Concurrent Basal Cell and Squamous Cell Carcinomas Associated with Hydroxyurea Therapy

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SUMMARY We report a case of a 76-year-old woman with concurrent onset of two primary cutaneous malignancies, one at the fourth finger and another at the dorsum of the same hand. The patient was on long-term therapy with hydroxyurea (HU) for polycythemia vera. Histopathologic and immunohistochemical studies revealed two different malignant cutaneous lesions, i.e. basal cell carcinoma (positive for bcl-2 and negative for vimentin, EMA and CK5/6) and poorly differentiated sarcomatoid squamous cell carcinoma (positive for vimentin, EMA and cytokeratins CK5/6, and negative for bcl-2). In addition, p53 was positive in approximately 50% of squamous cell carcinoma cells and in almost all basal cell carcinoma cells. The presence of low-risk human papillomavirus (HPV, types 6, 11) was verified by polymerase chain reaction, but only in the surrounding normal skin tissue, whereas HPV infection could not be detected in either carcinoma. In this patient, concurrence of two different skin carcinomas on sun-exposed skin, in the absence of HPV, suggest direct involvement of potentially mutagenic HU therapy, through influence on DNA synthesis and repair mechanisms, in conjunction with ultraviolet exposure. Therefore, we suggest that in patients on HU therapy with cutaneous side effects, referral to a dermatologist should be obligatory.

KEY WORDS: basal cell carcinoma, squamous cell carcinoma, hydroxyurea therapy

INTRODUCTION

Hydroxyurea (HU) is an antimetabolite, a ribonucleotide diphosphate reductase inhibitor used for treatment of myeloproliferative disorders such as chronic myeloid leukemia, polycythemia vera or essential thrombocythemia. It has also been used in the management of other disorders, such as sickle cell disease, thalassemia and psoriasis, and to inhibit viral replication of human deficiency virus (HIV) in infected patients (1). Increasing indications and recent revival of HU therapy make it a moderately used drug in clinical practice increasing the need for clinical awareness of the problem of cutaneous and other side effects of HU.

Although HU is in general well tolerated, patients on long-term therapy may experience a number of side effects, including mucocutaneous changes (xerosis, dark brown pigmentation of skin folds and nails, ichthyosiform lesions, malleolar ulcers, oral mucositis and ulcers, atrophy of the skin, "hydroxyurea dermopathy") and/or skin and oral carcinomas (2-8).

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Although HU is an antimetabolite interfering with DNA synthesis and DNA repair mechanisms, thus exhibiting the oncogenic effect due to the interaction between the drug and DNA, other possible co-carcinogenic factors could include ultraviolet radiation and human papillomavirus (HPV) infections. It is well known that HPV may play an important role in the pathogenesis of skin cancer (9,10). Virus infection and UVB exposure seem to act in synergy to induce HPV associated skin cancer (11). In order to elucidate the possible role of different etiologic factors in the skin carcinogenesis in patients on long-term HU therapy, we examined the presence of HPV-DNA in two concurrent skin cancers.

CASE REPORT

We report a case of 76-year-old woman suffering from polycythemia vera since 1986. Initially she was treated with venesection, and subsequently with HU therapy, since 1990, maintaining a good control of the disease. During treatment, she experienced cutaneous abnormalities, including atrophy and skin dryness, ichthyosiform lesions, oral ulcers, nail and skin hyperpigmentation, especially involving sun-exposed skin areas and nails. The patient was previously treated with cryotherapy for actinic keratoses on her face in 2004, but was not referred to dermatologist for regular check-up. In the same year, she also developed two ulcerations on the lower part of her left leg that persisted and were treated by the patient herself. On her regular follow up visit in September 2006, she disclosed two cutaneous changes on her left hand, partly ulcerated on the forth finger and on the dorsum of the left hand, 1.8-2 cm in diameter, and multiple keratoses on the dorsa of the hands. She was referred to dermatologist and physical examination revealed multiple actinic keratoses present on her face. The skin was generally xerotic and hyperpigmented with poikilodermatous changes on the dorsa of the hands and fingers, melanonychia, and two ulcerations persisting on her left lower leg. According to the patient's report, the two prominent lesions on the left hand appeared simultaneously about 8-10 months before (before September 2006) as a keratotic area a few millimeters in diameter. These lesions were neglected by the patient and therefore progressed forming indurated tumor lesions, partly ulcerated and covered by an adherent crust on the surface.

In October 2006, the patient was referred to Department of Surgery for extirpation of both skin lesions. Histopathology and immunohistochemistry showed two morphologically different malignant cutaneous tumors, i.e. basal cell carcinoma (BCC; positive for bcl-2, and negative for vimentin, EMA and CK 5/6) and poorly differentiated sarcomatoid squamous cell carcinoma (SCC; positive for vimentin, EMA and cytokeratins (CK) 5/6, and negative for bcl-2). In addition, p53 was positive in approximately 50% of SCC cells and in almost all BCC cells (Fig. 1). Regional lymph node metastases as well as signs of a systemic disease were excluded by lymph node ultrasound and PET-CT scan.

