CASE REPORT

Delayed-onset heparin-induced skin necrosis: a rare complication of perioperative heparin therapy

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SUMMARY

An uncommon case of delayed-onset dalteparin-induced skin necrosis in an 83-year-old Caucasian female patient associated with heparin-induced thrombocytopenia (HIT) presenting on day 30 following dalteparin therapy is reported. Investigations revealed mild thrombocytopenia with normal protein C, protein S, coagulation screen and positive test for heparin–platelet factor-4 antibody. Clinical diagnosis of heparin-induced skin necrosis with HIT was made. Dalteparin injection was discontinued promptly and substituted with fondaparinux therapy. The patient achieved good recovery following cessation of dalteparin therapy and was subsequently discharged.

BACKGROUND

Heparin is the most commonly prescribed medication for prophylaxis and treatment for thromboembolic events.¹ Skin necrosis is a rare complication of heparin therapy associated with serious thrombotic sequelae and increased morbidity. However, the true incidence is likely underestimated due to under-reporting.² Cases of heparin-induced skin necrosis have been reported to occur between 1 and 17 days after initiation of heparin therapy.³ An uncommon case of delayed-onset dalteparin-induced skin necrosis associated with heparin-induced thrombocytopenia (HIT) is presented.

CASE PRESENTATION

An 83-year-old Caucasian woman was admitted to the orthopaedic unit for dynamic hip screw fixation surgery after suffering from an intertrochanteric fracture of the right neck of femur. Her medical histories include type 2 diabetes mellitus, osteoporosis, hypothyroidism and a high body mass index (BMI 35 kg/m²). A daily dose of 5000 units of dalteparin injection was administered subcutaneously since the first day of admission and continued postoperatively. After 30 days of dalteparin injection, multiple tender erythematous subcutaneous nodules were noted at the injection sites of the lower abdomen. An initial diagnosis of subcutaneous haematoma was made. Her skin condition continued to deteriorate, and she developed multiple tender blistering lesions measuring 5×4 cm, 4×4 cm, 4×3 cm and 3×2 cm with areas of necrosis in the span of 5 days (figures 1 and 2). No other lesion was found on distant sites. Dermatologist's opinion was sought on day 35, and the

clinical diagnosis of heparin-induced skin necrosis was made.

INVESTIGATIONS

The patient's platelet count was noted to be $290 \times 10^9/L$ on admission. Her platelet count on the day of review is $142 \times 10^9/L$ with normal protein C, protein S and coagulation screen. Ultrasound scan of the abdomen demonstrated thickening of the subcutaneous layer with no underlying haematoma or collection.

DIFFERENTIAL DIAGNOSIS

Anti-heparin–platelet factor-4 antibody ELISA was positive at optical density (OD) of 2.4 OD units, and HIT was diagnosed. Ristocetin-induced platelet aggregation assay (RIPA) and platelet serotonin-release assay (SRA) were not performed.

TREATMENT

Dalteparin injection was discontinued on day 35 and switched to daily fondaparinux injection at a dose of 2.5 mg.

OUTCOME AND FOLLOW-UP

Satisfactory healing of the skin lesions was achieved after 30 days following discontinuation of heparin therapy (figure 3). Surgical debridement was not indicated in her case, and she was subsequently discharged on day 65.

DISCUSSION

Low-molecular-weight heparins (LMWHs) have been widely used in surgical practice as effective prophylaxis and treatment for thromboembolic disorders due to its superiority in safety profile and easy administration.^{1 3} Cases of heparin-induced skin lesions have been increasingly reported and more frequently observed with subcutaneous heparin therapy. Female sex, high BMI (>25 kg/m²) and long duration of heparin therapy (>9 days) have been identified to be the risk factors for developing heparin-induced skin lesions, and the incidence is estimated to be as high as 7.5%.² However, little is known about the incidence of LMWH-induced skin necrosis.

Skin necrosis normally develops between 5 and 11 days following LMWH therapy, and cases occurring beyond 11 days are extremely rare.³ HIT can develop alongside, often between 5 and 14 days after heparin therapy.⁴ Rare case of delayed-onset HIT up to 40 days after cessation of heparin

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Figure 1 Multiple violaceous blisters occurring at the injection sites.

therapy has been reported.⁵ The risk of developing thrombotic complications (systemic thromboembolism, skin necrosis) persists even after cessation of heparin therapy as the circulating HIT antibodies developed could remain in the bloodstream for up to 3 months.⁶ Our case demonstrated an uncommon delayed presentation of heparin-induced skin necrosis at day 30 following dalteparin therapy associated with HIT.

