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IN FOCUS

Heparin-induced non-necrotizing skin lesions: rarely associated with heparin-induced thrombocytopenia

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Summary. *Background:* Recently, there has been an increasing number of reports regarding adverse skin reactions to subcutaneous heparin administration. Case series have implied that heparin-induced skin lesions are predominantly associated with life-threatening heparin-induced thrombocytopenia (HIT) in at least 22% of patients. Skin lesions, therefore, have been included in clinical scores for HIT. *Objectives:* To determine the association of heparin-induced skin lesions with HIT. This would have a pivotal impact on further anticoagulatory management in patients with heparin-induced skin lesions. *Patients/Methods:* In our observational cohort study, 87 consecutive patients with heparin-induced skin lesions (85 occurring during low-molecular-weight heparin administration) were evaluated using a standardized internal protocol, including HIT diagnostics (heparin-platelet factor 4-ELISA, heparin-induced platelet activation assay), platelet count monitoring, clinical/sonographical screening for thrombosis, skin allergy testing and, if necessary, histology. *Results:* None of the observed heparin-induced skin lesions was due to HIT; all lesions were caused by delayed-type IV-hypersensitivity reactions (DTH) instead. Even the cutaneous reaction in one patient with concomitant HIT could be classified histologically as DTH reaction, amounting to an association of heparin-induced skin lesions and HIT in 1.2% (1/87; 95% confidence interval, 0.00–0.06). *Conclusion:* Heparin-induced skin lesions associated with use of low-molecular-weight heparins do not seem to be strongly associated with a systemic immunologic reaction in terms of HIT and might rather be due to DTH reactions than due to microvascular thrombosis. Hence, we propose refining existing pretest probability scores for HIT, unless underlying causes have been clarified.

Keywords: allergy, delayed-type hypersensitivity reaction, heparin, heparin-induced skin lesions, heparin-induced thrombocytopenia.

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[2]In this paper the term 'heparin' – if not further specified – refers to both unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH).

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Introduction

Heparins[2] are commonly used for prophylaxis and treatment of thromboembolic diseases. Heparin-induced skin lesions belong to the most frequently observed adverse effects of subcutaneous heparin therapy [1]. They may result from a lymphocyte-mediated delayed-type IV-allergic hypersensitivity reaction (DTH) [2] or heparin-induced thrombocytopenia (HIT) that is caused by antigenic anti-platelet factor 4 (PF4)/heparin-complexes [3]. Both start as erythematous lesions that, in the case of HIT, may turn to cutaneous necrosis or livedo reticularis due to microvascular dermal thrombosis [4]. In comparison, allergic type I and type III reactions to heparin are very rare [5,6]. Contrary to previous assumptions, recent evidence yields a marked increase of heparin-induced skin lesions [7]. Some authors suggest that heparin-induced skin lesions are predominantly associated with HIT [8,9]. Therefore, skin lesions have been included in a clinical pretest scoring system for the diagnosis of HIT [10]. Given this association can be sustained, this would have a pivotal impact

on the management of heparin-induced skin lesions because HIT requires mandatory alternative anticoagulation with non-heparin anticoagulants in order to prevent possibly fatal thromboembolic events [11,12]. Hence, this study was designed to determine the association of heparin-induced skin lesions with HIT by prospectively screening patients who developed skin lesions under current subcutaneous heparin therapy.

Patients and methods

Patients

Between January 2004 and June 2009, 87 patients (69 female, 18 male) from the Departments of Internal Medicine and Dermatology at the Goethe University Hospital Frankfurt/Main aged 18 years or older with heparin-induced skin lesions under subcutaneous heparin application for prophylactic or therapeutic indications underwent a standardized internal protocol for assessment of heparin-induced skin lesions including laboratory HIT diagnostics, platelet count monitoring, clinical and sonographical screening for thromboembolic events, and, if necessary, histology. To determine the underlying cause of skin lesions when HIT was ruled out, skin allergy testing was performed. To minimize bias patients were seen by two investigators and/or skin lesions were photodocumented. Biopsies were evaluated by two dermatopathologists. Also laboratory HIT-diagnostics were mostly performed in duplicate and interpreted in context with the patient's clinical data. Twenty-four patients were derived from a previous incidence-finding study on the incidence of DTH with heparins [7] and were, for the purpose of this study, sub-analysed regarding their association with HIT to enhance our findings.

