Hydroxyurea Associated Leg Ulcer Succesfully Treated with Hyperbaric Oxygen in a Diabetic Patient

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Key words
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- leg ulcer
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Abstract

Oxygen tension in healing tissues is heterogeneous. Increased oxygen mostly stimulates repair mechanisms and enhances tissue healing. Hyperbaric oxygen therapy increases blood and tissue oxygen content and may help maintain cellular integrity and function. Hydroxyurea (HU) is a cytotoxic agent, which leads to inactivation of ribonucleotide reductase, inhibition of cellular DNA synthesis, and cell death in the S phase. HU induced leg ulcers occur after use of this agent for a long time and at higher cumulative doses. Here we describe a diabetic patient with foot ulcer associated with HU treatment for polycythemia vera, who was treated successfully with hyperbaric oxygen and general wound care after discontinuation of HU. Faster improvement of leg ulcer in our patient compared to literature regarding HU withdrawal as single therapy suggests that hyperbaric oxygen may be helpful in the management of HU associated leg ulcers, especially in diabetic subjects.

Introduction

Hydroxyurea (HU) is an antineoplastic agent, which is indicated in the treatment of various hematological disorders and solid tumors. HU inhibits DNA synthesis via inactivation of ribonucleotide reductase in actively dividing cells, and causes cell death in the S phase [1].

Systemic side effects of HU are rare, dose dependent, and mostly reversible. However, dermatological side effects of HU are relatively common. Hyperpigmentation, photosensitivity, partial alopecia, scaling, brown discoloration of the nails, erythema and desquamation of the face and hands, oral ulceration, and stomatitis may be seen in the course of treatment with HU [1,2]. Leg ulcers due to HU are seen less frequently and are less well described than other dermatological side effects of the drug. HU associated leg ulcers are commonly located near the malleoli, are painful, and usually resolve after cessation of the drug [2]. There are reports suggesting that various therapies such as prostaglandin E1 [3], topical basic fibroblast growth factor therapy [4], and topical granulocyte-macrophage colony stimulating factor [5] may be helpful in the management of HU associated ulcers when they are added to standard wound care. Local application of autologous bone marrow cells [6] may also promote wound healing in diabetic foot ulcers.

Hyperbaric oxygen therapy is designed to greatly increase tissue oxygen tension. It involves breathing 100% oxygen at pressures greater than one atmosphere by using a pressurized treatment chamber. It is used as an adjuvant therapy in patients with certain types of wounds including diabetics [7]. Hyperbaric oxygen treatment is beneficial for diabetic ulcers, where the regional vascular system is intact or only partly damaged, but the tissue needs nutritive flow and oxygen supply because of local factors such as injury or infection [8].

Here we report a HU associated leg ulcer in a diabetic man, which was successfully treated with hyperbaric oxygen.

Case

A 63 year old male was referred in 2001 to department of hematology at our hospital for the evaluation of polycythemia. Investigation lead to the diagnosis of polycythemia vera and he was treated with HU. His blood cell count was controlled between target values by a total daily dose

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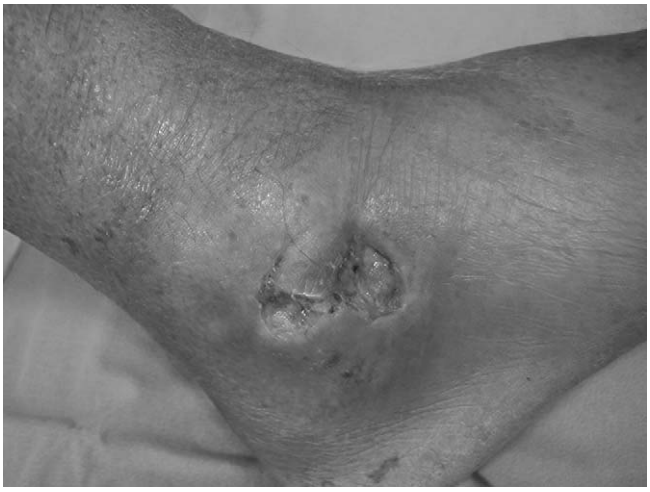

