

Recurrent urticaria lesions in a heparin-allergic patient: Most likely another form of "recall urticaria"

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Abstract. In this report we describe a female patient with a history of heparin allergy and recurrent urticaria lesions at definite locations where the heparin injections were administered previously.

Key Words: heparin, recall urticaria.

Introduction

Treatment with heparin is sometimes associated with adverse effects. One of them, although rare, is skin reactions at injection site, including skin necrosis, urticaria and eczematous lesions [1]. In this report we describe a female patient with a history of heparin allergy and recurrent urticaria lesions at definite locations where the heparin injections were administered previously.

Case:

A 30-year-old woman was referred to our clinic because of recurrent urticaria lesions lasting two years. Her symptoms recurred approximately three times per week and were limited to the triceps region. None of the other parts of body was affected.

Some two years ago, she had been diagnosed antiphospholipid antibody syndrome (APS) after her first pregnancy, which was terminated with fetal loss at the 7th month. During her second pregnancy she was treated with 10,000 IU per day of subcutaneous heparin (Liquemine injectable flacon, 5000 IU/ml, Roche). After delivery, heparin was discontinued and replaced with

daily aspirin. She is still receiving aspirin 300 mg per day regularly.

She stated she was beginning to experience erythematous itchy plaques at the injection site after every heparin injection 6 weeks following treatment initiation. She had probably developed allergy to heparin, since this kind of reactions may be seen sometimes with heparin [2]. Unfortunately, she did not inform her physician about these reactions, and fortunately, completed the heparin treatment and her gestation without anaphylaxis, despite the recurrent and progressive local reactions (Fig.1).

The medical history clearly pointed out allergy to heparin. Furthermore, the complaints stated, urticaria at definite regions of the body, may also be related to this allergy. Therefore, the patient was investigated for heparin allergy: skin tests were performed with the heparin preparation which was administered before.

At the first step, epidermal testing (skin prick test=SPT) was applied with undiluted heparin. Histamine as positive control (10 mg/ml, Stallergens S.A., France), and standardized diluent as negative control (0.9% sodium chloride and 0.4% phenol, Center Laboratories, Port Washington, USA) were used. SPT with heparin resulted negative.

At the second step, intracutaneous tests were performed with 1:10,000, 1:1000 and 1:100 dilutions of