Determination of HIT antibodies

All patients were tested twice for HIT antibodies with an antigen assay (heparin-PF4 – ELISA; Asserachrom HPIA®, Diagnostica Stago, Paris, France) and a functional assay (heparin-induced platelet activation assay – HIPA) as described elsewhere [13–15]: first, when they presented with heparin-induced skin lesions, and again 7 ± 1 days afterwards in order to detect delayed antibody development.

Monitoring of platelet counts

Platelet counts were determined to recognize a decrease of ≥ 30% in comparison to the pretreatment values at onset of skin lesions and again 7 ± 1 days afterwards.

Screening for thromboembolic complications

All patients were screened clinically for signs of a new or progressive thrombosis according to the Wells-Score [16] at the onset of skin lesions and during follow-up visits. Patients with underlying thrombosis (diagnosed ≤ 4 weeks before) were routinely subjected to compression ultrasonography [17] to rule out recurrent or progressive thrombosis.

Skin allergy testing

Patients with heparin-induced skin lesions were exposed to a series of prick, intracutaneous and epicutaneous skin allergy tests against a panel of undiluted antithrombotic agents as described elsewhere [15] only after exclusion of HIT. In the case of negative test results or refusal for extended allergologic testing, patients underwent subcutaneous provocation.

Statistics

Age and time of onset of skin lesions under heparin therapy were calculated as mean ± SD. Any missing data were completed during follow-up visits. Sample size calculation was performed with BIAS 8.4.6.® software (Epsilon, Hochheim Darmstadt, Germany) and based on the association of HIT with heparin-induced skin lesions in minimally 22% of patients [8]. A sample size of 81 patients was calculated in order to determine this association with a precision of minimally ± 10% and a confidence interval of 0.95.

Results

Characteristics of the study cohort

We present data from 87 patients with an average age of 47.1 ± 18.5 years with heparin-induced skin lesions at the injection site (Table S1). The sex ratio was 4:1 (69 females, 18 males). Skin lesions presented mainly as infiltrated erythematous plaques, mostly pruritic, sometimes burning or with emergence of papulovesicles (Fig. 1). A generalized skin rash was seen in seven patients. None developed a skin necrosis in the further course (Table S1). The median time for onset of skin lesions after the start of subcutaneous heparin therapy was 10 days (range 1 to 309 days). We identified 11 patients with

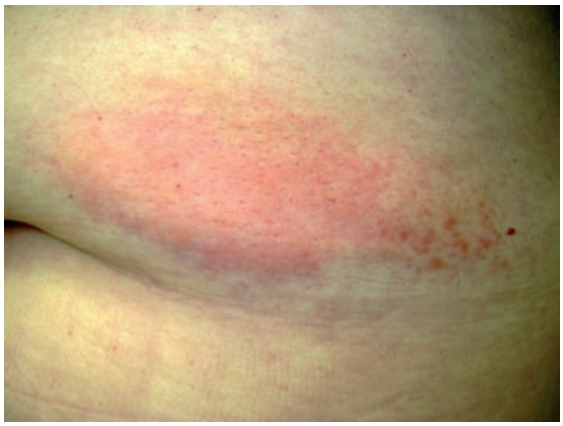

Fig. 1. Clinical presentation of a patient with a DTH reaction to nadroparin. The patient complained about pruritus and burning at the injection areas, which show an erythematous plaque.

early onset of skin lesions < 4 days after the start of therapy; all had been exposed to heparins within the past 3 months. Thirty-five patients had a prophylactic and 52 patients had a therapeutic indication (Table S1). Most patients were treated with a low-molecular-weight heparin (LMWH) preparation, especially nadroparin (63.2%) and enoxaparin (20.7%), and a few with dalteparin and certoparin; only two patients (2.3%) had received unfractionated heparin (calciparin). In total, five patients were not enrolled into the study because of refusal (1), discharge prior to examination (2) and skin lesions due to other dermatological diseases (2).

