

MULTIPLE KERATOACANTHOMATA

A Unique Case and Review of the Current Classification

B. J. Reid and M. J. Cheesbrough

Department of Dermatology, Royal Infirmary, Edinburgh, Scotland

Abstract. A case of multiple keratoacanthomata is described, with involvement of the palms and soles, and erosive lesions of the eyelids and penis. Several lesions healed spontaneously, leaving circular scars. Some were atypical clinically, taking the form of keratotic tumours. Methotrexate produced marked improvement of all lesions but had to be abandoned because of thrombocytopenia. The current classification of keratoacanthomata is reviewed.

Key words: Multiple keratoacanthomata; Keratoacanthoma; Neoplasms

One of the most important phenomena, so far unexplained, in the field of Cancer Research, is the spontaneous regression of malignant tumours. The keratoacanthoma, histologically like a squamous cell carcinoma, but subsiding without treatment, is clearly an important model for research in this area. Patients with multiple keratoacanthomata are fortunately rare. The factors involved in these cases may well be of general importance in the study of tumour development; however, the classification of the clinical types of multiple keratoacanthomata leaves much to be desired. We present here a review of the current classification, and the detailed investigation of a patient who does not really fit into this scheme.

CASE HISTORY

A 62-year-old male retired crane driver had suffered from psoriasis for 30 years and this had been controlled by simple topical measures.

In July, 1973, he noticed a change in his psoriasis which had become increasingly warty over the knees, elbows, back and shins. This feature cleared promptly after application of tar and dithranol pastes, but a circular keratotic lesion was noticed on the lateral aspect of the right ankle overlying a patch of psoriasis. This did not respond either

to these measures or to 3% salicylic acid ointment applied for several weeks on an in-patient basis.

During 1974 and 1975 many other keratotic areas developed on the legs, right sole, palms, back, scrotum and eyelids. The eyelid lesions ulcerated progressively and a peri-meatal ulcer appeared on the glans penis. Those on the soles and legs were tender.

On examination in June, 1975, bilateral ectropion was seen, with crusted ulcers on both upper lids, involving the lid margins. The left upper lid gradually became eroded, leaving a 'v' shaped notch (Fig. 1) but closure was preserved. Eyelashes were lost from the affected areas and the lids were oedematous. The left lower lid had an ulcer 1.8 cm in diameter with a raised, rolled margin, suggestive of a basal cell carcinoma. Both eyeballs were normal.

The glans penis was ulcerated around the urethral meatus, and five keratotic tumours similar to the skin tumours were present on the scrotum. A sloughing circinate lesion of the prepuce developed behind the corona (Fig. 2).

The back, legs, soles and palms bore 19 circular, raised keratotic tumours averaging 2.3 cm in diameter (Figs. 3, 4). Those on the hands were smaller at 0.8-1.2 cm in diameter. There was evidence of self-healing on the arms and legs, leaving pale flat circular scars. Several lesions were typical of keratoacanthomata (Fig. 5). Findings at general examination were normal and there was no lymphadenopathy.

The patient's general health was good apart from neck pains due to cervical spondylosis. He had taken no drugs containing iodine or bromine and "did not believe in taking tablets". His skin condition was not related to sunlight or occupational factors.

In the past he had bilateral Kunt-Szymanowski operations for ectropion in December, 1965, and for pleurisy with effusion in February, 1973.

Family history

His brother has psoriasis but no-one in the family is known to have multiple skin tumours.

Investigations

The following were normal or negative: full blood count; antinuclear factor; LE cells; blood urea and electrolytes; liver function tests; serum proteins; virology screen;



Fig. 1. Left upper lid.

VDRL; serum bromide; protein-bound iodine; total inorganic iodine; X-rays of chest, abdomen and sacro-iliac joints; electrocardiograph.

Direct immunofluorescence of normal and abnormal skin, autoantibody screen and serum antibodies to epidermal basement membrane and intercellular cement substance were all negative.

Immunological screen. The following were normal: blood lymphocyte and neutrophil counts; neutrophil function as shown by chemotaxis and the nitroblue tetrazolium



Fig. 2. Circinate lesion of the prepuce.



Fig. 3. Tumours on the back.

test; serum immunoglobulins; complement components (CH50, C3 and C4); neutrophil candida killing was abnormally low; in vivo tests for skin delayed-type hypersensitivity (Candida 0.02 ml 0.5%, SKSD 5 units, trichophyton 0.05 ml and PPD 1/100 all gave positive reactions. Mumps 1 CFU gave no reaction).

The HLA type was shown to be: 2, 10, 17, w10.

Bacteriology. 8 out of 15 swabs from ulcerated lesions grew coagulase-positive *Staphylococcus aureus*.

