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CASE REPORT

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Low-molecular-weight heparin-induced skin necrosis

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Abstract We report a case of low-molecular-weight heparin (LMWH)-induced skin necrosis in a patient with chronic lymphatic leukemia. The patient had heparin-PF4 antibodies and the heparin-induced platelet activation (HIPA) test was positive, but platelet counts remained normal. Analysis of seven cases of LMWH-induced skin necrosis revealed that this complication occurred mostly in patients previously exposed to heparin, and that severe problems such as thrombocytopenia or thromboembolic complications were rare. This is in contrast to skin necrosis induced by unfractionated heparin (UFH), where a substantially higher number of patients suffered from thrombocytopenia and thromboembolism. In addition, most patients with UFH-induced skin necrosis were not pretreated with heparin. Therefore, it is possible that LMWH is less immunogenic than UFH and requires repeated exposure for induction of skin necrosis.

Key words Low-molecular-weight heparin · Unfractionated heparin · Skin necrosis

Introduction

Low-molecular-weight heparins (LMWH) play an increasingly important role in the prophylaxis and treatment of thromboembolic disorders [26] and have several advantages over unfractionated heparin (UFH). These include a more predictable pharmacokinetic behavior, which leads to a greater antithrombotic efficacy at a lower risk of hemorrhage and a lower risk of heparin-induced thrombocytopenia [25] and osteoporosis after long-term treatment [14]. Skin necrosis is an extremly rare complication of treatment with UFH [4, 6, 8, 11, 20, 22, 24, 27, 28] but has also been observed in a small number of cases after treatment with LMWH [3, 5, 12, 15, 17, 19].

We report on a patient with heparin-induced skin necrosis induced by a LMWH. On the basis of the published cases of heparin-induced skin necrosis, we compare the clinical and laboratory features of UFH- and LMWH-induced skin necrosis.

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Materials and methods

Heparin-PF4 antibodies were determined with a commercial ELISA (Asserachrom STAGO, Asnieres-Sur Seine, France). The test was performed according to the instructions of the company. The heparin-induced platelet activation (HIPA) test was performed according to Greinacher [7].

Published reports of heparin-induced skin necrosis were identified by a literature search using *medline* and quotations in relevant papers.

To evaluate the statistical significance of differences between LMWH- and UFH-induced skin necrosis, the chi-square test was applied. Results were considered significantly different when p was < 0.05.

Case report

A 54-year-old man suffered from B-cell chronic lymphatic leukemia (CLL) stage IV. In 1994 he had been treated with fludarabine. Fludarabine treatment was discontinued because he developed autoimmune hemolytic anemia. He was splenectomized in 1995 because of massive splenomegaly and thrombocytopenia. Following splenectomy, his platelet count normalized and there were no signs of autoimmune hemolytic anemia. The patient was then treated with chlorambucil/prednisone, which was only moderately effective. Since his leukocyte counts were almost 200,000/μl and the Coombs test was negative, fludarabine was restarted in 1997. This treatment was very effective, with a reduction of the leukocyte count from 200,000/μl to 30,000/μl after the first cycle. After this cycle the patient had to be admitted because of high fever. Since he was bed-ridden, he received low-dose heparin prophylaxis (5000 units Fragmin once daily, subcutaneously). The patient had been treated with the same and other LMWH preparations (Enoxaparin, Sandoparin) 2 years earlier. The LMWH was injected in the outer circumference of the right thigh; 24 h after

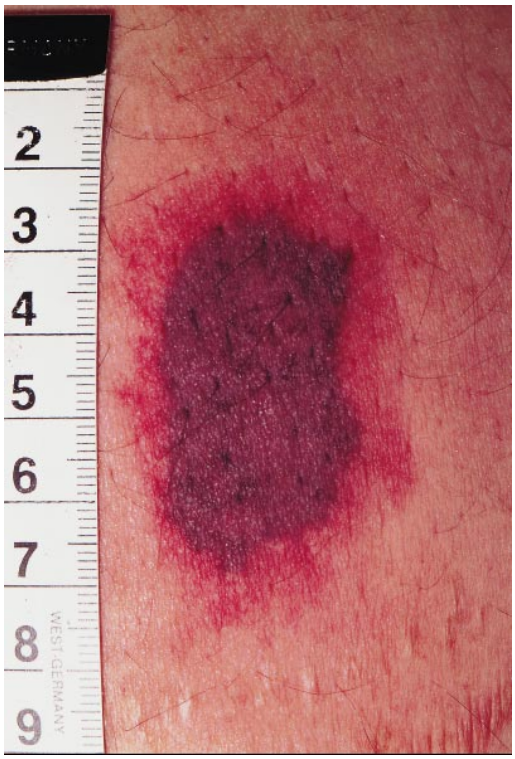

Fig. 1. Skin necrosis surrounded by erythema after subcutaneous injection of LMWH into the abdominal wall

the first injection an erythema approximately 5 cm in diameter developed. The erythema increased to 10 cm during the following days and was slightly painful. The injection site was changed to the left thigh and no local reaction occurred. On the eighth day of treatment with LMWH a bluish-black area was detectable at the center of the erythema on the right thigh. The next day, a central necrosis of 2×1.5 cm developed. On this day the patient had already received another injection into the abdominal wall. Three hours after this injection he complained of pain at the injection site, and within the following hours an erythema developed. On the next day a skin necrosis developed rapidly which was similar to that on the right thigh (Fig. 1). The injection site on the left thigh remained normal. LMWH was withdrawn. The lesions were treated locally, and healing was complete after approximately 2 months. No skin grafting was required.

