Heparin-Induced Bullous Hemorrhagic Dermatosis

Samreen Choudhry, BA; Patricia M. Fishman, MD; Claudia Hernandez, MD

Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) have been used for years in the prophylaxis and treatment of thromboembolic disease. Cutaneous reactions to heparin include hematomas, ecchymoses, erythematous plaques, nodules, skin necrosis, contact dermatitis, and urticaria, all occurring more commonly at local subcutaneous injection sites. Generalized cutaneous reactions are more rare. We report the case of a man with no known risk factors who developed intraepidermal hemorrhagic bullae on distant sites after receiving intravenous UFH for suspected pulmonary embolism. He was diagnosed with heparin-induced bullous hemorrhagic dermatosis and recovered without further complications after discontinuation of the heparin. This case reveals that widespread cutaneous reactions to heparin may occur, though they are rare.

Cutis. 2013;91:93-98.

Unfractionated heparin (UFH) and more recently low-molecular-weight heparin (LMWH) have been used clinically for the last 70 years, primarily for prevention of venous thrombosis and pulmonary embolism. Both forms produce their major anticoagulant effects by activating antithrombin III. Several adverse reactions to heparin have been discussed, with bullous eruptions rarely reported.[1] We present a case of a male patient who presented with a bullous hemorrhagic eruption following the administration of intravenous UFH.

From the University of Illinois at Chicago. Ms. Choudhry is from the College of Medicine, Dr. Fishman is from the Department of Pathology, and Dr. Hernandez is from the Department of Dermatology.

The authors report no conflict of interest.

Correspondence: Claudia Hernandez, MD, University of Illinois at Chicago, Department of Dermatology (MC 624), 808 S Wood St, Room 376 CME, Chicago, IL 60612 (claudiah@uic.edu).

Case Report

An 83-year-old man with a body mass index of 24 presented with gradually worsening shortness of breath and edema of the lower extremities of 2 days' duration. His medical history was remarkable for coronary artery disease, congestive heart failure secondary to ischemic cardiomyopathy, atrial fibrillation, chronic obstructive pulmonary disease, and hypothyroidism. His current medications included a fluticasone propionate metered-dose inhaler, aspirin (81 mg), furosemide, hydralazine hydrochloride, isosorbide dinitrate, levothyroxine sodium, metoprolol succinate, simvastatin, and tiotropium bromide.

Duplex Doppler scan of the lower extremities was obtained along with a ventilation-perfusion scan, which showed a low to moderate probability for pulmonary embolism; however, because of the medical team's high suspicion for pulmonary embolism as well as the patient's atrial fibrillation, coumadin was initiated, which was bridged with UFH. The patient received an initial loading dose of 5000 U of heparin followed by heparin sodium administered as a continuous intravenous infusion (800 U/hour for 6 days). Five days after starting the anticoagulants, the patient developed numerous scattered clusters of tense hemorrhagic bullae on his left arm, flank, bilateral thighs, and anterior aspect of the lower left leg. Physical examination revealed tense hemorrhagic bullae ranging from 0.5- to 1-cm in size on otherwise normal skin (Figures 1 and 2). The bullae were asymptomatic but bled easily upon trauma or scratching. No other atypical cutaneous findings, including oral lesions, were noted. Our differential diagnoses included drug-induced bullae, atypical bullous dermatoses including bullous pemphigoid, bullous variant of erythema multiforme, and septic phenomenon. Erythema multiforme was unlikely given the specific distribution of the lesions and minimal inflammation, and septic phenomenon was ruled out because the patient was afebrile with no leukocytosis and sparsely distributed bullae.

A punch biopsy specimen was obtained from the left thigh, which revealed a tense subcorneal

Figure 1. Clustered hemorrhagic bullae on thigh.

