Heparin-induced thrombocytopenia: a rare presentation with skin necrosis

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Abstract

Heparin-induced thrombocytopenia is the most clinically relevant non-hemorrhagic complication of heparin and is characterized by the presence of anti-platelet factor 4 (PF4)/heparin-immunoglobulin G (IgG) antibodies. The circulating PF4/heparin-IgG immune complex binds to platelets *via* their FcγIIa receptors, activating them and promoting their aggregation, with consequent platelet consumption, thrombocytopenia, and thrombotic phenomena. Despite thrombocytopenia, this condition is not typically associated with bleeding complications. Instead, thrombosis is the most serious complication of heparin-induced thrombocytopenia, contributing to increased morbidity and mortality. Thrombotic events can be venous and arterial, such as deep vein thrombosis, pulmonary embolism, myocardial infarction, and thrombotic stroke. Skin necrosis at the site of heparin injections is a rare but well-described manifestation of heparin-induced thrombocytopenia. We report a case of heparin-induced thrombocytopenia presented as skin necrosis, highlighting the importance of recognizing this potentially fatal condition and the need for an immediate cessation of all sources of heparin and its replacement by other anticoagulants.

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Introduction

Heparin has been widely used in medical practice for prophylaxis and treatment of thromboembolic diseases.[1] Heparin-induced thrombocytopenia (HIT) is the most clinically relevant non-hemorrhagic complication of heparin, with an estimated incidence of about 0.1% to 5% in exposed patients.[2] Despite the complex pathophysiology, HIT has an immunological mechanism caused by circulating antibodies directed to complexes of heparin and platelet factor 4 (PF4). In a minority of patients, these circulating anti-PF4/heparin-immunoglobulin G (IgG) antibodies lead to clinically relevant thrombotic and potentially fatal events. Thrombosis can be both venous (the most common) and arterial and includes conditions such as deep vein thrombosis, pulmonary embolism, myocardial infarction, thrombotic stroke, and limb artery occlusion.[1-3] Thrombocytopenia is often present and can be manifested as an absolute drop in platelet count or a 30% to 50% relative decline in baseline platelet count and is not typically associated with bleeding complications.[2,3]

Recognizing this pathology is very important because when there is an early suspicion, we can positively change its prognosis, interrupting the harmful agent and reversing the pro-thrombotic state. As we can see in our case report, the necrotic skin lesion represents an atypical but well-described presentation of this rare disease and is, therefore, easily misdiagnosed, exposing the patient to a high and avoidable thrombotic risk.

Case Report

A 70-year-old woman with a history of multiple vascular risk factors (hypertension, type 2 diabetes mellitus, dyslipidemia) and chronic obstructive pulmonary disease (COPD) was admitted to our hospital's intensive care unit after cardiac arrest due to cardiac arrhythmia, namely complete atrioventricular block, with pacemaker implantation. There was a rapid cardiac recovery with res-

