Case Report

# Enoxaparin-induced cutaneous panniculitis in a pregnant female

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## ABSTRACT

Low-molecular-weight heparins (LMWHs) are currently used as an antithrombotic prophylactic therapy during pregnancy and in post-surgery patients. The safety of various drugs in pregnancy has always been a matter of concern. Enoxaparin, being associated with low fetal and neonatal complications, is used extensively to improve the outcomes in high-risk pregnancies. The duration of treatment with LMWH in pregnancy is generally long; hence, strict monitoring of side effects should be done. We report a case of a 25-year-old pregnant female who experienced painful, erythematous skin necrosis and panniculitis after prophylactic administration of enoxaparin at multiple sites subcutaneously.

**Key words:** Enoxaparin, Low-molecular-weight heparin, Panniculitis, Skin necrosis

Enoxaparin-induced cutaneous panniculitis is an unusual complication of heparin injections either at the site of injection administration or at distant sites, leading to the death of cells and extensive necrotizing skin wounds [1]. Low-molecular-weight heparin (LMWH)-induced skin reactions include ecchymosis, erythema, rash with eosinophilia, urticaria with angioedema, erythematous plaques, and necrosis [2,3]. The rationale of reporting such rare adverse drug reactions due to LMWH holds strong implications to safeguard patients from developing serious disease conditions. Noxious effects also help us monitor the misuse and overuse of such agents.

## CASE REPORT

A 25-year-old primigravida 30+3 weeks, with gestational hypothyroidism and oligohydramnios with intrauterine growth retardation, developed pustular swelling in the left palm, followed by the bilateral thighs and anterior abdominal wall after receiving multiple doses of enoxaparin subcutaneous injections on the bilateral thighs. She had also applied heparin sodium and benzyl nicotinate ointment, following which she had blister formation on the abdomen, which ruptured spontaneously. She then underwent a venous Doppler of the upper left limb, which revealed superficial thrombophlebitis in the distal basilic vein, and was advised admission.

On examination, the patient had pallor, with a normal systemic examination, the uterus was relaxed, 30-week size, with a cephalic lie, and fetal heart sounds were regular. A tender abscess was present above the elbow joint with pus oozing out (Fig. 1a). A 5×4 cm erythematous swelling was present over the volar aspect of the distal aspect of the left wrist. A 6×4 cm erythematous abscess was present over the umbilicus (Fig. 1b). A 5×3 cm erythematous abscess was present over the anterior abdominal wall, and a 5×4 cm erythematous abscess was present over the right thigh with a 0.25×0.25 cm papule over the right thigh (Fig. 1c).

Routine investigations were done to rule out infection, which showed anemia (Hb–8.7 g/dL) with a normal leukocyte and platelet count. Renal function tests were normal. Liver function tests showed hypoalbuminemia (2.6 g/dL). Blood cultures and urine routine, microscopy, and cultures were sterile. C-reactive protein was positive (150 mg/L), and serum procalcitonin was within normal limits. Pus Gram stain revealed Gram-negative bacilli; however, routine cultures were sterile.

Enoxaparin was stopped, and the patient was started on intravenous injections of piperacillin and tazobactam. In view of anemia and hypoalbuminemia, blood products were transfused, and albumin was given. Regular ultrasounds for fetal well-being and fetal Doppler flows were normal. The patient was further worked up for antiphospholipid antibody syndrome and heparin-induced thrombocytopenia. Fibrinogen was increased (8.31 g/L), D-dimer was slightly increased to 0.56 ug/mL, and anti-factor Xa activity was zero. Protein C and Protein S functional assays were normal. Heparin-induced thrombocytopenia gel card was positive. The platelet aggregation test, which is confirmatory for heparin-induced

**Access this article online**

Received - 27 May 2023
Initial Review - 10 June 2023
Accepted - 25 July 2023

**DOI:** 10.32677/ijcr.v9i8.4071

**Quick Response code**

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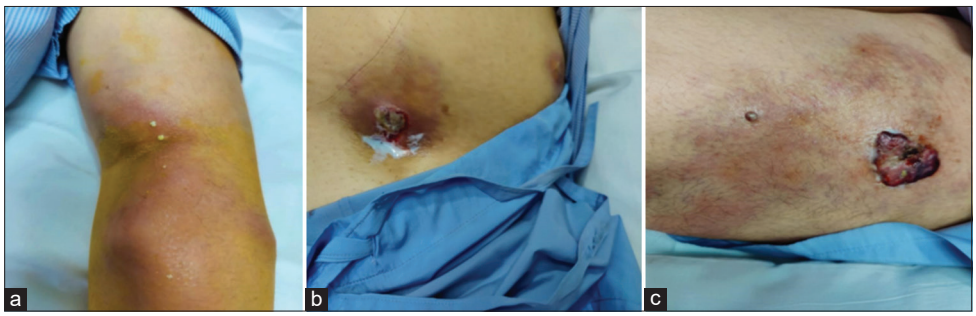