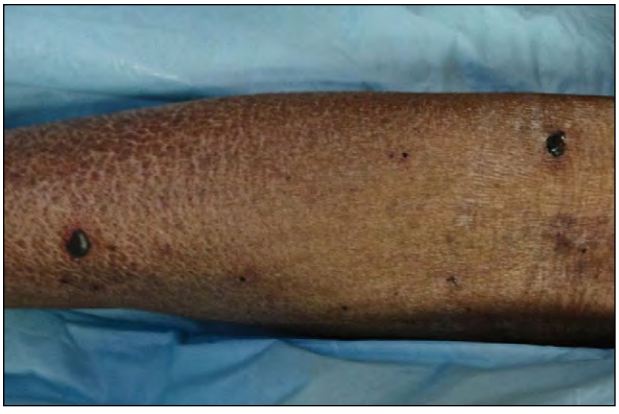

Figure 2. Widespread bullae on left forearm that was distant from heparin infusion site.

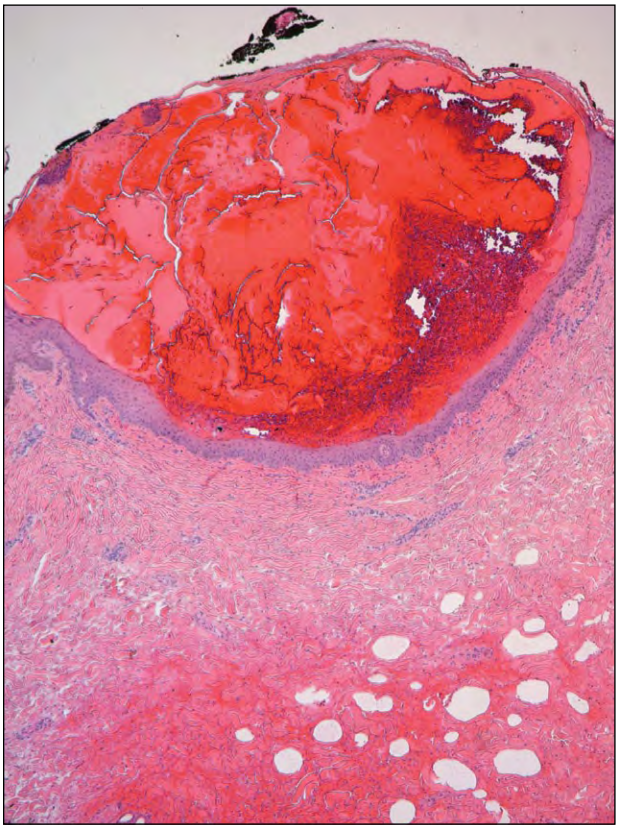

Figure 3. Tense intraepidermal blister filled with red blood cells (H&E, original magnification ×40).

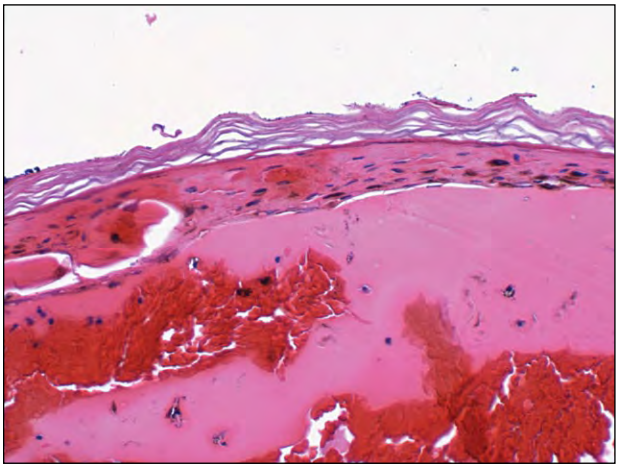

Figure 4. Higher-power view demonstrating intraepithelial location of bulla (H&E, original magnification ×200).

intraepidermal bulla filled with serum and red blood cells. The underlying dermis showed no evidence of vasculitis or thrombi (Figures 3 and 4).

