Enoxaparin-Induced Hemorrhagic Bullae at Sites of Trauma and Endothelial Pathology

Michael L. Garner, MD; Laura G. Pruitt, MD; Joseph Nenow, MD; Charles Phillips, MD

To the Editor:

A 67-year-old man with diabetes mellitus was admitted to the hospital for exacerbation of congestive heart failure and atrial flutter with rapid ventricular response. He subsequently developed a non-ST segment elevation myocardial infarction and was started on subcutaneous enoxaparin 110 mg twice daily. On day 9 of hospitalization, small "blood blisters" on the legs were noted by the nurse, and dermatology was consulted.

Physical examination revealed tense hemorrhagic bullae with erythematous haloes scattered over the arms and legs and to a lesser extent on the trunk. The bullae were most concentrated at the surrounding subcutaneous injection sites of insulin and enoxaparin with secondary bruising (Figure 1). The lesions also were present on the legs, where pitting edema and capillaritis also were appreciated (Figure 2).

Laboratory workup for heparin-induced thrombocytopenia was negative. A diagnosis of enoxaparin-associated hemorrhagic bullae was made. Biopsy was recommended, but the patient declined based on anecdotal reports that the bullae typically self-resolve.

The enoxaparin was discontinued 7 days after the dermatology consultation, and the patient was transitioned to apixaban. A review of the medical record during the dermatology consultation revealed he had been on aspirin (81–385 mg/d) for 13 years prior to admission and had received prophylactic enoxaparin (40 mg/d) while hospitalized 2 and 7 years prior to the current episode of hemorrhagic bullae.

The patient declined outpatient dermatology follow-up; however, his cardiologist noted that the skin lesions had resolved at a 3-week postdischarge

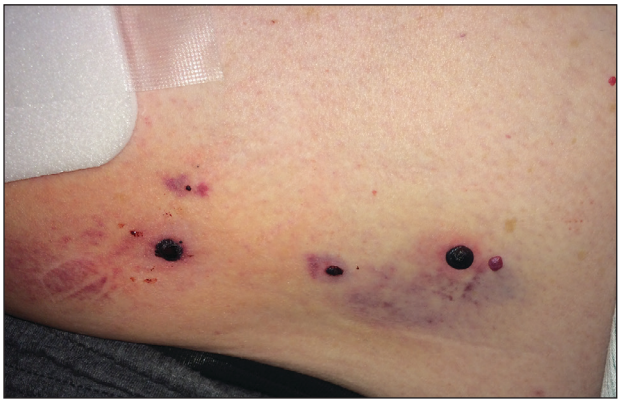

FIGURE 1. Enoxaparin-induced hemorrhagic bullae of the right flank with surrounding traumatic purpura.

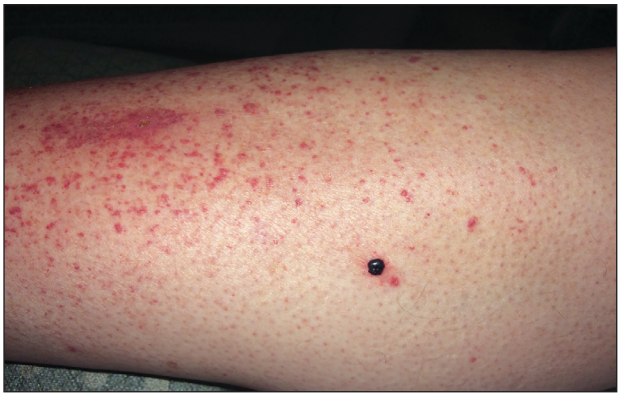

FIGURE 2. Enoxaparin-induced hemorrhagic bullae of the right lower leg with capillaritis and pitting edema.

From the Brody School of Medicine, East Carolina University, Greenville, North Carolina.
Dr. Garner is a medical advisor for Baek Clinical. Drs. Pruitt, Nenow, and Phillips report no conflict of interest.
Correspondence: Michael L. Garner, MD, 517 Moye Blvd, Greenville, NC 27834 (garner85@gmail.com).
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appointment. Approximately 5 months after discharge, the patient was re-treated by the cardiologist with enoxaparin 110 mg twice daily for 3 days to bridge to warfarin after he developed a deep vein thrombosis while taking apixaban. He did not develop hemorrhagic bullae upon retreatment with enoxaparin.

Heparin-induced hemorrhagic bullous dermatosis (HBD) has been associated with administration of both unfractionated and low-molecular-weight heparin.[1] The condition typically develops 5 to 21 days after initiation of heparin as asymptomatic, purple-to-black bullae, sometimes with an erythematous halo.[2,3] The arms and legs are the most common location, but the exact pathogenesis of the lesions remains unknown.[3,4] Most cases resolve within weeks of discontinuing heparin, although some reports have suggested that discontinuation is unnecessary.[3,4]

Histopathologic analysis shows intraepidermal or subepidermal bullae with red blood cells and fibrin in the absence of vasculitis and intravascular thrombi.[1,4] Immunofluorescence studies are negative.[3] In a comprehensive review of HBD, the investigators hypothesized that the pathogenesis may be related to noninflammatory to pauci-inflammatory activation of basement membrane zone proteases or possibly epithelial or endothelial fragility in conjunction with trauma that causes disruption of the vascular endothelium (eg, subcutaneous injections, vasculitis).[4]

Our case is of particular interest because the bullae were strikingly limited to sites of subcutaneous injection and surrounding areas along with coexistent endothelial pathology on the lower legs (capillaritis and pitting edema). These clinical observations support trauma from the injections and altered endothelia as pathogenetic factors in HBD.

Of interest, our patient had 2 prior hospitalizations during which he received prophylactic enoxaparin and did not develop hemorrhagic bullae. Furthermore, repeat exposure to therapeutic dosing of enoxaparin with a shorter duration did not result in recurrence of HBD. This suggests that heparin dosing and duration of therapy also might be involved in the development of HBD.

Our hope is that future reports of HBD will address the presence or absence of coexistent cutaneous pathology, such as edema, stasis dermatitis, bruising, and capillaritis, along with heparin dosing, duration, and prior exposure to heparin treatment so that risk factors and pathogenesis can be further investigated. We also agree with Snow et al[4] that HBD should be included as an outcome in future trials of heparin therapy.

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