HEPARIN-INDUCED DELAYED-TYPE HYPERSENSITIVITY REACTION: TWO CASE REPORTS AND MANAGEMENT STRATEGIES

Mehmet Hoxha[1,2], Ester Ndreu[2]

[1] Faculty of Medicine, University of Medicine, Tirana, Albania
[2] University Hospital Center "Mother Teresa", Tirana, Albania
Corresponding E-mail: esterndreu3@gmail.com

ABSTRACT

Background: Heparin-induced delayed-type hypersensitivity reaction (HIDHR) is a rare but clinically significant adverse effect of low molecular weight heparins (LMWHs). It represents a type IV hypersensitivity reaction mediated by T lymphocytes and typically occurs 1-3 weeks after treatment initiation. Clinically, it presents with pruritic erythematous plaques at injection sites, sometimes spreading beyond. Early recognition is essential to avoid complications and to ensure safe anticoagulant substitution**.**

Case Report: We report two cases of HIDHR in different clinical settings. The first case involves a 30-year-old pregnant woman in her first trimester receiving enoxaparin for thromboprophylaxis who developed pruritic erythematous plaques at injection sites that subsequently spread to the trunk after three weeks of therapy. Platelet count remained normal. Enoxaparin was discontinued and replaced with unfractionated heparin, leading to complete resolution of lesions within 10 days. The second case describes a 65-year-old woman after total abdominal hysterectomy who was treated with fraxiparine and developed similar lesions after three weeks. The drug was discontinued and replaced with fondaparinux, resulting in complete resolution within two weeks. Patch testing confirmed the diagnosis in the second case, while the first diagnosis was based on clinical and histopathological findings.

Conclusion: HIDHR is an uncommon but important complication of LMWH therapy, with consistent immunologic mechanisms across different clinical contexts. Early discontinuation of the offending agent and substitution with alternatives such as unfractionated heparin or fondaparinux ensures safe and effective anticoagulation. Awareness of this condition and potential cross-reactivity among LMWHs is essential for optimal patient management.

Keywords: Heparin-induced delayed-type hypersensitivity reaction; Low-Molecular-Weight Heparin; Drug Hypersensitivity; Enoxaparin; Fondaparinux.

REAKSION HIPERSENSITIV I TIPIT TË VONUAR I INDUKTUAR NGA HEPARINA: DY RASTE KLINIKE DHE STRATEGJITË E MENAXHIMIT

ABSTRAKT

Hyrje: Reaksioni i vonuar i hipersensibilitetit i induktuar nga heparina (HIDHR) është një efekt anësor i rrallë por klinikisht i rëndësishëm i heparinave me peshë molekulare të ulët

(LMWH). Ai përfaqëson një reaksion të tipit IV të ndërmjetësuar nga limfocitet T dhe zakonisht shfaqet 1–3 javë pas fillimit të trajtimit, me pllaka eritematoze dhe prurit në vendin e injeksionit. Njohja e hershme është thelbësore për të shmangur komplikacionet dhe për të zgjedhur një alternativë të sigurt antikoagulante.

Prezantimi rasteve: Paraqesim dy raste me HIDHR në kontekste të ndryshme klinike. Rasti i parë është një grua 30-vjeçare në tremujorin e parë të shtatzënisë, e trajtuar me enoksaparinë për tromboprofilaksi, e cila zhvilloi pllaka eritematoze me kruarje në vendet e injeksionit, me përhapje në trung pas tre javësh trajtimi. Numri i trombociteve ishte normal. Terapia u ndërpre dhe u zëvendësua me heparinë të pafraksionuar, me përmirësim të plotë të lezioneve brenda 10 ditësh. Rasti i dytë është një grua 65-vjeçare pas histerektomie abdominale totale, në trajtim me fraxiparinë, e cila zhvilloi manifestime të ngjashme pas tre javësh. Medikamenti u ndërpre dhe u zëvendësua me fondaparinuks, duke çuar në rezolucion të plotë të lezioneve brenda dy javësh. Në rastin e dytë, "patch" testi konfirmoi diagnozën, ndërsa në rastin e parë diagnoza u bazua në gjetjet klinike dhe histopatologjike.

Përfundime: HIDHR është një komplikacion i rrallë por i rëndësishëm i LMWH-ve me një mekanizëm imunologjik të përbashkët në kontekste të ndryshme klinike. Ndërprerja e hershme e medikamentit shkaktar dhe zëvendësimi me alternativa si heparina e pafraksionuar ose fondaparinuksi sigurojnë një trajtim të sigurt dhe efektiv. Rritja e ndërgjegjësimit për këtë gjendje dhe për mundësinë e reaksioneve të kryqëzuara është thelbësore për menaxhim optimal.

