

Case Report

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Enoxaparin-induced bullous hemorrhagic dermatosis adjacent to and distant from the injection site: A case report**Amir Hossein Hassani¹; Zahra Hooshanginezhad²; Mojtaba Rezaei³; Fatemeh Azizi^{4*}**¹Medical Student, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.²Clinical Cardiologist, Shiraz University of Medical Sciences, Shiraz, Iran.³Medical Doctor, Tropical and infectious disease research center, Hormozgan, Iran.⁴Clinical Cardiologist, Cardiology Department, Alzahra Hospital, Shiraz University of Medical Sciences. Shiraz, Iran.***Corresponding Author: Fatemeh Azizi, MD**Department of Cardiology, Alzahra Hospital, Shiraz
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Abstract

Background: Bullous hemorrhagic dermatosis is a rare and benign adverse effect happening on days 5-21 of treatment with heparin and Enoxaparin. It can be localized or generalized and occur in places adjacent to and distant from the subcutaneous injection site. It is mostly happening in the extremities, followed by the trunk and abdomen, and is very rare on the head and neck. Our reported case had lesions on the forehead, neck, trunk, abdomen, and extremities

Case presentation: Here we present a 84-year-old man with multiple Bullous hemorrhagic dermatosis on the neck, abdomen, and extremities after subcutaneous injection of enoxaparin. It is a rare presentation of a rare adverse effect of low molecular weight heparin.

Conclusions: Bullous hemorrhagic dermatosis is a rare and benign adverse effect of heparin and LMWH that can occur mostly on extremities followed by the abdomen, trunk, and rarely head and neck after 5-12 days of treatment. Doctors should be acquainted with this condition's dermatologic picture and reassure the patients about it since it mostly follows a benign course

Keywords: Enoxaparin; Low molecular weight heparin; Bullous hemorrhagic dermatosis.

Abbreviations: LMWH: Low Molecular Weight Heparin.

Background

Enoxaparin is Low Molecular Weight Heparin (LMWH), widely used as an anticoagulant factor inhibiting Xa and IIa factors in the hemostasis cascade [1]. Enoxaparin is used to prevent and treat venous thromboembolism and treat ischemic heart disease [2]. Subcutaneous administration of heparin molecules such as Enoxaparin has been associated with multiple dermatologic adverse reactions such as hypersensitivity reactions,

skin necrosis, and indurated erythematous lesions with central eschar due to intradermal microvascular thrombosis following heparin-induced thrombocytopenia [3].

Bullous hemorrhagic dermatosis is a rare subcutaneous heparin and LMWH administration sideeffect that mainly develops within 5-21 days of treatment and mostly follows a benign course. This complication was reported as either generalized or localized and usually is seen in sites distant from the injection

site. It is mostly happening in the extremities, followed by the trunk and abdomen, and is very rare on the head and neck. Our reported case had lesions on the neck, abdomen, and extremities [4,5].

This condition is believed to be self-limited; however, since it sometimes has a frightening appearance, physicians must be aware of the complication to reassure the patients [6]. So far, most of the case reports have depicted this complication on extremities; however, in our patient, this enoxaparin-induced bullous hemorrhagic dermatosis was found on the forehead, neck, abdomen, and trunk in places adjacent to and distant from the injection site and on abdominal fat.

Case presentation

The patient was an 84-years old gentleman with a history of systemic hypertension who came to our emergency department with a chief complaint of typical chest pain. He had been receiving losartan 25 mg twice a day. The patient was admitted with a Non-ST segment elevation myocardial infarction diagnosis due to his positive Troponin and ST-coving and T-wave inversion in his electrocardiogram (Figure 1). During his course of hospitalization, he was started on ASA, Clopidogrel, and therapeutic enoxaparin (60 mg twice daily, in the periumbilical region) for five days. On the fifth day of admission, he developed multiple asymptomatic lesions on the forehead, neck, chest wall, and abdomen (Figure 2) and a single tense hemorrhagic bullous on the periumbilical area near the injection site (Figure 3).

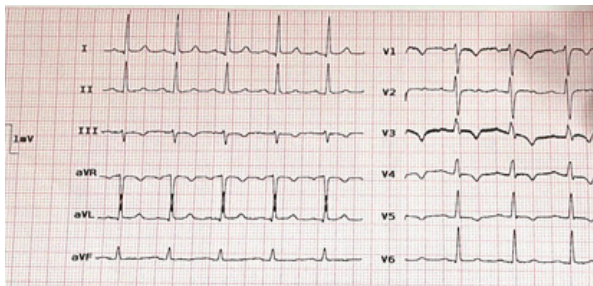


Figure 1: Electrocardiogram.

