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Oral Isotretinoin Therapy

Use in a Patient With Multiple Cutaneous Squamous Cell Carcinomas and Keratoacanthomas

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• An 83-year-old woman with multiple squamous cell carcinomas and keratoacanthomas of the legs was treated with orally administered isotretinoin (13 *cis*-retinoic acid). Complete regression of the tumors was noted during the initial six-month treatment period. In the subsequent 36 months, four new cutaneous tumors were excised. There have been no recurrences of lesions that regressed while the patient was receiving retinoid therapy.

(*Arch Dermatol* 1984;120:1215-1217)

Retinoids are chemically related to vitamin A and have many biologic effects, including antitumor actions, particularly against cutaneous neoplasms.¹⁻⁷ In the present study, oral isotretinoin (13 *cis*-retinoic acid) therapy without surgery was used to treat a patient with multiple cutaneous squamous cell carcinomas (SCCs) and keratoacanthomas (KAs).

REPORT OF A CASE

An 83-year-old woman had a skin tumor develop on the left forearm in 1975 at the age of 77 years. The biopsy specimen disclosed SCC. Over the next four years, 19 additional tumors on the legs, arms, and forearms developed; these were subsequently excised and found to be either SCC (Fig 1) or KA.

The patient was first seen by one of us (R.C.M.) in 1980 for six well-defined, hyperkeratotic, approximately 1.5- to 2.5-cm nodules on the lower legs. Biopsy specimens of two

of these tumors disclosed the microscopic findings of SCC, and a third disclosed the changes of a KA (Fig 2). The remaining three lesions were removed without microscopic examination because of the clinical similarity to the lesions from which biopsy specimens had been taken. Over the next three months, the patient noted the appearance of approximately 20 additional 0.5- to 2.0-cm papules and nodules over the legs and was referred to the University of Arizona Health Sciences Center, Tucson, for oral isotretinoin therapy. At no time prior to the initiation of retinoid treatment did any of her tumors spontaneously remit.

The patient was in otherwise good health and was taking no medications. She gave no history of exposure to arsenic or other potential carcinogens. There was no family history of a similar cutaneous problem.

Examination of the skin disclosed multiple 0.5- to 2.0-cm papules and nodules, all arising from an erythematous base. Many of the lesions had central keratotic plugs, and some of the lesions had erosions or shallow ulcerations (Fig 3, top).

METHODS

After informed consent had been obtained in accordance with established hospital procedures, the patient began to take isotretinoin, 2 mg/kg/day. She continued with this regimen for six months and underwent monthly complete blood cell counts, serum liver function studies, and serum triglyceride and cholesterol levels.

RESULTS

Within two weeks of starting oral isotretinoin therapy, many of the smaller lesions had flattened considerably and by six weeks had resolved completely. The larger tumors showed noticeable regression after six weeks, and all but a single lesion on the posterior calf had disappeared after six months of therapy (Fig 3, bottom). The solitary remaining tumor was excised after the six-month retinoid

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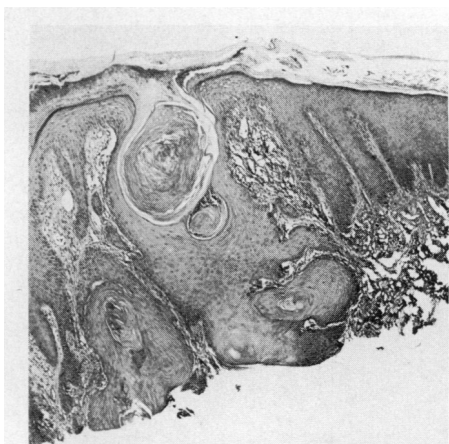


Fig 1.—Biopsy specimen of cutaneous squamous cell carcinoma shows invasion of dermis by epidermal masses with horn pearls (hematoxylin-eosin, original magnification $\times 45$).

