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Hydroxyurea-induced cutaneous squamous cell carcinoma: A case report

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Abstract

BACKGROUND

Hydroxyurea (HU) is a non-alkylating antineoplastic agent that is active in the S-phase of the cell cycle and inhibits the enzyme ribonucleoside reductase. HU is currently used to treat leukemia, sickle cell anemia, psoriasis, and chronic myeloproliferative disorders. Although HU is easy to use and effective and has high tolerance, there have been numerous reports of cutaneous complications during long-term therapy with HU.

CASE SUMMARY

We report a 67-year-old woman on long-term HU therapy for primary myelofibrosis who developed concurrent skin lesions during treatment. The first skin lesion appeared on the dorsum of her right hand in 2015. Despite continuous use of HU, her cutaneous changes were neglected. Approximately 3 years ago, she had multiple nodular and keratotic lesions on both hands with sharp margins, branny desquamation, and dotted hyperpigmentation. Furthermore, she developed acutely numerous ulcerative lesions on her hands and legs. Topical wound therapy with dressing changes and parenteral antibiotics was applied for management of the lesions. Most of the wounds healed after HU withdrawal. Lesions on both hands were replaced by scabs. Nevertheless, the wound on her left ankle reached 9 cm × 7 cm in size in January 2018. Pathology confirmed well-differentiated squamous cell carcinoma at the ulcer area. In addition, her left foot was severely affected and radical surgery with a below-the-knee amputation was suggested followed by preventive right groin nodal dissection.

CONCLUSION

In patients receiving continuous HU therapy, close dermatologic follow-up is critical for the early diagnosis and selection of appropriate treatment for cutaneous lesions.

Key words: Hydroxyurea; Squamous cell carcinoma; Primary Myelofibrosis; Case report

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Core tip: Long-term hydroxyurea (HU) therapy is a rare cause of cutaneous squamous cell carcinoma (cSCC). To our knowledge, fewer than 20 cases of HU-related cSCC have been reported. Recognizing patterns of HU-associated cSCC is important for surgeons and dermatologists. Moreover, early diagnosis and evaluation are critical for determining optimal treatment regimens. We review the reported cases of cSCC and discuss the pathogenic mechanisms.

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INTRODUCTION

Hydroxyurea (HU) is a non-alkylating antineoplastic agent first synthesized in 1869 by Dressler and Stein. It is currently used to treat leukemia, sickle cell anemia, psoriasis, and chronic myeloproliferative disorders^[1]. Following a large-scale drug screen, it has also been used as an anti-tumor agent for the management of head and neck cancers, malignant melanoma, and brain tumors. Moreover, HU is listed as an “essential medicine” by the World Health Organization^[2].

HU is a well-established inhibitor of DNA synthesis. It is mainly active in the S-phase of the cell cycle by suppressing ribonucleoside reductase, which plays a vital role in catalyzing the synthesis of deoxyribonucleotides from ribonucleotides^[1]. Inactivation of ribonucleoside reductase can slow the movement of DNA polymerase at replication forks and decreases deoxyribonucleotide triphosphate levels^[3]. Hence, HU depletes intracellular deoxynucleotide pools, which leads to impairment of DNA synthesis and repair.

There have been numerous reports of cutaneous complications during long-term maintenance therapy with HU. Common cutaneous side effects include hyperpigmentation, xerosis, alopecia, atrophy of the skin, nail changes, facial and acral erythema, palmar or plantar keratoderma, and leg ulcers^[4]. However, to date, fewer than 20 cases of HU-related cutaneous squamous cell carcinoma (cSCC) have been reported. Early diagnosis and evaluation are critical for determining optimal treatment regimens. Herein, we describe an additional case of cSCC associated with long-term HU therapy.

CASE PRESENTATION

Chief complaints

A 67-year-old Asian woman with a history of primary myelofibrosis presented with a painful non-healing chronic ulcer on her left ankle of 2 years duration.

History of present illness

The patient had primary myelofibrosis for 20 years and was initially treated with HU at a dose of 1 g/d.

History of past illness

Appendectomy was performed 10 years ago.

Personal and family history

The patient had no significant family history.

Physical examination upon admission

There was extensive photodamage and atrophy on the dorsal hands. The lesions on the hands consisted of multiple scabs, the largest scab on the right hand measured 1 cm × 2 cm (Figure 1). The irregularly shaped ulcer on the left ankle was 9 cm × 7 cm in size with an ill-defined margin (Figure 2).

