Heparin induced bullous hemorrhagic dermatosis at a site distant from the injection. A report of five cases*

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DOI: http://dx.doi.org/10.1590/abd1806-4841.20165418

Heparins both unfractionated and low-molecular-weight are associated with some cutaneous complications including hematomas, ecchymosis, erythematous plaques, nodules, skin necrosis, contact dermatitis and urticaria, all occurring more commonly at local subcutaneous injection sites. First reported at 2006 by Perrinaud et al, bullous hemorrhagic dermatosis is a rare cutaneous reaction to heparin in which hemorrhagic intraepidermal bullae appear in areas distant from the heparin injection sites and of which there are less than 20 cases described in the literature.

We present 5 cases of heparin induced bullous hemorrhagic dermatosis at a site distant from the injection. The characteristics of each patient are detailed in table 1. All the patients were male with mean age of 74 years, in treatment with enoxaparin at different doses. Patients 3 and 4 were also taking antiplatelet drugs. The onset of bullae was 8-20 days after the beginning of the heparin therapy and the lesions were asymptomatic in all cases. Biopsy was performed in the 5 cases, showing intraepidermic blister filled with red blood cells, without any signs of vasculitis or vessels thrombosis, and heparin-induced bullous hemorrhagic dermatoses was diagnosed (Figure 1A). Laboratory tests' results, blood count and coagulation studies were normal. Patients 2, 3, and 4 had pruritic conditions previous to the onset of lesions; therefore they scratched their skin. We observed that these patients presented more lesions and that they were more disseminated than in those patients without pruritus. What is more relevant, in patients 2, 3 and 4 some of the lesions had a linear, Koebner-like, arrangement (Figure 1B). Strikingly, patient 3 developed new lesions on the stitches at the site of biopsy (Figure 1C). Patient 5 had no pruritic condition, but the appearance of the lesions was clearly associated to an occasional scratch on the area.

In three of our five cases we maintained the treatment; two of them self-resolved without discontinuation but treatment was changed in patient 2 because new lesions kept appearing, but it also had a complete resolution within few weeks. The reaction to heparin seemed to be retarded as proved by the late onset of the bullae, ranging from 8 to 20 days after the beginning of the heparin therapy. This data is also consistent with the reports previously published.

The pathogenesis of this condition is unclear. Since some patients were receiving high doses of heparin it has been proposed a dose-related reaction. In our series only one patient received very high doses of heparin, and two patients received low dose. Other authors also agree with this observation, being unlikely an overdose phenomenon. A synergic mechanism has also been proposed for

Received on 23.11.2015
Approved by the Advisory Board and accepted for publication on 18.06.2016

* Study performed at the Department of Dermatology, 12 de Octubre University Hospital, Madrid, Spain.
Financial Support: None.
Conflict of Interest: None.

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Diagnosis for table 1: hemorrhagic dermatosis at sites distant from subcutaneous injections of heparin.

**TABLE 1: Bullous hemorrhagic dermatosis at sites distant from subcutaneous injections of heparin. Clinical features**

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Sex</th>
<th>Age</th>
<th>Relevant comorbidities</th>
<th>Previous use of heparin</th>
<th>Diagnosis for heparin use</th>
<th>Other anticoagulants</th>
<th>Heparin type and doses</th>
<th>Latency</th>
<th>Number of bullae</th>
<th>Pruritus/other skin diseases</th>
<th>Linear lesions or Koebner phenomenon</th>
<th>Lesion location</th>
<th>Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>90</td>
<td>Aortic stenosis</td>
<td>Yes</td>
<td>Aortic valve replacement</td>
<td>No</td>
<td>Enoxaparin 80mg/12h</td>
<td>8 days</td>
<td>&lt; 5</td>
<td>No</td>
<td>No</td>
<td>Ankle and wrist</td>
<td>2 weeks; Heparin maintained</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>65</td>
<td>Cryptogenic organizing pneumonia</td>
<td>No</td>
<td>Atrial fibrillation</td>
<td>No</td>
<td>Enoxaparin 60mg/12h</td>
<td>9 days</td>
<td>&gt; 30</td>
<td>Yes. Renal insufficiency causing pruritus</td>
<td>Yes</td>
<td>Lower and upper extremities</td>
<td>2 months. After 1 month and a half change treatment to tinzaparin. Resolution 2 weeks after.</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>64</td>
<td>Ischemic cardiomyopathy</td>
<td>Yes</td>
<td>Study previous to heart transplantation</td>
<td>Aspirin 100mg/d</td>
<td>Enoxaparin 60mg/12h</td>
<td>7 days</td>
<td>&gt; 30</td>
<td>Yes. Xeroderma</td>
<td>Yes</td>
<td>Lower and upper extremities</td>
<td>3 weeks; Heparin maintained</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>89</td>
<td>Cardiac decompensation</td>
<td>No</td>
<td>Atrial fibrillation</td>
<td>Aspirin 300mg/d</td>
<td>Enoxaparin 40mg/12h</td>
<td>10 days</td>
<td>&gt; 100</td>
<td>Yes. Chronic urticaria</td>
<td>Yes</td>
<td>Lower and upper extremities, scalp and upper part of the back</td>
<td>3 weeks; Heparin suspended</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>74</td>
<td>Systemic amyloidosis</td>
<td>Yes</td>
<td>Atrial fibrillation</td>
<td>No</td>
<td>Enoxaparin 40mg/12h</td>
<td>20 days</td>
<td>&lt; 5</td>
<td>No</td>
<td>No</td>
<td>Hand and leg</td>
<td>2 weeks; Heparin suspended</td>
</tr>
</tbody>
</table>

In fact, disseminated lesions in patients suffering from pruritic conditions and Koebner phenomenon occurs in this disease dermatology are unexplained, however, cases also occurred without anticoagulants and amiodarone. In previous reports also show histology does not support this theory. Previous reports also show Koebner-like arrangement in patients treated with one or more anticoagulants or amiodarone, however, cases also occurred without anticoagulants and amiodarone. Histopathologic findings: subepidermal blister filled with red blood cells. Case 1. A: Linear arrangement of the lesions on the arm in which the lesions were given. Case 2. B: Linear arrangement of the lesions on the arm in which the lesions were given. Case 3. C: Linear arrangement of the lesions on the arm in which the lesions were given.
REFERENCES


How to cite this article: Gargallo V, Romero Tous Romero F, Rodríguez-Peralto JL, Zarco C. Heparin induced bullous hemorrhagic dermatosis at a site distant from the injection. A report of five cases. An Bras Dermatol. 2016;91(6):857-9.