Hydroxyurea-Induced Cutaneous Ulcers in a Sickle Cell Disease Patient

Dear Editor,

Hydroxyurea (HU), an oral antineoplastic drug, is commonly used in the treatment of various hematologic disorders such as chronic myelogenous leukemia (CML), polycythemia vera, and sickle cell disease (SCD). It is usually well tolerated; however, long-term administration of HU has been associated with cutaneous side effects such as alopecia, diffuse hyperpigmentation, erythema, skin atrophy, and nail changes.[1] Here, we report a rare case of cutaneous ulceration in a patient of SCD following prolonged administration of HU.

A 21-year-old, non-smoking male presented with three painful, shallow ulcers over the lower part of the left leg and dorsum of the right foot for three months. He was a known case of SCD and was on HU 1 g/day for 2 years. There was no history of any vaso-occlusive event or trauma prior to the development of ulcers. Clinical examination revealed presence of one ulcer of size 3 × 1 cm over the dorsum of the right foot and two well-defined ulcers of size 1 × 1 cm, one over the lower left leg and other over the left lateral malleolus [Figure 1a and b]. Ulcers were tender on palpation, and serous discharge was present on the floor of the ulcer, along with hyperpigmentation of the surrounding skin. There was no evidence of peripheral neuropathy or varicose veins in both legs, and lower limb pulsations were well felt. Complete blood count revealed mild anemia, and other routine investigations including bacterial gram staining and culture, viral markers such as HIV, HBsAg, and anti-HCV antibodies were negative. Initially, local wound care and dressing were advised, but that failed to heal the ulcers, so a possibility of HU-induced cutaneous ulceration was considered and the drug was discontinued. All ulcers healed promptly within 6 weeks without any other intervention and with no appearance of any new ulcer [Figure 2a and b].

HU is a cytostatic drug, widely used in chronic myeloproliferative disorders and is the only US food and drug administration–approved oral drug for the treatment of SCD.[2] HU is an inhibitor of DNA replication. The activity of HU is most prominent in the S-phase of the cell cycle, where it prevents the synthesis of daughter strands of DNA by blocking ribonucleotide reductase, and, as a result, causes cell cycle arrest.[3] Stahl and Silber were the first to report HU-related skin ulcers in 1985. Leg ulcers represent up to 30% of all dermatologically relevant adverse events in HU treatment reported worldwide.[4,5]

The pathomechanism of the genesis of HU-induced cutaneous ulcers remains poorly understood, and seems to be multifactorial. HU can cause cumulative toxicity on the basal layer of the epidermis via inhibition of DNA synthesis. It has been postulated that ulcers may be the result of leukocytoclastic vasculitis or arterial microthrombi related to platelet dysregulation.[5] A recent study has revealed that HU can lead to increases in red blood cell volume and a reduction in red blood cell susceptibility to deformation. Therefore, it may cause impaired microcirculation and cutaneous anoxia, which then lead to ulcerative skin lesions, and severe pain.[8]

The treatment of choice for hydroxyurea-induced leg ulcers is discontinuation of the drug. The healing of hydroxyurea-induced leg ulcers have been described as slow (1-9 months) but spontaneous in 85% of patients after discontinuation of hydroxyurea therapy.[6] Other options for therapy include topical application of granulocyte macrophage colony-stimulating factor (GM-CSF), recombinant human erythropoietin, apligraft, prostaglandin E1, and pentoxifylline.[7,8] A case report of a successful treatment with hyperbaric oxygen has also been reported.[9]

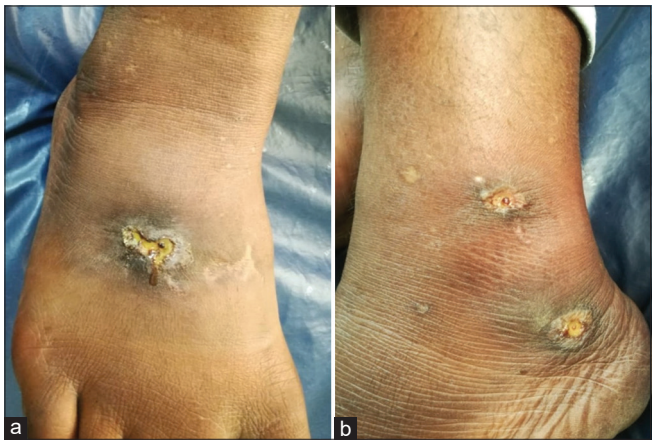

Figure 1: (a) An ulcer of size 3 × 1 cm over the dorsum of right foot (b) two well-defined ulcers of size 1 × 1 cm over lower part of left leg and over left lateral malleolus

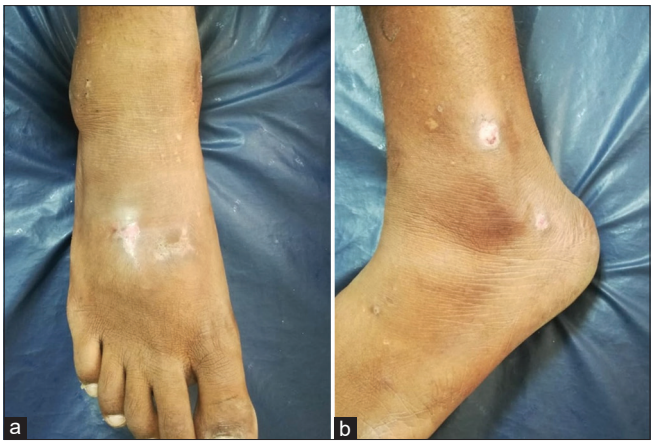

Figure 2: (a) Healed ulcer site over the dorsum of right foot after stopping hydroxyurea (b) over left lower leg and left lateral malleolus

A leg ulcer, which has a complex pathogenesis, has also been recognized as a complication of SCD itself, and medial malleolus is a more commonly involved site than lateral malleolus. Less common sites are the anterior tibial area, dorsum of the foot, and achilles tendon. These SCD-induced ulcerations are associated with advanced SCD vasculopathy.[10]

Our patient had ulceration mainly around the left lateral malleoli and dorsum of the right foot. The patient neither had a history of SCD crisis nor had any signs of vasculopathy clinically. The appearance of ulcers after commencing HU, with failure of these ulcers to respond to local wound care made us suspicious about the possibility of HU-induced ulceration. We also observed improvement in the perilesional hyperpigmentation after stopping the drug, which is suggestive of progressive but reversible cellular damage.

Leg ulceration is one of the adverse effects seen in patients with SCD during HU therapy. The differentiation of HU-induced ulceration from SCD ulceration is often difficult. Advanced topical treatment options mentioned above are not feasible in a resource-poor country like India, and discontinuation of the drug should be considered for optimal healing of ulcers.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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