Fjalë kyç: Reaksioni i mbindjeshmërisë së vonuar i induktuar nga heparina; Heparina me peshë molekulare të ulët; Mbindjeshmëria ndaj barnave; Enoksaparina; Fondaparinuks.

INTRODUCTION

Low molecular weight heparins (LMWHs) are widely used anticoagulants in clinical practice, particularly in pregnancy and perioperative settings, due to their predictable pharmacokinetics, ease of administration, and lower risk of heparin-induced thrombocytopenia compared to unfractionated heparin (UFH) [1,2]. Despite their favorable safety profile, LMWHs may be associated with rare adverse effects, including delayed-type hypersensitivity reactions Heparin-induced delayed-type hypersensitivity reaction (HIDHR) is an uncommon cutaneous adverse reaction mediated by T lymphocytes and classified as a type IV hypersensitivity reaction [2,6]. It typically occurs 1–3 weeks after initiation of therapy and presents as pruritic erythematous plaques at injection sites, which may occasionally generalize [5]. Histopathological findings usually reveal perivascular lymphocytic infiltrates with eosinophils, supporting an immune-mediated mechanism [6].The pathogenesis of HIDHR involves the role of LMWHs as haptens that bind to endogenous proteins, leading to sensitization and subsequent immune activation upon repeated exposure [6]. An important clinical challenge is the high rate of cross-reactivity among different LMWHs, reported in more than 50% of cases, which limits therapeutic alternatives [7]. Consequently, switching between LMWHs is not generally recommended. Early recognition of HIDHR is essential to avoid progression of skin lesions and to ensure safe continuation of

anticoagulation therapy. Alternative anticoagulants such as UFH or fondaparinux are often used depending on the clinical context, including pregnancy status [1,5,7].In this report, we present two cases of HIDHR occurring in different clinical settings, highlighting their similar clinical presentation and underlying immunologic mechanisms, as well as management strategies.

CASE PRESENTATION

A 30-year-old woman in the first trimester of pregnancy was started on enoxaparin 40 mg once daily for thromboprophylaxis due to increased thrombotic risk in pregnancy. After three weeks of treatment, she developed pruritic, erythematous plaques at the injection sites on the abdomen, with subsequent spread to the trunk. Cutaneous lesions are shown in Figure 1. There were no systemic symptoms. Laboratory findings showed a normal platelet count and no eosinophilia.

Dermatology consultation was performed, and a skin biopsy revealed perivascular lymphocytic infiltrates with eosinophils, consistent with a delayed-type hypersensitivity reaction. Based on clinical and histopathological findings, HIDHR was diagnosed. Enoxaparin was discontinued and replaced with unfractionated heparin. Treatment with topical corticosteroids and oral antihistamines led to complete resolution within 10 days.

Patch testing was not performed during pregnancy due to safety considerations and was not completed postpartum due to limited follow-up.

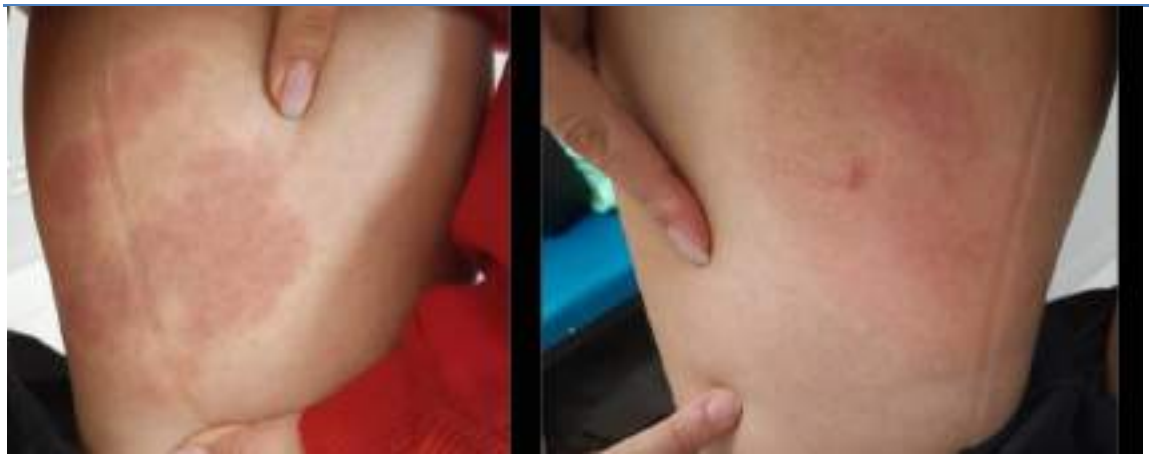

Figure 1. Erythematous pruritic plaques at enoxaparin injection sites in Case 1.

