplastin time (PTT) reaches the therapeutic range; the PTT is in the therapeutic range when it is approximately 2 times the control value.

The patient had a difficult course after the initiation of heparin therapy. Because she could not be weaned from the ventilator, a tracheostomy with concurrent percutaneous gastrostomy was performed. During the next few days, the patient's mental status improved; however, she continued to be dependent on the ventilator.

Warfarin therapy. By the ninth hospital day, the patient continued to have intermittent atrial fibrillation. The atrial fibrillation, the lower extremity DVTs, and her long-term confinement to bed prompted a decision to convert the heparin to warfarin; after the warfarin took effect, the heparin was to be discontinued. The patient initially received 5 mg of warfarin, orally, each evening for 2 days, and the dose was decreased to 4 mg the third evening after an initial increase in her international normalized ratio (INR), from 1.0 to 1.6. Our target for the INR was 2.0 to 2.5 times the control value. However, the following morning, the patient's

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Figure 1. (A) An erythematous skin lesion, approximately 15 cm by 10 cm, on the case patient's right hip. (B) A similar lesion on the patient's left thigh.

INR was greater than 5.6 on repeat analysis, and the warfarin was withheld. The INR remained greater than 5.4 for 2 days after the warfarin was stopped; at that time, the heparin infusion was also discontinued. The heparin infusion had previously been maintained with therapeutic PTTs, without difficulty.

Skin lesions. By the sixth day after warfarin had first been administered, an erythematous skin lesion, approximately 15 cm by 10 cm, was noted on the patient's right hip and a similar one was noted on her left thigh (**Figure 1**); the patient reported intense localized pain bilaterally. An initial concern regarding a possible decubitus variant was dismissed because of the lesions' presence in non-weight-bearing locations, as well as the skin-protective air mattress used by the patient, peau d'orange skin changes, intense pain, and development of ecchymosis and bullae within the lesions within 6 hours. A literature search was performed for treatment recommendations.

Further treatment. The patient was given 10 mg of vitamin K, intravenously, and 2 U of fresh frozen plasma (FFP) to reverse the effects of the warfarin.¹ She was also given 15,000 U of heparin via intravenous bolus, and continuous heparin infusion therapy was reinstated to prevent hypercoagulability. The maintenance dosage of the heparin was set according to a weight-based regimen, to rapidly increase the PTT to 2 to 3 times the control value.² Subsequently, the patient bled superficially at her tracheostomy site (< 200 mL), and the bleeding was controlled with direct pressure. The patient was given an additional 5 mg of vitamin K, intravenously. The heparin infusion was discontinued, and a third unit of FFP was administered. No further bleeding occurred. A disseminated intravascular coagulopathy panel was negative, and the patient's mental status did not deteriorate.

Wound care. Local wound care was provided to prevent bullae rupture, and low-molecular-weight heparin was administered, subcutaneously, for DVT prophylaxis. The bullae fluid, which was cultured at the request of an infectious disease consultant, was negative for aerobic and anaerobic bacteria, acid-fast bacilli, and fungi. Consultation with a dermatologist confirmed that the lesions were consistent with WISN, and the dermatologist agreed with the plan of local wound care pending a determination of the severity of the patient's condition and future definitive care.

To improve our understanding of the spectrum of tissue damage associated with WISN, the dermatologist equated the spectrum to that observed with partial to full-thickness burns and used a grading scale commonly used with decubitus ulcers (grade I to IV). However, the consultant did not know of any formal grading scale for WISN.

Patient outcome. The intensity of pain experienced by the patient rapidly decreased during the next 3 or 4 days after the start of the wound care, and the skin lesions matured quickly. There was some increase in the size of the bullae and only superficial sloughing (grade I) in the areas that had encompassed the bullae, leaving clean, well-demarcated margins, with serosanguinous crusting and granulation tissue at the bases. By this time, the sizes of the lesions on her legs were as follows: right leg, 1.5 × 2.5 cm; left leg, 6 × 8 cm. The patient was subsequently transferred to a long-term ventilator facility with ongoing local wound care consisting of daily dressing changes and topical antibiotic ointment application.

