

Successful treatment of hydroxyurea-associated chronic leg ulcers associated with squamous cell carcinoma

Hydroxyurea (HU) is an anti-neoplastic drug used in the treatment of chronic myeloproliferative neoplasms (MPNs). HU is associated with cutaneous adverse effects, whereas severe complications such as leg ulcers and non-melanoma skin cancers (NMSCs) are rare and only observed after long-term treatment. We herein report a patient with essential thrombocythemia (ET) treated chronically with HU, and who developed refractory bilateral leg ulcers complicated by squamous cell carcinoma (SCC) over both heels. The patient was successfully managed by multiple debridement stages and skin grafting surgeries.

HU is generally used to treat myeloproliferative disorders, particularly essential thrombocythemia (ET) and polycythemia vera (PV).^{1,2} Common cutaneous side effects include xerosis, hyperpigmentation of the skin folds and nails, alopecia, scaling, skin atrophy, lichen-planus and dermatomyositis-like eruptions. In addition, rare and more severe cutaneous manifestations, such as non-healing leg ulcers and cutaneous malignancies have been reported in a few studies and case reports.^{3–5} Chronic non-healing ulcers are at increased risk of harboring squamous cell carcinoma (SCC).⁶ Several cases of HU-related cutaneous SCCs have been reported.^{3,7–14} The synergistic action of long-term HU and ultraviolet (UV) light exposures are

strongly implicated in the development of cutaneous SCC.¹⁵ This report demonstrates a successful multidisciplinary management of HU-induced bilateral chronic leg ulcers associated with SCC.

CASE PRESENTATION

A 60-year-old Caucasian woman presented to our clinic for evaluation of thrombocytosis ($900 \times 10^9/L$) that was incidentally discovered after suffering a myocardial infarction. Bone marrow evaluation revealed hypercellularity with increased megakaryocytes. The patient had diploid karyotype, and molecular analysis revealed JAK2 V617F mutation with no BCR-ABL fusion gene. The diagnosis of ET was made based on the World Health Orga-

nization (WHO) 2008 criteria. She was started on low dose aspirin and HU.

In the fifth year of HU treatment, she developed painful erythematous, ulcerated plaques over the plantar aspect of bilateral feet (Fig. 1). HU was discontinued and she was switched to anagrelide. However, she was unable to tolerate it and was shifted to peginterferon α -2a (Pegasys®) with subsequent improvement. Nevertheless, the leg ulcers did not heal completely after HU discontinuation. Three years later, the patient developed painful fleshy erythematous papules within the heel ulcers. A punch biopsy revealed an infiltrating and keratinizing SCC with focal areas of SCC in-situ (Bowen's disease). Bilateral surgical excision revealed



Figure 1. Bilateral cutaneous ulceration over the plantar aspect of the soles after five years of HU therapy.

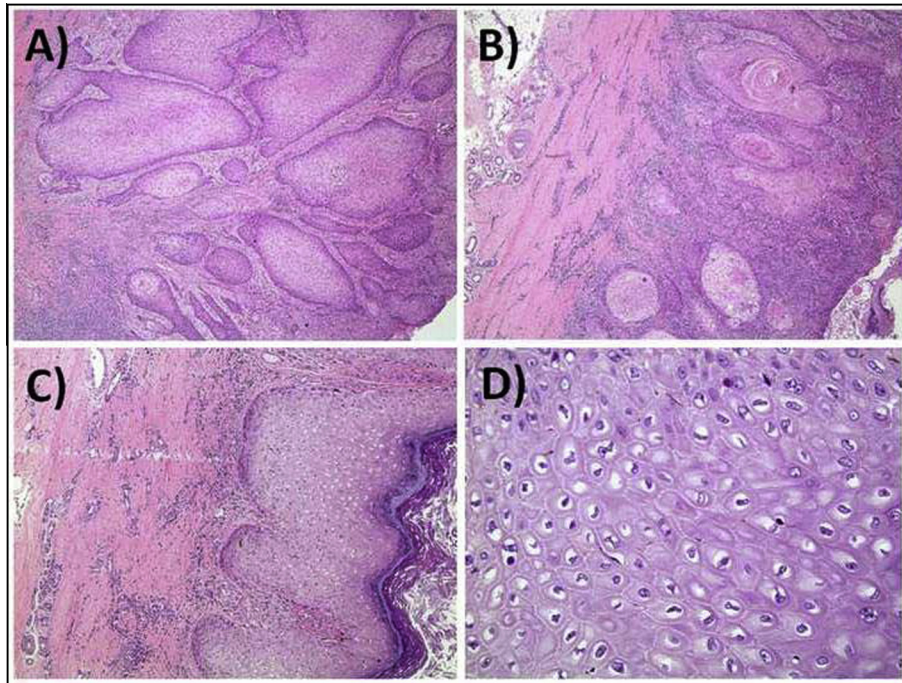


Figure 2. (A and B) Invasive moderately-differentiated keratinizing SCC involving the dermis, with an associated ulcer (mag 40×). (C and D) Areas of SCC in-situ (Bowen's disease) (mag 100× and 400×).



Figure 3. Complete resolution of skin lesions after three surgical debridement and skin grafting surgeries.

the same pathologic changes (Fig. 2). After one surgical debridement and two grafting procedures, the patient had complete resolution of the lesions, and no recurrence with three years of follow-up (Fig. 3).

DISCUSSION

HU is the approved first-line therapy for patients with high risk ET and PV.^{1,2,16} Only ten case reports

in the literature illustrate an association between long-term HU therapy and SCC in Ph-negative MPNs patients (Table 1). Among them, only one case described a chronic leg ulcer with malignant degeneration into SCC.¹¹

Discontinuation of HU is the cornerstone of treatment of HU-related ulcers. Dermatologic examination should be emphasized during long-term HU therapy. This report highlights the importance

of repeated skin ulcer biopsies in patients on HU, especially if the ulcers persist despite HU discontinuation. This early intervention is crucial for the early diagnosis of skin cancer and for prompt management. Furthermore, any diagnosed skin cancer should be addressed by a multidisciplinary team approach.

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