Case 2

A 65-year-old woman underwent total abdominal hysterectomy and received fraxiparine 0.4 mL (3800 IU anti-Xa) once daily for postoperative thromboprophylaxis. After approximately three weeks, she developed pruritic erythematous plaques at the injection sites, extending to the trunk (Fig. 2). No systemic symptoms were present. Laboratory evaluation showed a normal platelet count and mild eosinophilia.

A dermatology consultation was obtained, and a skin biopsy demonstrated perivascular lymphocytic infiltration with eosinophils, supporting a diagnosis of delayed-type hypersensitivity. Fraxiparine was discontinued and replaced with fondaparinux.

Topical corticosteroid therapy resulted in complete resolution of lesions within two weeks. Patch testing performed four months later was positive for fraxiparine and negative for fondaparinux.

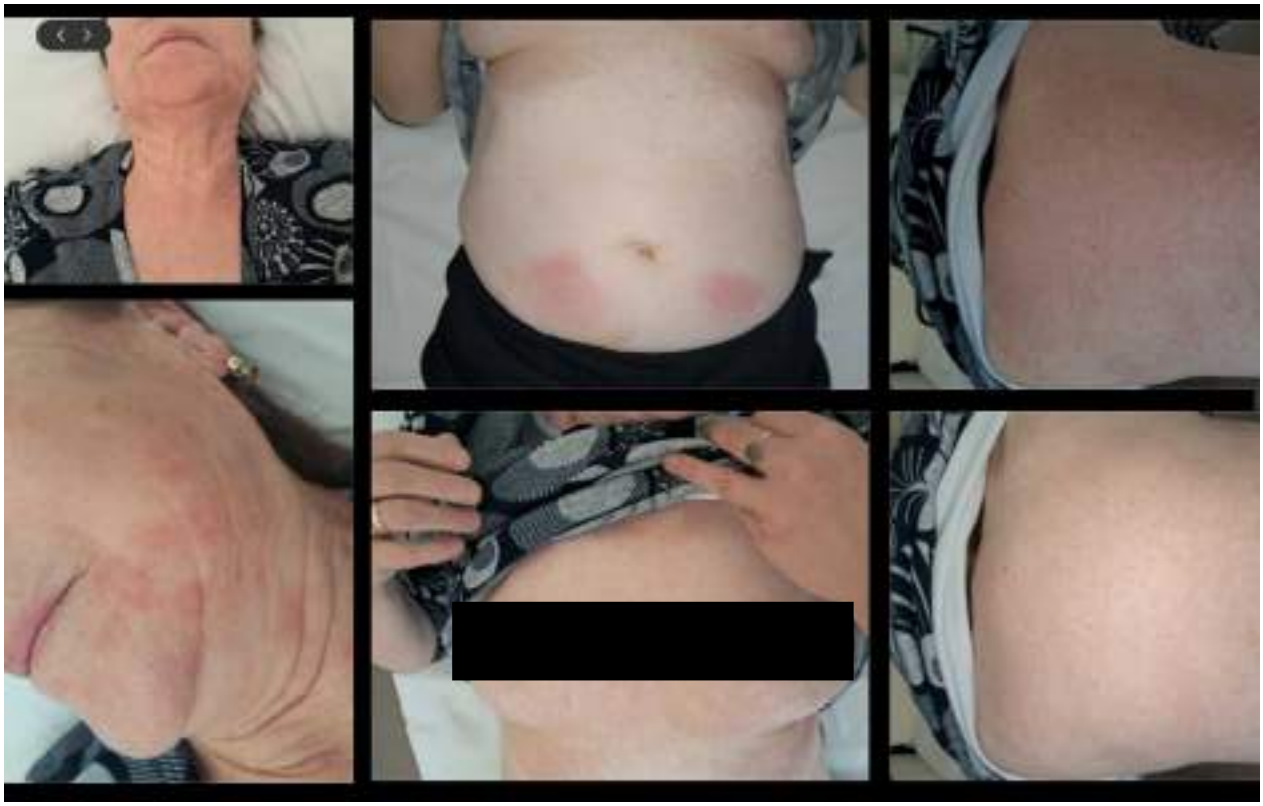

Figure 2. Cutaneous lesions associated with fraxiparine-induced delayed hypersensitivity in Case 2.