Lesions of heparin-induced skin necrosis typically present initially with tender erythematous tense subcutaneous nodules, which rapidly increase in size and develop areas of blister and ulcer with subsequent skin necrosis as it was in our case. Skin biopsy of these lesions typically demonstrates areas of necrotic tissues, infarctions, clots or evidence of vasculitis. The diagnosis of heparin-induced skin necrosis is made on clinical basis and aided by skin biopsy, test for heparin/platelet factor-4 antibody and blood test demonstrating thrombocytopenia. Functional tests, such as RIPA and SRA can also be performed to measure platelet activity. Cases of heparin-induced skin necrosis without the presence of HIT and heparin–platelet factor-4 antibodies have been infrequently reported.³

HIT typically presents with a platelet count below $100 \times 10^9/L$.⁴ However, overt thrombocytopenia is not characteristically seen in skin necrosis associated with HIT.³ Most of the patients who develop heparin-induced skin necrosis associated with positive heparin–platelet factor-4 antibodies present with platelet count above $150 \times 10^9/L$ or mild thrombocytopenia ($100\text{--}150 \times 10^9/L$).³ Relative reduction in platelet count of more than 50% from baseline is diagnostic for HIT as demonstrated in our case.⁴

Figure 2 Violaceous blisters on periumbilical region.

Figure 3 Resolution of skin lesions after 30 days following discontinuation of heparin therapy.

High BMI could be a potential predisposing factor for developing delayed-onset heparin-induced skin necrosis as residue heparin can persist in excess subcutaneous fat tissue with poor blood circulation. Females may be at increased risk of developing heparin-induced skin necrosis as a result of higher percentage of body fat mass compared with males. Delayed-onset heparin-induced skin necrosis is a diagnostic challenge and is probably least recognised due to under-reporting. Serious systemic involvements and thrombotic events have been noted in cases of delayed-onset heparin-induced skin necrosis.⁷ The HIT antibodies developed can remain in the blood circulation for up to 3 months.⁶ Patients with positive HIT antibodies are at risk of developing delayed thrombotic complications. Immediate discontinuation of heparin injections and substitution with appropriate anticoagulants are crucial as life-threatening complications can potentially develop due to internal clot formation and extensive skin involvement.^{7–9}

Current evidence recommends switching to non-heparin anticoagulant (argatroban, danaparoid) for suspected HIT.¹⁰ Extreme vigilance is required when switching to oral anticoagulant. Cases of venous gangrene associated with warfarin (coumarins) use in the presence of HIT syndrome have been described.³ Prophylactic fondaparinux demonstrated similar efficacy and safety profile as danaparoid and argatroban when full anticoagulation is not indicated.¹⁰ Platelet transfusion

Learning points

- ▶ Delayed-onset heparin-induced skin necrosis is a rare complication of heparin therapy associated with serious systemic involvements and thrombotic events.
- ▶ In patients with positive heparin–platelet factor-4 antibodies, the risk of developing thrombotic complications (systemic thromboembolism, skin necrosis) persists even after cessation of heparin therapy for up to 3 months.
- ▶ Skin necrosis associated with heparin-induced thrombocytopenia (HIT) often occurs without overt fall in platelet count.
- ▶ Absence of absolute thrombocytopenia ($<150 \times 10^9/L$) does not exclude the diagnosis of HIT.
- ▶ Prophylactic fondaparinux is a safe and effective substitute in patients presenting with heparin-induced skin necrosis when full anticoagulation is not indicated.

is generally not advised as it may aggravate HIT-induced prothrombotic state.⁴

Complete recovery is generally expected with cessation of heparin therapy. However, fatal cases of heparin-induced skin necrosis as a result of infection and systemic organ failure have been described.^{8,9} Surgical debridement may be indicated in poor-healing lesions to remove necrotic skin, and skin graft could be performed in patients with large area of skin loss.

In summary, delayed-onset heparin-induced skin necrosis is the least recognised adverse reaction of heparin therapy associated with devastating thromboembolic events and could potentially be fatal. Careful monitoring should be executed in all patients receiving heparin treatment to aid early detection of complications and limit disease progression.

Contributors WKG is involved in retrieving patient information including history, examination findings and results of investigations, as well as writing up of case report and obtaining patient consent.

Competing interests None declared.

Patient consent Obtained.

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