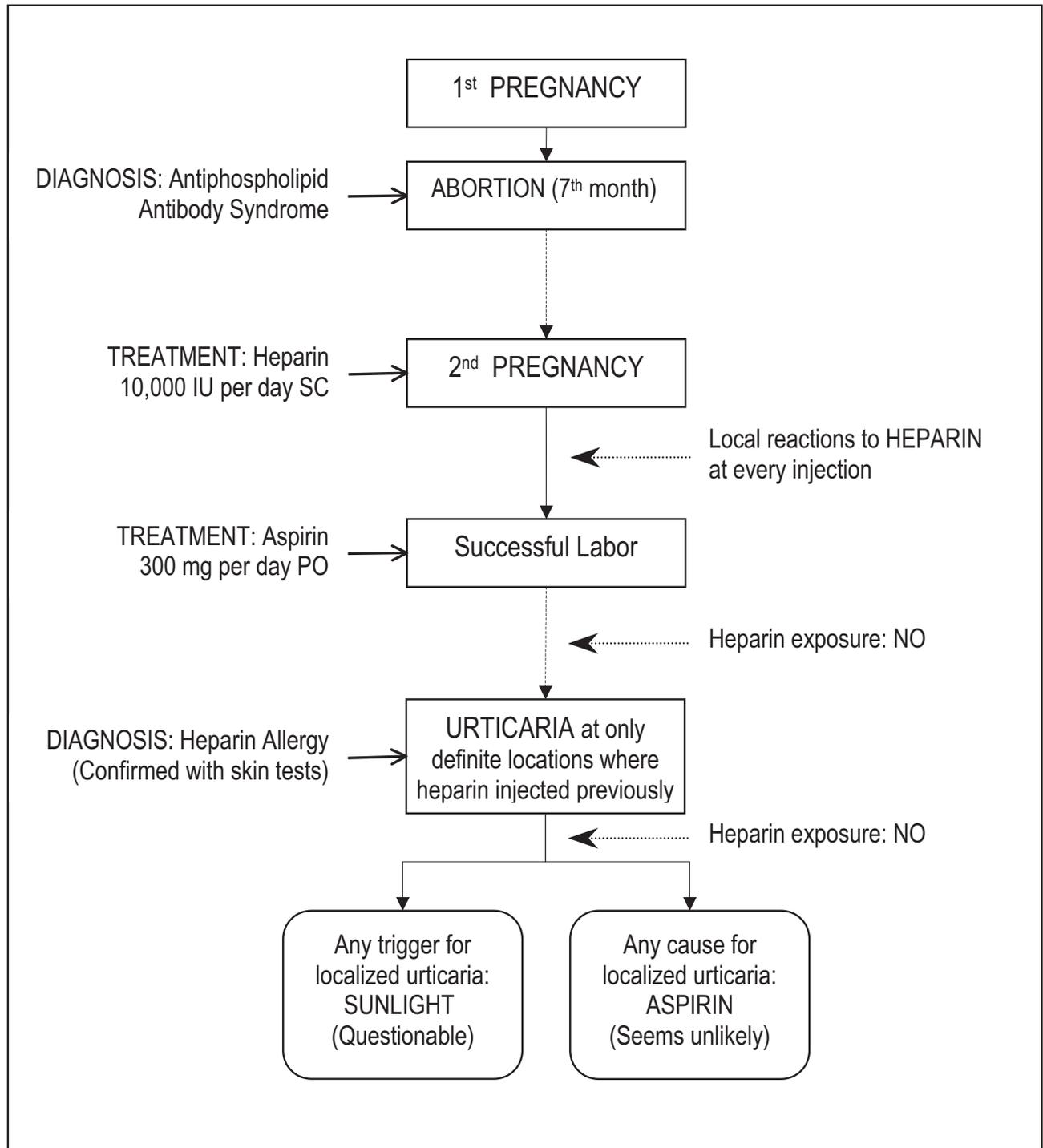


Figure 1. Summary of the case.

heparin, in sequence. Diluent and histamine solutions (1/10,000, Allergopharma, Reinbek, Germany) were used as negative and positive controls. Cutaneous responses were evaluated after 15 minutes and the patient was also warned about late phase reactions such as skin necrosis related to intracutaneous heparin [2]. The test was negative at 1:10,000 dilution and questionable at 1:1000 dilution. Strongly positive response was obtained at the final dilution

of heparin (1:100). The test was valid because the negative control was negative and histamine was positive.

In addition to immediate wheal and flare reaction obtained with heparin, an unusual reaction occurred about an hour after the skin tests: The patient described itch on the contralateral arm, that was not used for heparin testing. The only symptom was pruritus and no lesion was developed.

In accordance with skin testing procedures with drugs, possible irritant skin reaction to the drug used (heparin) was also investigated. Five healthy volunteers without history of heparin use and also without dermographism were subjected to intracutaneous test using the same dilution of heparin as for the patient, after having given informed consent. The results were negative in all tested controls.

Discussion

Detailed interview and diagnostic approaches established two different situations: Chronic urticaria with unusual presentation which is regularly recurring on a definite part of the body, and allergy to heparin. Since her lesions were appearing on both upper arms where heparin injections were performed previously, this unusual occurrence was indicative of a specific condition: recall urticaria.

According to the current medical literature records, "recall urticaria" was first published by Kelso et al. in 1994 [3]. Despite the lack of previously published papers, this kind of reactions has been known by years in the clinical practice. Kelso et al. used this term to define an unusual reaction occurred in their two patients receiving allergen immunotherapy injections. Both patients developed local reactions on their opposite arms after an injection, while there were no reactions on the allergen injected arms. They suggested that this response arose from long lasting local changes at the site of allergy injections.

Thereafter, two other patients with recall urticaria were described and published by Karaayvaz and Ozanguc, from our Allergy Clinic [4, 5]. And the last case, which was related to a peptide-based vaccine was reported by Rinn et al. in 1999 [6]. To our knowledge, there are only four published case reports about recall urticaria in the medical literature.

Our patient was allergic to heparin and her urticaria symptoms were limited only to heparin injected sites. In addition, she described an itching sensation on the contralateral arm after intracutaneous heparin injection. These findings were supportive of recall urticaria. However, this case was somewhat different from previously described recall urticaria cases. According to the current knowledge, exposure to sensitizing allergen with any route is necessary to develop the recall reactions. But our patient had not been receiving heparin or any related product for two years. The occurrence of urticaria on heparin injected sites without concurrent heparin exposure was difficult to explain. For this reason, we tried to find any factor and/or any mechanism that could cause her symptoms.

We re-interviewed the patient in detail to elicit other possible triggering factor(s). The only probable trigger was exposed: She stated that her urticaria symptoms sometimes recurred after direct exposure to sunlight.

We clearly know that ultraviolet rays may cause urticaria in some sun-sensitive patients. However, it is difficult to make a connection between sunlight exposure and urticaria at heparin injected site.

In the previously reported cases, two speculations about the mechanism of recall urticaria have been proposed: *First*, increased accumulations of mast cells at the site of allergen injections; *second*, the generation of more easily releasable mast cells at the injection sites. Degranulation of "over-responsive" mast cells may precipitate either by the distant injection of allergen or the systemic release of "histamine releasing factors" [3]. According to these hypotheses, accumulated and/or over-responsive mast cells at the allergen injection site may easily secrete their mediators by any proper stimulus. Although sunlight may be a stimulus for mast cell degranulation, it is difficult to make a connection between sunlight exposure and urticaria at heparin injected site.

There was another possible cause of urticaria in our patient: as noted before, she had been taking aspirin for approximately two years because of the diagnosis of APS. It is well documented that aspirin causes urticaria in sensitive individuals. However, aspirin-induced urticaria is almost always generalized, rather than localized on a definite region. Therefore, aspirin-induced localized urticaria in a heparin allergic patient seems unlikely.

As a result, we could not explain how the recall urticaria observed in our patient occurred. Despite the presence of some hypotheses, the underlying mechanism(s) of the "recall urticaria phenomenon" has not been clearly established until now. The case discussed, however, may provide a new point of view for the pathophysiology of the recall phenomenon.

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