

Heparin-induced bullous hemorrhagic dermatosis: A report of 3 cases



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INTRODUCTION

Heparin-induced bullous hemorrhagic dermatosis is an uncommonly reported reaction to heparin, with fewer than 40 cases reported in the English literature and first described in 2006 by Perrinaud et al.¹ The true incidence of bullous hemorrhagic dermatosis is likely higher because it is typically asymptomatic, has a relatively short course and favorable prognosis, and tends to spontaneously resolve regardless of whether heparin treatment is maintained, changed, or discontinued.^{2,3} The mechanism by which this presumed systemic adverse effect occurs remains unknown. Here we present 3 cases of heparin-induced bullous hemorrhagic dermatosis with different presentations at various stages and areas of involvement.

CASE REPORTS

Case 1

A 72-year-old woman with a history of bilateral pulmonary emboli, previously receiving apixaban, was admitted for treatment of a recently diagnosed primary central nervous system lymphoma. Three weeks after admission and starting subcutaneous enoxaparin, she was referred to the dermatology consultation service for evaluation of asymptomatic, bullous lesions on her legs, which began 1 week before. On examination, there were irregularly scattered, tense, hemorrhagic bullae and vesicles, each on a violaceous-erythematous base, concentrated on the anterolateral aspect of her lower legs (Fig 1). A few lesions had eroded, leaving trails of dried blood. There were also a few similar isolated hemorrhagic vesicles on her upper extremities. She had several small ecchymoses on her abdomen from

Abbreviations used:

PT: prothrombin time
 PTT: partial thromboplastin time
 RBC: red blood cell

subcutaneous enoxaparin injections. Laboratory studies showed a marginally low hemoglobin concentration of 11.8 g/dL (normal range 12.0-16.0 g/dL), normal platelet count of 159,000/ μ L (normal range 150,000-400,000/ μ L), normal prothrombin time (PT) of 12.5 seconds (normal range 11.5-14.5 seconds), normal partial thromboplastin time (PTT) of 24.1 seconds (normal range 23.0-36.0 seconds), and a normal international normalized ratio of 0.9. A clinical diagnosis of enoxaparin-induced bullous hemorrhagic dermatosis was made and confirmed by punch biopsy. The histopathology showed intraepidermal blisters containing red blood cells (RBCs), extravasated RBCs in the papillary dermis, and no signs of vasculitis or inflammatory infiltrate (Fig 2). The patient did not develop any new lesions while continuing enoxaparin, and improved during the following week.

Case 2

A 52-year-old female inpatient with atrial fibrillation and recurrent ventricular tachycardia caused by nonischemic cardiomyopathy with lamin A mutation was referred to the dermatology consultation service for evaluation of a new skin lesion on her face. She had been admitted 5 months before for ventricular tachycardia triggering implantable cardioverter-defibrillator discharges and evaluation for orthotopic

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Fig 1. Hemorrhagic bullae and vesicles on lower legs of the patient in case 1.

heart transplant. Before admission, she was receiving warfarin for atrial fibrillation, which began at approximately aged 30 years. Five days after admission, warfarin was switched to weight-based-protocol continuous intravenous unfractionated heparin infusion once her international normalized ratio was subtherapeutic. The heparin was maintained throughout her admission for atrial fibrillation and an intra-aortic balloon pump that was placed during this hospital course. The patient reported the onset of these lesions approximately 4 months after beginning the unfractionated heparin infusion.

Her medications at the dermatology consultation included heparin, aspirin, amiodarone, mexiletine, eplerenone, metolazone, daratumumab, and escitalopram.

