

CASE REPORT

ΕΝΔΙΑΦΕΡΟΥΣΑ ΠΕΡΙΠΤΩΣΗ

Enoxaparin-induced skin necrosis without heparin-induced thrombocytopenia

We report the case of a 73-year-old female who presented skin necrosis at enoxaparin injection sites after 11 days of treatment. We diagnosed enoxaparin-induced skin necrosis on clinical grounds, as the patient declined biopsy. Fondaparinux was substituted for the enoxaparin, and the lesions were managed conservatively. At follow-up the necrotic lesions had healed to a large degree. This case is uncommon in that laboratory findings excluded the presence of heparin-induced thrombocytopenia (HIT), and therefore the skin necrosis should be attributed to other mechanisms, such as type III hypersensitivity with vasculitis, or repeated local trauma and hemorrhage.

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Νέκρωση δέρματος από ενοξαπαρίνη, χωρίς συνοδό θρομβοπενία από ηπαρίνη

Περίληψη στο τέλος του άρθρου

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Up to one third of hospitalized patients receive heparin, either unfractionated heparin (UFH) or, more often, low molecular weight heparin products (LMWH), for treatment of various conditions such as acute coronary syndromes, including myocardial infarction and venous thromboembolism (VTE), and for VTE prophylaxis in medical and surgical inpatients, or as temporary replacement for oral anticoagulants (bridging).¹

Skin reactions to LMWH have been observed in 7.5% of medical inpatients, but LMWH-induced skin necrosis is a rare event that is usually associated with the heparin-induced thrombocytopenia (HIT) syndrome.^{2,3}

We present a case of LMWH-induced skin necrosis which was not associated with HIT. We think it is important that physicians be familiar with, and recognize, even the uncommon or rare adverse reactions to this commonly used class of medications.

CASE PRESENTATION

A 73-year-old Caucasian woman was admitted via the emergency department for treatment of cellulitis and chronic digital ischemia of the left foot.

The medical history included type 2 diabetes mellitus (DM), atrial fibrillation and heart failure. She had also been diagnosed with myelodysplastic syndrome, with refractory anemia for which she needed occasional red cell transfusions. Her medication included warfarin, valsartan, nebivolol, furosemide, vildagliptin and metformin.

We diagnosed acute bacterial skin and skin structure infection (ABSSI) along with chronic digital ischemia. The patient was treated with intravenous piperacillin-tazobactam and vancomycin, and for anticoagulation, the warfarin was switched to subcutaneous enoxaparin 12,000 IU/day.

On the 11th day of hospitalization, the patient presented two painful, erythematous lesions at LMWH injection sites on the right

arm and the abdominal wall, measuring 3.5×8 cm and 3×3 cm, respectively (figures 1A, 1B, 2). Initially, the lesions were attributed to heparin injection site hematomas, but during the next 48–72 hours the lesions developed into blisters with underlying necrosis, starting from the center and progressing peripherally. In addition, new lesions appeared on the subsequent injection sites.



Figure 1. Low molecular weight heparin skin necrosis in a 73-year-old woman. Skin lesion of the right arm at the site of enoxaparin injection. (A) initially, and (B) 72 hours later, with obvious necrosis.



Figure 2. Low molecular weight heparin skin necrosis in a 73-year-old Caucasian woman. Early skin lesion on the abdomen at the site of enoxaparin injection.

The differential diagnosis included HIT-associated skin necrosis, warfarin-induced skin necrosis and hematoma.

The platelet count at admission was $337 \times 10^9/L$ and on day 11 it reached $453 \times 10^9/L$. The patient had been taking warfarin, but the prothrombin time at admission was only slightly prolonged, at 14.30 sec with international normalized ratio (INR)=1.15. Warfarin-associated skin necrosis usually occurs during the initiation of warfarin in patients with thrombophilia. We excluded HIT because the patient had a low 4Ts score (two points for skin necrosis, no thrombocytopenia), and no antibodies against platelet factor-4 were detected with ELISA.

The lesions were initially erythematous and resembled injection site hematomas, but they quickly developed into necrotic blisters, a feature not observed in these hematomas.

After excluding other diagnostic entities, and as the patient declined skin biopsy, we diagnosed heparin-induced skin necrosis, based on the clinical characteristics of the lesions (i.e., necrotic lesions on enoxaparin injection sites).

On the 14th day, enoxaparin was discontinued, and replaced by fondaparinux 7.5 mg subcutaneously daily, after which no new lesions appeared, although the initial lesions developed into necrotic ulcers (fig. 1B). The patient was transferred to the Vascular Surgery Unit where she underwent amputation of the 3rd, 4th and 5th toes and was discharged home with no further complications. She was instructed to continue fondaparinux and it was planned to switch back to warfarin one week after discharge. At 2-month follow-up, the necrotic areas in the abdomen were completely healed and only a small ulcer on right arm lesion remained.

DISCUSSION

This patient was taking warfarin because of atrial fibrillation. On admission with cellulitis of the left foot, the anticoagulant was switched to LMWH in therapeutic doses, because she was undertreated with warfarin (INR=1.15) and she would have to receive antibiotics for at least 10 days.

