

## Multiple Keratoacanthomas, Giant Keratoacanthoma and Keratoacanthoma Centrifugum Marginatum: Development in a Single Patient and Treatment with Oral Isotretinoin

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A 78-year-old man is described, who over 18 years developed three different types of keratoacanthoma: multiple keratoacanthomas, keratoacanthoma centrifugum marginatum and giant keratoacanthoma. Histological examination of the different neoplasms showed similar changes, all typical of a keratoacanthoma. In situ hybridisation revealed no human papilloma virus in the tumours. Complete examination showed no associated internal malignancy. After repeated surgical treatment oral isotretinoin treatment was administered (1 mg/kg per day). This treatment produced clearing of existing keratoacanthomas and, during a period of 2 months, further keratoacanthoma formation was completely suppressed. Treatment was stopped after 3 months by the patient because of side-effects. Numerous keratoacanthomas developed during the following 6 weeks. **Key words:** retinoids; human papilloma virus; self-healing squamous cell carcinomata; Ferguson Smith.

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Keratoacanthoma is a tumour with uncertain clinical behaviour, which may be viewed as an aborted cancer that only rarely evolves into an aggressive squamous cell carcinoma (1). The solitary keratoacanthoma is the most common type, growing rapidly and tending to resolve spontaneously. In addition, multiple keratoacanthomas and even rarer variants such as keratoacanthoma centrifugum marginatum and giant keratoacanthoma have been reported. There are many reported types of multiple keratoacanthomas, including the Ferguson Smith type and Muir-Torre type and others whose classification is unclear and may overlap. We here describe a patient showing the clinical characteristics of these three variants. Treatment with isotretinoin was initiated because of the great number of lesions.

### CASE REPORT

In October 1986, we evaluated a 60-year-old man with a 10-year history of a giant keratoacanthoma on the back of his left hand. The lesion was excised three times but recurred rapidly (Fig. 1). After the fourth excision in November 1991, the surgical site has remained free of tumour. At this time the patient had another keratoacanthoma documented on the right fifth finger. In July 1994 the patient presented again with multiple keratoacanthomas, including a large keratoacanthoma centrifugum marginatum in regression. No tumour was found on the right fifth finger. According to his description, the patient had developed about fifty tumours over the past 18 years, mainly on sun-exposed areas, which had regressed spontaneously with residual



Fig. 1. Giant keratoacanthoma, 5 × 3 cm, on the back of the left hand. The scars are the result of previous keratoacanthomas with spontaneous regression.

scarring. The patient's father had also suffered from similar skin changes on his arms. The patient has no siblings or children.

At presentation in our out-patient department in July 1994 the patient showed the following skin lesions: On the right thumb he had a 2 × 1.5 cm dome-shaped erythematous nodule with multiple fine telangiectasias and central necrosis. On the left third finger a 3 × 1.5 cm large crateriform lesion was present (Fig. 2), while on the left side of the chest a 4 × 3 cm nodule with central depression was found (Fig. 3). The back of the left and the right hand showed multiple characteristically puckered scars (Figs. 1 and 2). Two further dome-shaped nodules, as demonstrated in Fig. 4, were on the lower lip (2 × 1 cm) and the right cheek (1 × 1 cm), together with a 1 × 0.5 cm hyperpigmented plaque with central hypopigmentation representing a keratoacanthoma in regression on the left side of the chin.

Haemoglobin was 9.0 g/dl, serum protein 5.8 g/dl, and serum creat-



Fig. 2. Keratoacanthomas at various stages of development on both hands.



Fig. 3. Keratoacanthoma centrifugum marginatum on the left side of the chest.

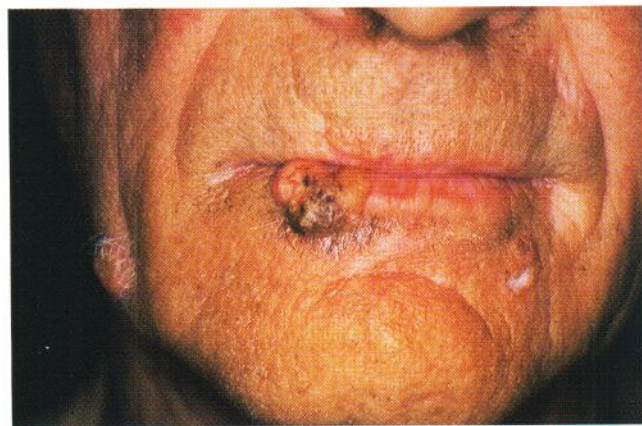


Fig. 4. Two mature keratoacanthomas on the lower lip, the right cheek and a keratoacanthoma in regression on the left side of the chin.

ine 1.95 mg/dl. Other routine laboratory test results, including determination of fasting serum triglyceride and cholesterol levels, were normal. The results of the following investigations were normal or negative: antinuclear antibodies, parietal cell antibodies and carcino-embryonal antigen. Results of the complete physical examination, including a thorough urological and otorhinolaryngological evaluation, showed no sign of other malignant tumours. Normal tests included stool guaiac tests, chest-ray, gastroscopy, infusion urography and abdominal ultrasound examination.