Histology. A total of 12 biopsies were taken from lesions on eyelids, legs, arms, trunk and penis; all showed pseudo-carcinomatous hyperplasia. The lesions were discrete, with a sharp change from normal to abnormal skin.



Fig. 4. Tumours on the sole.



Fig. 5. One tumour and several self-healing lesions on the leg.

One totally excised tumour had a 'stuck-on' appearance (Fig. 6) and there were lateral spurs (Fig. 7). There was marked hyperkeratosis forming a large central plug and focal parakeratosis. The epidermis showed irregular acanthosis with deeply placed horn pearls and occasional dyskeratotic cells. Many cells surrounding these horn pearls were pale and eosinophilic with cytoplasmic vacuolation (9). A chronic inflammatory dermal infiltrate was present and occasionally invaded the epidermal proliferations. Mitoses were infrequent. There was no deep dermal penetration by the infiltrate. Dermal vascularity was increased (Fig. 8).

Treatment and progress

Topical treatment with antibiotics and ichthammol paste and systemic flucloxacillin and prednisolone were ineffective, as were intralesional corticosteroid injections and a

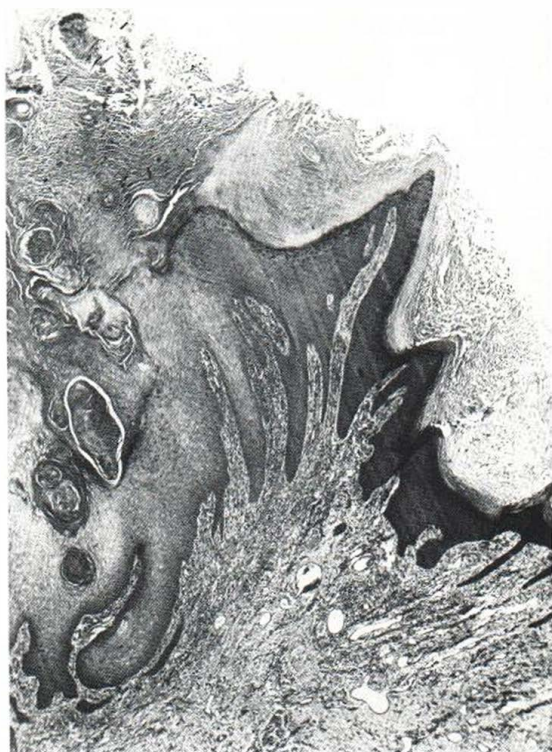


Fig. 7. Edge of lesion shown in Fig. 6 to show lateral spur. (H & E, $\times 25$.)

trial of iodine-free salt. Two lesions were curetted but recurred within 2 weeks.

Initially, plastic surgery was withheld in view of the mutilating procedures needed to treat the eyelids and penis, and the absence of frank malignancy. The cyc and penile lesions continued to deteriorate and for this reason, in January, 1976, he was given a trial of intravenous methotrexate 12.5 mg weekly, with dramatic and



Fig. 6. Excised lesion left lower leg. (H & E, $\times 7$.)

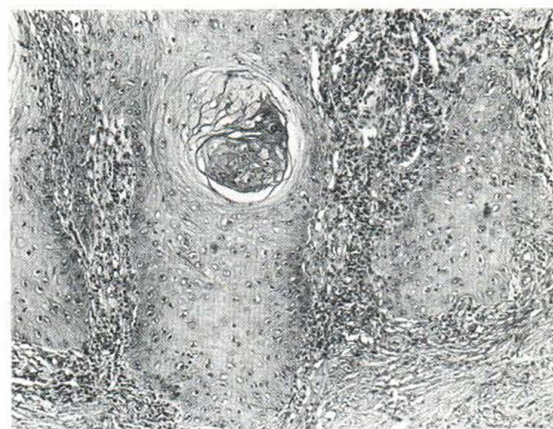


Fig. 8. Detail from lesion left lower eyelid. (H & E, $\times 41$.)

simultaneous improvement of all lesions, after two injections, following which he discharged himself from hospital. Methotrexate was then given orally in a single weekly dose of 15 mg, producing continued improvement in all tumours and complete clearance of the back lesions leaving flat scars. Towards the end of April, 1976, his platelets had gradually dropped to 40 000/cu.mm. and methotrexate therapy was stopped and has not been restarted.

The platelet count remained low until August, 1976, when a daily dose of 20 mg prednisolone increased the platelet count to 100 000/cu.mm. after only 2 weeks' treatment.

On 9th September, 1976, he had a partial amputation of the penis, performed because of the increasing discomfort and size of the penile tumours. At the same time six other troublesome lesions were excised: two on the sole of his right foot, one on the ulnar border of the left hand and three on the thigh.

