Hydroxyurea-Induced Leg Ulcers Treated With a Protease-Modulating Matrix

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Background: The development of painful leg ulcers in the ankle area is a rare and only partially described complication in patients receiving high-dose, long-term hydroxyurea treatment for myeloproliferative diseases. Several reports have described treatments for chronic wound management with this type of lesion.

Observations: We describe 2 patients who were diagnosed as having hydroxyurea-induced leg ulcers that were successfully treated with a freeze-dried sponge containing oxidized regenerated cellulose and bovine purified collagen. This dressing is able to modulate the activity of proteases such as plasmin, neutrophil-derived elastase, and matrix metalloproteinase by physically entrapping them and thus inhibiting their activity.

Conclusion: This case demonstrates that topical application of a matrix metalloproteinase modulator can be a successful and safe treatment option for patients with hydroxyurea-induced recalcitrant leg ulcers.

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Hydroxyurea is a hydroxylated derivative of urea that has been recognized since 1960 as an effective agent for treating cancer. It is an inhibitor of cellular DNA synthesis and promotes cell death in the S phase of the cell cycle through its inhibition of the enzyme ribonucleotide reductase. The most common indications for hydroxyurea therapy are chronic myeloid leukemia and gastrointestinal malignant melanoma. It has also been used in the management of other myeloproliferative disorders, sickle-cell disease, polycythemia vera, psoriasis, and to inhibit viral replication in human immunodeficiency virus disease. While the drug’s mode of action on bone marrow elements is well established, its effects on actively proliferating epithelial cells remain less well described.

Most adverse effects of hydroxyurea are mild and include fatigue, headache, nausea, vomiting, diarrhea, or fever. Rare and severe adverse effects appear to be linked to long-term administration and may be systemic (eg, leukopenia and anemia) or restricted to skin and mucous membranes (eg, stomatitis and diarrhea). Other dermatologic adverse effects are commonly reported with long-term daily therapy and include alopecia, hyperpigmentation, scaling, poikiloderma, atrophy of the skin and subcutaneous tissues, nail changes with multiple pigmented nail bands or brittleness, erythema and scaling of the face and acral sites stimulating chronic dermatomyositis, and lichen planus–like lesions or skin tumors on UV light–exposed areas.

Another rare and incompletely characterized complication, painful leg ulcers, has been described in patients with myeloproliferative diseases receiving high-dose, long-term hydroxyurea treatment. Poor response to traditional local and systemic therapy is a typical feature of hydroxyurea-induced leg ulcers, and discontinuation of treatment with the drug is often required to achieve complete wound healing.

Herein, we describe 2 cases of a pronounced association between hydroxyurea therapy and the development of painful leg ulcers unresponsive to standard treatment, as well as their successful treatment with local application of a sponge prepared from bovine collagen and oxidized regenerated cellulose (Promogran; Johnson & Johnson Wound Management, Piscataway, New Jersey).

Report of Cases

Case 1

In 1993, a 70-year-old woman was diagnosed as having thrombocythemia. In 1994, she began treatment with oral hy-
droxyurea (500 mg, twice a day) after failure of an anticoagulant therapy. In June 1999, painful ulcers developed in both lateral malleolar regions. Examination revealed 2 shallow, painful, well-defined ulcers with an adherent, yellow, fibrinous necrotic base and a livid border. The ulcers showed no signs of healing when treated with several local therapies such as gauzes impregnated with hydrogel, local hyperbaric oxygen, fibrinolytic ointment, and silver sulfadiazine cream. A full workup for venous and arterial assessment produced no abnormal results. In February 2000, because of high platelet values, hydroxyurea treatment was discontinued and oral busulfan therapy was started; this was maintained for 1 month. The size and severity of the ulcers partially reduced in 8 weeks with a topical hydrofiber dressing therapy.

In December 2001, the patient restarted therapy with oral hydroxyurea (500 mg, twice a day) because of high platelet values, and in April 2002, painful leg ulcers recurred in both lateral malleolar regions (Figure 1A). We successfully treated the ulcers by local application of Promogran dressing, which was applied on a wound bed moistened with isotonic sodium chloride solution and then covered with a nonadherent secondary dressing. Initially, we treated the ulcers with an application of the dressing every other day, and then twice weekly (Figure 1B). The treatment resulted in complete healing in 8 weeks, and the ulcers had not recurred at 1-year follow-up (Figure 1C).

CASE 2

An 82-year-old woman was diagnosed as having a polycythemia vera of 6 years’ duration. After 2 years of continuous treatment with oral hydroxyurea (1000-1500 mg/d), she developed a small painful ulcer on her right heel, distal to the medial malleolus. No preceding trauma was reported. Clinical examination and color Doppler evaluation showed venous dysfunction, but the patient could not tolerate any type of compression therapy. Treatment with hydroxyurea was stopped, and subcutaneous interferon alfa therapy was begun (5 × 10^6 IU every other day). The ulcer healed in 4 weeks under treatment with Promogran dressing twice a week.

