

## Hydroxyurea induced leg ulcer treated with HBOT



### Medical Science

**KEYWORDS:** Hyperbaric Oxygen Therapy; Non-Healing Ulcer; Hydroxy Urea; Polycythemia Vera.

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### INTRODUCTION

HBOT is used as adjunctive therapy for non-healing ulcer (NHU). It is an accepted indication for problem wounds by UHMS (Undersea hyperbaric medical society) [1]. Polycythemia Vera is a stem cell disorder characterized as a pan hyperplastic, malignant and neoplastic marrow disorder. It's most prominent feature is an elevated absolute red blood cells mass because of uncontrolled red cell production [2]. 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 [3]. Leg ulcers due to HU are seen less frequently and are commonly located near the malleoli, are painful, and usually resolve after cessation of the drug [4]. We report a case of leg ulcer associated with HU treatment for polycythemia vera who was treated with adjunctive hyperbaric oxygen at an Armed Forces tertiary care centre.

### CASE REPORT

A 63 years old lady known case of primary hypothyroidism and hypertension since 15 years on medication was incidentally diagnosed as a case of Polycythemia Vera 9 years back based on routine blood investigation and thereafter was started on regular treatment with hydroxyurea (HU). Her blood cell count was controlled by total daily dose of 1.5g of HU.

She reported to our centre three months ago with pain, erythema and ulceration over the right ankle. It started as a pin hole wound on the lateral aspect of right ankle and gradually progressed to a non-healing ulcer over 12 weeks. She complained of burning and throbbing pain at the ulcer site. There was no history of trauma. She was given standard treatment of wound care which did not result in any improvement.

Physical examination revealed a 4cmx3cmx1cm irregular ulcer over the lateral aspect of right ankle just below the lateral malleolus. The ulcer had sloping edges and the base was filled with thick slough with minimal discharge along with swelling of right ankle. The dorsalis pedis and posterior tibial pulses were felt normal and 2D color doppler did not reveal any vascular insufficiency. A plain radiograph of the leg showed no evidence of osteomyelitis. Blood examination was unremarkable except increased MCV (Table 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, acantholysis and granulomatous changes in the dermis consisting of proliferation of capillaries, fibroplasia and fat necrosis. It did not reveal evidence of vasculitis or malignancy. Culture of wound swab revealed gram positive cocci in pairs and clusters.

Parameter	Results
RBC Count	3.26 X 10 <sup>12</sup> Cells/L
Hb	13.2 g/dL
MCV	114.7 fL
MCH	40.3 pg
MCHC	35.3%
RDW	14.5%
WBC	10.29 X 10 <sup>9</sup> Cells/L
DLC	N78 L12 M08 E02
Platelets	357 X 10 <sup>9</sup> /L

**Table 1: Result of Hematological investigations**

The patient was started on HBOT at a pressure 2.4 ATA (atmospheres absolute) for 90 minutes six days a week in a multiplace chamber. Debridement of the wound was done initially and thereafter wound care and systematic antibiotics were continued by the primary treating surgeon. Hydroxyurea treatment was discontinued when considered as the etiological factor of leg ulcer in the patient and anagrelide was started instead. Phlebotomy was performed to control erythrocytosis due to polycythemia vera. Treatment was continued with alternative anagrelide.

Within 15 days of commencement of HBOT, gross reduction in the slough and pus in the wound was observed along with ingrowth of healing tissue from the ulcer margins. By 25 days of HBOT, the ulcer size had reduced to half the original size and healthy granulation tissue was observed in the ulcer base. Skin grafting was done at this time, uptake of which was satisfactory. HBOT was stopped at the end of 30 sittings.

### DISCUSSION

The mechanisms underlying the pathogenesis of the HU associated leg ulcer are not clearly defined. It is said that defective DNA repair mechanisms and cytotoxicity are 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 [3]. In addition, the pathogenesis of HU associated leg ulcers are related to ischemia due to intravascular thrombosis [7]. It has been observed that HU may induce pro-coagulation in the malleolar vessels and cause cutaneous atrophy. Velez et al [8] also considered macro-erythrocytosis 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 impairs 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 [9] 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 [3]. The most frequent location of HU associated ulcers are on the lower extremities, especially near the malleoli which would probably suggest that trauma may also be an initiating etiological factor. Best et al [4] 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 [6]. 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 microbicidal capacity of endogenous defense mechanisms. Other possible beneficial effects of hyperbaric oxygen are improved preservation of energy metabolism and reduction of edema [5, 6]. The long-term follow-up study results of Kalani et al [10] indicate that hyperbaric oxygen therapy accelerates the rate of healing, and reduces the need for amputation.

HBOT has been recognized as an adjunctive treatment for large number of problem wounds including diabetic wounds, vascular insufficiency ulcers, infected wounds, traumatic wounds, crush injuries, compromised skin grafts, thermal burns as well as radiation induced wounds [1]. In our case being reported, we managed HU-induced ulcer in the case of polycythemia vera which responded well to adjunctive HBOT.

## CONCLUSION

On the basis of our case report, we conclude that meticulous wound care and antibiotics may not be enough for the resolution of HU associated leg ulcer. Discontinuation of HU is essential and additional adjunctive hyperbaric oxygen therapy is likely to be beneficial for HU associated leg ulcers.

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