**Figure 1: Abscess present at the (a) elbow joint; (b) umbilicus; and (c) right thigh**

thrombocytopenia, came out to be negative. Antiphospholipid antibody syndrome workup was negative.

The patient underwent incision and drainage of multiple swellings over the left forearm and hand, followed by debridement of the abdomen and bilateral thigh wounds. After debridement, the samples sent for microbiological investigations such as pus and tissue gram stain, cultures, fungal cultures, tubercular cartridge-based nucleic acid amplification test, and microscopic tests were sterile. A tissue biopsy was sent, which revealed non-specific inflammatory lesions with neutrophils.

The patient was discharged with a vacuum-assisted closure *in situ* and oral antibiotics amoxicillin-clavulanic acid and clindamycin. She was readmitted again after 10 days, debridement and wound closure were done, and was discharged. The postoperative stitch site was healthy, and currently, she is doing well on follow-up.

## DISCUSSION

Enoxaparin is a commonly used LMWH to prevent thrombotic complications after surgery. It is given as a subcutaneous injection, which increases the antithrombin III action, inhibits coagulation factor Xa, and prevents the formation of thrombin and thereby fibrin clot [4].

In pregnancy, LMWH is used to safeguard the pregnancy and prevent fetal loss and pregnancy-related complications such as pre-eclampsia and fetal growth retardation. It is massively used in pregnancy as it does not trespass the placental barrier and ensures the safety of the fetus [5]. Mirgh and Bhave reported a case of a 29-year-old pregnant female who developed itching with erythematous plaques after 10 days of prophylactic enoxaparin administration in view of recurrent fetal losses. She was managed symptomatically, and the treatment was given in the form of antihistaminics and topical calamine lotion. Her lesions resolved after 4 weeks of the stoppage of enoxaparin [6].

It was also found that the risk factors leading to necrosis are female sex, obesity (BMI >30), young age, type of heparin used, and prolonged treatment period [7]. The patients who received doses of enoxaparin as venous thrombosis prophylaxis also developed skin necrosis in a span of days 5–11 of administration. These lesions initially began as tender plaques and then rapidly progressed to develop panniculitis [8]. There are a plethora of adverse effects of enoxaparin, skin changes being a rare drug reaction. Enoxaparin just like heparin can lead to necrosis of skin through antigen-antibody complex formation in blood vessels against platelets as occurs in heparin-induced thrombocytopenia syndrome. However, in our case, this was not the cause due to the absence of thrombocytopenia and a negative heparin-induced thrombocytopenia workup. Moreover, another possible mechanism could be that the LMWH gets collected in the subcutaneous tissue, resulting in adipose tissue necrosis and thereby panniculitis by the impediment of tissue blood circulation [9].

In patients with no heparin-induced thrombocytopenia syndrome, the pathogenesis of cutaneous necrosis might be vasculitis of the skin due to type III hypersensitivity reaction or type IV hypersensitivity reaction [10,11]. It has also been seen that Protein C and S deficiencies have an independent risk for the development of skin necrosis [12]. Treatment includes discontinuance of heparin injection, wound care, and debridement in cases of extensive skin involvement.

## CONCLUSION

Rarely, enoxaparin causes cutaneous manifestations as adverse effects. Prompt recognition of skin changes and stoppage of these medications at the earliest are warranted to prevent further development of complications.

## ACKNOWLEDGMENT

We would like to thank the patient and her family for giving us consent for using her clinical images.

We would like to thank Dr. Geeta Mediratta and Dr. Sharmistha Garg of the Department of Obstetrics and Gynecology and Dr. Bheem Singh Nanda of the Department of Plastic and Cosmetic Surgery with utmost gratitude for providing a constructive multidisciplinary approach in managing the patient.

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*Funding: Nil; Conflicts of interest: Nil.*

**How to cite this article:** Narula S, Kakar A, Gogia A, Batra T. Enoxaparin-induced cutaneous panniculitis in a pregnant female. Indian J Case Reports. 2023;9(8):239-241.