olution of cardiac electrical activity, and occlusive coronary disease was ruled out with cardiac catheterization, with serial echocardiographic evolution in favor of Takotsubo cardiomyopathy. On day 8 of her hospitalization, she was transferred to the general ward, where she received medical care following the diagnosis of acute exacerbation of her COPD. With no history of hospitalizations or exposure to any form of heparin product, the patient had received prophylactic enoxaparin (40 mg once daily) since admission to the hospital, and on day 11, she reported abdominal pain at the enoxaparin injection site. An elongated and painful necrotic lesion measuring 2×4 cm (Figure 1) with perilesional erythema in the right iliac fossa of the abdominal wall was documented. On the day of detection of the skin necrosis lesion, the platelet count was 404 $\times 10^3/\mu L$ and, in retrospective analysis, an initial drop in platelet count of more than 50% had occurred (Figure 2), with thrombocytopenia (the platelet count on admission was 350 $\times 10^3/\mu L$ and a minimum value of 147 $\times 10^3/\mu L$ was objectified on day 4 of prophylactic enoxaparin). Given the characteristics of the lesion, the time of presentation (day 11 of prophylactic enoxaparin), as well as the described platelet variation profile, skin necrosis as a presentation of HIT was suspected, and laboratory analyses were performed with anti-PF4/heparin antibodies detectable by immunoassay. No other thrombotic manifestations of HIT were observed. Other possible etiologies were reviewed. There was no history of recent subcutaneous or intramuscular drug administration other than enoxaparin or a traumatic context. No clinical evidence of other thrombotic phenomena, and no clinical or analytical clue supporting the hypothesis of cutaneous manifestation secondary to autoimmune or hematological diseases. Furthermore, no inflammatory syndrome or appearance of the lesion were in favor of a necrotic cutaneous infection. As soon as the diagnosis of HIT was suspected, enoxaparin was replaced by rivaroxaban 15 mg twice daily. At the same time, topical treatment was performed at the site of the lesion with fusidic acid. No surgical debridement of necrotic tissue was performed. The skin necrosis progressively improved with complete recovery during her hospitalization, and she was discharged with the recommendation to complete 3 months of anticoagulation with rivaroxaban. At the time of writing this report, the patient had already suspended anticoagulation more than one year before and remained asymptomatic, with no skin sequelae from this event or late thrombotic manifestations recorded.

Discussion

The pathophysiology of HIT, as mentioned before, begins with heparin administration and subsequent release of PF4, a cationic protein stored in platelet α granules, into circulation. In the bloodstream, PF4 interacts with negatively charged glycosaminoglycans, namely heparin, in endothelial cells, allowing the formation of PF4/heparin immunogenic complexes and leading to the generation of PF4/heparin antibodies. The circulating PF4/heparin-IgG immune complexes then bind platelets *via* FcγIIa receptors, causing their activation with the consequent release of prothrombotic platelet-derived microparticles and promoting their aggregation. This process eventually leads to thrombotic phenomena with platelet consumption and thrombocytopenia, which clinically defines HIT.[1-3] Different heparins have different affinities for PF4, resulting in different ratios of PF4/heparin complex formation and different incidences of HIT.[1] Unfractionated heparins (UFH) bind PF4 more strongly than low molecular weight heparins (LMWH), which explains why UFH is associated with a higher incidence of HIT and why LMWH are now preferred for thromboprophylaxis.[1,2] Despite this, IgG antibodies developed in patients receiving UFH often cross-react with LMWH and *vice versa*.[1]

Skin necrosis at the site of heparin injections is a rare but well-described condition, classically associated with HIT-positive antibodies and thrombocytopenia.[4-10] It is a manifestation of HIT, but other mechanisms, including allergic reactions and local trauma, may also be involved.[4] It typically occurs at injection sites; however, distant sites have been infrequently reported.[4,5] The size of necrotic areas varies but is usually small and circumscribed, with a maximum diameter of a few centimeters. The onset of heparin-induced skin necrosis is also variable, with reported cases developing between 1 and 17 days after heparin exposure, as occurred with our patient.[4]

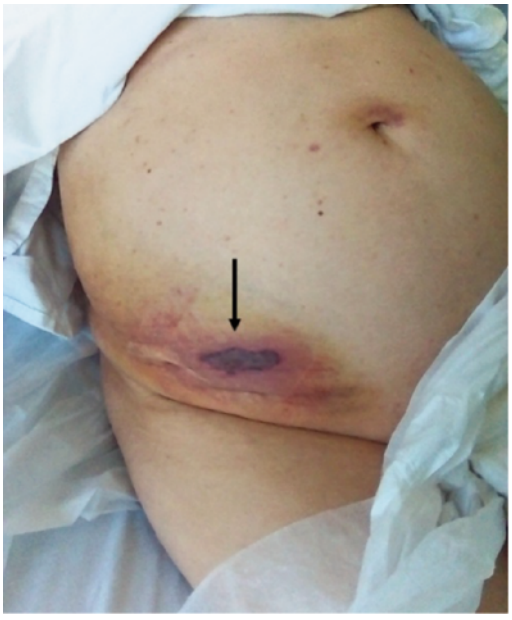

Figure 1. Painful necrotic lesion (arrow) with perilesional erythema in the right iliac fossa of the abdominal wall.

