Enoxaparin Induced Skin Lesions in Pregnancy: A Rare But Clinically Recognizable Association

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Abstract We report the case of a 29 year old pregnant female who experienced itching with erythematous plaques on prophylactic enoxaparin for recurrent fetal losses. These lesions generalized on rechallenge but erythema and itching gradually resolved after 4 weeks of discontinuation. Cutaneous adverse events with heparin have been reported (Villanueva et al. in *Actas Dermosifiliogr* 103:816–819, 2012; Neloska et al. in *Acta Dermatovenereol Croat* 23:223–224, 2015; Maldonado et al. in *Clin Exp Dermatol* 37:707–711, 2012; Schindewolf et al. in *Lancet* 380:1867–1879, 2012; Tassava and Warkentin in *Am J Hematol* 90:747–750, 2015), some specifically with enoxaparin (Villanueva et al. 2012; Neloska et al. 2015).

Keywords Enoxaparin · Pregnancy · Erythema · LMWH (low molecular weight heparin) · DTH—delayed type hypersensitivity · HIT—heparin induced thrombocytopenia

Abbreviations

4T Thrombocytopenia, timing of
score thrombocytopenia, thromboembolic
 complications and other causes of
 thrombocytopenia

BMI Body mass index
DTH Delayed type hypersensitivity
ELISA Enzyme linked immuno-sorbent assay
HIT Heparin induced thrombocytopenia
LMWH Low molecular weight heparin
UFH Unfractionated Heparin

Case

A 29 year old female, resident of Dubai, was started on prophylactic enoxaparin injection by her gynaecologist from sixth week of third pregnancy in view of recurrent first trimester spontaneous abortions. Ten days later, she experienced erythematous patches and itching at injection sites (Fig. 1). The lesion on abdomen was an erythematous plaque with an ill-defined hyperpigmented border which persisted despite a change in formulation. Five days after rechallenge, the lesions spread and involved the back and extremities i.e. at sites distant from enoxaparin injection (Fig. 2). After recurrence of lesions, she was referred to us. Enoxaparin was discontinued. There was no evidence of necrosis/thrombosis (no leg swelling, Homan's sign negative). Her workup for anti-phospholipid syndrome was negative.

Since our patient presented with typical features of itchy erythema without evidence of necrosis and a zero 4T score, a clinical diagnosis of enoxaparin induced DTH was made. Provocative testing was not done as she was pregnant. She was counseled for biopsy but she did not show intent. Symptomatic treatment was given with anti-histaminics and topical calamine lotion with regular ultrasound-doppler monitoring every 4 weeks. Her lesions showed gradual resolution of erythema and itching after

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Fig. 1 Erythematous plaque with ill-defined hyperpigmented border on abdomen

Fig. 2 Generalised erythema on the back on rechallenge predominantly involving the midline

4 weeks of stopping enoxaparin. There were residual skin coloured linear plaques and cobblestone papules on arms and extremities (Fig. 3). After 24 weeks, she travelled back to Dubai and her recent doppler scan at 29 weeks was normal.

Skin lesions due to heparin can be immune-mediated or non-immune-mediated reactions [3]. Of these, lymphocyte mediated DTH is the most common [4]. UFH increase the risk of such lesions. Hence, the ultra-low molecular weight pentasaccharide—fondaparinux is preferred. Risk factors

Fig. 3 Four weeks after discontinuation of enoxaparin, presence of skin coloured linear plaques and papules on forearm

comprise female sex, obesity (BMI > 30), young age, type of heparin (UFH, nadroparin) and prolonged treatment period [4].

Cutaneous DTH reactions usually present with an erythema associated with itching at injection sites. Generalisation occurs in 3–10 % of patients. HIT also presents with erythema but with subsequent necrosis—central black eschar surrounded by indurated erythema. However, HIT skin lesions are painful and non-itchy. Thrombocytopenia in HIT occurs in 85–90 % patients with an absolute thrombosis risk of 35–75 % (venous/arterial thromboembolism). Immediate hypersensitivity reactions are rare possibly because of improved purification, avoidance of preservatives or the anti-inflammatory properties of heparins [4].

Clinical presentation of erythema, itching, scaling, <4 points on 4T score with histological evidence of perivascular lymphohistiocytic infiltrate favours a DTH reaction. In contrast, erythema with pain/necrosis, >4 4T score with histological evidence of dermal microvascular thrombosis or positive serological assays (ELISA for Anti-heparin/PF-4 antibodies) favours HIT. The only reported laboratory test for a DTH reaction is a lymphocyte proliferation assay. Testing should preferably not be done during pregnancy. It can be done only 6 weeks after the clearance of all lesions and only when HIT has been excluded [4].

Figure 4 is an algorithm showing management of heparin-induced skin lesions. Symptomatic treatment consists of topical steroids or anti-histaminics. In case of surgery/emergency, intra-operative anticoagulation can be done with intravenous UFH. In contrast to HIT where UFH is contraindicated, the high tolerance to intravenous UFH might be because of differences in the immunologically separate compartment, skin, also defined as compartment allergy. Fondaparinux is an effective treatment option in pregnancy due to frequent cross reactivity. Newer oral anticoagulants are under investigation for use in pregnancy [4].

Fig. 4 Algorithm for management of heparin induced skin lesions [4]

Conclusion

Differentiation of HIT from DTH in a case of heparin induced skin lesions is essential. The presence of erythema with itching, scaling in an obese/pregnant female, <4 4T score and a positive lymphocyte proliferation assay or lympho-histiocytic infiltrate on histology favours a DTH reaction. Treatment options include Fondaparinux or intravenous UFH (in surgery/emergency) or oral anticoagulants—dabigatran/rivaroxaban (in non-pregnant patient).

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Compliance with Ethical Standards

Conflict of interest Dr. Sumeet Mirgh and Dr. Abhay Bhavde declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from the patient included in the case.

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