

Bullous Hemorrhagic Dermatitis Induced by Enoxaparin

Abstract

Bullous hemorrhagic dermatitis induced by enoxaparin is a rare, self-limiting, cutaneous adverse reaction causing no complications. In this report, we present a case where bullous hemorrhagic dermatitis developed at a location distant from the site of injection after using enoxaparin for 5 days for pulmonary venous thrombosis.

Keywords: Enoxaparin, hemorrhagic dermatitis, heparin

Introduction

Heparin is a common anticoagulant discovered in the 1930s.^[1] Enoxaparin is a member of low-molecular-weight heparins (LMWHs), inhibiting the action of factor Xa by binding to antithrombin III.^[2] The LMWHs including enoxaparin have been commonly used in the prophylaxis and treatment of thromboembolic diseases for the last 30 years.^[3] These agents are administered subcutaneously either once or twice a day, depending on the indications of the patient.^[2,3] These agents may lead to the formation of cutaneous lesions at the sites of injection. However, cases of heparin-induced hemorrhagic bullous dermatitis located distant from the sites of injection have been recently reported.^[4]

In this report, we present a case where bullous hemorrhagic dermatitis developed at a location distant from the site of injection after using enoxaparin for pulmonary venous thrombosis.

Case Report

A 72-year-old male patient presented with a history of systemic hypertension, diabetes mellitus, and hypercholesterolemia. The patient had been receiving metformin, enalapril, and simvastatin due to these complaints for the last 10 years. In addition, the patient had been receiving enoxaparin sodium therapy for pulmonary venous thrombosis for the last 1 week (80 mg subcutaneously every 12 h). Five days after the initiation of the enoxaparin therapy, the patient developed multiple asymptomatic

hemorrhagic vesico-bullous lesions on the right leg and right arm [Figure 1]. No hemorrhage was seen in any other part of the body and no lesions were detected in the sites of enoxaparin injections. Laboratory tests including whole blood count and biochemical and coagulation parameters (activated partial thromboplastin time, prothrombin time, international normalized ratio) and fibrinogen were normal. A punch biopsy was performed in the intact hemorrhagic bullous lesion on the right leg. Histopathologic examination revealed an intra-epidermal bulla filled with red blood cells. No vasculitic signs were detected [Figure 2]. Depending on the clinical and histopathologic findings, the patient was diagnosed as bullous hemorrhagic dermatitis induced by enoxaparin. The lesions resolved 1 week after the termination of the enoxaparin therapy.

Discussion

Enoxaparin is a member of LMWHs that are obtained from the depolarization of the standard heparin and include bemiparin, dalteparin, nadroparin, and tinzaparin.^[3] Enoxaparin is commonly used in the prophylaxis and treatment of thromboembolic diseases such as pulmonary venous thromboembolism and myocardial infarction.^[3,4] Subcutaneous heparin therapy leads to a number of side effects including hemorrhagic complications, heparin-induced thrombocytopenia, osteoporosis, alopecia, increased serum transaminase levels, and cutaneous reactions.^[5] Moreover, heparin

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Figure 1: Vesicles and bullae in the right leg

has been shown to be associated with various cutaneous side effects such as hematoma, ecchymosis, erythematous plaques, nodules, skin necrosis, contact dermatitis, and urticarial rash.^[1]

These cutaneous side effects may be localized or generalized and may occur at the early or late stage of the disease.^[2,4] Generalized cutaneous side effects are rare, however cases of LMWH-induced hemorrhagic bullous dermatosis located distant from the sites of injection have been recently reported.^[2,6] The etiology and pathogenesis of these lesions remains to be elucidated.^[7] In the past, hemorrhagic bullous dermatosis was considered to result from the preservatives in heparin; however, this reaction is currently considered to result from five distinct mechanisms including delayed hypersensitivity reaction, immune-mediated thrombocytopenia, type I allergic reaction, skin necrosis, and pustulosis.^[1,3]

The heparin-induced bullous hemorrhagic dermatosis is a rare occurrence and was first reported in three patients in 2006 by Perrinaud.^[8] In 2009, Beltraminelli *et al.*^[5], Thuillier *et al.*^[9] and Gonzales *et al.*^[10] reported four other patients with similar lesions. To date, a total of 23 patients have been reported with bullous hemorrhagic dermatosis induced by LMWHs.^[4]

In most of these patients, bullous hemorrhagic dermatosis was found to result from the use of enoxaparin, which is a commonly prescribed drug because it is practical, reliable, and requires no blood test or monitoring.^[4,5,7] The lesions of bullous hemorrhagic dermatosis typically occur within 5-21 days after the initiation of the heparin therapy and often present as tense, hemorrhagic bullae on the extremities and the abdomen.^[4,5] Normally, no lesions occur at the site of injection.^[4] These lesions are histopathologically characterized by intra-epidermal bullae with no vasculitic, thrombotic, or inflammatory changes, and these characteristics are used to rule out heparin-induced cutaneous reactions including skin necrosis,

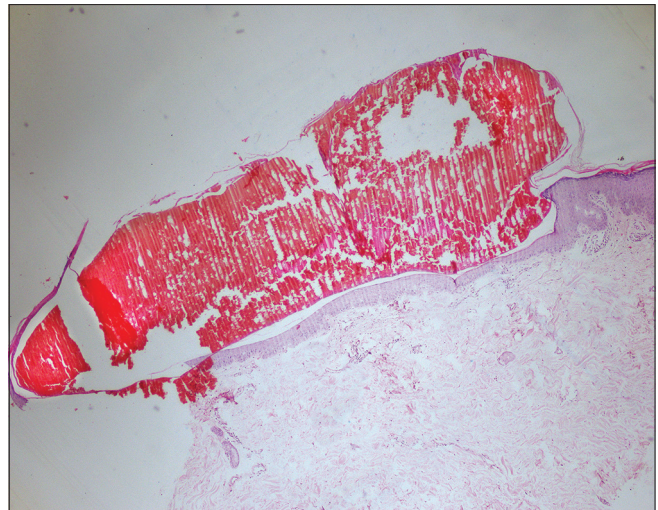


Figure 2: Intraepidermal bulla filled with red blood cells. No signs of vasculitis (H and E, ×40)

contact dermatitis, and urticarial.^[1,9] The pathogenesis of this condition remains unknown. The mechanism may be due to an idiosyncratic reaction caused by heparin because this drug was the only new drug temporarily associated with the eruption on the patients reported.^[4,9]

Various modalities have been used in the treatment of the lesions, and the discretion of the termination of the heparin therapy depends on the case presented.^[3] Several studies report that the lesions regress within 1-2 weeks in some patients despite continued use of LMWH therapy or shifting to an oral anticoagulant therapy.^[1,4,8] Several alternatives have been suggested regarding the termination of the heparin therapy: (1) the LMWH therapy can be terminated and an oral anticoagulant therapy can be initiated, (2) the LMWH therapy can be completely terminated, or (3) the LMWH therapy can be continued.^[4]

The heparin-induced bullous hemorrhagic dermatosis is a rare, self-limiting, cutaneous adverse reaction, which causes no complication and occurs at a location distant from the site of injection. Clinicians should be aware of the cutaneous side effects of these anticoagulants, which are commonly used in clinical practice.

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Conflicts of interest

There are no conflicts of interest

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