DISCUSSION

HIDHR is a rare but clinically relevant adverse reaction to LMWHs, mediated by a delayed-type (type IV) hypersensitivity mechanism involving sensitized T lymphocytes [1,3,6]. The characteristic onset 1–3 weeks after initiation of therapy reflects the time required for immune sensitization and subsequent elicitation upon repeated exposure [6].

Clinically, HIDHR typically presents with pruritic erythematous plaques at injection sites, which may extend beyond these areas, as observed in both of our patients [2,6]. The absence of thrombocytopenia helps distinguish HIDHR from heparin-induced thrombocytopenia, a potentially life-threatening immune-mediated complication [3]. In our cases, normal platelet counts supported the diagnosis of a localized cutaneous hypersensitivity reaction rather than HIT.

The differential diagnosis also includes cellulitis and other cutaneous drug reactions. Cellulitis is usually associated with localized pain, warmth, and systemic signs such as fever, and typically lacks the characteristic delayed onset and pruritus seen in HIDHR. Other injection-site reactions, including irritative or immediate hypersensitivity responses, tend to occur earlier after drug administration and are not mediated by a delayed T-cell response. In contrast, the timing, morphology, and histopathological findings in our patients were consistent with HIDHR.

The underlying pathophysiology involves LMWH molecules acting as haptens that bind to endogenous proteins, forming antigenic complexes that activate T cells [2,6]. Histological findings described in the literature include perivascular lymphocytic infiltrates with eosinophils, consistent with a delayed hypersensitivity response [6].

Management of HIDHR requires prompt discontinuation of the offending agent. Supportive treatment with topical corticosteroids and antihistamines is usually sufficient, while systemic corticosteroids are rarely needed [2,5]. Both patients in our report showed rapid clinical improvement following drug withdrawal and symptomatic therapy.

A major therapeutic challenge is the high rate of cross-reactivity among LMWHs, reported in more than half of cases [2,7]. For this reason, switching from one LMWH to another is generally discouraged. Instead, alternative anticoagulants should be considered based on patient-specific factors.

In pregnant patients, UFH is often the preferred alternative due to its safety and minimal cross-reactivity, as demonstrated in our first case [1,5]. In non-pregnant patients, fondaparinux represents an effective and well-tolerated option, with a low incidence of cross-reactivity [5]. Our second case supports this approach, as the patient tolerated fondaparinux without recurrence of symptoms.

Patch testing is a valuable tool for confirming delayed-type hypersensitivity to heparins and for assessing potential cross-reactivity [6]. However, it is not always feasible during the acute phase, particularly in pregnant patients, where it is often deferred due to safety and practical considerations. In our report, patch testing was performed only in the second case and supported the diagnosis. In contrast, in the first case, the diagnosis was based on clinical presentation and response to drug withdrawal. Although helpful, patch testing is not essential when clinical features and temporal association are typical.

The prognosis of HIDHR is excellent once the causative agent is discontinued, with most lesions resolving within one to two weeks [6]. However, failure to recognize this condition may lead to unnecessary continuation of the offending drug and worsening of symptoms.

Table 1. Recommended Anticoagulant Alternatives

Anticoagulant	**Pregnancy Safety**	**Cross-Reactivity**	**Comment**
Enoxaparin (LMWH)	Safe	High	First-line, may trigger HIDHR
Dalteparin (LMWH)	Safe	High	Similar to enoxaparin
UFH	Safe	Low	Preferred in pregnancy after HIDHR
Fondaparinux	Caution	Rare	Good alternative in non-pregnant patients
Warfarin	Contraindicated	N/A	Teratogenic

LIMITATIONS

This report has two main limitations. First, patch testing was not performed during pregnancy in one case due to safety and practical considerations, thereby delaying immunologic confirmation. Secondly, as a small case series, the findings may not be generalizable but provide clinically relevant insights into the recognition and management of HIDHR.

CONCLUSION

Heparin-induced delayed-type hypersensitivity reaction (HIDHR) is a rare but important complication of LMWH therapy. Early recognition and prompt discontinuation of the offending agent are essential for rapid resolution. Due to frequent cross-reactivity among LMWHs, alternative anticoagulants such as unfractionated heparin or fondaparinux should be considered. Increased clinical awareness is key to ensuring safe and effective management.

Conflict of Interest: The authors declare no conflict of interest.

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