The following laboratory results were pertinent: platelet count, 148,000/μL (reference range, 150,000−350,000/μL); international normalized ratio, 1.3 (reference range, 0.9–1.2); creatinine, 3.2 mg/dL (reference range, 0.6–1.2 mg/dL). After the administration of heparin and the subsequent skin eruption, the patient's hemoglobin count was 9.8 g/dL (reference range, 14.0−17.5 g/dL), his platelet count was 146,000/μL, the activated partial thromboplastin time was 90.6 seconds (reference range, 25−40 seconds), and the international normalized ratio was 1.8. He remained afebrile with a white blood cell count within reference range throughout his hospitalization.

Although bullous eruptions have been reported from treatment with furosemide, in this case the initiation of heparin temporarily was associated with the eruption. The patient was diagnosed with a heparin-induced bullous eruption. Discontinuation of heparin was recommended, and the patient's eruption resolved without incident. Subsequently, the patient was discharged and placed on a furosemide regimen (80 mg twice daily). The patient was scheduled to undergo antiplatelet factor 4 antibody and allergy testing as an outpatient but was lost to follow-up. Although these tests would have been valuable additions to the evidence supporting our diagnosis, the histopathology and temporal relationship between the heparin introduction and onset of the eruption are strong evidence for causation. The patient was discharged on a higher dose of furosemide, which was never discontinued, and had resolution of his bullae during this time, which does not support furosemide as the causative drug.

Comment

Heparins are a group of naturally occurring glycosaminoglycans utilized for the prevention and treatment of thrombo-occlusive and embolic disease due to their anticoagulant properties. Heparin is only effective in the presence of antithrombin III.[2] The heparin-antithrombin complex inactivates several coagulation enzymes including prothrombin (factor IIa) and factors IXa, Xa, XIa, and XIIa. Heparin also binds to platelet factor 4 and the vascular endothelium.[3] Although it is primarily considered an anticoagulant, heparin has several well-known effects, including angiogenesis regulation, lipoprotein lipase modulation, inhibition of vascular smooth muscle cell proliferation (after endothelial injury), and endothelial wall maintenance.[4] Endogenous heparin primarily is found in mast cells, basophils, and to a lesser extent in the endothelial cells of the vasculature.

The pathogenesis of heparin-induced cutaneous reactions is poorly understood; however, several theories exist. Initially, it was thought that the reaction was due to a preservative in heparin, but because LMWHs, which are free of preservatives, also have been associated with skin eruptions, this cause is unlikely.[5] Today it is believed that heparin-induced skin lesions might be caused by at least 5 mechanisms: delayed (type IV) hypersensitivity reactions, immune-mediated thrombocytopenia, type I allergic reactions, skin necrosis, and pustulosis.[1]

Not surprisingly, hemorrhage is the most common therapeutic complication. Bullous hemorrhagic eruption from heparins is a rare cutaneous side effect. Cutaneous reactions include skin necrosis, immunologically mediated eruptions, and bullae formation. Other known side effects include heparin-induced thrombocytopenia (HIT) complicated by bilateral adrenal hemorrhage, hypertransaminasemia, abnormal liver function, alopecia, and osteoporosis.[2,4] The 2 most commonly reported causes of heparin-induced skin lesions are immune-mediated HIT due to antiplatelet factor 4 antibodies and delayed hypersensitivity reactions. In 1995, Warkentin et al[6] demonstrated that HIT, associated thrombosis, and heparin-induced IgG antibodies are more common in patients treated with UFHs than LMWHs. Schindewolf et al[7] conducted an observational cohort study in which they verified that heparin-induced, nonnecrotizing skin lesions are not strongly associated with HIT, which previously had been suspected. The authors showed that nonnecrotizing skin lesions were most likely due to delayed hypersensitivity reactions and not life-threatening HIT.[7]

In addition to our patient's diminished kidney function, which may have increased the elimination half-life of heparin, the patient also was taking aspirin, an antiplatelet drug, which may have contributed to the cutaneous eruption. Aspirin use is a common feature among other reports of patients who had similar reactions to UFH and LMWH (Table). The antiplatelet effect of aspirin combined with the anticoagulant effect of heparin may have contributed to the hemorrhagic component of the eruption.[10] In fact, heparin has been shown to cause a relative prohemorrhagic tendency when coadministered with salicylates, most likely due to the combination of antiplatelet effect with clotting factor inhibition.[13]

