

Eczema-like plaques secondary to enoxaparin

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Low-molecular-weight heparins are used extensively in acute medicine. They are generally well tolerated but may cause a rare, eczema-like type IV hypersensitivity reaction. We report 3 cases of this eruption and speculate that it may be significantly under-reported due to misidentifying the causal drug, which may have serious consequences. We discuss treatment alternatives such as fondaparinux sodium, which may rarely cross-react.

Key words: eczema-like plaques; enoxaparin; fondaparinux sodium; low-molecular-weight heparins; type IV hypersensitivity. © Blackwell Munksgaard, 2006.

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Low-molecular-weight heparins (LMWHs) have been used for approximately 13 years and are now routinely used in protocols for the treatment of suspected myocardial infarction, unstable angina, deep vein thrombosis (DVT) and pulmonary embolus. No regular monitoring of clotting is required due to the predictability of their pharmacokinetics. The structure of enoxaparin is similar to that of the other LMWHs such as dalteparin and tinzaparin. Acute eczema-like plaque formation caused by heparin has been previously documented and is thought to be due to a type IV hypersensitivity reaction (1). LMWH have also been implicated in eczema-like eruptions as well as the more familiar skin manifestations of urticaria, bruising, angio-oedema, skin necrosis and, rarely, alopecia.

Case Report

Case 1

A 46-year-old man was given subcutaneous enoxaparin (1 mg/kg twice daily) for suspected acute coronary syndrome. 3 days later, he developed an itchy eruption initially over the right lower abdomen, adjacent to his subcutaneous LMWH injection site (Fig. 1). This later became generalized. The eruption was erythematous and scaly with some lichenified plaques, strongly resembling eczema. His medical team had wondered if this were a drug eruption to aspirin. Clinically, a reaction to enoxaparin was suspected. His eruption resolved a few days after enoxaparin was discontinued. Topical

0.05% clobetasol propionate ointment was used over the eczematous plaques until the resolution of his symptoms.

Case 2

A 68-year-old man was receiving DVT prophylaxis with subcutaneous enoxaparin at a dose of 20 mg daily after a splenectomy for idiopathic thrombocytopaenic purpura. 10 days after commencing enoxaparin, he developed an itchy, eczematous eruption over the chest and back, before it became generalized. Enoxaparin was discontinued immediately with resolution of the eruption within a week of treatment with emollients and topical corticosteroids.



Fig. 1. Eczematous eruption in the right lower abdomen adjacent to previous injection site.

Case 3

A 70-year-old man was referred for dermatology review for a suspected penicillin allergy. He was an in-patient following a left total knee replacement and was receiving prophylactic doses of subcutaneous enoxaparin at a dose of 40 mg daily due to his immobility. He had developed a wound infection, and 2 days before the onset of the rash, he was mistakenly given oral coamoxiclav for a wound infection, despite a documented penicillin allergy. The eczematous eruption had started over the ears and rapidly became generalized. On examination, there were confluent areas of erythema with some areas being papular or vesicular with lichenified plaques.

Skin biopsy showed marked oedema in the papillary dermis with a mixed inflammatory cell infiltrate and numerous eosinophils. The findings were of an eczematous drug eruption both clinically and histologically (Fig. 2)

The only drug common to these 3 cases was enoxaparin. The fact that the first case had initially developed his eczematous eruption adjacent

to the site of injection and the marked eosinophilia in cases 1 and 3 support this.

Patch testing of all 3 patients was undertaken on tape-stripped skin. Enoxaparin (Clexane[®] – Rhône-Poulenc Rorer, West Malling, UK) at a concentration of 100 mg/ml was used under 5 mm Finn[®] chambers (Epitest Oy, Tuusula, Finland) and Scanpor[®] tape (Norgesplaster, Vennesla, Norway) as well as unfractionated heparin at a concentration of 1000 U/ml. Readings were taken at days 2 and 4 and were negative in all 3 cases. Case 3, however, developed an eczematous eruption at a remote site in the axilla within 24 hr of the patch test. This site had previously been affected at original presentation. This is highly suggestive of a recall reaction, where subsequent exposure to antigen may evoke disease at remote sites previously affected by allergic contact dermatitis. Prick testing to enoxaparin (100 mg/ml) was negative with normal negative and positive controls in all 3 patients. After counselling each patient that the reaction might have recurred with subcutaneous challenge, all 3 patients declined to have this investigation.

