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To cite this article: Savaş Öztürk, Ilkay Can, Ilker Erden, Hadice Akyol & Ozgen Aslan Solmaz (2015) Enoxaparin-induced hemorrhagic bullous dermatosis in a leprosy patient, Cutaneous and Ocular Toxicology, 34:3, 254-256, DOI: [10.3109/15569527.2014.950381](https://doi.org/10.3109/15569527.2014.950381)

To link to this article: <http://dx.doi.org/10.3109/15569527.2014.950381>



Published online: 08 Sep 2014.



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CASE REPORT

Enoxaparin-induced hemorrhagic bullous dermatosis in a leprosy patient

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Abstract

Enoxaparin is a low-molecular-weight heparin that has been used widely to prevent and treat thromboembolic disorders for at least 30 years. The most common adverse skin reactions to enoxaparin are ecchymosis and skin necrosis due to vasculitis, urticaria, angioedema and erythema. Side effects from heparin administration are rare and usually located at the injection site. However, recent reports have suggested that they can also occur at a distance from the site of injection. Moreover, the etiopathogenesis has not been fully explained. In this article, we present a case of hemorrhagic bullous dermatosis associated with enoxaparin for the treatment of ischemic heart disease that developed in a patient with a past history of lepromatous leprosy.

Keywords

Dermatosis, enoxaparin, hemorrhagic bulla

History

Received 1 July 2014

Revised 18 July 2014

Accepted 26 July 2014

Published online 29 August 2014

Introduction

Heparin has been used as an anticoagulant agent since 1930. Low-molecular-weight heparins such as enoxaparin have been used for approximately 30 years in the prophylaxis and treatment of thromboembolic diseases^{1,2}. Enoxaparin is used once or twice daily, depending on the indication. Cutaneous complications associated with these anticoagulants include hematomas, ecchymosis, erythematous plaques, nodules, skin necrosis, contact dermatitis and urticaria, all occurring more commonly at local subcutaneous injection sites. The most common complications associated with heparin are hemorrhagic events. Generalized cutaneous reactions are rarely seen^{3,4}. However, it was recently reported that hemorrhagic bullous dermatosis caused by low-molecular-weight heparins may also occur at a distance from the site of injection⁵. The mechanism of hemorrhagic bullous dermatosis formation remains unexplained³. In a review of the literature, we found 19 cases of heparin-induced bullous hemorrhagic dermatosis. Here, we present a case of hemorrhagic bullous dermatosis that developed without thrombosis of the dermal vessels at a distance from the site of injection of enoxaparin for the treatment of ischemic heart disease in a patient with a past history of lepromatous leprosy.

Case report

A 73-year-old male with a past history of lepromatous leprosy was hospitalized for ischemic heart disease. His medical history revealed that in 1992 he was treated for leprosy according to the guidelines of the World Health Organization. Four years prior, he had received a diagnosis of ischemic heart disease and been treated with ramipril and clopidogrel. During his most recent admission, he had been started on treatment with enoxaparin sodium (60 mg administered subcutaneously in the abdominal region every 12 h) for unstable angina pectoris. Enoxaparin was the only new drug introduced on admission. Six days after starting enoxaparin therapy, the patient noted multiple hemorrhagic blisters on his left palmar area that grew rapidly and dried to become crusted nodules. The patient did not report bleeding in any other area of his body. The patient reported that 6 days before the lesions appeared, he had started treatment with enoxaparin. There were no other symptoms. A dermatologic examination revealed multiple crusted nodules and hemorrhagic tense blisters on the patient's nonerythematous skin ranging in diameter from 2 mm to 2.5 cm on his left palmar area (Figure 1). No lesions were visible on the patient's abdomen at the sites of enoxaparin injection. No other atypical cutaneous findings, including mucosal lesions, petechial eruption, and purpura, were noted. The results of laboratory tests such as a complete blood count and coagulation studies, including prothrombin time, international normalized ratio, prothrombin activity, thromboplastin time, fibrinogen, antithrombin III, protein C, and protein S, were within normal limits. Based on the pre-diagnoses of hemorrhagic bullous dermatosis and bullous erythema multiforme, a 4-mm punch

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Figure 1. Hemorrhagic tense blisters on left palmar area.