Because interferon was not well tolerated, oral hydroxyurea was reinstated a few weeks later. Within 3 months, 2 painful ulcers had appeared on her right lateral malleolus. Both ulcers were circular and well demarcated at her first visit and became confluent in a single large lesion with a fibrinoid-necrotic base 48 hours later (Figure 2A). Topical application of Promogran dressing twice a week was restarted. The ulcers showed a progressive increase in the formation of granulation tissue after 2 weeks (Figure 2B) and were 85% healed in 6 weeks (Figure 2C).

COMMENT

Hydroxyurea is usually well tolerated and has a low toxic effect profile. However, cutaneous adverse effects such as diffuse hyperpigmentation, brown discoloration of nails, acral erythema, photosensitization, fixed drug eruption, alopecia, and oral ulceration have been described. Painful, difficult-to-heal leg ulcers associated with hydroxyurea therapy have been rarely reported. Montefusco and colleagues describe 17 patients who had hydroxyurea-related leg ulcers and achieved complete resolution or significant improvement after hydroxyurea therapy was discontinued. Another study described 4 patients with hydroxyurea-induced skin ulcers that eventually healed with appropriate wound care. Other authors describe the effectiveness of pentoxifylline and prostaglandin E1 in the treatment of leg ulcers in patients continuing systemic therapy with hydroxyurea. There is also a case report concerning the suc-
Successful treatment of these kind of lesions with the local application of Apligraf (Novartis, East Hanover, New Jersey), a tissue-engineered human skin equivalent.15

Herein we describe 2 patients who developed cutaneous leg ulcers while receiving long-term treatment with hydroxyurea. Our clinical experience confirms and clarifies the association between hydroxyurea therapy and the development of chronic leg ulcers, while our observations show that the patients who had hydroxyurea-induced leg ulcers developed hard-to-heal ulcers again when hydroxyurea treatment was resumed. We successfully treated the ulcers with local therapy by using Promogran dressing during the concomitant hydroxyurea treatment. In the beginning, we treated the ulcers with an application of the dressing every other day, and then twice weekly. The treatment resulted in complete healing in the first case and 85% healing in the second after 8 and 6 weeks of dressing application, respectively.

Other common features of these wounds include round shape and well-defined aspect at an early stage, high level of pain, and occurrence at the malleolar region. This localization may be caused by mechanical injury and trauma, but chronic and progressive cytologic damage is also involved due to the antimitabolic activity of the drug. The exact mechanisms by which hydroxyurea may lead to the formation of leg ulcers is still unclear, but long periods of exposure to the drug, latency in ulcer formation, chronic and slow ulcer enlargement, and healing after discontinuation of hydroxyurea therapy all suggest a chronic cumulative cytologic toxic effect of the medication.

Hydroxyurea selectively kills cells such as basal keratinocytes and inhibits collagen synthesis, so the drug itself could be considered a possible etiologic factor. However, platelet-derived inflammatory mediators related to the myeloproliferative disorders may play a part in the pathogenetic process. Usually cutaneous wounds develop spontaneously or after local previous trauma, and healing is possible only through discontinuation of the hydroxyurea treatment.16

Our study describes the successful treatment of hydroxyurea-induced leg ulcers with a novel material that modified the wound environment by significantly reducing the activity of proteases present in human chronic wound fluids. The treatment produced excellent pain relief in both patients, which was unexpected, and the mechanism of this benefit is unclear.

Promogran is a freeze-dried sponge containing oxidized regenerated cellulose and bovine purified collagen. This dressing lowers the activity of proteases such as plasmin, neutrophil-derived elastase, and matrix metalloproteinase by physically entrapping them and thus inhibiting their activity in diabetic foot ulcers.17 An alteration in the amount of these proteases plays a role in the occurrence of chronic wounds. This dressing inhibits the degradation of growth factors and the destruction of tissue, limiting the damage to collagen synthesis due to hydroxyurea. We believe that this rebalancing of the wound environment should hasten the wound repair process, diminish local pain, and consequently provide an efficacious treatment for hard-to-heal leg ulcers associated with hydroxyurea treatment. Local treatment was well tolerated compared with standard therapy and showed no adverse events.

In conclusion, we describe 2 patients with hydroxyurea-induced leg ulcers that responded to a protease-modulating matrix treatment. However, the use of this advanced dressing in the treatment of this atypical ulcer requires more evaluation in future studies.

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Figure 2. A, Large chronic wound with fibrinoid and necrotic tissue at baseline; B, after 2 weeks of treatment with Promogran dressing (Johnson & Johnson Wound Management, Piscataway, New Jersey); and C, after 6 weeks of treatment with Promogran.
the integrity of the data and the accuracy of the data analysis. Study concept and design: M. Romanelli. Acquisition of data: M. Romanelli and Dini. Drafting of the manuscript: M. Romanelli and Dini. Critical revision of the manuscript: P. Romanelli. Administrative, technical, and material support: Dini. Study supervision: P. Romanelli. Financial Disclosure: None reported.

REFERENCES