Laboratory diagnosis



Figure 1 Skin lesions on both hands.

Laboratory investigations showed that the patient had marked leukocytosis ($84.5 \times 10^9/\text{L}$), a raised neutrophil count ($60.8 \times 10^9/\text{L}$) and platelet count ($488 \times 10^9/\text{L}$), and a low erythrocyte count ($2.1 \times 10^{12}/\text{L}$).

FINAL DIAGNOSIS

A pathological examination of the surgical specimen revealed a well-differentiated squamous cell carcinoma with evidence of abundant cytoplasmic keratin pearls (Figure 3).

TREATMENT

Although surgeons considered performing resection of cSCC on her left foot and coverage with skin grafts, the operation was deemed too risky due to the high likelihood of failure and incomplete excision. Thus, the patient underwent a successful below-the-knee amputation followed by preventive right groin nodal dissection.

OUTCOME AND FOLLOW-UP

The postoperative course was uneventful with no recurrence after 12 mo of follow-up. Dermatologic changes on both hands secondary to HU therapy were extensively treated.

DISCUSSION

Long-term HU therapy is a rare cause of cSCC. In total, only 18 cases, including our patient, have been reported in the literature (Table 1). Disdier *et al*^[5] first reported a patient with cSCC after HU treatment in 1991. In these reports, four primary diseases (primary myelofibrosis, polycythemia vera, essential thrombocythemia, and chronic myelocytic leukemia) and a wide age range (from 45 to 81 years) were presented. There was no significant sex difference in these cases (10 of 18 cases were men). Lesions were commonly located on the scalp, face, and extremities. Most patients had no history of precursor lesions or skin cancers, which rendered HU as the most likely culprit. Patients with HU-related cSCC typically showed symptoms after a latency period of approximately 2 to 13 years. HU treatment withdrawal, Mohs surgery, multiple debridements, and ablation were usually necessary to heal leg ulcers, but in five cases, the above therapies did not result in wound closure. It is suggested that the skin toxicity of HU is a long-term cumulative process and will persist after drug withdrawal, which could be defined as late toxicity. However, the mechanisms underlying the occurrence of HU-related cSCC are mostly unknown, but two pathogenic mechanisms have been proposed to explain this association.

Ultraviolet (UV) irradiation is most likely the primary factor leading to the development of cSCC. *In vitro*, HU inhibits natural DNA repair in UV-irradiated human skin fibroblasts and directly induces chromosome damage, which further



Figure 2 Skin lesions on left ankle.

interferes with cell replication in the basal layer of the epidermis^[6,7]. *In vivo*, HU transforms free radical nitrogen oxides that may produce high oxidative stress in patients' epithelial tissues and cooperates with UV in DNA damage, peroxidation of membrane lipids, and signal transduction pathway changes^[8]. The synergistic effect of HU and UV radiation provides an ideal environment for the formation of cSCC. In addition, HU can markedly elevate p53 levels in basal layer keratinocytes, which increases the risk of skin cancers^[9]. This pathogenic mechanism could explain the occurrence of cSCC in photoexposed skin.

A chronic wound environment characterized by prolonged inflammation undoubtedly plays another critical role in HU-associated cSCC^[9]. Lower limb ulceration is a significant adverse reaction caused by long-term administration of HU. Several pathogenetic hypotheses (DNA inhibition theory, tarombokinesis, and microcirculation rheology theory) could explain the formation of lower limb ulcers. It is well-known that chronic skin damage, including ulcers, burn sites, and scars, is associated with an increased incidence of skin cancer^[10]. In addition to the case reported here, 11 articles refer to the presence of cSCC on extremities, which are different from the light exposure area. Hence, chronic inflammation may be another main cause of cSCC in these patients.

CONCLUSION

Taken together, these findings indicate that long-term HU administration can lead to the development of cSCC, probably through synergistic effects with UV or chronic inflammation. Hence, patients should be informed of the potential cutaneous toxicities of HU treatment in advance. Closer dermatologic follow-up is advisable, particularly in patients with continuous HU therapy and a long history of sun exposure. Moreover, regular protection against UV rays should be emphasized. When cSCC is identified, HU treatment withdrawal is necessary, and we recommend prompt replacement therapy as required. The skin toxicity of HU is considered late toxicity, and patients should be monitored for many years after HU discontinuation.