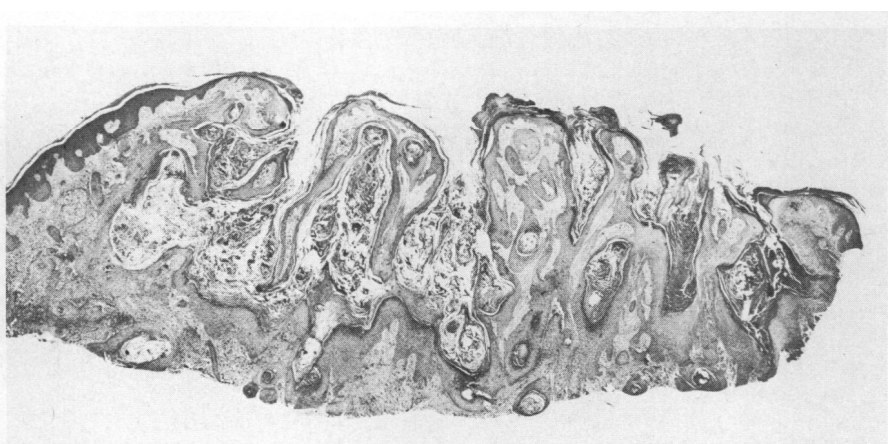
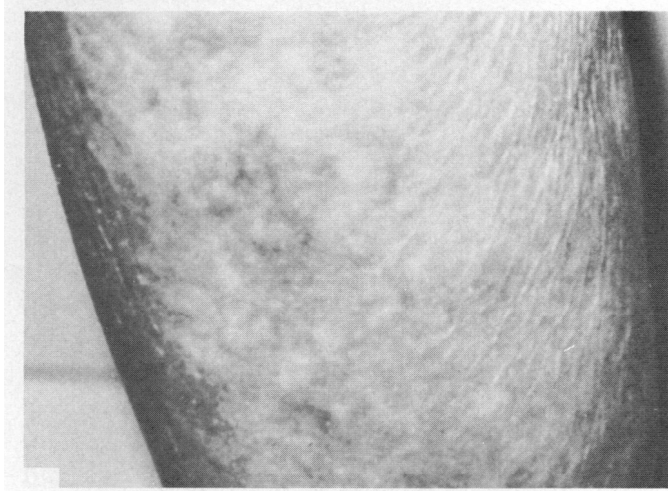


Fig 2.—Biopsy specimen of keratoacanthoma shows keratin-filled crater and irregular epidermal proliferation into dermis (hematoxylin-eosin, original magnification $\times 20$).

Fig 3.—Top, Patient's pretreatment condition with numerous tumors on right anterior leg. Bottom, Patient's right leg after six months of isotretinoin therapy. Tumors have resolved, leaving depressed hypopigmented scars.



treatment period. Microscopic examination disclosed that it was a KA.

In the succeeding 36 months after isotretinoin therapy was discontinued, three SCCs and one KA developed in areas not previously involved. These lesions were surgically removed.

COMMENT

A patient with multiple cutaneous SCCs and KAs responded to oral isotretinoin therapy with complete clearing of almost all lesions. Twenty tumors resolved completely over a six-month course of therapy with no recurrence of these lesions in the subsequent 36 months of observation. A preliminary report of this case was reported previously in tabular form without further description.⁸

A number of different mechanisms of retinoid antitumor action have been proposed, including effects on epithelial differentiation,⁹ steroid hormone-like effects in the nucleus,¹⁰ immunomodulation,^{11,12} membrane effects,¹³ and oncogene-interference properties.¹⁴ In addition, several clinical studies have demonstrated retinoid antineoplastic responses. Koch³ reported a 45% remission rate of multifocal and advanced leukoplakia of the oral mucosa with an aromatic retinoid. In 1982, Moriarity et al⁴ reported that 37 of 44 patients with actinic keratoses responded to four months of aromatic retinoic treatment. Peck et al⁵ noted regression of basal cell carcinomas with isotretinoin therapy. Levine and Meyskens⁶ reported the cases of two patients with multiple foci of cutaneous metastatic melanoma that responded to topical tretinoin (trans retinoic acid).⁶ Haydey et al⁷ successfully treated a patient with multiple KAs with oral isotretinoin therapy, which prevented the recurrence of tumors that had recently been surgically excised. Our case is the second one reported in which the patient had multiple KAs successfully treated with oral isotretinoin therapy; however, it differs from the first

report in that no pretherapy surgical excisions were needed to effect a cure.⁷

Our patient had only four additional lesions develop since therapy was discontinued. It is possible that the isotretinoin acted as a chemopreventive agent as well as a chemotherapeutic modality. The role of retinoids in cancer prevention has been suggested,¹⁵ and there are substantial in vitro data,¹⁶ and in vivo observations^{17,18} to support this contention.

Could these tumors have regressed spontaneously in spite of retinoid therapy? This is highly unlikely, since the patient had never had a previous lesion that

disappeared without therapy; the lesions regressed as a group shortly after treatment was begun, and the biologic behavior of SCC is such that it shows little or no tendency to spontaneous resolution. We believe that in selected cases of multiple KAs and/or SCCs, where surgical excision of the lesions is not possible, or feasible, isotretinoin may be a useful therapeutic modality.

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