4. LoVecchio F, Blackwell S, Stevens D. Outcome of chlorine exposure: a 5-year poison center experience in 598 patients. Eur J Emerg Med. 2005;12:109–10.
5. Hammond BG, Barbee SJ, Inoue T, Ishida N, Leviskas GJ, Stevens MW, et al. A review of toxicology studies on cyanurate and its chlorinated derivatives. Environ Health Perspect. 1986;69:287–92.
6. Differential diagnosis for annular lesions rash [Accessed October 22, 2009]. Available at: http://en.diagnosispro.com/differential_diagnosis-for/annular-lesions-rash/34066-154.html.
7. Brodsky B, Wormser U. Protection from toxicants. Curr Probl Dermatol. 2007;34:76-86.

F.J. Castellote-Varona

Unidad de Valoración y Cuidados Geriátricos, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain

E-mail address: franciscoj.castellote@carm.es

Fondaparinux and Lepirudin as Therapeutic Alternatives in a Disseminated Eczematous Skin Reaction to Low-Molecular-Weight Heparin

Fondaparinux y lepirudina como alternativas terapéuticas ante una reacción cutánea eccematosa diseminada a heparina de bajo peso molecular

To the Editor:

Low-molecular-weight heparins are obtained by depolymerization of conventional heparin; these heparins are part of the anticoagulant armamentarium and are widely used as therapy or prophylaxis in thromboembolic conditions. They are used at the initiation of long-term oral anticoagulant therapy and are the treatment of choice for the substitution of oral therapy before invasive diagnostic or therapeutic procedures. Reactions such as ecchymoses are commonly observed at the injection sites; eczematous plaques are seen less often.

We present a patient who developed an eczematous skin reaction related to Clexane (enoxaparin); intradermal tests revealed delayed-type hypersensitivity and subcutaneous challenge confirmed cross-reactivity to unfractionated heparin and other low-molecular-weight heparins available at our hospital.

An 80-year-old woman with paroxysmal atrial fibrillation and a double aortic valve lesion was receiving oral anticoagulation with Sintrom (acenocoumarol). She was admitted for cardiac catheterization (as part of the work-up for valve repair) and the oral anticoagulant was switched to subcutaneous Clexane at a dose of 40 mg/24 h. Four days after starting the new treatment, pruritic erythematous papules appeared in the periumbilical region, coinciding with the sites of injection, and tended to coalesce to form plaques (Figure 1); dyshidrosiform lesions were also observed on the palms (Figure 2). Following 48 hours of replacement therapy with intravenous sodium heparin, the lesions became disseminated. Skin biopsy showed spongiosis with mild eosinophilia. The patient recalled a similar acute local reaction when she was admitted on a previous occasion due to the onset of atrial fibrillation and received subcutaneous Clexane prior to oral anticoagulation; the reaction resolved after the oral therapy was started.

Because a delayed-type hypersensitivity reaction to enoxaparin was suspected, heparin was discontinued and

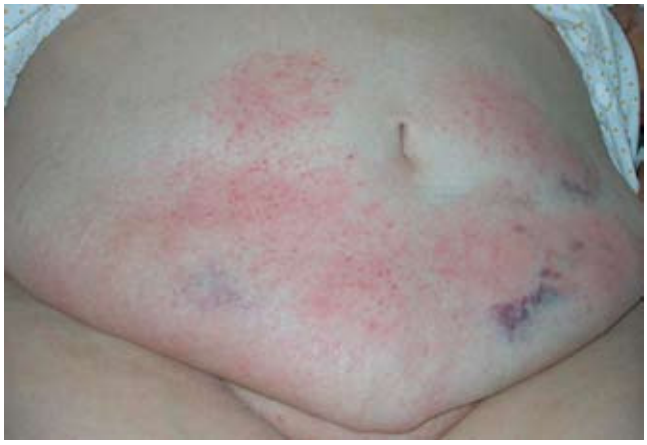

Figure 1 Periumbilical eczematous lesions in the areas where subcutaneous enoxaparin was administered.

