# Bullous Hemorrhagic Dermatosis in a 65-year-old Filipino Woman Secondary to Enoxaparin: A Case Report

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## ABSTRACT

Bullous hemorrhagic dermatosis (BHD) is a rare cutaneous manifestation characterized by tense hemorrhagic bullae that appear at sites distant from low molecular weight heparin (LMWH) injections, typically within seven days of exposure. As of March 2022, only 94 cases have been reported. It most commonly affects elderly males with predisposing factors for thromboembolism, such as carcinoma, and usually involves the extremities.

This case highlights the importance of maintaining a high index of suspicion for bullous hemorrhagic dermatosis (BHD) in patients receiving low molecular weight heparin, even beyond the typical 7-day window and in demographics not commonly affected. Early recognition and prompt discontinuation of the offending agent, as demonstrated in this atypical presentation involving a Filipino elderly woman with multiple comorbidities and no malignancy, can lead to favorable outcomes. Clinicians should be aware of this rare but reversible complication to avoid misdiagnosis and ensure appropriate management.

*Keywords: bullous hemorrhagic dermatosis, Filipino, low molecular weight heparin, enoxaparin, case report*

## INTRODUCTION

This is an unusual case of bullous hemorrhagic dermatosis (BHD) in a 65-year-old Filipino woman with multiple comorbidities, including type 2 diabetes mellitus, hypertension, and end-stage renal disease (ESRD), but without a history of malignancy or known hypercoagulable state. In contrast to typical presentations, hemorrhagic bullae developed approximately one month after initiation of enoxaparin therapy. This case broadens the clinical spectrum of BHD and highlights the importance of considering this diagnosis even in atypical patient populations and delayed onset presentations.

Bullous hemorrhagic dermatosis is a rare adverse drug effect usually secondary to LMWH. In a study reported by Uceda-Martin et al., they reported a total of 94 cases of BHD. Enoxaparin, an LMWH resulting as a by-product from the depolymerization of heparin, is commonly used among patients in the hospital for the prevention of venous thromboembolism. Side effects of enoxaparin range from bleeding, the most common, to ecchymoses, skin necrosis, and even urticaria.[1-3] These may even occur among those treated with warfarin and unfractionated heparin. This case is unique because the onset of the lesion was one month after exposure to LMWH which developed as a tense, hemorrhagic bullae involving not only the right extremity but also the abdomen.

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## CASE PRESENTATION

A 65-year-old Filipino elderly female patient admitted to the intensive care unit (ICU) was referred to a dermatologist due to the appearance of a large, dark, tense, fluid-filled bullae which was initially on her right knee and then involving the abdomen. Before her transfer to the ICU, she was rushed to the emergency room due to her fever associated with decreased sensorium. Upon arrival, she was noted to be unresponsive, with no pulse and breathing, thus cardiopulmonary resuscitation was performed. Resuscitation attempts continued for 10 minutes. Post-arrest, the patient remained hypotensive and unresponsive. IV resuscitation was given, broad-spectrum antibiotics were started, blood cultures were taken, and further workup was done. Due to the persistent hypotension, vasopressors were initiated and the patient was transferred to the ICU. She was a non-smoker and a non-alcoholic beverage drinker. She had type 2 diabetes mellitus, hypertension, and ESRD. She had an orthopedic operation due to a fall years prior and was given apixaban, a direct oral anticoagulant (DOAC), as prophylaxis for venous thromboembolism. She had no cutaneous reactions from the DOAC. She had no history of cancer, myocardial infarction, or a hypercoagulable state. Pertinent family history was hypertension and type 2 diabetes mellitus on the paternal side. She was bed-bound, with no response to external stimuli and no spontaneous movements. Hypoxic-ischemic encephalopathy was considered. Her lack of spontaneous movements increased her risk of venous thromboembolism, thus prophylaxis with LMWH was contemplated. Baseline platelet count, prothrombin time, and partial thromboplastin time taken at the emergency room were normal. Enoxaparin 40 mg once a day subcutaneously was given.