On examination, there was an asymptomatic, solitary, 4-mm, hemorrhagic vesicle on a background of uninvolved skin on the right malar aspect of her face (Fig 3). She had similarly asymptomatic discrete lesions at various stages of healing, ranging from 1 to 4 mm, irregularly scattered on areas of her shoulders, lower abdomen, back, and left dorsal aspect of her hand. Older hemorrhagic vesicles were dark and well crusted over, with sharp demarcation from uninvolved surrounding skin. Newer evolving lesions were subtly lobular with underlying areas of erythema that had not yet crusted and were better appreciated under dermoscopy (Fig 4). Results of laboratory studies showed a low hemoglobin concentration of 9.1 g/dL (normal range 12.0-16.0 g/dL), normal platelet count of 178,000/ μ L (normal range 150,000-400,000/ μ L), normal PT of 13.8 seconds (normal range 11.5-14.5 seconds), an elevated PTT of 82.2 seconds (normal range 23.0-36.0 seconds), and a normal international normalized ratio of 1.1. Given the history and clinical presentation, a diagnosis of heparin-induced bullous hemorrhagic dermatosis and recommendation to continue heparin therapy was made. A punch biopsy of a newer

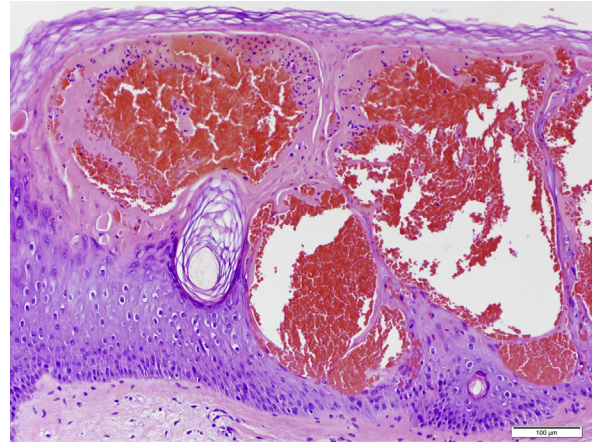


Fig 2. Case 1 histopathology showing intraepidermal blisters containing red blood cells and extravasated red blood cells. There were no signs of vasculitis, thrombosis, or inflammatory infiltrate.



Fig 3. Case 2 clinical presentation, right malar aspect of the face with solitary hemorrhagic vesicle.

lesion on the left upper aspect of her back showed intraepidermal blisters containing RBCs, extravasated RBCs in the papillary dermis, and no signs of vasculitis or inflammatory infiltrate (Fig 5). The lesions were monitored and spontaneously resolved by 3 weeks.

Case 3

A 45-year-old man with end-stage renal disease requiring hemodialysis was admitted for treatment of his valvular heart disease, and was also referred to the dermatology consultation service for evaluation of asymptomatic hemorrhagic lesions on his hands and legs. The patient estimated the onset of the lesions to be at least several weeks ago. He received subcutaneous heparin injections with his hemodialysis 3 times weekly. On examination, there were scattered, small, well-demarcated, hemorrhagic, crusted papules with surrounding erythema on his hands and bilateral aspect of his lower legs (Fig 6). His laboratory studies showed a low hemoglobin concentration of 7.8 g/dL (normal range

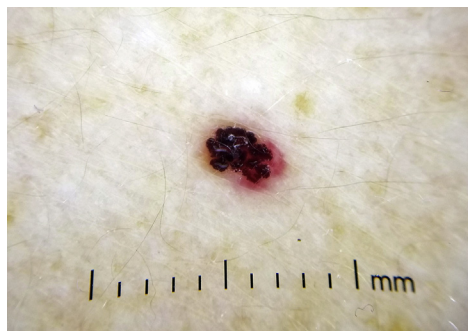


Fig 4. Case 2 dermatoscopic photograph of early hemorrhagic vesicle at left upper aspect of the back.

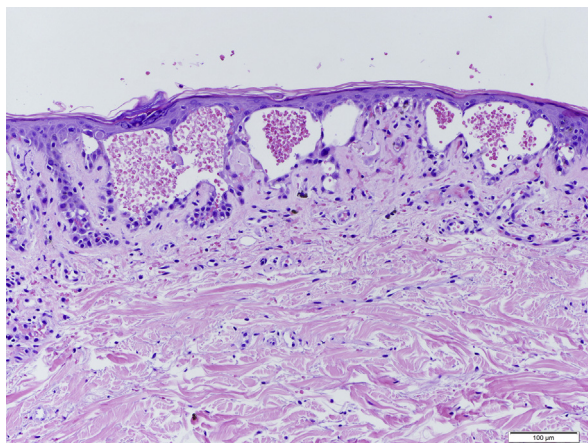


Fig 5. Case 2 histopathology showing intraepidermal blisters containing red blood cells, extravasated red blood cells, and no signs of vasculitis, thrombosis, or inflammatory infiltrate.