Fig. 1 Ulcer on the right lateral malleolus of the patient

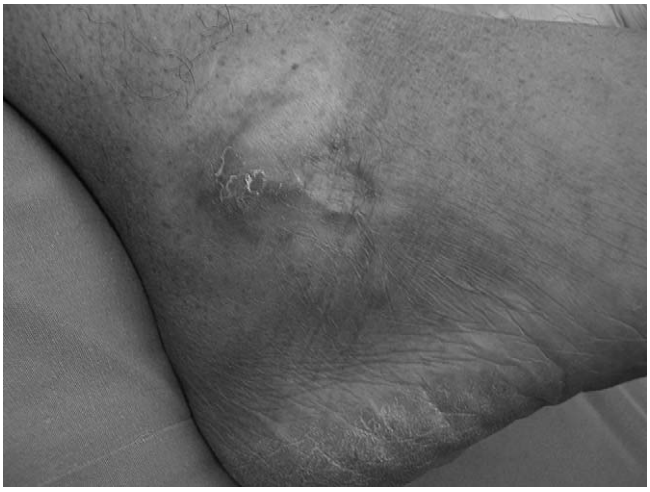

Fig. 2 The ulcer resolved almost completely with hyperbaric oxygen and general wound care after discontinuation of HU

of 1.5 g. The cumulative dose of HU used for this patient was 0.91 g/kg.

He reported to an outpatient clinic 7 months ago with complaints of pain, erythma, and ulcer over right lateral malleolus. He did not recall any trauma. He was given various topical wound dressing including mupirocin and oral antibiotics but the lesion failed to heal. Despite local debridment and wound care, no improvement was observed. Skin grafting of the area over the lateral tibia was performed. Although the wound from graft region on the tibia healed well, the malleolar wound did not improved. Repeated debridement, oral antibiotics, and local wound care failed to promote healing. He was referred to us for hospitalization and further investigation.

He had an 8 year history of type-2 diabetes. He was treated with oral antidiabetics for 3 years, and thereafter with insulin. His HbA_{1C} was 5.8%, controlled on a basal-bolus regime of regular insulin and NPH. He had mild proliferative diabetic retinopathy. He didn't have any other microvascular complications of diabetes. There was no history of ischemic heart disease and other macrovascular complications of diabetes. The patient was a nonsmoker, and he did not consume alcohol.

Physical examination revealed a 3×4 cm shallow, irregular ulceration on the right lateral malleolus. Skin atrophy and minimal edema were seen around the lesion as well as elsewhere on the foot (**Fig. 1**). The dorsalis pedis and posterior tibial pulses were easily palpable. Monofilament (10 g) testing revealed no peripheral neuropathy. No gross foot deformities were apparent. There was no radiological evidence of vascular insufficiency and no culture evidence of infection. A plain radiograph showed no evidence of osteomyelitis. Venous Doppler ultrasound was not associated with venous insufficiency.

Blood examination revealed a red blood cell count of $3.05 \times 10^{12} L^{-1}$ (normal: $4.0–5.77 \times 10^{12} L^{-1}$), hemoglobin concentration: 12.3 g/dl (normal: 13.5–17.5 g/dl), mean corpuscular volume of 125.9 (normal: 80.7–95.59, white cell count of $4.9 \times 10^{9} L^{-1}$ (normal: $4–10.3 \times 10^{9} L^{-1}$) with a differential of 71% segmented neutrophils, 18% lymphocytes, 8% monocytes, 2% eosinophils, and platelet count $357 \times 10^{9} L^{-1}$ (normal: $156–373 \times 10^{9} L^{-1}$). Peripheral blood smear revealed macrocytosis. Serum C-reactive protein, erythrocyte sedimentation rate, kidney and liver function tests, and urinalysis were within normal limits. Biopsy of the ulcer showed pseudoepithelial hyperplasia in the epidermis, acantolysis and granulomatous changes in the dermis consisting of proliferation of capillaries, fibroplasia and fat necrosis. It did not reveal evidence of vasculitis or malignancy.

HU treatment was discontinued, when considered as the etiological factor of leg ulcer in the patient. Hyperbaric oxygen therapy was initiated two days after withdrawal of HU. He underwent 90 minutes daily sessions of 100% O_2 breathing in a multiplace hyperbaric chamber pressured at 2.5 absolute atmosphere air for 30 days. Wound care and surgical debridement were also performed. Systemic antibiotics were given empirically until blood and tissue culture results were obtained. After cultures indicated that there was no evidence of infection, antibiotics were discontinued. The ulcer resolved almost completely within 35 days (**Fig. 2**). Phlebotomy was performed to control erythrocytosis due to polycythemia vera. Since extreme thrombocytosis developed, the treatment was continued with anegrelide. No ulcer episode was observed after treatment with anegrelide during follow-up period.