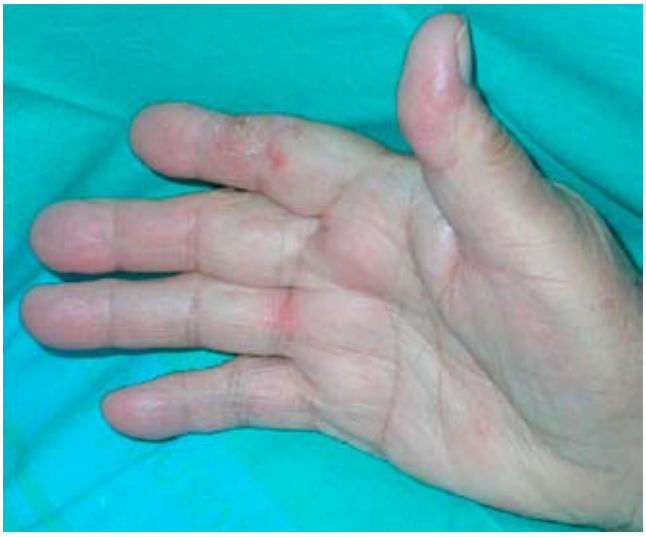

Figure 2 Dyshidrosiform lesions on the palm of the right hand.

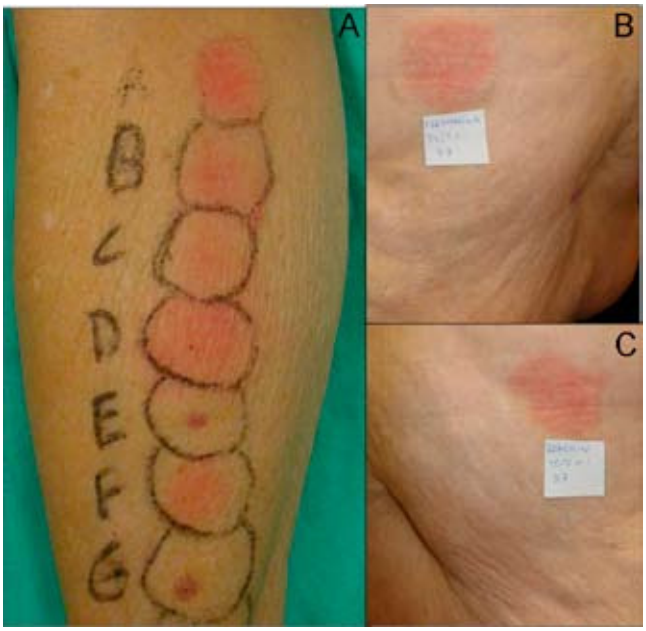

Figure 3 A, Intradermal tests on the right forearm, reading at 7 days: positive for A (Hibor [bemiparin], D (Clexane [enoxaparin]), and F (sodium heparin); inconclusive for B (Fragmin [dalteparin]) and C (Fraxiparina [nadroparin]); and negative for E (Arixtra [fondaparinux]) and G (Refludin® [lepirudin]). B, Positive Fraxiparina challenge test at 7 days. C, Positive Fragmin challenge test at 7 days.

oral anticoagulation was resumed. The patient also required oral and topical corticosteroid therapy until the lesions resolved 3 weeks later. Patch tests were performed using the standard Spanish Contact Dermatitis Research Group (GEIDAC) series, Chemotechnique cosmetic series, and heparins (sodium heparin and the low-molecular-weight heparins available at our hospital), Arixtra (fondaparinux), and Refludin (lepirudin), but no relevant positive reactions were observed at 48 and 96 hours. Intradermal tests were negative at 30 minutes and at 48 and 96 hours; however, the reading at 7 days (Figure 3A) was positive for Hibor (bemiparin), Clexane, and sodium heparin, inconclusive for Fragmin (dalteparin) and Fraxiparina (nadroparin), and negative for Arixtra and Refludin. Challenge tests using subcutaneous injection were performed in the case of compounds with an inconclusive or negative result in the intradermal tests and were positive for Fragmin and Fraxiparina at 7 days (Figures 3B and 3C), and negative for Arixtra and Refludin.

Our patient presented an eczematous skin reaction to enoxaparin, initially localized to the areas of puncture and later disseminated, possibly due to cross-reactivity with sodium heparin. Intradermal tests showed delayed hypersensitivity to enoxaparin, as well as cross-reactivity to unfractionated heparin and other low-molecular-weight heparins available at our hospital; the results were subsequently confirmed by challenge tests. The negative test results for Arixtra (synthetic heparin pentasaccharide) and Refludin (synthetic hirudin analog) indicated that either could be used to substitute oral anticoagulant therapy in this patient.