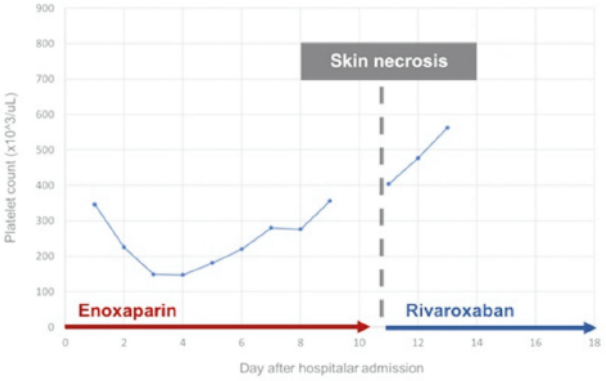

Figure 2. Temporal correlation between enoxaparin and platelet count during hospitalization.

HIT's diagnosis is made by integrating clinical features and laboratory detection of anti-PF4/heparin IgG antibodies.[1-3] The 4T scoring system can be used to identify patients at high, intermediate, or low risk of developing HIT.[1,2] Retrospectively, our patient had a platelet count drop of >50% with a nadir of ≥20 $\times 10^3/\mu L$ (2 points on the 4T scoring system) 4 days after heparin exposure, with no known past exposure (0 points). No other apparent cause of thrombocytopenia was recognized (2 points), and a well-circumscribed skin necrosis lesion was present (2 points). A score of 6 points predicted a high probability of a HIT diagnosis.

Laboratory detection of anti-PF4/heparin IgG antibodies includes both immunoassays (which detect the presence of anti-PF4/heparin antibodies but not their ability to bind and activate platelets) and functional assays (which assess the ability of anti-PF4/heparin antibodies to bind and activate platelets and thus cause the clinical HIT syndrome).[2,3] Only the former was available in our hospital laboratory. Based on the 4T score and the positive immunoassay, we assumed the diagnosis of HIT presented as skin necrosis. On the day the skin necrosis was detected, the patient presented with thrombocytosis. We believe that the initial drop in platelet count was followed by a progressive elevation due to concomitant exacerbation of her COPD.

HIT treatment includes immediate cessation of all heparin formulations, which is insufficient to stop current thrombotic events or prevent future ones.[1] As this entity provides a pro-thrombotic state, even in the absence of thrombotic manifestations, alternative anticoagulation should be given using parenteral anticoagulants (such as argatroban, bivalirudin, danaparoid, and fondaparinux) or direct oral anticoagulants (such as rivaroxaban, apixaban, edoxaban, and dabigatran). As vitamin K antagonists can lead to a reduction in protein C, they should be avoided initially as they may worsen thrombosis.[1-3,11] We immediately stopped enoxaparin administration and started anticoagulant treatment with rivaroxaban. Anticoagulation duration after an episode of HIT has not been defined in any prospective study, but some guidelines recommend a therapeutic anticoagulation dose of 4 weeks in patients with isolated HIT and 3 months for patients with HIT with thrombosis.[3,12]

Conclusions

Heparin is an anticoagulant widely used in medical practice, and HIT is the most relevant adverse reaction due to the high risk of life-threatening thrombotic manifestations. Heparin injection site necrosis is a rare thrombotic complication of this condition. The 4T scoring system can help identify the likelihood of HIT, and laboratory studies can confirm the diagnosis. The authors would like to alert healthcare providers to this rare presentation as a possibility of HIT since its recognition requires exclusion or even early detection of other thrombotic and potentially fatal events and demands immediate therapeutic measures, including prompt discontinuation of all sources of heparin and initiation of other types of anticoagulation.

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