Introduction

Hydroxyurea is an antitumoral agent currently used in the treatment of various diseases, mainly chronic myeloproliferative disorders. The appearance of a dermatomyositis-like rash and ulcers on the lower limbs is a rare adverse reaction that develops in patients undergoing long-term hydroxyurea therapy. The fact that such lesions do not respond to standard treatments and characteristically resolve spontaneously when hydroxyurea is withdrawn means that it is important that dermatologists be aware of the drug’s role as the causal agent. However, patients with such a reaction have generally received multiple treatments for periods of time ranging from months to several years before hydroxyurea is suspected as the origin of the dermatological disorders.

Case Description

We describe the case of a 76-year-old woman who was diagnosed with essential thrombocythemia in 1994. Since diagnosis, the patient had been receiving hydroxyurea (Hydra, 500 mg, twice daily), folic acid (Acfol, 5 mg/d),
Martorell-Calatayud A et al. Multiple Painful, Treatment-Resistant Leg Ulcers Associated With Dermatomyositis-Like Lesions Over the Interphalangeal Joints Induced by Hydroxyurea

and acenocoumarol (Sintrom Uno, 2 mg/d). In 1999 she consulted her hematologist due to the appearance of an ulcer with a long-axis diameter of 7 cm on her right ankle. Several treatments were used, including hydrocolloid dressings, antibiotic therapy, and topical and systemic corticosteroid therapy. As the lesion did not respond, a total skin graft was performed in 2001, 2 years after the initiation of treatment. In 2002 the ulcer reappeared in the area of the graft and new lesions developed on the side of the right ankle. At that point, the hematologist replaced hydroxyurea, which was showing a slight decrease in efficacy, with busulphan. What was striking from the dermatological point of view was that 2 months after the withdrawal of hydroxyurea, the skin lesions resolved completely, with no additional treatment. Unfortunately, the patient did not tolerate the alternative therapy and 1 year after she had begun busulphan treatment, hydroxyurea at the initial dosage had to be reintroduced. In 2007 she was referred to our department due to the reappearance of the earlier lesions and the appearance of new ulcers on the lower right leg, from the ankle to the heel. These ulcers were extremely painful, were well delimited by an atrophic epidermis, and had a yellowish-white adherent base. The largest lesion was 7 cm × 3 cm, and the smaller ones tended to coalesce, producing elongated stellate patterns (Figure 1). In the physical examination, ochre dermatitis was observed on both lower limbs, with normal and symmetrical peripheral pulses in both extremities. The patient also reported nonpruritic scaly erythematous lesions affecting the back of the interphalangeal joints of both hands (Figure 2). This chronic inflammatory process had begun 3 years after initiation of hydroxyurea therapy and had developed parallel to the development of the skin ulcers. Biopsy samples were taken from the edge of the ulcer and from one of the papules located over the interphalangeal joints of the hands. The biopsy of the edge of the largest ulcer showed nonspecific changes, while the biopsy of the sample from the back of the hand showed changes consistent with dermatomyositis, including mild hydropic degeneration of the base and a slight lymphocytic infiltration in the superficial and middle dermis, along with moderate interstitial deposition of mucin. Once the origin of the chronic ulcerative process had been established, hydroxyurea was withdrawn. During the period preceding the withdrawal of hydroxyurea, the lesions had been treated every 2 days by applying first powdered bovine collagen (Catrix) and then a nonadhesive hydrocolloid dressing (extra-fine Varihesive). These measures led to the stabilization of all the lesions and the closure of some of them. After 2 months of these topical treatments, we began to gradually replace hydroxyurea with interferon α 2a (Roferon, 6 million units per day). This resulted in a gradual improvement of both the cutaneous ulcers and the lesions on the back of the hand.

