

Enoxaparin-Induced Generalized Exanthem

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Adverse cutaneous reactions to low molecular weight heparin (LMWH) are uncommon in the literature. They are usually localized reactions such as ecchymoses, erythematous plaques, and nodules. Only one case of a generalized maculopapular rash with enoxaparin has been reported in Europe. To our knowledge, this is the first case reported in the English literature of a generalized exanthem due to subcutaneous injection of enoxaparin.

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Enoxaparin and other low molecular weight heparins (LMWHs) are widely used to treat and prevent thromboembolic disorders. Rare adverse skin reactions to LMWH are largely confined to the localized sites of injections and include ecchymoses, erythematous plaques, and nodules.¹⁻³ Previous reports of generalized skin rash due to high molecular weight heparin (HMWH) given intravenously and subcutaneously have been well described.⁴⁻⁷ Only one case of a generalized skin reaction to enoxaparin has been reported in Europe.⁸ We report the first case of a generalized maculopapular rash due to subcutaneous enoxaparin injections in the English literature.

Case Report

A 53-year-old white woman with morbid obesity and a history of deep venous thromboses, pulmonary emboli, and cor pulmonale developed a generalized pruritic rash on the fourth day of therapy with subcutaneous enoxaparin injections. The patient had been admitted to the hospital for a deep venous thrombosis in her leg. She initially was

given intravenous heparin for 5 days, and then was switched to oral warfarin for anticoagulation. Warfarin was administered for one week but was discontinued because a Greenfield filter placement was being considered. She was then started on subcutaneous enoxaparin, 100 mg twice a day. By day 4 of enoxaparin administration, a rash appeared on the malar area of the face that quickly spread to the trunk and proximal extremities over the next few days. Tender lesions at injection sites on the abdomen also were noted. The patient had no known history of allergies to any medications prior to this episode. She denied any similar rash in the past. She had received heparin during previous hospitalizations without any adverse reactions. She denied receiving enoxaparin before this hospital stay. Her other medications included folic acid, metoprolol tartrate, amiodarone hydrochloride, acetaminophen with codeine, and albuterol inhaler, all of which she had been taking for many months to years. The patient was given albumin intravenously during the early part of her hospitalization for oliguria. No new medications were started prior to her admission.

On physical examination, there was a generalized blanching erythematous maculopapular rash, with marked accentuation on the nose and cheeks (Figures 1 and 2). There were tender ecchymotic nodules on the abdomen at the sites of previous enoxaparin injections. No mucous membrane lesions were seen.

Results of laboratory studies, including complete blood cell count, blood chemistries, and transaminases, were within normal limits. There was no eosinophilia. Antinuclear antibodies were negative. Results of a skin biopsy of the maculopapular rash demonstrated a superficial perivascular infiltrate with lymphocytes and a few eosinophils (Figure 3). The clinical presentation and histologic findings were consistent with a drug eruption.

All medications were halted, and 60 mg of oral prednisone was started. The rash began to resolve 3 days later. Prednisone was tapered, and all of the patient's long-standing medications were restarted.

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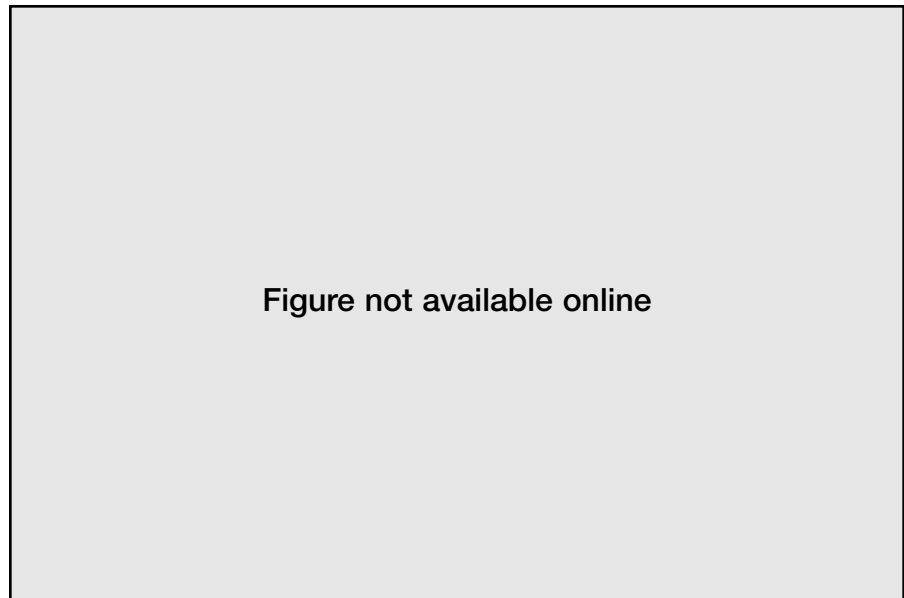


Figure 1. Erythema with marked accentuation on the nose and cheeks.



Figure 2. Erythematous macules and papules on the trunk and extremities.

The patient also was restarted on warfarin for anticoagulation. There was no recurrence of the rash. A provocation test with enoxaparin was offered, but the patient declined.