Obesity, diabetes mellitus, and treatment with broad-spectrum antibiotics seem to increase the risk for thrombocytopenia, skin necrosis, and thrombotic events in patients being treated with heparin, which usually is the result of heparin-induced formation of platelet aggregating immunoglobulins in these patients.[14] Other risk factors that have been identified include a body mass index greater than 25, treatment with heparin for more than 9 days, and female sex.[1] Interestingly, our patient did not exhibit any of these risk factors, which emphasizes that these reactions can occur in any patient, making it difficult to reliably predict which patients will have an adverse reaction. Cutaneous necrosis secondary to heparin administration may serve as a warning of the potentially lethal complications of intravenous heparin use. Heparin therapy should be discontinued in patients who develop skin necrosis or thrombocytopenia, and oral anticoagulation should be considered as an alternative.[14]

Conclusion

Our patient recovered quickly and completely after discontinuing treatment with heparin, but patients

Anticoagulant-Induced Bullous Hemorrhagic Dermatoses

Reference (Year)	Patient	History of Anticoagulant Use	Cutaneous Manifestation	Skin Biopsy	Direct Immunofluorescence	Outcome
Horn et al[8] (1981)	53-year-old man	Initiation of warfarin therapy	Skin necrosis on left flank and buttock; formed multiple hemorrhagic bullae	NA	NA	Eventually required skin grafting
	70-year-old man	Warfarin dose of 10 mg daily reduced to 2.5 mg daily	Bullous violaceous lesions on lower left leg and foot	NA	NA	Warfarin discontinued
Dyson et al[9] (2004)	62-year-old woman	Subcutaneous LMWH (enoxaparin sodium)	Multiple broad-based tense bullae on erythematous bases and healing erosions on left buttock	Subepidermal blister with eosinophils lining base, compatible with bullous pemphigoid	Negative	Enoxaparin was replaced with oral warfarin and eruption resolved within 2 weeks
	31-year-old man	Subcutaneous LMWH (enoxaparin sodium)	2 weeks after initiation of treatment, tense bullae developed on both lower extremities	Subepidermal blister with eosinophils lining base, compatible with bullous pemphigoid	Negative	Enoxaparin was discontinued and lesions resolved within 1 week
Perrinaud et al[10] (2006)	75-year-old male	Subcutaneous LMWH (dalteparin sodium: 100 U/kg twice daily)	5 days later, ~50 tense hemorrhagic bullae on normal skin	Intraepidermal bullae filled with RBCs, normal blood vessels, and moderate perivascular lymphohistiocytic infiltrate	Negative	Patient died of cerebral hemorrhage possibly related to vitamin K overdose
	82-year-old woman	Subcutaneous LMWH tinzaparin (175 U/kg once daily) for 11 days	5-day history of tense hemorrhagic bulla on extremities	Intraepidermal blister filled with RBCs, with early stages of necrosis of the roof and no vessel involvement	Negative	After heparin treatment was withdrawn, skin lesions resolved within 10 days