HIT-antibody testing and other sequelae of HIT

HIT-antibody testing HIT could be diagnosed in one of 87 patients, amounting to a 1.2% incidence (CI = 0.0–6.4%) of HIT in patients with heparin-induced skin lesions. This one patient with erythematous skin lesions at heparin injection sites starting 10 days after initiation of an anticoagulatory therapy with nadroparin due to brachiocephalical and subclavian vein thrombosis tested positive with both ELISA (OD: 3.14 [0.01–0.5]) and HIPA assay (Table 1). A drop in platelet count of 34% (269 nL^{-1} vs. 177 nL^{-1} platelets) was detected when she presented in our department on day 15.

Two of 87 patients were tested weakly positive (OD: 0.55/0.68) for HIT antibodies in the first ELISA assay, one became negative in the second screening for HIT antibodies after 7 days while the other one remained weakly positive (OD: 0.58) (Table 1). HIPA testing was repeatedly negative in both patients and no other clinical symptoms of HIT were observed.

Eighty-four of 87 patients tested negative with both HIT assays at the onset of skin lesions. Seventy of these 87 patients underwent a second testing for HIT antibodies 7 ± 1 days afterwards, in which 68 of 70 patients tested negative with both HIT assays (Table 1). Seventeen of 87 patients were lost to follow-up for the second testing.

Heparin-induced skin lesions Skin biopsy of the patient with HIT revealed a lympho-histiocytary infiltrate without dermal microvascular thrombosis. Thus, it was identified as DTH reaction but not as beginning HIT-induced skin necrosis due to dermal microvascular thrombosis (Fig. 2). Clinically, skin lesions disappeared in this patient within 5 days after start of alternative anticoagulation with fondaparinux followed by s.c. lepirudin [18].

In both patients with initially positive ELISA, skin allergy testing with reexposition to heparin was possible without complications. None of the 87 patients developed skin necrosis and all cutaneous lesions disappeared after switching therapy to a different LMWH or to fondaparinux.

Thromboembolic events Neither the 84 patients with negative laboratory HIT-diagnostics nor the two patients who initially had a positive ELISA nor the single patient with confirmed HIT showed clinical signs and symptoms for associated new or progressive thromboembolic events. Sonographically, neither the patient with HIT nor 26/39 patients with underlying thrombosis showed sonographical signs for thrombosis progression in routinely performed control examinations. The remaining 13/39 patients who did not undergo repeat sonography did not show clinical signs for thrombosis progression.

Drop in platelet count Five patients, including the patient with HIT but not the two patients with positive ELISA, showed a drop in platelet count of ≥ 30% at the onset of symptoms or during the follow-up. With the exception of the patient with HIT, these events were related to different underlying diseases (sepsis, chemotherapy).

Results of skin allergy testing

In 69 of 87 subjects, DTH was confirmed by skin allergy testing performed as detailed above. Eighteen patients were not subjected to skin allergy testing because of pregnancy, refusal, or contraindication because of HIT (one patient). Nevertheless, skin lesions in these patients were considered as DTH reaction based on clinical appearance, time of onset, histological findings and further clinical observation because no skin necrosis developed and symptoms disappeared after switching to another LMWH or fondaparinux (Table S2).

Discussion

Beginning cutaneous reactions due to HIT or DTH, respectively, under subcutaneous heparin therapy may be similar (Table S3) [1,7]. They are characterized by an infiltrated erythematous plaque [1,7,15]. Another diagnostic dilemma is that the typical onset of skin lesions for both entities is within the first 2 weeks after start of therapy [1,12]. Only when skin lesions appear after day 14, is HIT rather unlikely although delayed-onset type HIT occurs in 3–5% of all HIT cases [12]. Quick assessment is pivotal because HIT can lead to fatal thromboembolism and skin necrosis, whereas DTH is often

Table 1 Results of HIT diagnostics and of other possible sequelae of HIT in patients with heparin-induced skin lesions

	Heparin/PF4 ELISA negative HIPA negative	Heparin/PF4 ELISA positive HIPA negative	Heparin/PF4 ELISA positive HIPA positive	Platelet drop	New or progressive thrombosis
First testing at onset of skin lesions	84/87	2/87	1/87	5/87	0/87
Second testing after 7 ± 1 days	68/70	1/70	1/70		

