letter to editor

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

Hydroxyurea (HU) is an antineoplastic 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 (900×10^9/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 Organization (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

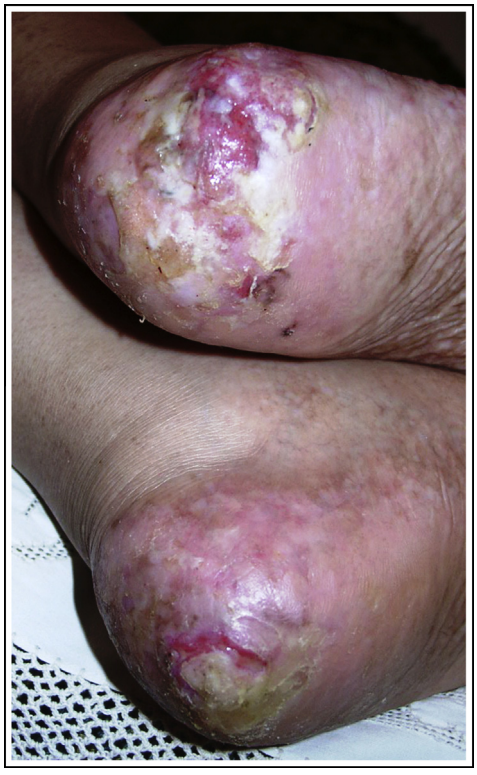

Figure 1. Bilateral cutaneous ulceration over the plantar aspect of the soles after five years of HU therapy.

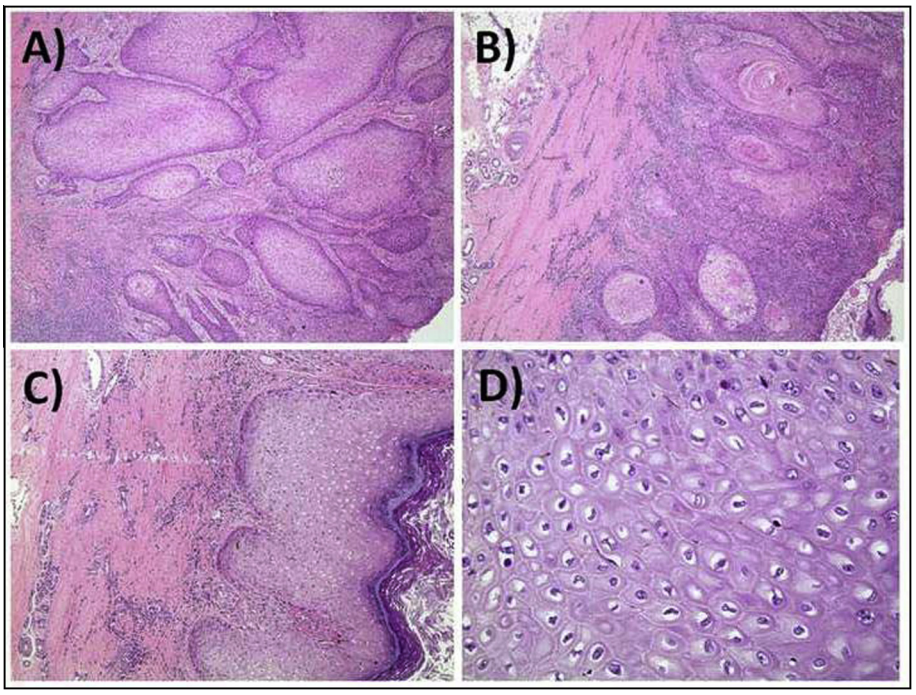

Figure 2. (A and B) Invasive moderately-differentiated keratinizing SCC involving the dermis, with an associated ulcer (mag 40×). (C and D) Areas of SCC in-situ (Bowen's disease) (mag 100× and 400×).

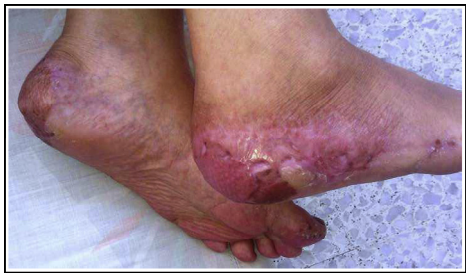

Figure 3. Complete resolution of skin lesions after three surgical debridement and skin grafting surgeries.

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.

Table 1. Hydroxyurea related skin squamous cell carcinoma in Ph-negative MPNs patients.

