Case Report

Multiple Skin Cancers Associated With Hydroxyurea Therapy

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The association of multiple cutaneous cancers and long-term use of hydroxyurea is now being recognized. In this article, we describe the development of multiple skin tumors in two patients who were receiving hydroxyurea therapy. These cases illustrate the late onset of subsequent skin cancers despite discontinuation of therapy. As hydroxyurea continues to have a prominent role in the treatment of myeloproliferative diseases, clinicians must be aware of the increased risk of multiple skin cancers and use preventive and skin cancer screening practices in patients with these diseases.

Mayo Clin Proc 1998;73:961-963

Hydroxyurea is an antimetabolite whose major action is the inhibition of ribonucleotide reductase. It is commonly used in the treatment of myeloproliferative disorders, but other uses have been proposed, including in the reduction of painful sickle cell crises, in the treatment of psoriasis, and as a radiosensitizer for multiple cancers.[1-3] Common cutaneous side effects of long-term therapy consist of hyperpigmentation, scaling, partial alopecia, atrophy of the skin and subcutaneous tissues, and nail changes. Erythema of the face and hands has also occurred; lower extremity ulcerations are less common.[4-6] Recently, cases have been reported that suggest an association between long-term hydroxyurea therapy and multiple skin tumors.[7-9] Herein we describe two additional cases of multiple cutaneous cancers associated with long-term hydroxyurea therapy; in one case, the tumors appeared more than 4 years after discontinuation of therapy.

REPORT OF CASES

Case 1

A 59-year-old woman with essential thrombocythemia was treated with hydroxyurea for 8 years, which was effective in controlling her platelet count. After she had received hydroxyurea for 6½ years, a scaly red patch, 0.5 cm, had developed on her face. Two biopsy specimens were obtained, and actinic keratosis was diagnosed. Six months later, another scaly lesion had developed on her face, and she had scaling of her palms and soles. At that time, she was referred for further assessment and was found to have a scaly eroded plaque, 15 by 17 mm, on her right cheek, multiple red scaly macules as large as 5 mm on both cheeks, facial telangiectasia, dry white scaling of her palms and soles, and pink-red flat papules over the bony prominences on the dorsal aspects of her hands. The hydroxyurea treatment was discontinued, and anagrelide therapy was initiated. The previous biopsy specimens from her right cheek were reexamined, and the diagnosis was changed to squamous cell carcinoma in situ; a grade 1 squamous cell carcinoma was excised. A lesion in her left nasolabial fold showed squamous cell carcinoma in situ and was removed. On her right hand, atop the first metacarpophalangeal joint, a 5-mm punch biopsy revealed squamous cell carcinoma with dermal mucinosis, telangiectasia, and solar elastolysis; findings on direct immunofluorescence microscopy were consistent with lichen planus. Five weeks later, the patient underwent electrodesiccation and curettage of a 10- by 6-mm basal cell carcinoma on her left mid-cheek area, a 6- by 3-mm infiltrating basal cell carcinoma on the right lower medial aspect of her cheek, and an 8- by 8-mm squamous cell carcinoma on her midchest. Two months later, a 6-mm nodular basal cell carcinoma was excised from her right upper lip, and a 4-mm squamous cell carcinoma in situ was removed from her left lower cheek. Four actinic keratotic lesions were also removed. Two months later, six additional actinic keratoses were removed from her face and dorsal aspects of her right hand, but no more skin cancers were detected.

Case 2

Chronic myelogenous leukemia was diagnosed in a 50-year-old woman after abnormalities were found on routine blood cell counts in April 1987. Hydroxyurea therapy was initiated. She did well for 6 months, after which multiple ulcers developed on her legs and recurred during the next 3 years despite usual treatment. She also had red scaly areas on her palms, fingers, and arms. In September 1991, after she had received hydroxyurea therapy at a dosage of 2.5 g