The penile stump slowly healed, but further tumours have continued to develop and treatment consists of soothing dressings.

DISCUSSION

Differential diagnosis

Other possible causes were considered as an explanation of this patient's lesions.

Verrucose psoriasis (2) was excluded on histological grounds. Pyoderma gangrenosum is usually solitary and on the face but was considered because of the frequent cultures of *Staphylococcus aureus* from lesional swabs and the appearance of the eye lesions. However, the histology was inconsistent with this condition and no improvement followed the use of appropriate topical and systemic antibiotics. Pseudo-carcinomatous hyperplasia may occur with chronic granulomata such as tuberculosis and syphilis, but no granulomata were seen in this case, and serology for syphilis proved negative.

The lesions were not clinically suggestive of pyoderma gangrenosum. Bromine and iodine may cause pseudo-carcinomatous hyperplasia and keratotic lesions may occur, but there was no drug history of halogen-containing agents; serum bromide, protein-bound iodine, total inorganic iodine were normal and no improvement followed the use of iodine-free salt. Keratoderma blennorrhagica is excluded on histological grounds and the characteristic HLA antigens in this condition were not found.

A clinical diagnosis of multiple keratoacanthomata was made on the grounds of appearance of the lesions, the occurrence of self-healing and the histological findings of pseudo-carcinomatous hyperplasia, lateral spurring and

central plug formation. It is known that tar treatment of psoriasis can lead to keratoacanthoma formation (3), but this had only been used for a short time, in 1973 after the appearance of the initial tumour in our case.

Vickers & Ghadially (16) reported a case of multiple keratoacanthomata occurring during an attack of psoriasis. In their case the tumours developed on psoriatic plaques, as did the initial lesion in our patient.

The histological characteristics of malignancy are frequently seen in keratoacanthomata; including nuclear abnormalities, abnormal mitoses, horn pearls, and multiple keratoacanthomata may persist for three years or more (6). In the long run, only the fate of the lesions may be admissible evidence of malignancy (4). No frank signs of malignancy were present in the biopsy specimens from our patient.

Review of classification

Baer & Kopf (1) classify keratoacanthomata as follows: 1) solitary, 2) multiple keratoacanthomata—Ferguson Smith type, 3) multiple keratoacanthomata—Grzybowski type.

Ferguson Smith (5, 13, 14) described in three patients lesions similar to those of our patient, but occurring at an earlier age; they were self-healing, leaving pitted scars which were destructive on the face. A familial tendency was noted by Sommerville & Milne (15). Rook & Moffat (11) reviewed the 23 cases in the world literature.

Grzybowski (7) described the case of a middle-aged man who developed hundreds of eruptive tumours "varying in size from a nearly invisible point to the size of a bean". The lesions evolved over 4 to 8 months and healed spontaneously, leaving pitted scars. The case differed from Ferguson Smith's by the larger number of lesions and involvement of the oral mucosa and palate by multiple papules. A similar case with thousands of eruptive self-healing tumours was described by Witten & Zak (18).

Rossmann et al. (12) noted palm and sole involvement in their case of eruptive keratoacanthomata. In these sites, where hair follicles are lacking, they suggested that "derivation from other cutaneous appendages must be considered in the pathogenesis of these tumours". Winkelmann & Brown (17) reviewed seven cases in the world literature, including three of their own, of eruptive keratoacantho-

mata. Clinical features which they emphasised were: palm and sole involvement in six and bilateral ectropion. This complications, which might lead to corneal ulceration, was noted in two of their three patients. Medium-sized lesions were recommended for biopsy as being most likely to give the typical histology of an actively growing keratoacanthoma.

Our case differs from the Ferguson Smith type in that self-healing was slow, the absence of a family history, and in the involvement of palm, soles, eyes and glans penis. It differs from the Grzybowski type in the clinical appearance (fewer and larger lesions) and limited self-healing. The most similar case to ours was described by Kopf (8). This 35-year-old patient had had multiple keratoacanthomata since the age of 10. He was severely disabled after amputation of the fingers because of painful subungual lesions. He also had difficulty in walking and driving, due to painful sole lesions. Methorexate was ineffective both topically and systemically.

Detailed immunological investigations on our patient have disclosed no abnormality—with the exception of abnormally reduced neutrophil killing. No immunological studies on multiple keratoacanthomata appear to have been published; however, Ramselaar & van der Meer (10) studied 11 patients with solitary keratoacanthomata in a search for immunological mechanisms which might have been involved in the spontaneous regression of lesions. Their results were quite negative.

In the absence of convincing signs of malignancy, we submit this as an unusual case of multiple keratoacanthomata.

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M. J. Cheesbrough, M.B.
Department of Dermatology
General Hospital
Nottingham NG1 6HA
England