Discussion

All of our patients were male, and none were obese. Only 1 male case of eczema-like plaques to enoxaparin has been reported previously (2), with most of the patients being obese. None of our patients had concomitant thrombocytopenia. It is possible that the reaction in case 3 was due to penicillin; however, eczematous reactions are not normally seen either clinically or histologically with penicillin allergy.

It seems most likely that eczema-like eruptions due to various heparins reflect a type IV hypersensitivity reaction. Patch and prick tests are unreliable in this setting, and subcutaneous provocation is thought the best means to investigate these patients (3). In the literature, specifically regarding enoxaparin, patch test results have been variable (4–7). This perhaps reflects differing methodologies such as the use of scarification. Prick test results are also variable, although the presumed mechanism of delayed hypersensitivity should mean that immediate hypersensitivity reactions are negative. Establishing a diagnosis of enoxaparin sensitivity is critical in our patients, who would be likely to encounter enoxaparin or other LMWHs again in acute medicine.

Eczema-like plaques result due to binding of the heparin molecule to dermal protein, triggering a delayed-type hypersensitivity reaction. All

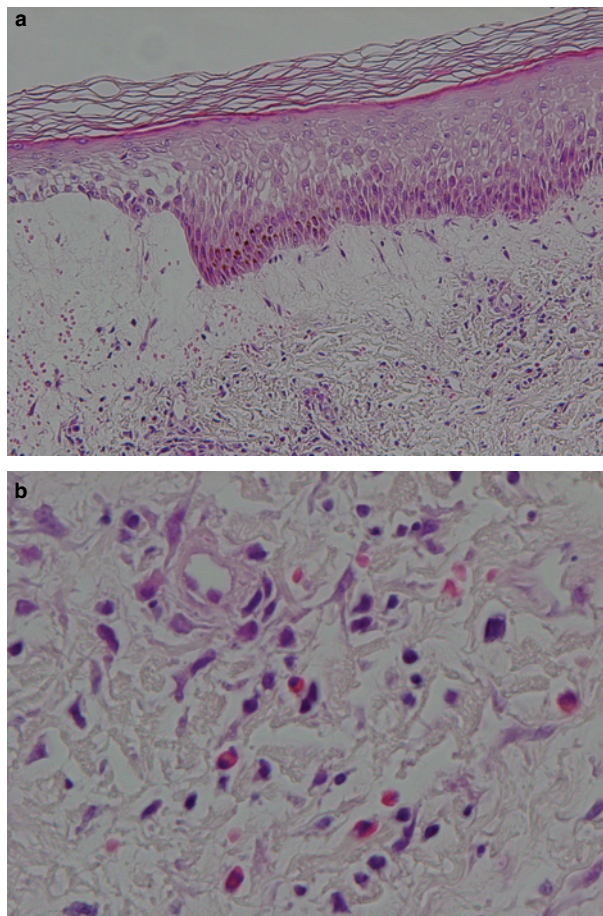


Fig. 2. (a) Marked oedema and spongiosis on skin biopsy. (b) Numerous eosinophils in the dermis.

heparins should be avoided in such individuals due to cross reactivity. Alternatives which may be used include fondaparinux sodium, a synthetic pentasaccharide, or recombinant hirudins. Unfortunately, both of these agents themselves may cause type IV hypersensitivity reactions (8, 9). Fondaparinux specifically may cross-react in those with established heparin and semisynthetic heparinoid allergy, although on the small number investigated ($n = 7$), this effect seems to be rare (10).

Eczema-like eruptions may be under-reported because patients may be commenced concomitantly on other medications such as aspirin, warfarin and beta-blockers and the eruption may be mistaken for a drug eruption to these agents.

LMWH is used extensively in acute medicine. Eczema-like eruptions associated with LMWH, and particularly with enoxaparin, may be more frequent than previously recognized. Patch testing LMWH is difficult because the molecules are large. Other cases documented commonly report negative results on patch testing. Our cases emphasize the need for accurate diagnosis by the assisting physician to prevent the potentially fatal consequences of erroneously discontinuing drugs such as aspirin in acute medical patients.

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