Authors	No. of cases	Disease	Age/sex	HU dose	HU duration	Description of skin SCC	Other HU related toxicity	Treatment	Outcome
Saraceno et al.[7]	1	PMF	81/M	1 g/d	6 months	Multiple face and extremities skin SCC	– Actinic keratoses – Keratoacanthomas – Nail changes	– Imiquimod cream 5% – HU was not stopped	– CR of skin SCC – Nail unchanged – New skin lesions
Hoff et al.[8]	1	PV	86/F	*n*/a	8 years	SCC in the lower leg	– Actinic keratoses – Painful ulcers	– HU was stopped – Cryotherapy for keratoses – Excision for SCC	– CR of skin SCC and actinic keratoses
Schleubinger et al.[9]	1	ET	80/F	750 mg/d	13 years	Multiple SCC of the face	– Multiple large – Hyperkeratoses	*n*/a	n/a
Zaccaria et al.[10]	1	ET	73/M	1 g/d	12 years	Five SCC of the face	– Dermatomyositis-like eruption together with a leg ulceration – Poikilodermatouskeratotic lesions	– HU was stopped – Excision of face SCC – Busulfan 8 mg/day	– Resolution of all skin lesions after 3 month of HU withdrawal
Stone et al.[11]	1	PV	62/F	*n*/a	9 years	Left heel SCC on top of non healing ulcer	– Non healing ulcer of the left heel – Face basal cell carcinoma	– HU was stopped – Multiple surgical debridement	Complete healing of the wound after multidisciplinary treatment
Callot-Mellot et al.[3]	2	1-ET 2-PV	1–64/M 2–69/F	Cumulative doses between 650 and 3600 g	1–5.5 years 2–8.5 years	1–3 skin SCC 2- In situ SCC on dorsal face of a finger	1- Xerosis, melanonychia, actinic keratosis. 2- Hyperpigmentation, keratoderma, erythema, actinic keratosis	1- Surgical excision and discontinuation of HU 2- Surgical excision without discontinuation of HU	1- No recurrence after 3 years follow up 2- No recurrence
Salmon-Ehr et al.[12]	1	PV	73/M	*n*/a	10 years	One ear SCC	Multiple actinic keratosis	HU was stopped Surgical excision Busulfan was introduced	– No recurrence Clearance of actinic – Keratosis 14 months after HU discontinuation
Best and Pettit et al.[13]	1	ET	59/F	*n*/a	8 years	4 face SCC	Multiple actinic keratosisLichen planus like lesionsMultiple basal cell carcinoma	HU was stopped Anagrelide was introduced	Improvement after HU discontinuation
Esteve et al.[14]	1	PV	83/F	1 g/day	13 years	7 skin SCC	– Oral SCC – Xerosis – Atrophic erythematous lesions and ulcers on hands	HU was stopped	New SCC despite HU discontinuation

PMF, primary myelofibrosis; SCC, squamous cell carcinoma; ET, essential thrombocythemia; PV, polycythemia vera; CR, complete remission; HU, hydroxyurea.

CONFLICT OF INTEREST

None.

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REFERENCES

1. Cortelazzo S, Finazzi G, Ruggeri M, Vestri O, Galli M, Rodeghiero F, et al.. Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. N Engl J Med 1995;332(17):1132–6.
2. Najean Y, Rain JD. Treatment of polycythemia vera: the use of hydroxyurea and pipobroman in 292 patients under the age of 65 years. Blood 1997;90(9):3370–7.
3. Callot-Mellot C, Bodemer C, Chosidow O, Frances C, Azgui Z, Varet B, et al.. Cutaneous carcinoma during long-term hydroxyurea therapy: a report of 5 cases. Arch Dermatol 1996;132(11):1395–7.
4. Salmon-Ehr V, Leborgne G, Vilque JP, Potron G, Bernard P. Secondary cutaneous effects of hydroxyurea: prospective study of 26 patients from a dermatologic consultation. Rev Med Internet 2000;21(1):30–4 Article in French.
5. Antonioli E, Guglielmelli P, Pieri L, Finazzi M, Rumi E, Martinelli V, et al.. Hydroxyurea-related toxicity in 3411 patients with Ph'-negative MPN. Am J Hematol 2012;87(5):552–4.
6. Baldursson BT, Hedblad MA, Beitner H, Lindelöf B. Squamous cell carcinoma complicating chronic venous leg ulceration: a study of the histopathology, course and survival in patients. Br J Dermatol 1999;140(6):1148–52.
7. Saraceno R, Teoli M, Chimenti S. Hydroxyurea associated with concomitant occurrence of diffuse longitudinal melanonychia and multiple squamous cell carcinomas in an elderly subject. Clin Ther 2008;30(7):1324–9.
8. Hoff NP, Akanay-Diesel S, Pippirs U, Schulte KW, Hanneken S. Cutaneous side effects of hydroxyurea treatment for polycythemia vera. Hautarzt 2009;60(10):783–7 Article in German.
9. Schleussinger TM, Dyall-Smith D, Field LM. Hydroxyurea-associated squamous dysplasia in a monozygotic twin. J Am Acad Dermatol 2011;65(3):679–80.
10. Zaccaria E, Cozzani E, Parodi A. Secondary cutaneous effects of hydroxyurea: possible pathogenetic mechanisms. J Dermatolog Treat 2006;17(3):176–8.
11. Stone T, Berger A, Blumberg S, O'Neill D, Ross F, McMeeking A, et al.. A multidisciplinary team approach to hydroxyurea-associated chronic wound with squamous cell carcinoma. Int Wound J 2012;9(3):324–9.
12. Salmon-Ehr V, Grosieux C, Potron G, Kalis B. Multiple actinic keratosis and skin tumors secondary to hydroxyurea treatment. Dermatology 1998;196(2):274.
13. Best PJ, Petitt RM. Multiple skin cancers associated with hydroxyurea therapy. Mayo Clin Proc 1998;73(10):961–3.
14. Estève E, Georgescu V, Heitzmann P, Martin L. Multiple skin and mouth squamous cell carcinomas related to long-term treatment with hydroxyurea. Ann Dermatol Venereol 2001;128(8–9):919–21 Article in French.
15. Kalajian AH, Cely SJ, Malone JC, Burruss JB, Callen JP. Hydroxyurea-associated dermatomyositis-like eruption demonstrating abnormal epidermal p53 expression: a potential premalignant manifestation of chronic hydroxyurea and UV radiation exposure. Arch Dermatol 2010;146(3):305–10.
16. Harrison CN, Campbell PJ, Buck G, Wheatley K, East CL, Bareford D, et al.. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. N Engl J Med 2005;353(1):33–45.