Heparin-induced thrombocytopenia (HIT) is a life-threatening immune complication of exposure to unfractionated heparin or low molecular weight heparins (LMWH) that occurs independently of the dose in a small percentage of patients. The clinical case and diagnosis of HIT, which started as skin necrosis will be discussed here.

A 75-year-old obese woman (weight 98 kg, height 164 cm, BMI 36.4 kg/m²) was hospitalized due to unexplained chronic abdominal pain and jaundice. Although on admission there were no clinical signs of deep venous thrombosis, she was prescribed a prophylactic dose of nadroparin 2850 U s/c; as she was motionless and after a few days of investigations, she was diagnosed with metastatic neoplasia of liver and intrahepatic ducts. After 8 days, a one 20 cm area of nonpalpable purpura with surrounding erythema and hemorrhagic vesicles on the central abdominal part was noticed (Figure 1). There was no pruritus or surrounding pain. The platelet count was decreased from 217,000/microl at hospitalization to 68,000/microl when the skin necrosis developed. Protein S, protein C, prothrombin time, and thrombin time were normal. Commercial diagnostic test kit for PF4/heparin antibodies identification of all isotypes was used (*ID-PaGIA Heparin/PF4 Antibody Test* (DiaMed GmbH). Two different titrations were made (1:4 and 1:32) and both of them were positive.

Based on the clinical picture, nadroparin-induced skin necrosis was diagnosed. We also clinically suspected a
high probability (appr. 50%) of type II heparin-induced thrombocytopenia (HIT) as a score of 7 points according to the 4T’s HIT score system was calculated (Table 1). A high 4T score and positive PF4/heparin antibodies led to high suspicion of HIT, although platelet functional tests were not performed. All contact with heparin (including catheter washing) and LMWH were stopped. For 1 week, the patient was without anticoagulation, and then pain and edema developed in the right upper leg. Lower extremity Doppler ultrasound confirmed acute iliofemoral thrombosis of the right leg, thus anticoagulation was required. After changing nadroparin to fondaparinux and later on to oral apixaban, the lesions improved and eventually healed (Figure 2). Platelet count was returned to normal 11 days after discontinuation of nadroparin (Table 2).

Skin necrosis is a rare complication of LMWH; although for unfractionated heparin injections, it is a well-described complication. In the literature, dalteparin and enoxaparin are mostly described LMWH, which cause HIT, nadroparin-induced skin necrosis is rarely published. Skin necrosis immediately suggests the presence of HIT as this develops due to intradermal microvascular thromboses. The absolute risk for HIT is 0.2% with LMWH and 2.6% with unfractionated heparin. Often, the first manifestation of HIT is thrombocytopenia, occurring in up to 90% of those affected. Thrombosis occurs in up to 50% of patients, more frequently due to venous than to arterial thrombi, and can lead to skin necrosis and organ infarction. Mortality from HIT, mostly due to thrombosis, in the past was as high as 20%, and approximately 10% of patients required amputations or suffered other major morbidities. In the recent study, it was found that thrombotic events were only venous in patients with LMWH-induced HIT, while some patients in the unfractionated heparin HIT group experienced arterial events.

**TABLE 1** 4 Ts score calculation for estimating the pretest probability of heparin-induced thrombocytopenia (HIT) in the patient

| 4 Ts score parameters |  |
|-----------------------|--|
| Thrombocytopenia       |  |
| PLT decrease >50% AND nadir ≥20,000/microL AND no surgery within preceding 3 days | 2 points |
| Timing of onset after heparin exposure |  |
| 8 days | 2 points |
| Thrombosis or other clinical sequelae |  |
| Confirmed skin necrosis | 2 points |
| Other causes for thrombocytopenia |  |
| Possible (eg, neoplasm) | 1 point |
| Interpretation |  |
| 6–8 points—High HIT probability (approximately 50%). |

Note: Adapted from: Lo GK, Juhl D, Warkentin TE, et al. Evaluation of pretest clinical score (4 T’s) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. J Thromb Haemost 2006; 4:759.
The mortality rate was nil in the LMWH group. Protein C and protein S deficiencies greatly increase the risk of skin necrosis and should be measured if skin necrosis follows LMWH injection.

Heparin or LMWH-induced skin necrosis is generally a benign condition, which resolves after stopping the culprit drug, but skin necrosis can just be a part of clinical spectrum of thrombotic complications, which are potentially life-threatening. The decisive diagnostic procedure in heparin-induced necrosis is HIT antibody testing, diagnostic procedure in heparin-induced necrosis, PF4/heparin antibodies and by diagnosis confirmation by platelet functional test, histological examination if necessary and the chronological connection between the initiation of heparin/LMWH and appearance of skin necrosis, thrombocytopenia, which usually occurs 5–10 days later at the site of injection (although there is the description of distant lesions development). Clinical and laboratory evidence in evaluating patients for HIT should be always considered.