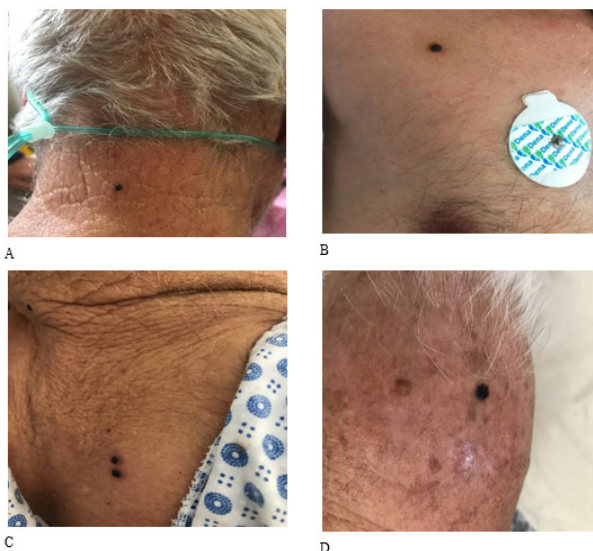


Figure 2: Enoxaparin-induced bullous hemorrhagic dermatosis on A: Posterior neck B: Chest wall C: Neck D: Forehead.

Laboratory tests, including complete blood cell count and biochemical and coagulation panel (activated partial thromboplastin time, prothrombin time, international normalized ratio) and liver function test and serum electrolytes have been checked and were within normal range. Biopsy wasn't performed due to the typical clinical appearance of lesions, and the patient was diagnosed with bullous hemorrhagic dermatosis induced by enoxaparin.

No abnormal bleeding was seen in the patient, and the physical examination of his mucous membranes was normal.

Enoxaparin was discontinued for the patient, lesions continued to resolve, and after three weeks, no sign of enoxaparin-induced bullous hemorrhagic dermatosis was found on the patient's body. This was a relatively rare case in which enoxaparin-induced bullous hemorrhagic dermatosis is seen on the trunk of a patient both adjacent to and distant from the injection site of Enoxaparin.

Discussion

In this article, we reported a case of enoxaparin-induced bullous hemorrhagic dermatosis in places adjacent to and distant from the injection site. Bullous hemorrhagic dermatosis is a rare complication of various heparin molecules first described by Perrinaud et al [7]. They reported this condition in three patients, two of whom received low molecular weight heparin (Dalteparin and Tinzaparin), while the other received heparin calcium. All of the dermatological lesions appeared distant from the injection site. The treatment was continued in the patient receiving heparin calcium, and the lesions were resolved spontaneously. The treatment was discontinued in the patient receiving Tinzaparin, and the lesion disappeared within ten days. The other patient expired due to cerebral hemorrhage, possibly consequent of Vitamin K antagonist overdose.

Less than thirty enoxaparin-induced bullous hemorrhagic dermatosis cases have been previously reported [8,9]. The patients ranged from 38 to 90 years old. In the cases who stayed alive after treatment of their underlying disease, the bullous hemorrhagic dermatosis resolved regardless of the continuation or discontinuation of enoxaparin. Pathologic investigation can confirm the diagnosis by ruling out other entities. Although skin biopsy was not performed in our study, previous literature has shown that the bulla is intraepidermal and subcorneal [5]. No significant change was detected in complete blood counts, coagulation panels, liver function tests, or serum electrolytes in the reported cases. In our case, no significant difference was seen in the laboratory results either.

The underlying pathogenesis of heparin-induced bullous hemorrhagic dermatosis is yet to be found. Multiple hypotheses are postulated in this regard. Gonzalez et al. and Thuillier et al. found eosinophilic infiltration in the dermis underneath the bulla and proposed hypersensitivity reactions as a possible mechanism for bullous hemorrhagic dermatosis formation [10,11]. Anticoagulant overdose and idiosyncratic reactions are the other possible etiologies [12,13]. In the previous literature, no vasculitis feature was seen in pathology specimens.

Regarding managing heparin-induced bullous hemorrhagic dermatosis, the lesions can resolve despite the continuation

or discontinuation of heparin therapy; however, the evidence on this matter is not enough to draw a wholesome conclusion. Consequently, the decision to continue or discontinue heparin or LMWH should be individualized.

Conclusions

Bullous hemorrhagic dermatosis is a rare and benign adverse effect of heparin and LMWH that can occur mostly on extremities followed by the abdomen, trunk, and rarely head and neck after 5-12 days of treatment. Doctors should be acquainted with this condition's dermatologic picture and reassure the patients about it since it mostly follows a benign course. Management of this adverse effect should be an individualized decision since further research is needed to have a generalizable conclusion regarding the treatment of this condition.

Declarations

Ethics approval and consent to participate: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Shiraz University of Medical Sciences, Iran. Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

Consent to publication: Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

Availability of data and material: The data presented in this study are available on request from the corresponding author.

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Author contributions:

1. Amir Hossein Hassani: investigation, resources, writing case report, review, editing

2. Zahra Hooshanginezhad: validation, investigation, review, and editing.

3. Mojtaba Rezaei: Collecting data, investigation, review.

4. Fatemeh Azizi: Collecting data, investigation, resources, writing case report, review, editing, supervision.

All authors have read and agreed to the published version of the manuscript

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