The test for heparin-PF4-induced antibodies was positive on day 16 after the first injection of LMWH. The HIPA test was slightly abnormal at day 16 and day 28 after the first injection of LMWH. The platelet counts were monitored very closely and there was no change at all. The levels of protein C, protein S, and antithrombin were normal, and no anticardiolipin antibodies were detected.

Discussion

This patient had a typical but very rare complication of heparin treatment – heparin-induced skin necrosis. Although no prospective studies have been performed, this complication appears to be extremely rare, since only a limited number of cases of UFH-induced skin necrosis and seven cases (including our case) after

Table 1 Published cases of LMWH-induced skin necrosis

	Cordoliani et al. 1987	Montserrat et al. 1990	Ojeda et al. 1992	Ballestra et al. 1994	Real et al. 1995	Lefebvre et al. 1997	present case
Age (years)	54	61	68	87	68	69	54
Sex	f	m	f	f	m	f	m
Preparation	Fraxiparin	Dalteparin	Fraxiparin	Lowli-quemin	Dalteparin	Enoxaparin	Dalteparin
Indication for treatment	prophylaxis	prophylaxis	prophylaxis	prophylaxis	DVT	prophylaxis	prophylaxis
Previous exposure to heparin	no	?	?	yes*	yes	yes	yes
				LMWH	UFH iv	LMWH	LMWH
Day of onset after injection of LMWH	10	10	5	7	8	1	8
Localization of skin necrosis	thigh	abdominal wall	?	thigh	abdominal wall	thigh	thigh, abdominal wall
Antibodies to heparin	nd	nd	nd	+(HIPA)	nd	nd	+(HIPA, ELISA)
Platelet count	normal	normal	normal	decreased	normal	normal	normal
Thromboembolic complications	no	no	no**	no	no	no	no
Subsequent therapy with heparin	UFH	UFH iv	UFH iv	no	UFH iv	no	no
Side effects of subsequent heparin therapy	no	no	no	–	no	–	–
Underlying disease	obesity, alcoholism	hip replacement	hip replacement	myocardial-infarction, anemia, transfusions	bladder-carcinoma, asthma	obesity, alcoholic-cirrhosis, diabetes	CLL, AIHA, fever, transfusions

* personal communication; ** DVT developed while the patient was on oral coumarine anticoagulation; nd: not done; AIHA, autoimmune hemolytic anemia

Table 2 Comparison of cases of LMWH-versus UFH-induced skin necrosis

	LMWH [3, 5, 12, 15, 17, 19]	UFH [4, 6, 8, 11, 20, 22, 24, 27, 28]
Age median (range)	65.9 (54–87)	58.9 (36–81)
Sex:female:male	4:3	11:4
Indication for heparin therapy prophylaxis:treatment	6:1	12:3
Previous exposure to heparin	4/5	2/8
Day of onset after starting of heparin treatment (range)	7.0 (1–10)	6.7 (3–11)
Antibodies to heparin	2/2	8/8
Thrombocytopenia	1/7	5/11
Thromboembolic complications	0/7	5/15
Subsequent heparin therapy	4/7	6/11
Side effects of subsequent heparin therapy	0/4	4/6

LMWH have been reported. In addition, a number of cases of erythematous skin reactions after administration of UFH [9, 10, 21, 23, 24] and LMWH [9, 10, 13, 18, 21] have been described. In the seven cases of LMWH skin necrosis (Table 1) the lesion developed after about 1 week of treatment, starting with painful erythema and progressing within a short time to necrosis. With one exception [3], there were no systemic complications such as thrombocytopenia or thromboembolism. Interestingly, we demonstrated heparin-PF4 antibodies in the ELISA, and the HIPA test in our patient was positive. These antibodies are typically found in patients with heparin-induced thrombocytopenia [1] but may also occur in patients who have received heparin without any complications [2].

We were interested in analyzing and comparing the features of patients with UFH- and LMWH-induced skin necrosis (Table 2). Patients with UFH- and LMWH-induced skin necrosis were of similar age, with a female preponderance, and in most cases heparin was given prophylactically. There was also no difference in the time of onset of skin reactions from start of heparin treatment (approximately 1 week in both patient groups). Antibodies to heparin-PF4 or an abnormal HIPA test were detected in the two patients with LMWH-induced skin necrosis in whom these tests were carried out [3] and in all patients with UFH-induced skin necrosis [4, 11, 22, 24, 27]. There are three features in which UFH- and LMWH-induced skin necrosis may differ: (a) Almost all patients who had skin necrosis after LMWH had had previous treatment with UFH or LMWH, while this was the case in only two of eight patients with UFH skin necrosis. (b) Thrombocytopenia seems to be more common in patients with UFH-induced skin necrosis. (c) Thromboembolic complications occurred in none of the patients after LMWH skin necrosis but in five of 15 patients with UFH-induced skin necrosis. However, all of these differences are not statistically significant ($p > 0.05$). Further studies are needed to ensure that there really are differences between UFH- and LMWH-induced skin necrosis.

The patients with UFH- or LMWH-induced skin necrosis had a variety of underlying diseases or conditions and various indications for heparin. One explanation for the development of this obviously antibody-related complication in our patient may be the fact that he suffered from a disease (CLL) in which autoimmune phenomena are common. It is well known that fludarabine may trigger the formation of autoantibodies against blood cells [16]. It can be speculated that the antibody which is directed against a platelet protein (platelet factor 4)-heparin complex was a (rare) consequence of fludarabine treatment.

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