Reference (Year)	Patient	History of Anticoagulant Use	Cutaneous Manifestation	Skin Biopsy	Direct Immunofluorescence	Outcome
Perrinaud et al[10] (2006) (continued)	64-year-old man	Furosemide and heparin calcium; high dose of heparin 2 days before first bulla appeared	21 days after initiation of treatment, 10 tense hemorrhagic bullae appeared on forearms and ankles	Intraepidermal bulla filled with RBCs without blood vessel involvement; anti-HPF4 antibodies present	Negative	Skin lesions resolved despite continuation of heparin; patient died of septic shock few weeks later
Thuillier et al[11] (2009)	51-year-old patient	Subcutaneous enoxaparin sodium was initiated and replaced later by tinzaparin sodium	48 hours after initiation of treatment, annular, erythematous, and vesicular plaques erupted at the injection sites; hemorrhagic bullae appeared on abdominal area	Intraepidermal blister filled with RBCs	Negative	Skin lesions disappeared 10 days after discontinuation of LMWH
Gonzales et al[12] (2009)	88-year-old man	Subcutaneous enoxaparin sodium and warfarin	Numerous blood-filled vesicles and bullae (0.2–1.5 cm) on the anterolateral lower extremities without any visible lesions at sites of injections on the abdomen	Subcorneal collection of RBCs within an intact vesicle and neutrophils and eosinophils within the dermis without evidence of vasculitis	NA	Eruption resolved after discontinuation of heparin
Current case	83-year-old man	Loading dose of 5000 U of heparin followed by heparin sodium	5 days after initiation of treatment, the patient developed scattered clusters of tense hemorrhagic bullae on the extremities ranging from 0.5–1 cm	Subcorneal/intraepidermal bulla filled with serum and RBCs without evidence of vasculitis or thrombi in underlying dermis	NA	Eruption resolved after discontinuation of heparin

Abbreviations: NA, not applicable; LMWH, low-molecular-weight heparin; RBC, red blood cell; HPF4, heparin-platelet factor 4.

who continue heparin therapy may experience substantial morbidity.

REFERENCES

1. Schindewolf M, Schwaner S, Wolter M, et al. Incidence and causes of heparin-induced skin lesions [published online ahead of print September 29, 2008]. *CMAJ*. 2009;181:477-481.
2. Verstraete M. Pharmacotherapeutic aspects of unfractionated and low molecular weight heparins. *Drugs*. 1990;40:498-530.
3. Hirsh J, Watkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest*. 2001;119:64S-94S.
4. Freedman MD. Pharmacodynamics, clinical indications, and adverse effects of heparin. *J Clin Pharmacol*. 1992;32:584-596.
5. Nelson-Piercy C. Hazards of heparin: allergy, heparin-induced thrombocytopenia and osteoporosis. *Baillieres Clin Obstet Gynaecol*. 1997;11:489-509.
6. Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med*. 1995;332:1330-1335.
7. Schindewolf M, Kroll H, Ackermann H, et al. Heparin-induced non-necrotizing skin lesions: rarely associated with heparin-induced thrombocytopenia [published online ahead of print February 1, 2010]. *J Thromb Haemost*. 2010;8:1486-1491.
8. Horn JR, Danziger LH, Davis RJ. Warfarin-induced skin necrosis: report of four cases. *Am J Hosp Pharm*. 1981;38:1763-1768.
9. Dyson SW, Lin C, Jaworsky C. Enoxaparin sodium-induced bullous pemphigoid-like eruption: a report of 2 cases. *J Am Acad Dermatol*. 2004;51:141-142.
10. Perrinaud A, Jacobi D, Machet MC, et al. Bullous hemorrhagic dermatosis occurring at sites distant from subcutaneous injections of heparin: three cases. *J Am Acad Dermatol*. 2006;54(suppl 2):S5-S7.
11. Thuillier D, Chaby G, Dadban A, et al. Low-molecular-weight heparin-induced bullous haemorrhagic dermatosis associated with cell-mediated hypersensitivity [in French] [published online ahead of print February 28, 2009]. *Ann Dermatol Venereol*. 2009;136:705-708.
12. Gonzales UP, Scott GA, Briones AJ, et al. Remote hemorrhagic bullae occurring in a patient treated with subcutaneous heparin. *Arch Dermatol*. 2009;145:604-605.
13. Walker AM, Jick H. Predictors of bleeding during heparin therapy. *JAMA*. 1980;244:1209-1212.
14. Levine LE, Bernstein JE, Soltani K, et al. Heparin-induced cutaneous necrosis unrelated to injection sites. a sign of potentially lethal complications. *Arch Dermatol*. 1983;119:400-403.