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per day for 4 years and 5 months, a basal cell carcinoma, 21 by 11 mm, on the left nasal ala was excised. Four months later, a squamous cell carcinoma, 4 by 4 mm, appeared on her left upper lip. The hydroxyurea therapy was discontinued because of concern that it was causing the leg ulcers. Interferon alfa therapy was initiated. Two months later, the scaly areas on her hands had diminished, and 6-thioguanine was added for control of her myeloproliferative disorder. Eight months after discontinuation of the hydroxyurea therapy, all leg ulcers had resolved. Two months later, interstitial lung disease developed, consistent with bronchiolitis obliterans organizing pneumonia that was thought to be due to the 6-thioguanine. Thus, use of 6-thioguanine was discontinued, and radiophosphorus (^{32}P) was instituted in January 1995. Anagrelide was initiated and was then discontinued in favor of busulfan. In May 1995, multiple squamous cell carcinomas developed on the patient's hands: a 6-mm lesion on the right fourth digit, a 5-mm lesion on the right fifth digit, a 7-mm lesion on the left second digit, a 6-mm lesion on the left third digit, and a 28- by 30-mm lesion on the dorsal aspect of her right second finger (Fig. 1). All lesions were excised, and the right index finger was grafted. Two months later, she had development of a 12- by 9-mm squamous cell carcinoma on her left first finger. Four months later, a new squamous cell carcinoma had developed on her left fourth finger, and she was noted to be in blast crisis. No more skin cancers were evident at the time of her death 3 months later.

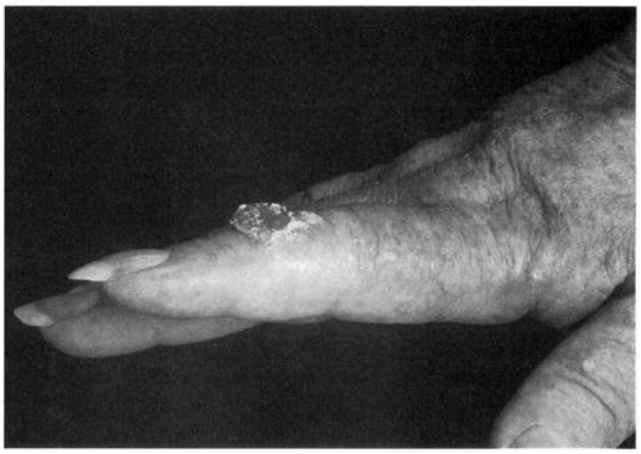

Fig. 1. One of five concurrent squamous cell carcinomas that developed in a 57-year-old woman with chronic myelogenous leukemia after discontinuation of hydroxyurea therapy. Carcinoma was 28 by 30 mm, and skin grafting was necessary after its removal.

DISCUSSION

The cutaneous cancers associated with the use of hydroxyurea are often multiple and include both squamous cell carcinomas and basal cell carcinomas. They typically appear on sun-exposed surfaces and may occur in patients who have other cutaneous manifestations of hydroxyurea therapy.

Although the association between cutaneous cancers and hydroxyurea therapy has been recognized infrequently, some cases in the literature have similar features. In the case report by Papi and associates,[7] a man receiving hydroxyurea therapy had development of multiple squamous cell and basal cell carcinomas of the skin. This patient had other dermatologic side effects from hydroxyurea therapy, including a leg ulcer, erythematosquamous and atrophic lesions on the knuckles and wrists, and actinic keratoses. Other similarities between our cases and the case described by Papi and colleagues[7] include development of skin cancers several months after discontinuation of hydroxyurea therapy. Another report that raised the possibility of hydroxyurea therapy associated with multiple squamous cell carcinomas described a man with chronic myeloid leukemia who was treated for 4 years with hydroxyurea therapy, after which multiple cancers developed on his scalp.[8] Finally, a report described five patients who had been receiving hydroxyurea therapy for a mean duration of 6.5 years, in whom basal cell carcinomas or squamous cell carcinomas developed.[9] No recurrences were noted, but use of hydroxyurea was discontinued in four of the five patients. Although these reports suggest an association between hydroxyurea and skin cancer, a causative role cannot be clearly defined because skin cancers are common. Additionally, multiple other confounders, such as sun exposure and skin type, must be addressed in future studies. Despite these limitations, recognizing this potential interaction may help facilitate cancer screening and the discontinuation of hydroxyurea therapy if multiple skin cancers develop.

Laboratory data support the role of hydroxyurea in promoting premalignant and malignant skin lesions. Hydroxyurea is a potent inhibitor of DNA synthesis and has been shown in experimental models to induce chromosomal damage and inhibit DNA repair in ultraviolet-irradiated cells.[10,11] Hydroxyurea has also been shown in animal models to enhance carcinogenesis produced by substances such as *N*-methyl-*N*-nitrosourea.[12]

Recognizing the ability of hydroxyurea to promote skin cancers has important clinical implications. A thorough examination of the skin of patients receiving hydroxyurea is imperative. Furthermore, patients must be observed for many years after discontinuation of hydroxyurea therapy because of the apparent prolonged duration of the risk of skin cancers.

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