Reversible Leg Ulcer due to Hydroxyurea in a Case of Chronic Myeloid Leukemia

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Abstract
The cutaneous side effects of hydroxyurea are lesser known complication of long term hydroxyurea therapy in myeloproliferative disorders. We report a non-diabetic patient, who developed hydroxyurea dermopathy (leg ulcers) during long-term treatment with hydroxyurea for chronic myeloid leukemia (CML). The time course of the development of ulcers and its healing suggests that these resulted from the direct toxicity of hydroxyurea. We aim to increase clinical awareness of this problem.

INTRODUCTION
Hydroxyurea is a hydroxylated derivative of urea which is recognized as an effective antineoplastic drug. It inhibits cellular DNA synthesis and promotes cell death in the S-phase of cell cycle through its action on enzyme ribonucleotide reductase. Its effect on actively proliferating epithelial and epidermal cells are fairly common and include hyperpigmentation, scaling erythema, partial alopecia and desquamation of face and hands. Our patient presents as an extremely instructive case in view of extensive and debilitating leg ulceration that developed secondary to hydroxyurea therapy.

CASE REPORT
Patient RP 29 years male, non-smoker visited Leukemia Clinic on May 1999 with complaints of weight loss, pain in abdomen and weakness for two months. On examination, patient had pallor, splenomegaly of about 10 centimeter and mild hepatomegaly. There was no lymphadenopathy and respiratory, CVS and CNS examination was normal. There was no past history of diabetes mellitus, hypertension, tuberculosis or syphilis. There was no history suggestive of drug hypersensitivity, autoimmune disorder or peripheral vascular disease. On investigation, he had hemoglobin (Hb) of 7.5 mg/dl; total leukocyte count of 38,000/cu mm. Peripheral blood revealed neutrophils 81%; lymphocytes 10%, basophils 2%, metamyelocytes 2%, myelocytes 1%, promyelocytes 3% and blasts 1%. The bone marrow findings were suggestive of chronic myeloid leukemia (chronic phase). Cytogenetically patient was Philadelphia chromosome positive.

Patient was put on hydroxyurea therapy (1.0-1.5 gram per day) and hematinics. He was under regular follow up and the hydroxyurea dosages were adjusted according to the total leukocyte count (TLC).

Patient was asymptomatic on the therapy for two years. Since May 2001, he needed larger dosage of hydroxyurea (1.5-2.0 gram per day) to achieve clinico-hematological control. In June 2001, he developed a painful ulcer over lateral malleolus of left foot with purulent discharge (Fig. 1). Ulcer was single, circular in shape with irregular crescentic border. There was black discoloration of the skin in the surrounding area. Skin around ulcer was normal in temperature. There was no bleeding from the ulcer, varicosities involving the limb or evidence of stasis dermatitis. Peripheral pulses like posterior tibial artery and dorsalis pedis artery were normally palpable. Patient was managed with antibiotics (Ciprofloxacin+Tinidazole) along with local antiseptic dressing. The total leukocyte count was 37,000/cu mm. Other, investigations demonstrated Hb as 10.0 gm%, RBS 102 mg/dl, B. urea 20 mg/dl, S. creatinine 0.8 mg/dl, S. LDH 156 IU/L, S. protein 7.2 gm/dl, S. albumin 4.0 gm/dl. APTT was comparable with the control. ANA, antiphospholipid antibody and VDRL test were found negative. Hydroxyurea was continued as 1.5-2.0 gram daily. The ulcer did not heal. Subsequently the patient was advised biopsy of the ulcer. Biopsy did not reveal any evidence of malignant infiltration. Hydroxyurea was continued in lower dosages.

In September 2001, he came with complaint of ulcer of the same nature on his right foot along with swelling and difficulty in walking. Total leukocyte count became much higher than in the previous month. He was advised culture for the growth of microorganisms in the discharge from ulcer region. The culture did not reveal growth of any microorganism. X-ray of the involved area showed no bony abnormality. In view of
the possibility of hydroxyurea induced ulcer, former was substituted by busulphan. Ulcers progressively healed following the cessation of hydroxyurea within 6-8 weeks (Fig. 2). The total leukocyte count was controlled on busulphan. During follow-up, he developed myeloid blast crises and died.

**DISCUSSION**

Hydroxyurea is commonly used in the treatment of various types of hematological disorders. The drug inhibits the cellular DNA synthesis and promotes cell death in the S phase of the cell cycle. Dermatological side effects of hydroxyurea are fairly common which include brown discoloration, hyperpigmentation, scaling of nails, stomatitis, erythema, desquamation of face and hands and partial alopecia. A rare complication is leg ulceration. Pathogenesis is currently unknown and seems to be multifactorial. Concomitant arterial or venous disease may play a contributing role in the development of these types of ulcers. Hence differentiation between disease-related and hydroxyurea treatment-induced leg ulcer may not always be possible. Doaud et al suggested that cessation of therapy was necessary for healing or improvement of the lesion. It is thought that hydroxyurea, an antineoplastic agent with selective cytotoxicity for cells that divide most actively (such as those of the skin) causes these ulcerations through impairment of normal wound healing in areas of common trauma. The ulcer is thought to result from the cumulative toxicity of hydroxyurea on basal layer of epidermis due to inhibition of DNA synthesis. This is supported by the auto radiographic study, which revealed large areas of absent epidermal uptake of titrated thymidine.

Most patients who develop leg ulcers received over 1 gram of hydroxyurea per day for at least one year. Treatment is difficult and usually requires cessation of hydroxyurea therapy.

We present this case to highlight the potential cutaneous side effects of hydroxyurea therapy and to increase clinical awareness of the problem.

**REFERENCES**