Within the first seven days of initiation of anticoagulation, no bleeding episodes nor hemorrhagic lesions were noted as seen in the literature. After a month of receiving enoxaparin 40mg once daily, she started to develop tense, hemorrhagic bullae on her right knee, which gradually enlarged as enoxaparin was continued (Figures 1 and 2). She also developed the same lesion on her abdomen (Figure 3). No mucosal lesions were noted. The development of the hemorrhagic bullae distant from the site of injection with enoxaparin was highly suggestive of bullous hemorrhagic dermatosis. At this point however, the patient was bed-bound and comatose. The poor prognostic condition of the patient and financial constraints were important considerations as to why biopsy was no longer performed. The platelet count and coagulation profile, a month after admission, were repeated and were normal.

Differential diagnoses considered in this case were bullous drug reactions and bullous pemphigoid.

Bullous drug reactions are the result of medication exposure. Many conditions present with bullous eruptions, such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Recently, both SJS and TEN have been categorized as epidermal necrolysis (EN). EN may occur at any age, but is commonly seen in elderly individuals above 65 years old. EN is characterized by erythematous skin, epidermal detachment, and mucous membrane erosion. Bullae, which may be hemorrhagic, may develop and coalesce. It is usually accompanied by fever and malaise. The most common group of drugs reported to be highly associated with EN are allopurinol, sulfonamides, carbamazepine, lamotrigine, phenobarbital, phenytoin, non-steroid anti-inflammatory drugs (NSAIDS) of the oxicam type, e.g., meloxicam, and nevirapine.[4]

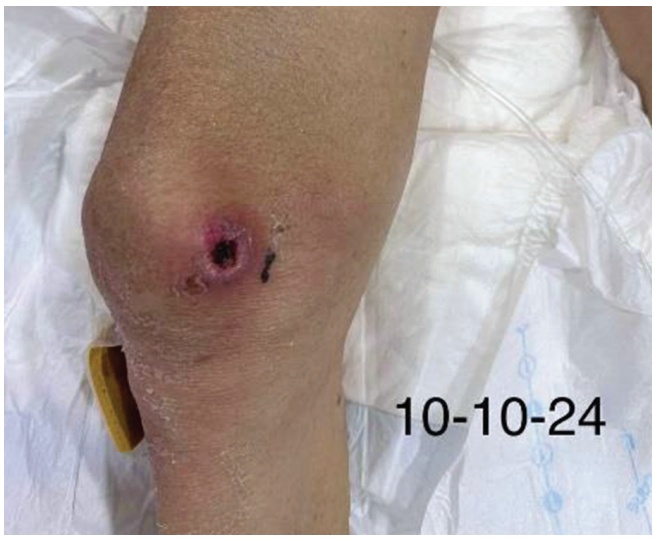


**Figure 1.** Medial aspect of the right knee showing a round, dark, vesicle with an erythematous border after one month of enoxaparin administration.

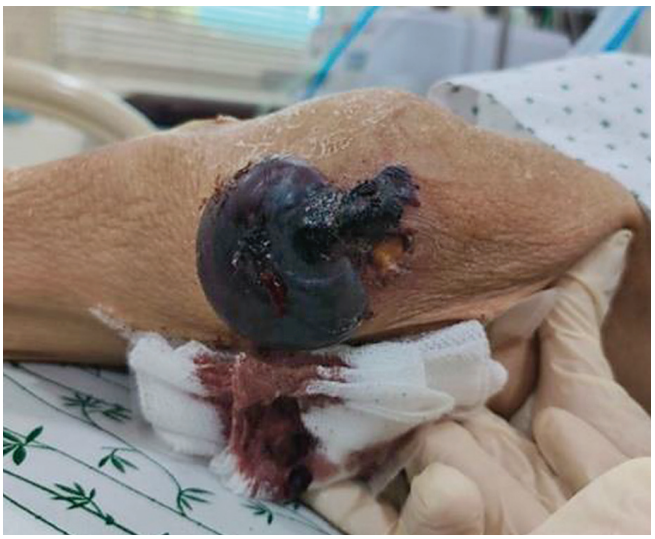

**Figure 2.** Medial aspect of the right knee now showing a round, dark, tense, hemorrhagic bullae one day after its initial appearance.