The appearance of an eczematous reaction at the site of subcutaneous injections of low-molecular-weight heparin is attributed to a delayed-type hypersensitivity to the molecule.[1] The incidence of this adverse event is unknown; however, it appears to be uncommon if we consider the extent to which these drugs are used. The antigenic determinants of heparin have not yet been identified, but the compound may behave like a hapten, needing to bind to structural proteins in the dermis or subcutaneous tissue to acquire antigenic properties.[2,3] Because conventional heparin is structurally related to low-molecular-weight heparins and fondaparinux, these latter drugs should be discontinued whenever a delayed-type hypersensitivity reaction to one of the compounds is detected, and any possible cross-reactions should be investigated before replacement therapy is started.[4-6] Lepirudin was recently introduced as a therapeutic alternative in cases of heparin hypersensitivity because it is structurally unrelated and shows no cross-reactivity with heparin or its derivatives.[7]

In order to confirm the diagnosis of delayed hypersensitivity to heparin, intradermal tests, considered to be the most sensitive, should be performed, along with subcutaneous challenge tests (gold standard); all possible therapeutic alternatives (unfractionated heparin, low-molecular-weight heparins, ultra-low-molecular-weight heparins, and synthetic hirudin analogs) should be tested and readings should be taken at 7 days.[8] Patch testing is of extremely limited use, and false negative results are common because the molecules are large and do not penetrate the epidermis.[9]

References

1. Bircher AJ, Fluckiger R, Buchner SA. Eczematous infiltrated plaques to subcutaneous heparin: a type IV allergic reaction. Br J Dermatol. 1990;123:507-14.
2. Jappe U, Juschka U, Kuner N, Hausen BM, Krohn K. Fondaparinux: a suitable alternative in cases of delayed-type allergy to heparins and semisynthetic heparinoids? A study of 7 cases. Contact Dermatitis. 2004;51:67-72.
3. Fields RM, Peppo W. The use of intravenous recombinant hirudin in the treatment of deep vein thrombosis in a patient with an acute heparin allergy. Ann Emerg Med. 2002;40:155-8.
4. Bircher AJ, Harr T, Hohenstein L, Tsakiris DA. Hypersensitivity reactions to anticoagulant drugs: diagnosis and management options. Allergy. 2006;61:1432-40.
5. Grims RH, Weger W, Reiter H, Arbab E, Kranke B, Aberer W. Delayed-type hypersensitivity to low molecular weight heparins and heparinoids: cross-reactivity does not depend on molecular weight. Br J Dermatol. 2007;157:514-7.
6. Maetzke J, Hinrichs R, Schneider LA, Scharffetter-Kochanek K. Unexpected delayed-type hypersensitivity skin reactions to the ultra-low-molecular-weight heparin fondaparinux. Allergy. 2005;60:413-5.
7. Koch P, Münbinger T, Rupp-John C, Uhl K. Delayed-type hypersensitivity skin reactions caused by subcutaneous unfractionated and low-molecular-weight heparins: tolerance

of a new recombinant hirudin. J Am Acad Dermatol. 2000;42: 612-9.
8. Palacios Colom L, Alcántara Villar M, Anguita Carazo JL, Ruiz Villaverde R, Quiralte Enríquez J. Delayed-type hypersensitivity to heparins: different patterns of cross-reactivity. Contact Dermatitis. 2008;59:375-7.
9. Nino M, Patruno C, Zagaria O, Balato N. Allergic contact dermatitis from heparin-containing gel: use of scratch patch test for diagnosis. Dermatitis. 2009;20:171-2.

D.I. Santiago Sánchez-Mateos,* C. Eguren, D. de Argila, and J. Sánchez-Pérez

Servicio de Dermatología, Hospital de la Princesa, Madrid, Spain

*Corresponding author.
E-mail address: dianass_m@yahoo.es
(D.I. Santiago Sánchez-Mateos).

Sweet Syndrome in a Pregnant Woman

Síndrome de Sweet asociado al embarazo

To the Editor:

A 33-year-old woman, a primigravid at 16 weeks' gestation, came to our outpatient clinic due to the sudden appearance of a hot, infiltrated, edematous erythematous plaque, with clusters of pustules, and areas of crusting and desquamation (Figure 1). The lesion had appeared on the anterior aspect of her right thigh 4 days earlier. The patient had no relevant past medical history and no record of abortion, and her pregnancy was developing normally. Coinciding with the appearance of the lesion, she had been feeling feverish, and complained of pruritus and pain in the area; she thought the lesion might have been the result of an insect bite. She was diagnosed with cellulitis and was prescribed an oral antibiotic, an aqueous solution of 3 sulfates (copper, zinc, and potassium), and topical corticosteroids. The thigh lesion gradually improved, but 10 days after the first visit, the patient returned to the clinic with 2 similar plaques (1 on a wrist and 1 on the abdomen), urticarial in appearance, and characterized by intense pruritus (Figure 2).

