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LETTER TO EDITOR

Heparin-induced bullous hemorrhagic dermatosis☆

Keywords Heparin; Bullous; Adverse reaction; Hemorrhagic; Dermoscopy

Abbreviation

SARS-CoV-2 severe acute respiratory syndrome coronavirus 2

Introduction

Non-fractional heparin and low-molecular weight heparin are frequently used in the treatment and prevention of thrombotic disorders [1]. Recently, they are widely used in the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, several cutaneous adverse reactions to heparin are reported such as: hematoma, ecchymosis, skin necrosis, urticaria [2]. Bullous hemorrhagic dermatosis is a rare reaction associated with heparin. It was first described in 2006, with less than 90 cases reported through literature [2,3]. We report a case of bullous hemorrhagic dermatosis occurring 4 days after the introduction of heparin therapy.

Case report

A 75-year-old man, with a history of high blood pressure, chronic obstructive pulmonary disease and atrial fibrillation treated by digoxin 0.25 mg, aspirin 250 mg and inhaled corticosteroids, was referred to the Cardiology Emergency Department for chest pain. The diagnosis of acute coronary syndrome was established and the patient was treated by thrombolyse within the first hour. He received unfractionated heparin as a loading dose followed by low-molecular-weight heparin (enoxaparin) at curative dose (6000 UI [60 mg]/0.6 mL twice per day).

After four days, the patient developed bubbles and hemorrhagic vesicles, with a diameter varying from 0.5 to 1.5 cm, on both arms and legs. These lesions were located far from the heparin injection sites. Some bubbles were eroded, giving way to bright red blood (Fig. 1a). Light-polarized dermoscopy examination confirmed the hemorrhagic character of these bubbles and vesicles (Fig. 1b and c). Mucous membranes were healthy. Biological examinations (especially blood formula numeration, hepatic and renal functions) were within normal levels. Hemostasis evaluation showed a low prothrombin time level and a prolongated kaolin clotting time. D-dimere, factor V, protein C and fibrinogen were within normal levels. Anti-PF4 antibodies were not detected. Anti-Xa activity was slightly elevated. The diagnosis of heparin-induced bullous hemorrhagic dermatosis was evoked. The decision was to withdraw the heparin and monitor the patient closely. Ten days later, a complete healing of skin lesions, associated with normalized coagulation laboratory results, was observed and no new bubble was noted.

Discussion

Clinical lesions of our patient were typical and the diagnosis of bullous hemorrhagic dermatosis reaction to heparin was supported by the average duration to onset which was in accordance with previous reported cases, ranging from 1 to 30 days [4]. We retained the imputability of heparin as very suggestive (C3S3I4) [5]. The main differential diagnoses include leukocytoclastic vasculitis and heparin-induced skin necrosis which can be easily ruled out based on clinical presentation, dermoscopy features and even skin biopsy.

The mechanism of bullous hemorrhagic dermatosis remains unknown. Proposed hypotheses included over-anticoagulation, hypersensitivity, and idiosyncratic reaction [1]. Our patient developed a disorder in coagulation laboratory results which were normalized 10 days after heparin-withdrawal. So, over-anticoagulation seems to be as a possible mechanism in the development of bullous hemorrhagic dermatosis in our patient.

Bullous hemorrhagic dermatosis often occurs on extremities with a male predominance, as well as in our patient [1,4].

This dermatosis has a good prognosis [1]. In fact, lesions can disappear even when heparin treatment is continued [4]. However, the risk of intracranial hemorrhage has been rarely reported in association with bullous hemorrhagic dermatosis [6]. In our case, heparin-withdrawal was mandatory because of the high number of bubbles, the risk of cutaneous infection and the modification of coagulation study results. Finally, it seems that bullous hemorrhagic dermatosis is under-reported because heparin is extensively used and skin lesions are asymptomatic and spontaneously disappear. Awareness of bullous hemorrhagic dermatosis can help and reassure clinicians in the management of patients with anticoagulant treatments, noting its currently favorable prognosis. However, further studies are needed to better understand the mechanism.

☆ This case has been declared to pharmacovigilance center of Monastir (Tunisia) on 29 March 2021 under the number 25/21.

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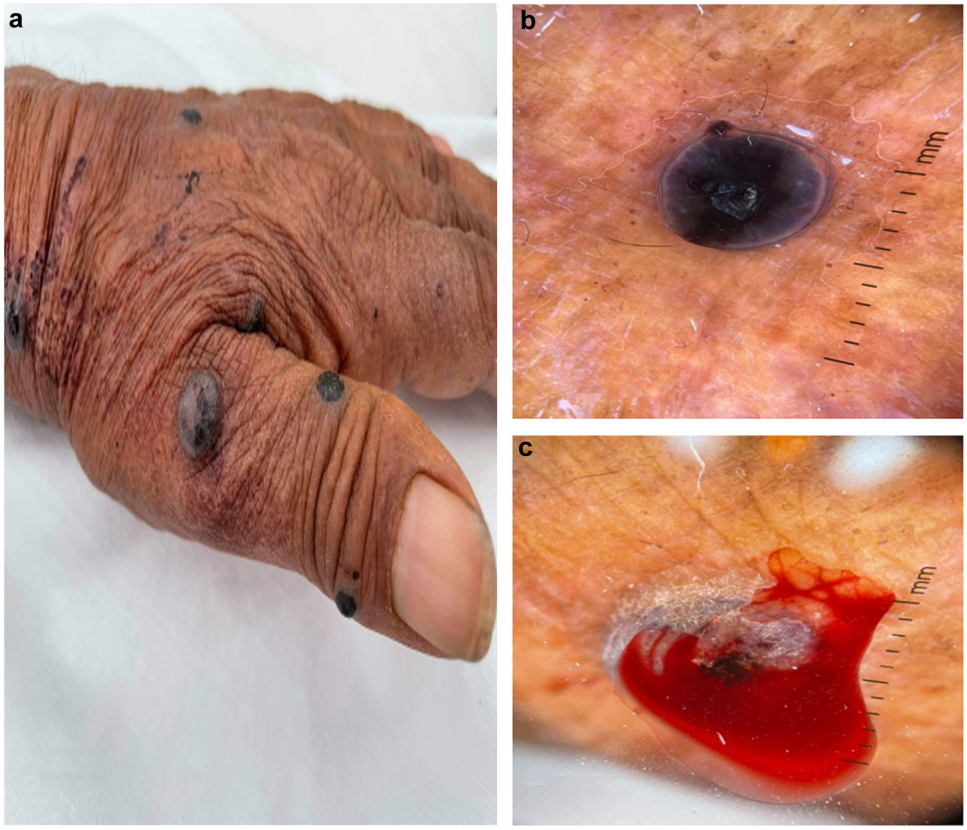

Figure 1. Multiple hemorrhagic bubbles on the left hand (a). Dermoscopy showing hemorrhagic bubble (b). Dermoscopy of an eroded bubble illustrating bright red blood (c).

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Disclosure of interest

The authors declare that they have no competing interest.

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