Hydroxyurea Ulcers of Unusual Location: A Case Report and Review of the Literature

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Abstract

Introduction

Hydroxyurea is a cytotoxic drug that has been used for decades for the treatment of various entities, mostly hematological, especially polycythemia vera.

Its side effects are varied, including dermatological ones, ranging from skin xerosis, hyperpigmentation, lesions like dermatomyositis, and even a relationship with premalignant processes (actinic keratosis) and non-melanoma cancer (squamous, basal cell, Merkel, and oral tumors).

Case presentation

In this paper, we report a clinical case of a relatively frequent adverse effect of hydroxyurea, ulcers, but of extraordinary localization and clinical presentation. Specifically, in our patient, the location was both hands, associated dermatomyositis-like lesions and nail hyperpigmentation, skin changes also related to hydroxyurea. The therapeutic response with withdrawal was spectacular.

Conclusions

The association of ulcers with taking hydroxyurea is well known. Most of the time, these appear in the lower limbs, and in patients with chronic vascular pathology. However, in some patients in some patients, it can present atypically. Knowledge of this condition is vitally important for the hematologist and the dermatologist to ensure adequate care.

Introduction

Hydroxyurea (hydroxycarbamine) is a pharmacological agent used since the middle of the last century in various hematological entities, including polycythemia vera, chronic myeloid leukemia or sickle cell anemia [1].

Among its potential adverse effects (including hematologic, infections, gastrointestinal, hepatics, renals, neurologics, pulmonary...), we find cutaneous ones. Half a century ago, Kennedy et al [2] reported several of the same in a series of 20 patients treated with hydroxyurea for chronic myeloid leukemia, including: partial alopecia, increased pigmentation, scaling, nail changes, and facial and hand erythema.

In addition, Daoud [3] proposed a term, exclusive to patients with associated hematological malignancy, called "hydroxyurea dermopathy", characterized by an erythematous, crusty rash with lichenoid papules like Gottroni's in dermatomyositis, on the dorsum of the fingers.

They are also reported to be associated with premalignant processes (actinic keratosis) and non-melanoma cancer (squamous, basal cell, Merkel, and oral tumors) [4].
Case Presentation

We describe the case of a 74-year man diagnosed six years before of polycythemia vera after two routine analytics with thrombocytosis and poliglobulia separated by one year.

Patient did not report splenomegaly or another clinic. Rest of the analytics was correct.

Peripheric blood frotis did not have any abnormality.

Analyses reported Janus Kinase-2 (JAK-2) positive and narrow biopsy reported cellularity of the three series increased, especially the megakaryocytes and it was compatible with polycythemia vera.

Karyotype was normal.

After these results, hematologists started treatment with hydroxyurea 500mg/12 hours and acetylsalicylic acid 100mg/24 hours with rapidly amelioration and was asymptomatic and with improvement in their routine controls.

Nevertheless, three years after the beginning of the treatment, the patient started with edema and tumefaction of his two hands and the developing of numerous painful ulcers on palmar and dorsal aspect of the hand.

Initially, the clinic was attributed to chilblains due to the cold and it was recommended to avoid exposure. Given the lack of improvement, he was initially referred to Rheumatology, who considered the condition part of his underlying disease and prescribed symptomatic treatment.

Finally, the patient was referred to Dermatology.

On examination, ulcers were observed, 7–8 in number on the dorsal side and 2–3 on the palmar side, with a very well-defined border, minimally painful to the touch and with a crusty surface. Also, he presented small erythematous-violaceous papules on the back of the hands and pigmentation at the nail level (Fig. 1a-d).

Given the suspicion of ulcers due to prolonged treatment with hydroxyurea, a punch biopsy was performed, and its discontinuation was indicated, starting second-line treatment with ruxolitinib 10mg/12 hours, with rapid improvement, leaving a remnant after one month of treatment and with total disappearance of the lesions two months after treatment (Fig. 2a-b).

Review Of The Literature And Conclusions

Among hydroxyurea skin side effects are ulcers, which were first described by Stahl and Silber in 1985\textsuperscript{5}. Their prevalence ranges between 3.5 and 5% in large cohort studies [6, 7]. In a recent review by Quattrone et al [8], it was found that these were more frequent in women, with a mean age of 62.7 years and the majority had hematological patients (polycythemia vera and chronic myeloid leukemia).
They usually have a well-defined border, with a surrounding whitish or erythematous halo and a dry superficial crust. On many occasions, they are clinically painful [7, 9].

Although most ulcers due to hydroxyurea are in the lower limbs, some cases of localization in the upper body, including the hands, have been described, as occurred in the clinical case that we present [10, 11].

It has been described various histopathologic findings in hydroxyurea-induced ulcers: leukocytoclastic vasculitis, lymphocytic infiltration, formation of thrombi, thickening of vessel walls, dermal fibrosis and hyperkeratosis [8].

However, the diagnosis is clinical, and is corroborated by the discontinuation of this medication, which, added to the local treatment of the ulcer, reports improvement rates of over 90%. Other treatments used have been local debridement [12], the use of healing materials such as dextranomer5, vasodilators such as prostaglandins E1 and I2 [13], topical antibiotic treatments [14] or enzymatic debridement materials such as collagenase [15].

Once the triggering factor has been eliminated, other lines can be used, including: anagrelide, phlebotomies, aspirin, interferon alfa, ruxolitinib, imatinib, cyclophosphamide, etc [16].

Through this clinical case, we wanted to highlight a relatively frequent adverse effect, but with a very atypical presentation, related to a drug used daily in the hematology field: hydroxyurea. Knowledge of these effects is vitally important for the hematologist to ensure adequate care.

Declarations

1. Funding

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“Compliance with ethical standards”:

2. Disclosure of potential conflicts of interest

1. The authors declare that there is no conflict of interest.

3. Research involving Human Participants and/or Animals and Ethics approval

- The recent work applies research on human beings, complying with the current regulations and approved by the Ethical Committee IIS La Fe El CEIm in terms of its composition, complying with the regulations of the Standard of Good Clinical Practices (CPMP/ICH/135 /95) and with Royal Decree 1090/2015.

- All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration
and its later amendments or comparable ethical standards.

4. Consent to participate and 5. Written consent for publication

- Written informed consent to participate and for publication was obtained from all individual participants included in the study. If additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

6. Availability of data and material

The data and material are available by the author in order of transparency in the investigation.

7. Code availability

Not applicable

8. Authors’ contributions

All authors declare their equal participation in the preparation of this work.

References


Figures
Figure 1

Lesions before discontinuation of hydroxyurea

(a and b): numerous ulcers with well-defined borders located on the dorsum of the fingers can be seen. Also, appreciate the reddish hue on the back of the interphalangeal and metacarpophalangeal joints, creating a "Pseudo-Gottron" pattern, like dermatomyositis. Note also nail brittleness and melanonychia, features also widely described in urea toxicity.

In (c), a dermatoscopic detail of the lesions can be seen, with ulcers with very well-defined borders, with a whitish halo surrounded by another more erythematous one on the outside. The appearance of the ulcer is crusty and dry.

In (d), detail of involvement in the palmar aspect.
Figure 2

Lesions after discontinuation of hydroxyurea

One month after discontinuation of therapy, the patient showed a notable improvement in the lesions (a), in the case of smaller and clinically asymptomatic ulcers.

In (b), improvement is also seen at the palmar level.