As possible diagnoses, we considered urticarial vasculitis, eosinophilic panniculitis, herpes gestationis, and Sweet syndrome. Blood tests revealed iron deficiency anemia, and leukocytosis of 12 000 cells/μL, both considered to be consistent with pregnancy. Samples taken for pathology study confirmed Sweet syndrome. Intense edema was observed in the upper dermis, accompanied by a predominantly perivascular neutrophilic inflammatory infiltrate, and a dense band-like inflammatory infiltrate in the papillary dermis (Figure 3). Treatment with 45 mg/d of deflazacort resolved the lesions in 10 days. The dose of corticosteroids was tapered over the following month, but the patient—22 weeks pregnant, and receiving 7.5 mg/d of deflazacort—returned with identical lesions at the same sites. Deflazacort was again prescribed at a dose of 45 mg/d for 15 days. The lesions resolved, and treatment was reduced to 10 mg on alternate days until vaginal delivery at 39 weeks without complications. Two years later the patient remains asymptomatic.

Sweet syndrome is named after Dr. Robert Douglas Sweet, who first described the disorder in 1964. Also known as acute febrile neutrophilic dermatosis, it has a worldwide distribution and is most common in women aged 30 to 50 years. Five subtypes have been identified: classical or idiopathic (71%); infection- or autoimmune-associated (15%), paraneoplastic (10%-20%); pregnancy-associated (2%); and drug-induced.[1]

The etiology is unknown. The fact that Sweet syndrome is predominantly a disorder of women and is associated with pregnancy and oral contraceptives would suggest a hormonal origin. Elevated estrogen and progestogen levels during pregnancy may be responsible for the vascular, cellular, microbiological, and immunological changes linked to the pathogenesis of pregnancy-associated Sweet syndrome.[2] Diagnosis is complicated by the fact that skin lesions are not always accompanied by the typical triad of fever, anemia, and leukocytosis with neutrophilia and an increased erythrocyte sedimentation rate. For this reason, we are of the opinion that Sweet syndrome is probably underdiagnosed.

The skin lesions typically present as clearly circumscribed, infiltrated erythematous papules and plaques, with marked edema. Vesicles and blisters may also be observed. Around 33% of patients relapse—as happened with our patient—as corticosteroid treatment is tapered off. Lesions tend to occur mostly on the upper part of the body, although, as happened with our patient, they may also appear elsewhere.[3]

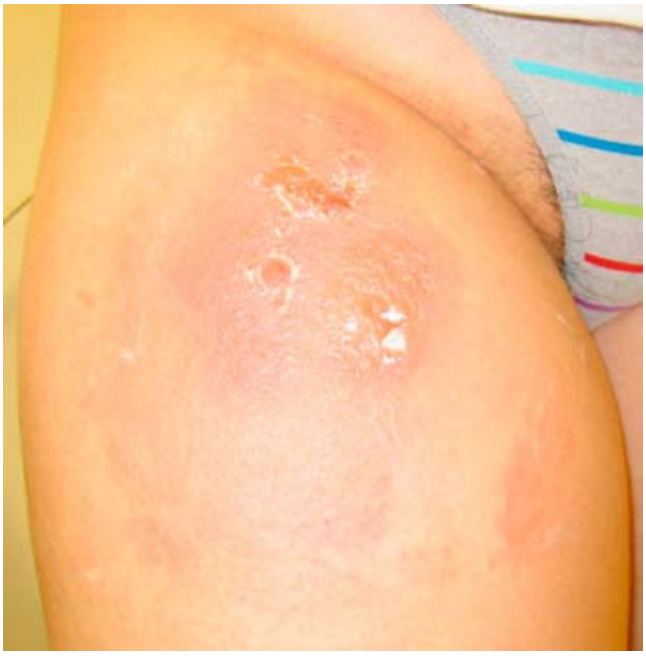

Figure 1 First episode. Hot, infiltrated, edematous e rythematous plaque on the right thigh, with clusters of pustules, and areas of crusting and desquamation.