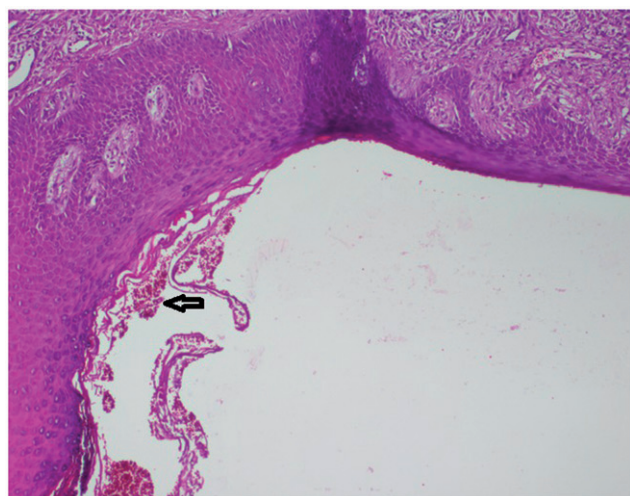


Figure 2. Intraepidermal bullae filled with red blood cells and fibrin deposits.

biopsy was taken from intact hemorrhagic bullae in the left palmar area. Histopathologic examination revealed tense subcorneal intraepidermal bullae filled with red blood cells and fibrin deposits. There was no inflammatory infiltrate, capillary thrombosis, or evidence of vasculitis (Figure 2). The patient was diagnosed with hemorrhagic bullous dermatosis according to the existing clinical and histopathologic findings. Enoxaparin treatment was maintained and the patient's lesions stabilized, crusted over, and healed spontaneously without sequelae within 2 weeks.

Discussion

Enoxaparin, obtained by the depolymerization of standard heparin, is used for prophylaxis and the treatment of thromboembolic diseases⁶. In recent years, the most frequent unwanted cutaneous side effects of heparins have been reported. These reactions are usually not life-threatening, but they require attention since they impair the compliance of patients and may lead to the discontinuation of important anticoagulant therapy⁷⁻¹⁰. Heparins can induce skin lesions;

however, the pathogenesis of heparin-induced cutaneous reactions is poorly understood. Initially, it was thought that the reaction was due to a preservative in the heparin; however, new low-molecular-weight heparins, which are free of preservatives, have also been associated with skin eruptions. Today, it is believed that heparin-induced skin lesions might be caused by at least five mechanisms: delayed hypersensitivity reactions, immune-mediated thrombocytopenia, type I allergic reactions, skin necrosis, and pustulosis^{10,11}. Traditionally, three types of cutaneous reactions were distinguished: urticarial lesions (immediate hypersensitivity reactions), erythematous papules and plaques (delayed hypersensitivity reactions), and skin necrosis⁷.

Hemorrhagic events are the most common therapeutic complication of heparins. The two most commonly reported causes of heparin-induced skin lesions are immune-mediated heparin-induced thrombocytopenia and delayed hypersensitivity reactions^{11,12}.

Bullous hemorrhagic dermatosis associated with subcutaneous heparin injections is rare, having first been reported in 2006. Perrinaud et al.⁵ described three patients with eruptions of tense, noninflammatory hemorrhagic blisters distributed in groups at a distance from the site of subcutaneous heparin injection. Since then, 19 patients with hemorrhagic bullous dermatosis associated with various low-molecular-weight heparins such as enoxaparin have been described. The bullae typically start from 5 to 21 days after the initiation of heparin therapy and have been noted mostly on the limbs and abdomen, appearing as nonpruritic, tense, hemorrhagic bullae on noninflamed skin. Intraepidermal bullae with a lack of thrombotic, vasculitic or inflammatory changes are key histopathologic features of this disease and thus can be used to exclude other heparin-induced cutaneous reactions, including skin necrosis, contact dermatitis and urticaria^{8,9,13,14}. In our case, bullous hemorrhagic eruptions in the left palmar formed 6 days after the initiation of enoxaparin therapy. Drug-induced bullae have been associated with furosemide, e-aminocaproic acid, and phenylbutazone. The histopathologic characteristics of these drug-induced reactions range from papillary dermis vessel thrombosis to vasculitis^{5,15,16}. The pathology in our case was different, including the lack of vasculitis and thrombosis. In our case, no abnormal results were obtained by routine hematologic or coagulation tests, and we decided to continue enoxaparin treatment because there were similar cases in the literature. Although enoxaparin treatment was maintained, the patient's lesions stabilized, crusted over and healed spontaneously without sequelae within 2 weeks.

In conclusion, reports of enoxaparin-induced hemorrhagic bullous dermatosis occurring at a distance from the site of injection are increasing; however, the condition usually resolves itself, even in patients who continue heparin therapy, implying that the condition is even more widespread than the literature suggests.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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