

## THE CLINICAL PICTURE

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# The Clinical Picture

## Purpuric lesion on the elbow

**A** 75-YEAR-OLD MAN was admitted to the hospital with new-onset atrial fibrillation. He underwent rate control, and a heparin infusion was started. Warfarin (Coumadin) 10 mg was added on the second hospital day. Two days later, the heparin infusion was discontinued when the international normalized ratio (INR) was in the therapeutic range.

On day 5, he developed a painful lesion on the left elbow, which progressed to multiple lesions on the forearms, abdomen, and lower legs. No history of trauma was noted. His INR was 5.2, and wound cultures were negative (FIGURE 1).

**Q:** Which is the most likely diagnosis?

- Pyoderma gangrenosum
- Cutaneous vasculitis
- Warfarin-induced skin necrosis
- Ecthyma gangrenosum
- Dermatitis herpetiformis

**A:** The most likely diagnosis is warfarin-induced skin necrosis, a rare paradoxical complication that occurs in 0.01% to 0.1% of patients receiving this drug.<sup>1</sup> Microthrombosis leads to necrosis of the skin and subcutaneous tissues, arising within 2 to 10 days after the start of anticoagulation therapy, although in rare cases it can occur months to years later.<sup>2,3</sup>

The most common risk factors include the unopposed use of warfarin (ie, unopposed by heparin at the start of therapy), using higher doses of warfarin during the initiation of anticoagulation, and inadequate overlap with an effective parenteral anticoagulant. Patients with protein C or S deficiency, heparin-induced thrombocytopenia,<sup>4</sup> resistance to acti-



**FIGURE 1**

vated protein C, antithrombin deficiency, and lupus anticoagulant have also been reported to be at risk.

The most common sites affected are areas with high subcutaneous fat content, such as the abdomen, thighs, breasts, and buttocks. Skin presentations can vary from dermal plaques to petechial lesions, which rapidly progress to well-demarcated, bluish-black, painful lesions and eventually to hemorrhagic bullae and necrosis.<sup>1</sup>

At the start of warfarin therapy, the levels of protein C and factor VII (with half-lives of 5 to 8 hours) fall faster than those of other vitamin-K-dependent factors (ie, factors II, IX, and X). This causes a transient imbalance in procoagulant and anticoagulant pathways favoring thrombosis of the microvasculature, with resulting necrosis. Patients with hereditary protein C deficiency are at higher risk.<sup>5</sup>

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Histologic review of lesions often shows venous thrombosis and diffuse necrosis of the dermis and subcutaneous tissue.<sup>2</sup>

Promptly stopping the warfarin and choosing alternative anticoagulation may help prevent further progression of this condition. Wound care, debridement, and sometimes skin grafting may be necessary, depending on the extent of the lesions. A rechallenge with warfarin is often difficult, but cases have been reported in which treatment was resumed without adverse consequences.<sup>6</sup> Avoiding large loading doses of warfarin, gradually increasing doses over an extended period (about 10 days),<sup>3</sup> and starting warfarin with a heparin bridge for at least 5 days (which was not done in this patient) would prevent the condition.

Early recognition, differentiation, and diagnosis are essential to minimize morbidity and to prevent death.

### ■ CASE CONTINUED

Warfarin was discontinued once the patient developed the skin lesions. He received vitamin K and fresh frozen plasma to normalize his INR, and he was started on a heparin infusion, after which the lesions began to heal. The patient refused a skin biopsy. Platelet counts remained stable during his hospital course. Pro-

tein C levels were not checked, given his recent use of warfarin. He was started on dabigatran (Pradaxa) and was discharged a week later.

### ■ THE OTHER DIAGNOSTIC CHOICES

**Pyoderma gangrenosum** is an uncommon ulcerative skin condition often associated with autoimmune disease. It usually starts at the site of a minor injury, more commonly on the legs, and gradually progresses to a painful ulcer.

**Cutaneous vasculitis** is an inflammation of small blood vessels characterized by palpable purpura. The lesions can resemble urticaria, petechia, or erythema multiforme. It is commonly associated with infection, drug therapy, inflammatory disease, and malignancy.

**Ecthyma gangrenosum** is an infection of skin caused by *Pseudomonas aeruginosa*. Usually, it presents as hemorrhagic pustules or infarct-like areas with surrounding erythema that evolve into necrotic ulcers surrounded by erythema.

**Dermatitis herpetiformis** is a chronic skin condition, presenting with fluid-filled blisters and commonly involving the neck, back, scalp, and elbows. This condition is associated with celiac disease, and the lesions are extremely pruritic. ■

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Wound care, debridement, and skin grafting may be necessary based on the extent of the lesions