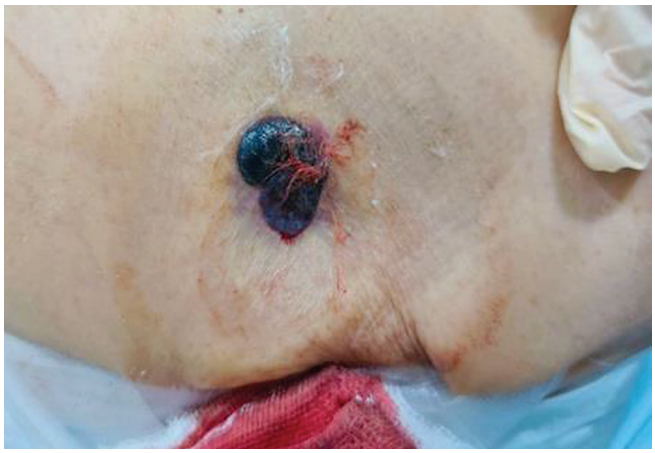

**Figure 3.** Left lower quadrant of the abdomen with dark, tense, hemorrhagic bullae one month after enoxaparin administration.

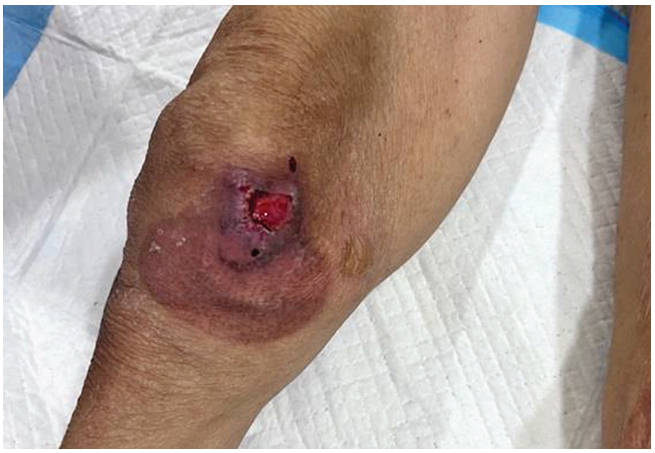

**Figure 4.** Medial aspect of the right knee two weeks after discontinuation of enoxaparin with noted resolution of bullae.

Bullous pemphigoid is the most common autoimmune bullous disorder which appears as tense or hemorrhagic bullae. Multiple comorbidities and drug exposures have been cited as potential triggers. It is seen in the 8th decade of life affecting both genders. It classically manifests with tense bullae superimposed on normal skin or on erythematous and edematous surfaces on the trunk and extremities and are intensely pruritic. The bullae may also be widespread and in clusters. In atypical presentations, they start as pruritic erythematous patches or plaques. In a report by Miyamoto et al., the drugs that were commonly reported to induce bullous pemphigoid were DPP-IV inhibitors, diuretics, antipsychotics, and checkpoint inhibitors. The diagnosis relies on a combination of clinical features with histopathology showing eosinophilic spongiosis with a mixed dermal inflammatory infiltrate.[5,6]

Enoxaparin was discontinued and shifted to a direct oral anticoagulant (DOAC). In this case, apixaban, 2.5 mg was given via nasogastric tube twice daily. Local wound care with daily change of sterile dressing soaked with 0.9 % saline solution was done. Two weeks later, the bullae on the right knee resolved in size and appearance, although the patient continued to be bed-bound with no response to external stimuli (Figure 4). The resolution of the bullae on the abdomen was not documented.