The lesions at the lower lip and the right cheek were treated surgically. The histological examination of these and four other previously excised tumours showed different stages of growth of keratoacanthomas. Most commonly the lesions were in the fully developed stage, showing a well circumscribed, symmetrical dome-shaped crateriform nodule with a central keratotic core. The surrounding epidermis typically formed a lip and the base of the tumour was flat or round. The tumour consisted of pleomorphic epithelial cells with focal keratinization; the nuclei varied in size and shape. Additionally, there were some mitotic figures. In the upper dermis and in the tumour proper there was an infiltration of lymphocytes, histiocytes and some neutrophils. Keratoacanthomas in the involution stage (Fig. 5) showed a flat base, a broad based crater, peritumoral scar formation and a lichenoid infiltrate. In situ hybridization revealed no HPV-related DNA.

Oral therapy with isotretinoin was started at a dosage of 1 mg/kg per day in August 1994. During the first 2 months of treatment, the keratoacanthomas disappeared and no new tumours developed. Yet in the 3rd month new keratoacanthomas developed on the left ear

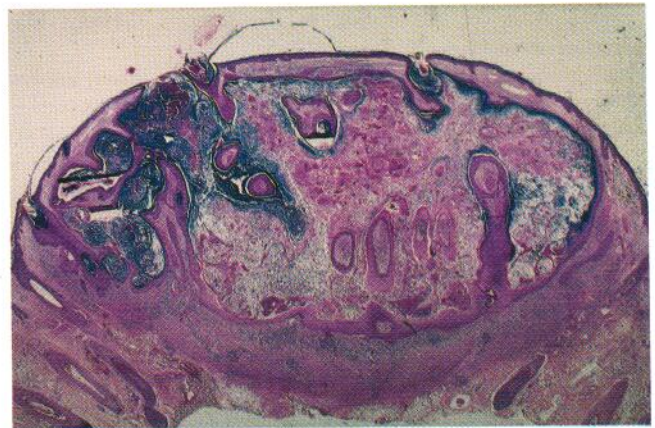


Fig. 5. Maturing keratoacanthoma with large keratin-filled core (hematoxylin-eosin stain).

and abdomen. After this period of 3 months, retinoid treatment was discontinued by the patient because of the side-effects, including painfully dry skin and frequent nosebleeds. Within the following 6 weeks five new keratoacanthomas developed at various sites of the face.

## DISCUSSION

Several types of keratoacanthomas have been described. Usually keratoacanthomas are solitary, but some patients have multiple lesions (1–3). Our patient showed a variety of keratoacanthomas: multiple ordinary lesions, a giant keratoacanthoma and a keratoacanthoma centrifugum marginatum. Initially from 1976 to 1991 he started with a giant keratoacanthoma which recurred and was treated surgically four times. After this, multiple keratoacanthomas appeared at other body sites, along with a keratoacanthoma centrifugum marginatum (3). The combination of these different variants is uncommon and has not, to our knowledge, been previously reported.

Association of multiple keratoacanthomas with carcinoma has been described by a variety of authors (1, 4–6). Despite extensive searching we found no internal malignancy in our patient. Multiple keratoacanthomas and sebaceous neoplasms may be a cutaneous sign of the Muir-Torre syndrome (7, 8). A very rare distinct type of keratoacanthomas was described by Ferguson Smith (9). He reported in 1934 a young Scottish male patient with multiple self-healing squamous carcinomas. This variant found in persons from Scotland or with Scottish ancestors is characterized by development of the tumours in adolescence and by autosomal dominant inheritance. These keratoacanthomas are frequently perioral and self-healing with atrophic scars, and their histological appearance may resemble squamous cell carcinoma. Other clinical variants of multiple keratoacanthomas include the Grzybowski type, the Witten Zak type and others (1). The classification of these variants is not standardized and often leads to confusion and overlapping. Our patient shows some characteristic clinical features of the Ferguson Smith type (autosomal dominant inheritance, perioral involvement, healing with scars), even though he has no Scottish ancestry. Therefore our patient could be classified as a non-Scottish Ferguson Smith type.

Giant keratoacanthoma and keratoacanthoma centrifugum marginatum are also rare variants. Keratoacanthoma centrifugum marginatum is characterized by progressive peripheral

growth with central healing of the tumour. Lesions may develop up to 20 cm and more (3).

Spontaneous regression of keratoacanthoma is well known. Patients suffering from multiple keratoacanthomas are nevertheless often handicapped by them, especially when they are situated in the face. Complete excision of solitary lesions is the therapy of choice. For the treatment of multiple recurring keratoacanthomas retinoids have been used successfully (10–12). Both isotretinoin (1.5 mg/kg/day) and etretinate (1 mg/kg/day) have been given with beneficial effects because of their well-known antikeratinizing effects, which occur by modulating the terminal differentiation of epidermal cells. The retarded development of keratoacanthomas in our patient during therapy with isotretinoin and the quick relapse after discontinuation of the treatment are notable and demonstrate the efficacy of isotretinoin treatment. Development of keratoacanthomas was considerably suppressed by the therapy. The experience in our patient with isotretinoin treatment, however, may underline the necessity of a large starting dose.

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