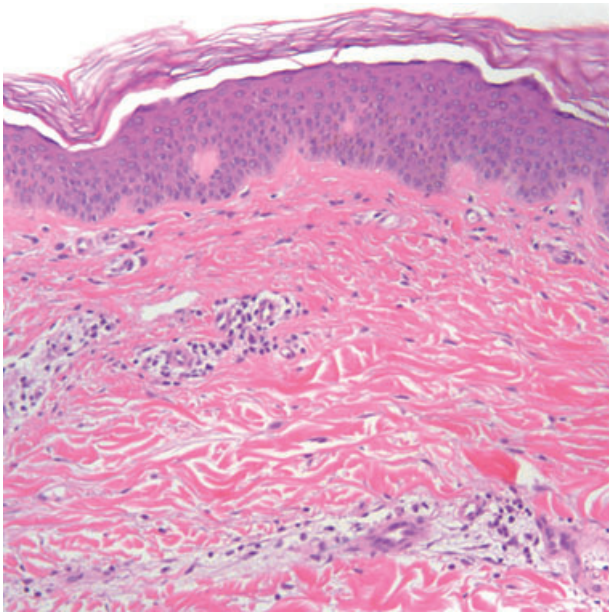

Fig. 2. Skin biopsy of a patient with heparin-induced skin lesions and concomitant HIT. The hematoxylin and eosin stained specimen shows a mainly perivascular dermal infiltration, predominantly with lymphocytes and to a low degree with eosinophils, which is typical for a DTH reaction. There are no microthromboses in dermal vessels (which, if present, would have suggested the presence of HIT). Thus, skin lesions in this patient were classified as DTH reaction and not as HIT. Magnification (UPlanFI ×20; Olympus Optical Co., Tokyo, Japan) is 200-fold. Sections were analyzed with a standard binocular light microscope (BX50F4; Olympus Optical Co.). Images were captured by Leica SP1 Pro (Leica Microsysems, Heidelberg, Germany) and imported into SilverFast software (LaserSoft Imaging AG, Kiel, Germany) as a series of JPEG files. Images were post-processed with Photoshop CS software (Adobe Systems Incorp, San Jose, CA, USA).

self-limiting [1,19]. Our results demonstrate that erythematous heparin-induced skin lesions that occur during LMWH therapy are rarely associated with HIT. Except for one patient with HIT, HIT as an explanation for skin lesions had been excluded clinically and serologically in all patients. As an underlying cause of the heparin-induced skin lesions, a DTH reaction could be confirmed clinically, allergologically and/or histologically in all patients, even in the patient with HIT. Hence, DTH must be considered the most frequent explanation for heparin-induced skin lesions in an unselected cohort of patients, at least when caused by LMWH therapy.

Comparison of study results with previous case series

To date, two reports suggested a strong relationship between heparin-induced skin lesions and a systemic immunologic response in terms of HIT. In one retrospective study, 3/9 patients with heparin-induced skin-lesions tested positive for HIT antibodies [8]. Two of these patients were diagnosed with HIT by positive HIPA-assay results, pointing to an incidence of HIT in 22% of patients with heparin-induced skin lesions. By eliminating the two patients where DTH was not allergologically confirmed, an even higher incidence of HIT (28.6%) results. In another study, all six patients with heparin-induced skin lesions tested positive for HIT antibodies [9]. Two out of six patients also showed two HIT sequelae (thrombocytopenia, thrombosis), and one out of six patients showed one HIT sequelae (adrenal hemorrhagic infarction). Thus, assuming HIT in these patients, this points to an incidence of HIT in 33 and 50%, respectively, of patients presenting with heparin-induced skin lesions. This study further showed an incidence of 100% of platelet-activating IgG-HIT antibodies, regardless of whether thrombocytopenia developed or not. Both studies [8,9] implicating HIT in a higher proportion of patients with heparin-induced skin lesions had primarily investigated patients treated with UFH [9], or both UFH and LMWH [8]. Thus, it remains uncertain whether our findings can be extrapolated to patients treated with UFH as only two of our patients were receiving UFH, while most patients were treated with LMWH.