In order to examine the presence of HPV-DNA in excised lesions, microdissection was used. Microdissection is a valuable tool for selection of cell populations from tissue sections under the light microscope for subsequent molecular analysis (12). Thus, tumor tissue was sectioned and mounted onto PALM® Membrane slides, 1-mm thick glass slides, as routinely done on glass slides. After mounting, the slides were dried overnight in the oven at 37 °C and hematoxylin/eosin (HE) stained for tissue visualization. Following staining, the slides were carefully examined and areas of interest were microdissected using PALM® Robot Microbeam laser microdissection system (P.A.L.M. GmbH, Bernierd, Germany) into separate tubes (tumor tissue and surrounding normal skin cells).

Dissected tissue was digested overnight with proteinase K (Machery-Nagel, Duren, Germany) and DNA was isolated using NucleoSpin®Tissue kit (Macharey-Nagel, Duren, Germany), according to the manufacturer's instructions.

Detection of HPV DNA was performed using GP5/GP6 general primers (13), and HPV positive samples

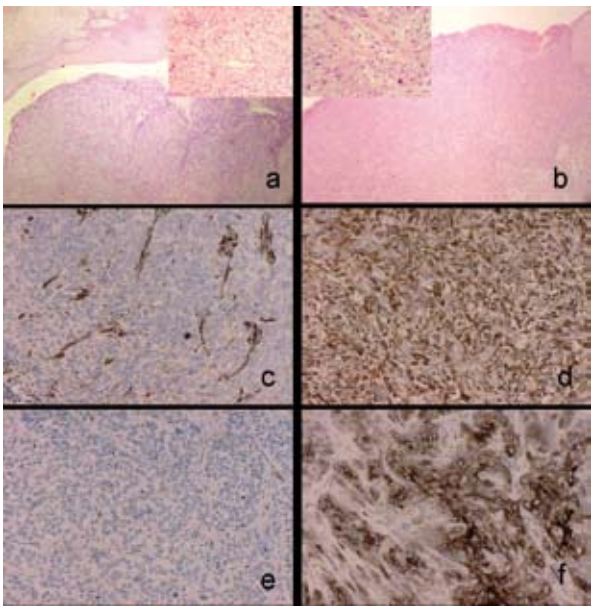

Figure 1. Basal cell (a) and poorly differentiated sarcomatoid squamous cell carcinoma (b) with immunohistochemical staining for vimentin (c and d) and EMA (e and f).

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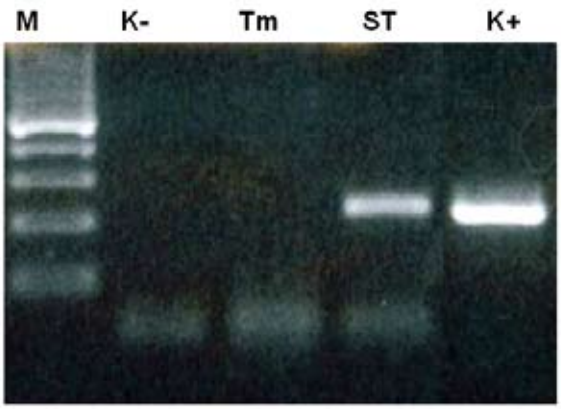

Figure 2. Products of PCR reaction with primers specific for low-risk HPV (genotypes 6,11) confirm the presence of low-risk HPV only in normal skin around the tumors (M, marker; K, negative control; Tm, tumor; ST, surrounding HPV infected tissue; K+, positive control).

were typed using type specific primers, amplifying sequences within E6/E7 open reading frame (Human Papillomavirus Typing Set, Takara Biomedicals, Japan). HPV infection could not be detected in either carcinoma. Polymerase chain reaction (PCR) confirmed the presence of low-risk HPV (with primers specific for types 6, 11) only in the surrounding normal skin tissue (Fig. 2).

DISCUSSION

The association of HU treatment with secondary skin tumors in sun exposed areas has been well documented in the literature and is recognized as a long-term side effect (2-4,6-8). Here we present a case of a 76-year-old woman suffering from polycythemia vera treated with HU for sixteen years, which led to the development of many cutaneous side effects including concurrence of two different cutaneous carcinomas, squamous cell carcinoma and basal cell carcinoma on the left hand. The lesions appeared at the beginning as a keratotic area and thus were neglected by the patient for a few months, which led to lesion progression.

Hydroxyurea inhibits cellular DNA synthesis and promotes cell death in the S phase of the cell cycle through its action on the enzyme ribonucleotide reductase. It interferes with DNA synthesis and DNA repair mechanisms after injury by external factors, such as ultraviolet radiation by reduction of intracellular deoxyribonucleotide pools *in vitro* (2). Hydroxyurea prevents incorporation of thymidine into DNA causing abnormalities in cell replication and reduces the ability of DNA for self repair upon exposure to irradiation, leading to accumulation of somatic mutations and chromosomal damage (2,4,14). Intrinsic mutagenic activity of HU has also been documented (6). Therefore, it is considered that DNA damage by HU may not only play a role in the anti-cancer activity, but also in carcinogenesis.