Discussion

Hydroxyurea is a cytoreductive agent that is usually well tolerated. However, long-term hydroxyurea therapy has been associated with adverse hematological and dermatological reactions (Table 1). The development of ulceration in the lower limbs (Figure 1) and the appearance of a dermatomyositis-like eruption on the back of the hands (Figure 2) are 2 of the rarest adverse reactions associated with the long-term administration of hydroxyurea. While the precise pathogenesis of this process is unknown, it is noteworthy that dermatomyositis-like lesions induced by hydroxyurea present clinical characteristics that are different from those induced by other drugs (Table 2).
first described by Montefusco et al in 1986, there has been an attempt to establish the various characteristics of this adverse reaction. Its exact pathogenesis has not yet been confirmed, but the antimetabolite action of hydroxyurea may slow keratinocyte turnover, causing the thinning of the epidermis and a decrease in the thickness of the basement membrane. In addition, the immunosuppressive effect of hydroxyurea induces pancytopenia and macrocythemia in 12% of patients, as well as a decrease in erythrocyte deformability, adding an ischemic component to the pathogenesis of this process. Finally, the possible involvement of platelets in the pathogenesis of this condition is based on the role of the drug as a mediator of inflammation through increased local production of serotonin (5-hydroxytryptamine), prostaglandins, and platelet aggregation factor. These factors increase vascular permeability and the local production of interleukin 1 and 8 and granulocyte-monocyte colony-stimulating factor, causing tissue damage. Chronic ulcerative lesions appear in patients between the ages of 38 and 90 years (mean age, 67 years), independent of sex. They are located on the lower limbs and tend to favor the perimalleolar region, followed by the pretibial region, and the back and sole of the foot. The ulcers have a fibrinous base and are well delimited by an erythematous and partially atrophic epidermis. Lesions are multiple in 70% of patients and are typically extremely painful. They appear long after the initiation of hydroxyurea therapy (between 2 and 15 years), with cumulative doses ranging from 1.4 to 5.5 kg. The histological study does not contribute useful information for the diagnosis of the condition. This type of ulcer does not respond to the usual measures applied in the management of venous and arterial ulcers. However, discontinuing hydroxyurea therapy leads to the spontaneous resolution of the lesion within 1 to 48 months (mean time, 10 months). Characteristically, the lesions reappear when hydroxyurea is reintroduced, thereby confirming that the drug was indeed the causal agent. At the present time, the development of ulcers secondary to hydroxyurea therapy for essential thrombocytosis is considered indicative of resistance or intolerance to the drug. For this reason, the recognition of hydroxyurea as the causal agent in a chronic ulcerative process will make it possible to manage this type of patient appropriately, essentially by withdrawing the drug. In recent years several therapeutic alternatives have been described that are useful in the management of those patients in whom hydroxyurea cannot be withdrawn. (Table 3).

### Conflicts of Interest
The authors declare no conflicts of interest.
Table 3. Alternative Therapies in Those Patients With Hydroxyurea-Induced Ulcers in Whom Treatment Cannot Be Discontinued

<table>
<thead>
<tr>
<th>Type of Therapy</th>
<th>Mechanism of Action</th>
<th>Mechanism of Action and Outcomes</th>
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<tbody>
<tr>
<td>Topical fibroblast growth factor spray</td>
<td>Neovascularization</td>
<td>Applied as a spray to the ulcers daily</td>
</tr>
<tr>
<td>(30 µg/application)</td>
<td></td>
<td><em>Outcome in 1 patient, with complete resolution of the lesion in 2 weeks</em>¹²</td>
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<tr>
<td>Topical granulocyte-monocyte colony-stimulating factor</td>
<td>Drug used for the prevention and treatment of mucositis and for the treatment of ulcers. Modulation of the action of monocytes and macrophages</td>
<td>Dilution of 5 µg/mL in 1-mL preloaded syringes</td>
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<tr>
<td></td>
<td></td>
<td>*Applied twice daily for 4-6 weeks.¹³</td>
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<td></td>
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<td>*Complete resolution in the 4 patients treated¹³</td>
</tr>
<tr>
<td>Proteinase modulators of the extracellular matrix</td>
<td>Inhibition of growth factor degradation and of the destruction of tissue by proteinases</td>
<td>First 2 weeks: Applied on alternate days.</td>
</tr>
<tr>
<td>(purified bovine collagen: Catrix, Promogran)</td>
<td></td>
<td>As of the second week: change to 2 days a week.</td>
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<td></td>
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<td>*Complete resolution in the 2 patients treated¹⁴</td>
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</tbody>
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*Published studies.

References