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AN UNUSUAL CASE OF TINZAPARIN-INDUCED HAEMORRHAGIC BULLOUS DERMATOSIS: DIAGNOSTIC AND THERAPEUTIC CHALLENGES

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ABSTRACT

Haemorrhagic bullous dermatosis is a rare (<0.5%), dose-independent complication of treatment with low molecular weight heparin (LMWH), often misdiagnosed as necrotizing fasciitis or vasculitis. The case presented here underscores the importance of clinicopathological correlation in anticoagulated patients. We present a 72-year-old woman with a history of hypertension who developed tender haemorrhagic bullae on her left leg 10 days after initiating tinzaparin (a low molecular weight heparin with 70 to 120 units of anti-factor Xa activity per mg) to treat pulmonary embolism. Histopathology revealed subepidermal haemorrhage with neutrophilic infiltrates but no fibrinoid necrosis/immune deposits. The bullae resolved rapidly after switching to apixaban and local wound care. This case revealed a number of diagnostic challenges. It is important to differentiate haemorrhagic bullous dermatosis from heparin-induced thrombocytopenia-associated skin necrosis by means of the platelet count (normal in our patient), as well as to exclude vasculitis (no leukocytoclastic in our patient) and bullous pemphigoid (no immunofluorescent deposits in biopsies from our patient). LMWH-induced bullous dermatosis requires high clinical suspicion. Early biopsy and switching to direct oral anticoagulants ensure favourable outcomes.

KEYWORDS

Tinzaparin adverse effects, haemorrhagic bullous dermatosis, low molecular weight heparin toxicity, anticoagulant-induced skin lesions

LEARNING POINTS

- Delayed onset (8-10 days post-initiation of low molecular weight heparin), dose independent.
- Haemorrhagic bullous dermatosis is not a hypersensitivity reaction.
- High-risk profile: age >70 years-old, estimated glomerular filtration rate <30 ml/min, concomitant steroids, or vascular fragility.

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INTRODUCTION/BACKGROUND

Low molecular weight heparin (LMWH) has become the anticoagulant therapy of choice for both prophylaxis and treatment of thrombotic disorders. It has effectively replaced unfractionated heparin in most clinical applications due to its superior pharmacokinetic profile and convenience of administration. Nevertheless, LMH is associated with several characteristic adverse effects, the most clinically significant of which are haemorrhagic complications (occurring in 1-4% of patients), a risk of dose-dependent osteoporosis following prolonged use (>3 months), transient elevation of liver enzymes (typically asymptomatic, but observed in 50-80% of cases), headache (2-8% incidence), and reversible alopecia. Localized reactions may also occur at the injection site (15-20% prevalence)[1,2].

Haemorrhagic bullae (or hemobullae) induced by LMWH constitute a rare cutaneous complication characterized by blistering haemorrhagic lesions at a distance from injection sites. It is clinically challenging to distinguish these bullae from hypersensitivity reactions, both diagnostically and therapeutically[1]. Thus, although this complication remains rare, its early identification helps prevent therapeutic errors. In this report, we present a case of haemorrhagic bullous dermatosis occurring in a location distant from the injection site in a patient treated with tinzaparin (a LMWH with 70 to 120 units of anti-factor Xa activity per mg) for acute bilateral pulmonary embolism.

CASE DESCRIPTION

A 72-year-old white European woman with a medical history of systemic hypertension and chronic obstructive pulmonary disease was admitted to our department for post-intensive-care management of septic shock linked to pulmonary (*Serratia marcescens* pneumonia) and cutaneous (non-necrotizing dermo hypodermatitis without confirmed infectious cause) origins associated with bilateral pulmonary embolism. The latter was treated with tinzaparin (16,000 UI). At the time of presentation, in addition to tinzaparin, her medications included amitriptyline, salbutamol, furosemide and nebivolol. She had a history of chronic skin ulcers on both legs (since 1993). Examination of the skin revealed mixed-aetiology (arterial and venous) skin ulcers on her left leg with stasis dermatitis, bilateral venous varicosities and eczematous skin rash. At presentation, there were no haemorrhagic bullae.

Initial workup revealed a normal complete blood count, unremarkable liver function tests (aspartate, aminotransferase/alanine, aminotransferase/bilirubin), preserved renal function (creatinine 0.58 mg/dl, estimated glomerular filtration rate 108 ml/min), absence of coagulopathy (prothrombin time (PT)/international normalised ratio (INR) 1.15, activated partial thromboplastin time (aPTT) 1.07.

On the tenth day following tinzaparin initiation, the patient developed a first haemorrhagic bulla on the left leg without trauma *(Fig. 1)*. The outcome was favourable after drainage of the bulla. However, a second haemorrhagic bulla appeared, also on the left leg, when the patient was mobilized to a standing position *(Fig. 1)*.

Histological examination showed spongiotic epidermis with regenerative features, associated with lymphocyte exocytosis. The underlying dermis was oedematous and showed capillary hyperplasia associated with a diffuse, polymorphic inflammatory infiltrate and red blood cell extravasation, without fibrinoid necrosis. Direct immunofluorescence revealed no deposits of IgA, IgG, or C3. No coagulation disorders were detected (PT/INR 1.15, aPTT 1.07), and platelet levels were within normal limits.

The patient's wounds were initially treated locally using non-adhesive hydro cellular dressings and application of a multi-layer compression bandage. Her treatment was switched from LMWH to apixaban, 5 mg twice daily, with strict bed rest for 14 days.

After one week, the patient's condition had markedly improved, although post-bullous skin erosion remained *(Fig. 2)*. No further haemorrhagic bullae were observed to form following discontinuation of tinzaparin combined with local wound care.



Figure 1. Physical examination revealed two haemorrhagic bullae with chronic skin ulcers on the left leg.



Figure 2. Persistent post-bullous skin erosions without haemorrhagic bullae.

DISCUSSION

The haemorrhagic bullae that developed at a distance from the injection site in our patient treated for bilateral pulmonary embolism with tinzaparin can arise from various causes. Skin biopsies were of key importance for differential diagnosis. Drug-induced bullous eruption was ruled out as histological analysis showed an absence of CD8+ T-cell-predominant lichenoid interface dermatitis, and insignificant dermal oedema[1]. Bullous pemphigoid was also ruled out based on the lack of histological evidence of subepidermal blistering or neutrophil/eosinophil-predominant infiltrates[2]. Physical examination revealed no signs of trauma at blister sites[1].

Although the exact pathogenesis remains unclear, with regard to reactions to heparin-related molecules, the preservative hypothesis[3] is being supplanted by multifactorial models as our understanding evolves. Some established mechanisms include heparin-induced thrombocytopenia -associated thrombocytopenia with microthrombosis[3], IgE-mediated type I reactions[4], direct endothelial toxicity causing necrosis[5], and sterile pustulosis due to IL-1β activation[6]. Thus, there is no need to test for allergies when faced with LMWH-induced haemorrhagic bullae as this complication is caused by mechanical factors rather than immunological or allergic mechanisms.

Recent retrospective studies and clinical cases have clearly identified at-risk populations: patients older than 75 years (OR=4.2), with renal insufficiency (glomerular filtration rate <30 ml/min, OR=5.6) or diabetes, with a mean time to onset of 8-10 days after treatment initiation[4-7].

The additional risk factors observed in our case include advanced age and skin fragility (chronic skin ulcers). The haemorrhagic bullae appeared spontaneously, with no preceding trauma or report of mechanical injury. LMWH-induced bullous dermatosis requires high clinical suspicion. Early biopsy and switching to direct oral anticoagulants ensure favourable outcomes.

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