In patients with suspected HIT and a high-probability 4Ts score, the ASH guideline panel recommends discontinuation of heparin and initiation of a non-heparin anticoagulant at therapeutic intensity. When a non-heparin anticoagulant is being selected, the ASH guideline panel suggests argatroban, bivalirudin, danaparoid, fondaparinux, or a direct acting oral anticoagulants (DOAC). The choice of agent may be influenced by drug factors (eg, cost and ability to monitor the anticoagulant effect), patient factors (kidney and liver function, bleeding risk, and clinical stability), and the experience of the clinician. This is supported by a multi-centric retrospective case series of HIT patients treated with either rivaroxaban or apixaban during the acute HIT phase. No patient experienced major or clinically relevant non-major bleeding or thrombosis that could be related to DOAC treatment during follow-up. The literature review found similarly favorable results when apixaban and dabigatran were used to treat acute HIT.

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**CONFLICTS OF INTEREST**

The authors state no conflict of interest.

**AUTHOR CONTRIBUTION**

Laura Malinauskiene involved in conception and design, writing the manuscript, revising, and final approval of the version to be published. Laima Aleksandraviciute involved in drafting the manuscript, and final approval of the version to be published. Lina Kryzauskaite involved in analysis and interpretation of data, and final approval of the version to be published. Ilona Savlan involved in acquisition of data and final approval of the version to be published. Each author participated sufficiently in the work to take public responsibility for appropriate portions of the content.

**ETHICAL APPROVAL**

The patient signed an informed consent form.

**CONSENT**

The patients in this manuscript have given written informed consent to publication of their case details.

**DATA AVAILABILITY STATEMENT**

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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**REFERENCES**

1. Handschin AE, Trentz O, Kock HJ, Wanner GA. Low molecular weight heparin-induced skin necrosis - a systematic review. Langenbecks Arch Surg. 2005;390:249-254.
2. Pasha AK, McBane II RD. Heparin skin necrosis in heparin-induced thrombocytopenia. Mayo Clin Proc. 2021;96(9):2492.

3. Carrillo Pérez DL, Peña-Romero AG, Díaz-González JM, Domínguez-Cherit J. Nadroparin-induced skin necrosis: clinical manifestation of HIT-2 even in the absence of thrombocytopenia. BMJ Case Rep. 2016;2016:bcr2016215288.

4. Pramateftakis MG, Kanellos D, Psomas S, Kanellos I. Nadroparine-induced skin necrosis on a patient with essential thrombocytahemia: a case report. Cases J. 2009;2:6458.

5. Yombi JC, Belkhir L, De Baere T, Dubuc JE, Hainaut P. Low-molecular-weight heparin-induced skin necrosis: about 2 cases. Acta Clin Belg. 2009;64:228-230.

6. Coelho J, Izadi D, Gujral S. Enoxaparin-induced skin necrosis. Eplasty. 2016;16:ic40.

7. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood. 2005;106:2710-2715.

8. Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. Am J Med. 1996;10:502-507.

9. Warkentin TE, Sheppard JA, Heels-Ansdell D, et al. Heparin-induced thrombocytopenia in medical surgical critical illness. Chest. 2013;144:848-858.

10. Nand S, Wong W, Yuen B, et al. Heparin-induced thrombocytopenia with thrombosis: incidence, analysis of risk factors, and clinical outcomes in 108 consecutive patients treated at a single institution. Am J Hematol. 1997;56:12-16.

11. Boshkov LK, Warkentin TE, Hayward CP, Andrew M, Kelton JG. Heparin-induced thrombocytopenia and thrombosis: clinical and laboratory studies. Br J Haematol. 1993;84:322-328.

12. Gruel Y, Vayne C, Rollin J, et al. Comparative analysis of a French prospective series of 144 patients with heparin-induced thrombocytopenia (FRIGTIH) and the literature. Thromb Haemost. 2020;120(7):1096-1107.

13. Gucalp A, Parameswaran R, Lacouture M, Abou-Alfa G, Soff G. Skin necrosis induced by generic enoxaparin. Am J Hematol. 2013;88:339.

14. Warkentin TE, Greinacher A, Gruel Y, Aster RH, Chong BH, scientific and standardization committee of the international society on thrombosis and haemostasis. Laboratory testing for heparin-induced thrombocytopenia: a conceptual framework and implications for diagnosis. J Thromb Haemost. 2011;9(12):2498-2500.

15. Cuker A, Arepally GM, Chong BH, et al. American society of hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv. 2018;2(22):3360-3392. doi: 10.1182/bloodadvances.2018024489

16. Carré J, Guérineau H, Le Beller C, et al. Direct oral anticoagulants as successful treatment of heparin-induced thrombocytopenia: a Parisian retrospective case series. Front Med (Lausanne). 2021;8:713649.

17. Warkentin TE, Pai M, Linkins LA. Direct oral anticoagulants for treatment of HIT: update of Hamilton experience and literature review. Blood. 2017;130(9):1104-1113.

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