Discussion

The mechanisms underlying the pathogenesis of the HU associated leg ulcer are not clearly defined. Defective DNA repair mechanisms and cytotoxicity may be responsible for the leg ulcer. Keratinocytes having high proliferation rates are the most sensitive cell type in the skin to be damaged due to cytotoxic agents [1]. Some authors argued that pathogenesis of HU associated leg ulcers are related to ischemia due to intravascular thrombosis [9]. It has been speculated that HU may induce procoagulation in the malleolar vessels and cause cutaneous atrophy. Velez et al. [10] also considered macroerythrocytosis as a pathogenic factor and hypothesized that the circulating red cell survival coincides with the duration required for healing after HU withdrawal. The megaloblastic changes of the erythrocytes due to HU may prohibit these cells from easily traversing the capillaries. This may impair blood flow in the microcirculation and cause relative ischemia in the basal layer of the skin, which requires more oxygen for proliferation. Engstrom et al. [11] reported that HU causes changes in red cell geometry and deformability, and may impair blood flow in the microcirculation. Another possible factor leading to risk for leg ulcer is hyperviscosity associated with blood dyscrasia in polycythemia vera [1].

The presence of coexisting disease, like diabetes in our case, makes the differential diagnosis of HU associated ulcer more difficult. The most frequent location of HU associated ulcers on lower extremities and especially near the malleoli suggests that trauma may be an initiating factor. Best et al. [2] reported that of the 18 ulcers in 14 patients, 10 (55.6%) were over the medial malleolus and 8 (44.4) were over the lateral malleolus.

Collagen synthesis by fibroblasts is critical in the healing of soft tissue wounds. It is dependent on efficient oxygen supply. Hyperbaric oxygen stimulates fibroblast proliferation and differentiation, increases collagen formation and cross-linking, augments neovascularization, and ameliorates leukocyte functions [8]. Hyperoxia can trigger the onset of signal transduction pathways regulating the gene expression of growth factors. Oxygen has direct activity against anaerobic organisms and can enhance microbiocidal capacity of endogenous defense mechanisms. Other possible beneficial effects of hyperbaric oxygen are improved preservation of energy metabolism and reduction of edema [7,8]. Controlled clinical trials suggest that hyperbaric oxygen treatment is associated with improvement outcomes when used as an adjunctive treatment for diabetic foot ulcers [7,12]. It has been reported that hyperbaric oxygen treatment reduces the incidence of major amputation in diabetic patients with gangrenous foot [13]. In a randomized prospective study, Kessler et al. [14] documented that hyperbaric oxygen, in addition to standard multidisciplinary management, doubles the mean healing rate of nonischemic foot ulcers in selected diabetic patients. The long-term follow-up study results of Kalani et al. [15] indicate that hyperbaric oxygen therapy accelerates the rate of healing, and reduces the need for amputation.

Healing times can be predicted in various types of wounds such as neuropathic diabetic foot ulcers [16]. HU associated leg ulcers usually resolve after cessation of the drug. Montefusco et al. [17] found complete resolution in 14 patients and marked improvement in 3 patients after discontinuation of HU in their study including 17 patients with HU associated leg ulcer. Best et al. [2] reported that the leg ulcers completely resolved in 12 patients of 14 after cessation of HU. The mean healing duration of the HU associated leg ulcers was reported as 4.3 months in the study of Montefesco et al. [17]. Sirieix et al. [1] reported that 80% of patients recovered completely after discontinuation of HU in a mean duration of 3 months (range: 1–24 months). The shorter duration of healing in our patient (35 days) compared to mean values from both studies suggest that hyperbaric oxygen treatment may have beneficial effects in the management of HU associated leg ulcers.

In conclusion, we suggest that meticulous wound care and antibiotics are not enough for the resolution of the HU associated leg ulcer. Discontinuation of HU is essential. Hyperbaric oxygen treatment may be beneficial to accelerate wound healing. Further studies are required to determine clinical benefit of hyperbaric oxygen treatment in the treatment of HU associated leg ulcers.

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