12.0-16.0 g/dL), normal platelet count of 169,000/ μ L (normal range 150,000-400,000/ μ L), an elevated PT of 18.1 seconds (normal range 11.5-14.5 seconds), normal PTT of 45.8 seconds (normal range 23.0-36.0 seconds), and a normal international normalized ratio of 1.5. A clinical diagnosis of heparin-induced bullous hemorrhagic dermatosis was made and the lesions continued to resolve during several weeks.

DISCUSSION

Known common adverse reactions to heparin include hematoma, ecchymosis, skin necrosis, urticaria, angioedema, and eczematous dermatitis.^{1,2} Bullous hemorrhagic dermatosis is typically associated with either unfractionated or low-molecular-weight heparin, by subcutaneous injection or continuous infusion, and much less commonly warfarin therapy.¹⁻⁸ Although the clinical lesions of bullous hemorrhagic dermatosis can be distinct, the differential diagnoses include leukocytoclastic



Fig 6. Case 3 clinical presentation, lower legs and feet showing scattered, well-demarcated, hemorrhagic, crusted papules with surrounding erythema.

vasculitis, heparin-induced skin necrosis, and warfarin necrosis. The clinical history and skin biopsy can distinguish between these entities if the diagnosis is in question. A brief review of recent reports of bullous hemorrhagic dermatosis in the English-language literature showed the mean age of patients to be 72 years (range 38 to 90 years), with a male-to-female ratio of 2.6:1. The most frequent sites of lesions were on the extremities alone, followed by the trunk and extremities, lesions on the head and neck being rare.¹⁻⁸ In reports that included size measurements, lesions ranged from 0.2 to 2.0 cm in diameter.^{3,4,7,8} The average duration to onset of lesions was 8.7 days, with a range of 1 to 30 days. Lesions usually resolved by 3 to 4 weeks from onset independent of whether heparin therapy was continued, discontinued, or changed to another anticoagulant therapy.¹⁻⁸ Laboratory and coagulation study results were typically unremarkable.^{1,4-8}

The duration to onset of bullous hemorrhagic dermatosis in case 1 was 2 weeks, which is consistent with most cases described in the literature. However, the onset of bullous hemorrhagic dermatosis in case 2 was unusual in its relative delay of 4 months after the start of unfractionated heparin therapy. The patient's lesions resolved spontaneously by 3 weeks

from presentation despite continuing required heparin therapy. Facial involvement with bullous hemorrhagic dermatosis, as in case 2, is uncommon. The onset of bullous hemorrhagic dermatosis in case 3 was less clear, but the lesions appeared to be in later stages and resolving. The mechanism of bullous hemorrhagic dermatosis remains unknown. Proposed hypotheses have included overanticoagulation, hypersensitivity, and idiosyncratic reaction. However, many patients had normal laboratory study results and were receiving monotherapy anticoagulation, and none demonstrated eosinophils or significant inflammatory infiltrate on biopsy.^{1,3,5,6}

Bullous hemorrhagic dermatosis likely has a higher incidence than suggested in the reported literature because heparin is widely used, and skin lesions of bullous hemorrhagic dermatosis are typically asymptomatic and spontaneously resolve within weeks. Optimal management of bullous hemorrhagic dermatosis remains unclear because reports in the literature are limited. It appears reasonable to maintain heparin therapy if indicated, if the patient is clinically improving without thrombotic or hemorrhagic complications, and if laboratory values remain within normal limits. Increased awareness of bullous hemorrhagic dermatosis can assist and reassure clinicians in managing patients' anticoagulation regimens, noting its currently favorable prognosis.

Further studies are needed to better characterize and understand the pathogenesis of bullous hemorrhagic dermatosis, what predisposes certain patients to this condition, and any unknown implications.

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