DISCUSSION

According to our literature review, skin necrosis occurs in 0.01% to 0.1% of patients receiving warfarin,

orally.³ It is more common among middle-aged, perimenopausal, obese women being treated for DVTs or pulmonary emboli.^{1,3} WISN has been postulated to be associated with deficiencies of protein C, protein S, factor VII, and antithrombin III.^{1,2,4} Also, there is a case report attributing WISN-like lesions to vitamin K deficiency in the absence of warfarin therapy.⁵

Clinical Manifestations

Patients may initially experience local paresthesias with an erythematous flush that is not well demarcated, followed by intense pain and the rapid development and coalescence of petechiae, with concomitant accumulation of subcutaneous edema resulting in a peau d'orange appearance. During the first 24 hours after the first sign of skin lesions, hemorrhagic bullae within the involved area may occur and signal irreversible tissue injury. Full-thickness skin necrosis is the end stage of cutaneous injury. Once the overlying eschar sloughs, the residual defect is revealed. The spectrum of tissue damage ranges from self-limited, superficial tissue loss capable of healing by spontaneous granulation, to injury requiring surgical débridement with skin grafting, to extreme tissue sloughing and loss with extensive deficits occasionally leading to amputation.¹

Location of the lesions varies. However, in women, the breasts are the most common sites, followed by the buttocks and thighs.¹ In men, chest involvement is rare, but sometimes the skin of the penis may be affected.¹ In addition to these sites, the trunk, face, and extremities may be involved in both men and women.

Diagnosis

At initial presentation, the lesion(s) of WISN must be differentiated from several conditions, such as gangrene,¹ decubitus ulcer,³ and a hematoma—a much more common complication of warfarin therapy.⁶ The differential diagnosis of skin lesions in patients receiving warfarin therapy is presented in **Table 1**. WISN is usually diagnosed clinically, based on patient symptoms, lesion appearance, clues in the patient's phenotype (eg, obesity, short stature, stocky build), and history of recent warfarin therapy. Approximately 83% to 90% of patients develop symptoms between days 3 and 6 of warfarin treatment.⁷ Although not required for diagnosis, skin biopsy will often reveal subepidermal hemorrhages with adjacent epidermal necrosis and congestion and thrombosis of superficial dermal capillaries.⁷

Treatment

Short-term treatment recommendations include the use of vitamin K, administered either subcuta-

Table 1. Differential Diagnosis of Skin Lesions in Patients Receiving Warfarin Therapy

Acute necrotizing fasciitis
Calciophylaxis (in patients undergoing renal dialysis)
Cellulitis
Cryofibrinogenemia
Decubitus ulcer
Disseminated intravascular coagulopathy with purpura fulminans
Ecthyma
Fournier's gangrene
Hematoma
Heparin-induced antiplatelet antibodies
Inflammatory breast cancer
Lupus anticoagulation-associated skin necrosis
Microembolization
Purple toe cholesterol embolism syndrome
Pyoderma gangrenosum

neously or intravenously (depending on patient stability and the extent of skin involvement), and FFP, with the objective of restoring vitamin K-dependent coagulation factors depleted by warfarin therapy. Based on a patient's underlying pathology prompting anticoagulation therapy, many clinicians also recommend resumption or continuance of heparin therapy by using a weight-based dosing protocol to maintain the PTT at 2 to 3 times the control value. Newer short-term therapies include purified protein C concentrate, for patients who are deficient in the protein, and prostacyclin, for which clinical and histologic improvements have been reported.¹

Long-term treatment includes local wound care and observation of the wound for signs of granulation tissue and healing. Some injuries require surgical débridement with skin grafting. In severe cases, amputation may be necessary.

Some clinicians have reported the recurrence of WISN in patients reintroduced to warfarin.^{2,3} Although such recurrence is rare, the cautious resumption of warfarin is recommended for patients with significant need for anticoagulant therapy. Long-term (subcutaneous) therapy with heparin is associated with osteoporosis and thrombocytopenia, as well as a very rare skin necrosis syndrome similar to WISN.⁷ Some clinicians suggest fractionated (low-molecular-weight) heparin as a more conservative method of anticoagulation therapy.⁷

Fractionated heparin has a more favorable adverse-effects profile compared with unfractionated heparin.⁷

Prevention

Several recommendations for preventing WISN have been advanced: (1) heparin should be continued until the INR is near the therapeutic range as a result of the warfarin therapy and vitamin K-dependent clotting factors have been consumed¹⁻¹²; (2) standard or low-dose warfarin should be used instead of initial large loading-doses; and (3) a clinician should be cautious when advancing the dosage of warfarin.

In our patient, the heparin remained therapeutic during the initiation of warfarin therapy, and the heparin was discontinued after 2 days of an INR greater than 5. The patient received a total of 14 mg of warfarin over 3 days, which reflected a decrease in dose the third day after an initial increase in the patient's INR.

CONCLUSION

Skin necrosis is a rare but serious complication of oral anticoagulation therapy with warfarin—there are only approximately 200 reports. WISN occurred in our patient despite our following literature-recommended precautions for the administration of warfarin. Practitioners should consider this reaction when suspicious skin lesions appear, regardless of the manner in which warfarin treatment was initiated. HP

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