## DISCUSSION

BHD is a non-immune dermatological eruption related to anticoagulation. Apart from LMWH, heparin, warfarin, and fondaparinux are also implicated as common causative agents. To date, there are no reports regarding DOACs with these skin lesions. BHD can present in both men and women, with the elderly making up the majority involving those ages 31-94 years old, with a mean age of 73.5. Our patient was 65 years old. In the same report, majority received enoxaparin.[2] It presents as intra-epidermal lesions arising distant from the site of administration and commonly involving the lower extremities, followed by the upper extremities, the trunk, and rarely the head. The interval between exposure with LMWH and BHD ranged from 6 hours to 30 days, with a mean of 8.4 days.[2,7] Our patient presented after one month of enoxaparin exposure. Most patients have no prior exposure to any anticoagulants.[7] The lesions are variable, from small to large, often tense, fluid-filled, and hemorrhagic. The diagnosis is made by a combination of clinical and histopathologic findings. Histopathology reveals intraepidermal blisters accompanied by eosinophils, with red blood cells but without microthrombi. The absence of microthrombi and vascular lesions is necessary as they rule out necrosis and vasculitis as the underlying cause.[8] The exact pathophysiology of BHD is still unclear although the most common explanation is probably because of a hypersensitivity reaction to LMWH. This is suggested by the presence of eosinophils within the dermal layer.[9] Enoxaparin is an LMWH formed as a by-product of the depolymerization of heparin. This explains why cross-reactivity among LMWH and standard heparin is not uncommon. The most frequently reported type of hypersensitivity reaction is the delayed type (Type IV).[10] Interestingly, the appearance of the lesions distant from the site of administration makes local adverse reactions unlikely to be the cause. Moreover, the preferential involvement of extremities is likely due to the combination of capillary fragility and higher frequency of trauma of the extremities. A causal link is suggested due to the temporal profile of the appearance of the lesions during heparin exposure, and disappearance after discontinuation of heparin.[11]

When LMWH is discontinued, the lesions spontaneously disappear within two weeks.[2] The management of BHD depends on the size and number of the lesions. Lesions are known to be self-limiting, whereas in other reports, they

usually resolve after discontinuation of LMWH exposure. Local wound care of the bullae and skin is advisable in its treatment. The outcome of BHD is favorable.[2,8] Further studies are needed to understand the exact mechanism of bullous hemorrhagic dermatosis, other predisposing risk factors, and complications.

## CONCLUSION

This case illustrates a rare and atypical presentation of bullous hemorrhagic dermatosis (BHD) in a critically ill, elderly Filipino woman with multiple comorbidities, who developed hemorrhagic bullae distant from enoxaparin injection sites approximately one month after initiation—well beyond the commonly reported time frame. While the clinical features strongly suggested BHD, diagnostic confirmation via biopsy was not pursued due to the patient's poor neurologic prognosis and financial constraints. The absence of mucosal involvement, normal coagulation parameters, and the resolution of lesions after discontinuation of enoxaparin further supported the diagnosis.

This case underscores the diagnostic challenge posed by cutaneous hemorrhagic eruptions in critically ill patients and highlights the need for heightened clinical awareness of BHD, especially in under-represented populations and atypical timelines. Given the limited number of reported cases in the literature and the overlap with other bullous conditions, more studies are needed to clarify the pathophysiology, risk factors, and clinical spectrum of BHD. Until then, clinicians should consider BHD in the differential diagnosis when hemorrhagic bullae arise in patients on LMWH, even in the absence of classic risk factors or timing, and weigh the risks and benefits of continuing anticoagulation therapy on a case-by-case basis.

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### Informed Consent

An approved informed consent was given to the husband to which he has read, signed, and received a copy. He understood that the results may be used for publication while assuring patient confidentiality.

### Statement of Authorship

The author certified fulfillment of ICMJE authorship criteria.

### Author Disclosure

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