Table 1 Hydroxyurea-related cutaneous squamous cell carcinoma

Ref.	Year	Age	Sex	Primary disease	HU dose	Latent period	Pathological distribution	Treatment	Prognosis
Saraceno <i>et al</i> ^[11]	2008	81	Male	PMF	1 g/d	6 mo	Face and extremity	Imiquimod cream 5% HU was not discontinued	CR of cSCC new skin lesions
Wen <i>et al</i> ^[12]	2014	55	Female	PMF	1 g/d	8 yr	Extremity	Imiquimod cream 5% Surgical excision and discontinuation of HU	/
Stone <i>et al</i> ^[9]	2012	62	Female	PV	1 g/d	10 yr	Left heel	Surgical excision and discontinuation of HU	Complete healing of the wound after multidisciplinary treatment
García-Martínez <i>et al</i> ^[13]	2012	67	Male	PV	2 g/d	12 yr	Beside the right ear	Surgical excision and discontinuation of HU	CR of cSCC
Hoff <i>et al</i> ^[14]	2009	68	Female	PV	/	8 yr	Lower legs	Surgical excision and discontinuation of HU	CR of cSCC
Best <i>et al</i> ^[15]	1998	59	Female	ET	/	8 yr	face and right hand	Surgical excision and discontinuation of HU	Improvement after HU discontinuation
Zaccaria <i>et al</i> ^[16]	2006	73	Male	ET	1 g/d	12 yr	face	Surgical excision and discontinuation of HU, Busulfan 8 mg/d	CR of cSCC
Schleußinger <i>et al</i> ^[17]	2011	80	Female	ET	0.75 g/d	13 yr	face	Surgical excision	/
Disdier <i>et al</i> ^[5]	1991	65	Male	CML	1 g/d	2 yr	face, scalp and both hands	Surgical excision and discontinuation of HU, radiotherapy	Continual progress
Best <i>et al</i> ^[15]	1998	50	Female	CML	2.5 g/d	5 yr	face and both hands	Surgical excision and discontinuation of HU	New skin lesions; Died
Stasi <i>et al</i> ^[18]	1992	70	Male	CML	5.5 g/d	4 yr	face, both hands and elbows	Imiquimod cream 5%; Surgical excision and discontinuation of HU	CR of cSCC; New skin lesions
Papi <i>et al</i> ^[19]	1993	70	Male	CML	1 g/d	3 yr	Face	Surgical excision and discontinuation of HU	Continual progress
Angeli-Besson <i>et al</i> ^[20]	1995	67	Male	CML	1 g/d	4 yr	Scalp	Localized electron beam therapy	Died
Aste <i>et al</i> ^[21]	2001	60	Male	CML	0.05-0.1 g/d	/	Face, scalp and back of hands	Surgical excision and discontinuation of HU	Continual progress
Pamuk <i>et al</i> ^[22]	2003	73	Male	CML	10 g/wk	3 yr	Left ear	Surgical excision and discontinuation of HU, radiotherapy	Died

Hao <i>et al</i> ^[23]	2013	45	Male	CML	0.4-0.8 g/d	11 yr	Both hands	Surgical excision and discontinuation of HU	Continual progress
Wang <i>et al</i> ^[24]	2013	66	Female	CML	2-2.5 g/d	5 yr	Left hand	Radiation treatment and discontinuation of HU	PR of cSCC

HU: Hydroxyurea; PMF: Primary myelofibrosis; PV: Polycythemia vera; ET: Essential thrombocythemia; CML: Chronic myelocytic leukemia; CR: Complete remission; PR: Partial response; cSCC: Cutaneous squamous cell carcinoma.

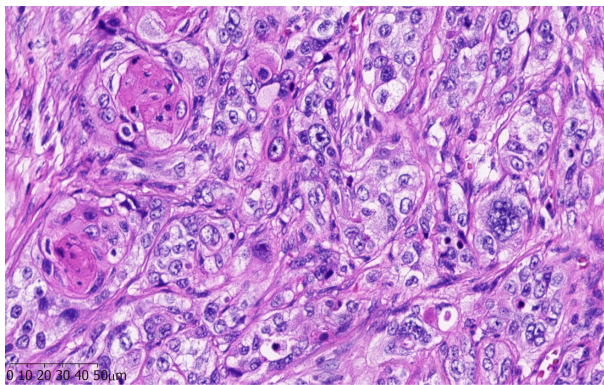


Figure 3 Pathologic findings indicating pure, well-differentiated squamous cell carcinoma with evidence of abundant cytoplasmic keratin pearls. Hematoxylin-eosin staining, original magnification × 400.

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