Comment

Heparin-induced skin reactions associated with subcutaneous administration have been well described in the literature.^{1,9,10} Typical lesions are erythematous, tender nodules at injection sites. Reports of reactions with different preparations of HMWH and LMWH have implicated the heparin molecule rather than preservatives as the causative

agent.^{2,11,12} Substitution of one heparin preparation for another does not prevent the recurrence of similar reactions in susceptible individuals.^{2,7,11,13}

Enoxaparin is the first LMWH to be marketed in the United States. LMWHs are derived from unfractionated heparin, a heterogeneous mixture of polysaccharide chains. Unfractionated heparin is prepared from ox lung and bovine and porcine intestinal mucosa.¹¹ Adverse effects are typically less common with LMWH than with unfractionated heparin, perhaps due to the smaller size of molecules, the greater homogeneity, and the exclusive porcine origin of LMWH.¹⁴

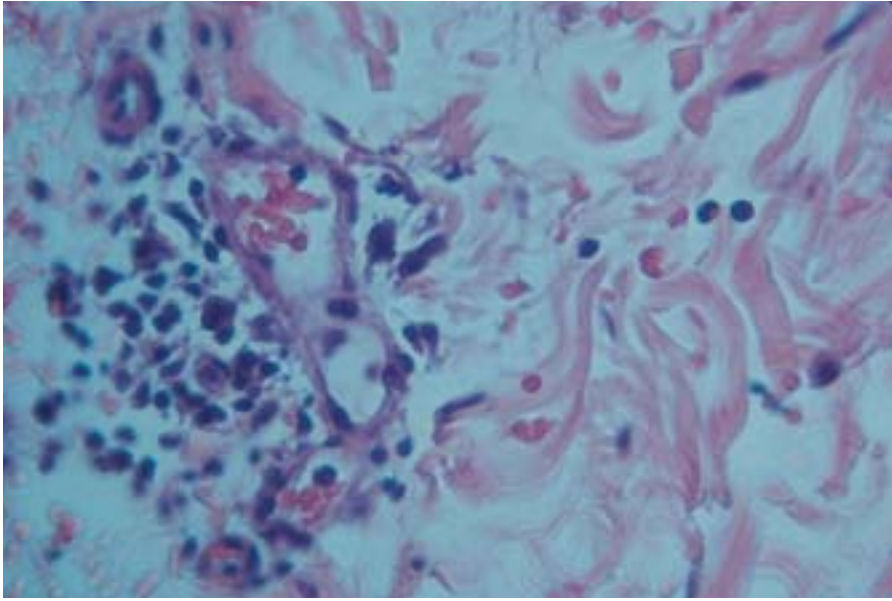


Figure 3. Perivascular lymphocytic infiltrate with eosinophils (H&E, original magnification $\times 400$).

Localized adverse cutaneous reactions to LMWH have been reported. Ecchymoses and hematomas are thought to be directly related to the pharmacologic effects of the agent.¹⁵ Urticaria is probably due to local histamine release or is a classic type-I immediate hypersensitivity reaction. Early cases of urticaria with heparin were thought to be due to sensitivity to contaminant proteins.¹⁶ In recent years, reports of urticarial reactions have been rare.³ One case of generalized urticaria and angioedema has been attributed to enoxaparin.¹⁷ Skin necrosis from unfractionated heparin at injection sites typically occurs after 5 to 9 days of treatment.⁹ Lesions also have been noted at distant sites from subcutaneous and intravenous administration of unfractionated heparin.^{18,19} Similar cases of skin necrosis at injection sites have been reported with LMWH.^{15,20} Enoxaparin-induced skin necrosis distant from injection sites has been described in a patient with diabetes.²¹ Some patients may develop heparin-induced thrombocytopenia and present with erythematous plaques that rapidly evolve into necrosis.¹² Occurring 6 to 10 days after the start of therapy, this condition is thought to be secondary to heparin-antiheparin IgG immune complexes that activate platelets and is more common in patients treated with unfractionated heparin than in patients on LMWH therapy.²²

Delayed-type hypersensitivity skin reactions at injection sites have been reported with all types of LMWH.^{23,24} Lesions are well-circumscribed, erythematous, infiltrated, or vesicular plaques. Female sex, obesity, diabetes, and prolonged application of the

drug are suspected risk factors for the development of sensitization to HMWH and LMWH.^{7,25}

To our knowledge, this is the first case reported in the English literature of a generalized exanthem due to subcutaneous injection of enoxaparin. The temporal relationship of the medication and onset of rash, the patient's erythematous nodules at enoxaparin injection sites, and the absence of recurrence after all other medications were restarted strongly implicate enoxaparin as the sole responsible agent for her generalized skin reaction. Incidentally, the patient was given albumin prior to the rash; however, the exceedingly rare, untoward reactions to albumin, such as nausea, fever, chills, or urticaria, usually disappear when the infusion is slowed or temporarily stopped. Our patient tolerated the albumin infusions without any adverse symptoms. In addition to being obese and female, our patient had been exposed to heparin multiple times in the past; thus, she shares the suspected risk factors that have been previously described in patients with localized hypersensitivity skin reactions to LMWH.

Lesions at the injection sites combined with the generalized rash that appeared 4 days after the onset of enoxaparin therapy suggest a type IV hypersensitivity reaction in this patient. A subcutaneous provocation test is considered the gold standard test for this condition.⁷ However, potential adverse effects such as anaphylactic shock or heparin-induced thrombocytopenia may occur.¹⁴ A provocation test was offered to the patient, but she declined.

There are several potential therapeutic alternatives to heparin therapy. Danaparoid sodium and

pentosan polysulfate have polysaccharide chains with structures chemically different from heparin. Danaparoid, however, is a mucopolysaccharide derived from porcine intestinal mucosa and may share the same allergens with heparin. Allergic reactions with danaparoid and pentosan polysulfate have been reported.^{4,6,26} Hirudin is another anticoagulation agent that the patient may tolerate because recombinant hirudins do not cross-react with HMWH or LMWH and heparinoids.^{13,27} Unfortunately, they too can cause delayed-type hypersensitivity reactions.⁵ At present, our patient is on warfarin therapy.

Skin hypersensitivity reactions to enoxaparin are considered rare. However, given the widespread use of this and other LMWHs, it is important for the clinician to suspect this diagnosis when evaluating localized, as well as generalized, cutaneous eruptions.

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