In addition to immunosuppression, ultraviolet exposure and a history of HU therapy, several other predisposing factors are also associated with the occurrence of skin carcinomas, most significantly HPV infection. Some epidemiological and experimental studies have suggested HPV subtypes as the potential causal agents in non-melanoma skin cancers (15,16). Therefore, in our patient, tumors were examined for the presence of HPV-DNA because of its carcinogenic role in skin tumor development. However, in the case presented, PCR confirmed the presence of low-risk HPV (types 6, 11) only in the surrounding normal skin tissue but not in either tumor tissue.

CONCLUSION

In conclusion, we report this case to draw attention to the fact that long-term HU therapy can lead to a variety of cutaneous manifestations, and to increase clinical awareness of the problem. It is clear that patients on long-term HU therapy may be exposed to an increased risk of developing cutaneous cancers, particularly on sun-exposed areas. This is probably due to direct HU influence on DNA synthesis and DNA repair mechanisms following ultraviolet radiation. We would like to stress the significance of patient awareness of the possible risks of HU treatment, but physicians should also be vigilant for signs of cutaneous adverse effect and should conduct regular physical examination in order to identify side effects at an early stage. We suggest that in patients on HU therapy with keratoses and cutaneous side effects, referral to a dermatologist should be obligatory.

References

1. Lori F, Lisziewicz J. Hydroxyurea: overview of clinical data and antiretroviral and immunomodulatory effects. Antivir Ther 1999;4 Suppl 3:101-8.
2. Young HS, Khan AS, Kendra JR, Coulson IH. The cutaneous side-effects of hydroxyurea. Clin Lab Haematol 2000;22:229-32.
3. 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;128:919-21.
4. De Benedittis M, Petruzzi M, Giardina C, Lo Muzio L, Favia G, Serpico R. Oral squamous cell carcin-

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oma during long-term treatment with hydroxyurea. Clin Exp Dermatol 2004;29:605-7.

5. Angeli-Besson C, Koeppel MC, Jacquet P, Andrac L, Sayag J. Multiple squamous-cell carcinomas of the scalp and chronic myeloid leukemia. Dermatology 1995;191:321-2.
6. Vassallo C, Passamonti F, Merante S, Ardigò M, Nolli G, Mangiacavalli S, *et al*. Muco-cutaneous changes during long-term therapy with hydroxyurea in chronic myeloid leukaemia. Clin Exp Dermatol 2001;26:141-8.
7. Papi M, Didona B, DePità O, Abruzzese E, Stasi R, Papa G, *et al*. Multiple skin tumors on light-exposed areas during long-term treatment with hydroxyurea. J Am Acad Dermatol 1993;28:485-6.
8. Stasi R, Cantonetti M, Abruzzese E, Papi M, Didona B, Cavalieri R, *et al*. Multiple skin tumors in long-term treatment with hydroxyurea. Eur J Haematol 1992;48:121-2.
9. Barr BB, Benton EC, Mc Laren K, Bunney MH, Smith IW, Blessig K, *et al.* Human papilloma virus infection and skin cancer in renal allograft recipients. Lancet 1989;1:124-9.
10. de Jong-Tieben LM, Berkhout RJ, ter Schegget J, Vermeer BJ, de Fijter JW, Bruijn JA, *et al*. The prevalence of human papillomavirus DNA in benign keratotic skin lesions of renal transplant recipients with and without a history of skin cancer is equally high: a clinical study to assess risk factors for keratotic skin lesions and skin cancer. Transplantation 2000;69:44-9.
11. Jackson S, Harwood C, Thomas M, Banks L, Storey A. Role of Bak in UV-induced apoptosis in skin cancer and abrogation by HPV E6 proteins. Genes Dev 2000;14(23):3065-73.
12. Micke P, Ostman A, Lundeberg J, Ponten F. Laser-assisted cell microdissection using the PALM system. Methods Mol Biol 2005;293:151-66.
13. Khan S, Jaffer NN, Khan MN, Rai MA, Shafiq M, Ali A, *et al*. Human papillomavirus subtype 16 is common in Pakistani women with cervical carcinoma. Int J Infect Dis 2007;11:313-7.
14. Sakano K, Oikawa S, Hasegawa K, Kawanishi S. Hydroxyurea induces site-specific DNA damage *via* formation of hydrogen peroxide and nitric oxide. Jpn J Cancer Res 2001;92:1166-74.
15. Batinac T, Zamolo G, Coklo M, Hadzisejdic I, Stemberger C, Zauhar G. Expression of cell cycle and apoptosis regulatory proteins in keratoacanthoma and squamous cell carcinoma. Pathol Res Pract 2006;202:599-607.
16. Harwood CA, Proby CM. Human papillomaviruses and non-melanoma skin cancer. Curr Opin Infect Dis 2002;15:101-14.
17. Pfister H. Chapter 8: Human papillomavirus and skin cancer. J Natl Cancer Inst Monogr 2003;31:52-6.