LMWH products have several advantages over UFH, including the subcutaneous route of administration, more convenient dosing schemes, no need for laboratory monitoring and a lower risk of side effects such as thrombocytopenia and osteoporosis.¹ Skin reactions, however, are a relatively frequent adverse effect of LMWH. One prospective study found that 7.5% of a cohort of 320 patients developed skin reactions. The majority of the patients (62.8%) received LMWH for prophylaxis. All the skin reactions reported consisted of eczematous plaques, mostly at the injection sites, identified as type IV delayed hypersensitivity reactions to heparin. In another study, the rate of skin reactions to LMWH was 39.0% in a cohort of 188 pregnant women receiving therapeutic doses of nadroparin.⁴

No case of heparin-induced skin necrosis was reported in the above-mentioned studies.^{3,4} This is a rare adverse event, although some authors suggest that it is under-reported.⁵ A systematic literature review, published in 2004, identified 21 cases of LMWH-induced skin necrosis. Skin necrosis occurred 7.6 ± 3.4 days (range 1–17) after initiation of LMWH administration. The lesions usually appeared on the injection sites, although in 5/21 patients they were located on distant areas. Clinically, the lesions begin as painful, erythematous and oedematous areas, which rapidly progress into necrotic blisters and finally ulcers. The lesions range in size from 2 to 20 cm. The clinical events in the case presented here (timing, distribution, appearance and size of the lesions) are in line with those described in the literature.

A significant number of cases of LMWH-induced skin necrosis occur in the context of HIT. In a relevant review, thrombocytopenia was present in 9/21 patients, while anti-PF4 antibodies were detected in 9/10 patients tested. In these cases, the probable mechanism for skin necrosis is microthrombosis of skin vessels due to HIT. This mechanism explains the appearance of skin lesions in areas other than the injection sites. Other reports challenge the association of HIT with LMWH-induced skin necrosis.⁶

Our patient tested negative for anti-PF4 antibodies and, in addition, her platelet count during hospitalization was either normal or slightly increased, apparently because of her infection. In patients without HIT syndrome, the possible mechanisms for the necrosis are skin vasculitis associated

with a type III hypersensitivity reaction (Arthus phenomenon, with immune-complexes on vascular endothelium) or a type IV hypersensitivity reaction (DTH).^{6,7} Proposed non-immune mediated mechanisms include repeated local trauma and hemorrhage, which increases tissue pressure, and leads to compression of small cutaneous arteries, ischemia and necrosis.⁵ Finally, local accumulation of heparin due to poor vascularization of the adipose tissue, may increase vascular damage.⁸ Unfortunately our patient declined skin biopsy, which would probably have provided insight into the underlying mechanism (e.g., the presence of vasculitis).

Management of LMWH-induced necrosis includes discontinuation of LMWH and switching to another anticoagulant, if necessary.^{5,9} In older reports, patients were switched to subcutaneous UFH, hirudin or even coumarin.^{2,10} If necrosis occurs in the context of HIT, however, UFH is contraindicated, and warfarin should be used only after initial anticoagulation with a non-heparin anticoagulant.⁹ We used fondaparinux here, but alternatives include danaparoid or bivalirudin. In most reports, conservative treatment has led to healing of the lesions, with occasional exceptions, usually involving large ulcers, for which surgical debridement was necessary.

In summary, LMWH-induced skin necrosis is a rare adverse event. In a significant number of cases it is associated with HIT, but it can occur with no evidence of HIT. Clinicians should be aware of the variation, in order not to misdiagnose this complication as injection site hematoma or hypersensitivity reaction.

ΠΕΡΙΛΗΨΗ

Νέκρωση δέρματος από ενοξαπαρίνη, χωρίς συνοδό θρομβοπενία από ηπαρίνη

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Γυναίκα 73 ετών εμφάνισε νέκρωση του δέρματος στις θέσεις ένεσης ενοξαπαρίνης μετά την 11η ημέρα θεραπείας. Η ασθενής αρνήθηκε να υποβληθεί σε βιοψία δέρματος και έτοι αφού αποκλείστηκαν άλλα πιθανά αίτια, διαγνώστηκε νέκρωση του δέρματος σχετιζόμενη με ενοξαπαρίνη. Η ενοξαπαρίνη διακόπηκε και η ασθενής τέθηκε υπό fondaparinux, ενώ οι δερματικές βλάβες αντιμετωπίστηκαν συντηρητικά. Κατά την επανεξέταση μετά την έξοδο από το νοσοκομείο οι βλάβες είχαν επουλωθεί σε μεγάλο βαθμό. Στην ασθενή αυτή αποκλείστηκε εργαστηριακά η θρομβοπενία από ηπαρίνη. Επομένως, η νέκρωση του δέρματος θα πρέπει να αποδοθεί σε άλλους μηχανισμούς, όπως η αντίδραση υπερευαισθησίας τύπου III με αγγειίτιδα ή το επανειλημμένο τοπικό τραύμα με αιμορραγία.

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