In our study, we identified one patient with heparin-induced skin lesions and concomitant HIT [18], resulting in an association of heparin-induced skin lesions with HIT in only 1.2% (1/87) (CI = 0.0–6.4%). Even in this patient with HIT, DTH was diagnosed by histology as the underlying cause of cutaneous reaction. Hence, none of the observed skin lesions in our study was caused by HIT. Two patients were unspecifically tested positive for HIT antibodies without any other HIT sequelae; skin allergy testing confirmed a DTH reaction. None of the other patients tested positive for platelet-activating antibodies (HIT-antibody-ELISA/HIPA) on occurrence of skin lesions and even during follow-up visits, resulting in a 3.5% (3/87) (CI = 0.7–9.7%) incidence of seroconversion. The discrepancy in our results most probably results from differences in patient recruitment in the aforementioned studies [8,9], that is, when patients suspected for HIT are screened for heparin-induced skin lesions that occur as frequent adverse side-effects of heparin therapy [1,7]. Thus, the high incidences of HIT in at least 22% of patients with heparin-induced skin lesions in these studies seem to be overestimated and may rather mirror the natural incidence of DTH following heparin use [7]. The discrepancy might also allow for a higher UFH usage in the early to mid 1990s when these studies were performed, and thus, a higher rate of seroconversion.

Clinical significance for HIT diagnostics

In none of 87 patients were heparin-induced skin lesions due to HIT, and none of the lesions progressed to cutaneous necrosis. Thus, before applying heparin-induced skin lesions in a clinical pretest probability score for HIT [10], they need to be evaluated concerning their underlying cause. Applying heparin-induced skin lesions in pretest probability scores together with a positive EIA reactivity without further investigation might easily render intermediate risk values of 4 or 5 and, thus, might lead to a slight overestimation of the risk of HIT [20]. Therefore, we propose to refine the well-established 4T's score for HIT (Thrombocytopenia, Timing, Thrombosis including skin lesions and oTher). Because 'erythematous non-necrotizing

skin lesions' almost always have another explanation than HIT and are normally due to DTH, we suggest scoring these lesions as '0' for the 4th 'T' category 'oTher', at least when LMWH is the inciting heparin preparation. This refinement ensures that erythematous skin lesions are usually scored as 'low' pretest probability for HIT (3 or fewer points). Still, the possibility of HIT remains open if there is an associated platelet count fall. The item 'skin necrosis' scored with '2' points would be not affected by that refinement because this might be a stronger indicator for HIT: at present there is no plausible and reasonable alternative explanation for dermal necrosis at heparin injection sites, besides HIT.

Limitations

Eighty-five out of 87 patients were receiving a LMWH preparation and only 2/87 patients were receiving UFH when skin lesions developed. Thus, our data do not rule out the possibility that scoring of non-necrotizing skin lesions that occur at sites of UFH administration should perhaps be scored differently than such skin lesions that occur at sites of LMWH administration.

Conclusion

Heparin-induced skin lesions associated with LMWH use do not seem to be strongly associated with a systemic immunologic reaction in terms of HIT (< 1.2%) or formation of platelet-activating HIT antibodies and might rather be due to a DTH reaction than due to microvascular thrombosis. Hence, we propose refining the pretest probability score for HIT [10] by weighting 'erythematous lesions' differently, for example by scoring 'oTher' as '0' points when the skin lesions are associated with LMWH use, given that our study indicates that such lesions can be definitively explained by DTH. Nevertheless, due to a possible fatal outcome in patients with HIT, close platelet count monitoring [12] and, if suspected, HIT diagnostics are recommended at onset of skin lesions.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Demographic characteristics and data about the initial onset of skin lesions, the indication for heparin therapy and the causative heparin for cutaneous lesions.

Table S2. Combination of cross-allergies in 19 patients with heparin-induced skin lesions who showed a cutaneous reaction to several heparins. The rest of the patients showed a positive skin reaction to only one heparin, that is, the heparin preparation implicated in causing the reaction.

Table S3. Main characteristics of heparin-induced skin lesions in immune heparin-induced thrombocytopenia (HIT) compared with cutaneous delayed-type IV-allergic hypersensitivity reaction (DTH) [21–28].

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