

## HYDROXYUREA INDUCED LEG ULCER IN A PATIENT OF CHRONIC MYELOID LEUKEMIA-A CASE REPORT

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**Abstract :** Dermatological side effects of long term hydroxyurea therapy used for chronic myeloid leukemia (CML) are not uncommon. But the development of leg ulcers is very rarely reported with its prolonged use. A 55 years old nondiabetic, non smoker male patient on long term use of hydroxyurea for the management of CML, who developed leg ulcer as complication, is being reported here for its rarity.

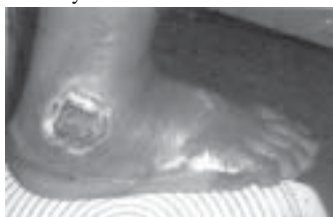
### INTRODUCTION

Hydroxyurea is a hydroxylated derivative of urea which is recognised 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<sup>1</sup>. The common cutaneous side effects of hydroxyurea include hyperpigmentation, scaling, erythema and partial alopecia etc.<sup>2</sup> But the development of leg ulcers is a rare complication<sup>3</sup>. A patient of chronic myeloid leukemia who developed leg ulceration secondary to hydroxyurea therapy is being presented here.

### CASE REPORT

A 55 years old male-non smoker and non-diabetic-presented with the complaints of weight loss, pain abdomen, lump in the abdomen and weakness for three months. On examination, he had pallor, massive splenomegaly of 14 cms, palpable below left costal margin and mild hepatomegaly. There was no lymphadenopathy. Examination of CVS, CNS and respiratory systems were normal. There was no past history of diabetes, hypertension, tuberculosis or syphilis. There was no history suggestive of drug hypersensitivity, autoimmune disorder or peripheral vascular diseases. His laboratory profile included Hb 9.8 gm/dl, TLC 105000/mm<sup>3</sup>, platelets 290000/mm<sup>3</sup>, ESR 90 mm at the end of first hour, FBS 90 mg/dl serum uric acid 6.2 mg/dl, Serum LDH 150 IU/L. Peripheral blood film examination revealed neutrophils 78%, lymphocytes 12%, basophils 2%, myelocytes 1%, metamyelocytes 2%, promyelocytes 3% and blasts 3%. The bone marrow was hypercellular with myeloid hyperplasia and 2% blasts. APTT was comparable with the control. ANA, antiphospholipid antibody and VDRL tests were negative. Liver and renal profile were normal. Cytogenetically he was Philadelphia chromosome positive. He was diagnosed to be a case of CML and put on hydroxyurea orally 1.5 g/day in divided doses along with hematinics. He was under regular follow up and doses of hydroxyurea were adjusted according to the WBC count.

Patient remained asymptomatic with this treatment for two and half years. Then he developed painful ulcer over right lateral malleolus with purulent discharge along with swelling of right lower leg (photograph). He was unable to walk. The ulcer was single, circular in shape with irregular crescentic border. There was black discoloration and extensive desquamation of the skin in the surrounding area. The skin around ulcer had normal temperature. There was no bleeding from the ulcer, varicosities involving the limb or evidence of stasis dermatitis. Peripheral pulses like posterior tibial and dorsalis pedis arteries were normally palpable. Biopsy of ulcer was negative for malignant infiltration. Patient was put on antibiotics and local dressing of wound. Culture from the wound did not reveal growth of any organism. X-ray of involved area did not show any abnormality.



Hydroxyurea was continued in the lower doses for 6 weeks but ulcer did not heal. Subsequently hydroxyurea was replaced by tablet Busulfan 4 mg orally daily and ulcer started healing progressively following the cessation of hydroxyurea within 8 weeks and patients improved symptomatically as well. The total leucocyte count was controlled on Busulfan. But he was lost on follow up.

### DISCUSSION

Hydroxyurea is commonly used in the treatment of various types of hematological disorders. Dermatological side effects of hydroxyurea include diffuse hyperpigmentation, brown discoloration, acral erythema, scaling of nails, stomatitis, erythema and partial alopecia<sup>4</sup>. A rare complication of leg ulceration was described by Montefusco et al<sup>3</sup>, subsequently Nguyen reported four cases<sup>4</sup> and Beast et al<sup>5</sup> reported fourteen cases. All of them improved after cessation of offending drug. No consistent correlation between the dose or duration of hydroxyurea therapy and occurrence of ulcers has been reported<sup>6</sup>. The mechanism of action of hydroxyurea is inhibition of cellular DNA synthesis leading to cell death in the S phase of the cell cycle. Damage also occur from free radical nitroxide intermediates and inhibition of DNA repair<sup>1</sup>. Basal keratinocytes are the most actively replicating cells of the epidermis and damage to keratinocyte by cytotoxic drugs is common. Epidermis atrophy may result from damage to basal keratinocyte<sup>7</sup>. Hydroxyurea induced leg ulcers could be due to impairment of normal wound healing in areas of common trauma resulting in non production of normal epidermis, stromal cells or epithelium<sup>8</sup>. Another mechanism of ulcer development may be cumulative toxicity of hydroxyurea on basal layer of epidermis due to inhibition of DNA synthesis<sup>1</sup>. This is supported by the autoradiographic study, which revealed large areas of absent epidermal uptake of titrated thymidine<sup>9</sup>. Most patients who developed leg ulcers received over 1 gram of hydroxyurea per day for atleast one year. But our patient remained asymptomatic till two and half years after which he developed leg ulceration. few cases of reversible hydroxyurea induced leg ulcers in patients of CML have been reported in the Indian literature<sup>10</sup> from various parts of the country. Probably this is the first case report from this part of the country to the best of our knowledge. Hence the case report.

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