BJD
British Journal of Dermatology

Rapidly-growing squamous cell carcinoma shortly after treatment with ingenol mebutate for actinic keratoses: report of two cases

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Summary

Actinic keratoses (AKs) are defined as cutaneous areas of atypical squamous transformation that are regarded as an early step in the continuum of alterations leading from normal skin to invasive and metastatic squamous cell carcinoma (SCC). AKs are classified as precancerous lesions by some authors and *in situ* SCC by others. The rate of evolution of a given AK to an invasive SCC has been estimated as 0·075–0·096% per lesion per year. These rates are similar to those estimated for gynaecological intraepithelial neoplasia. We describe two cases of SCC with rapid onset that developed after the application of ingenol mebutate gel for the treatment of AKs.

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Accepted for publication
7 July 2015

Funding sources
None.

Conflicts of interest
RG collaborates with scientific and academical support, with several pharmaceutical firms, including Almirall, Ferrer, Isdin, La Roche Posay, Leo Pharma, Pierre Fabre and Procter and Gamble among, sporadically, others.

DOI 10.1111/bjd.14054

What's already known about this topic?

- Ingenol mebutate is a recently approved treatment for actinic keratoses.
- No severe treatment-related side-effects have yet been reported.

What does this study add?

- We herein report the first two cases of squamous cell carcinoma that appeared rapidly after treatment with ingenol mebutate.
- Knowledge of the less frequent and/or severe side-effects of a new medication is important to raise awareness of the possible emergence of new cases.

Actinic keratoses (AKs) are keratotic lesions occurring on chronically sun-exposed adult skin. They represent focal areas of abnormal keratinocyte proliferation and differentiation that carry a relatively low risk of progression to invasive squamous cell carcinoma (SCC). AKs are classified as precancerous lesions by some authors and *in situ* SCC by others. AKs are widely considered to be premalignant lesions although they have low individual potential for invasive malignancy and higher potential for spontaneous regression.[1] In recent years, however, there has been an effort to redefine AKs as malignant neoplasms, because these lesions might essentially represent intraepithelial SCCs in evolution. Although not all AKs become SCCs, AKs are the initial lesion in a disease continuum that may progress to SCC.[2]

Mathematical models predict that for an individual with an average of 7·7 AKs, the probability of at least one transforming within a 10-year period is approximately 10%.[3]

Treatment of AKs is usually classified as lesion-directed (e.g. cryosurgery, curettage and electrodesiccation, shave excision, laser ablation) or field-directed (e.g. photodynamic therapy, topical pharmacotherapy). In the management of multiple AKs, topical therapy should be preferred to more destructive and/or invasive treatments in consideration of the field effect, which allows treatment of both visible and subclinical lesions.[4] A Cochrane review concluded that, among field-directed treatments, 5-fluorouracil, imiquimod, diclofenac gel and ingenol mebutate showed similar efficacy with different profiles of adverse events and cosmetic outcomes.[5] Ingenol mebutate gel (Picato® gel LEO Pharma, Princes Risborough, U.K.) is the most recent medication for AKs that has been approved by the Food and Drug Administration and the European Medicines Authority.

We have recently seen two patients with a surprisingly rapid growing SCC shortly after the application of ingenol mebutate for AKs.

Case reports

Case 1

A 95-year-old Spanish woman presented to our dermatology clinic with an erythematous, flat, rough lesion on the forehead. She had no history of skin cancer, immunosuppressive drugs or relevant medical conditions. With a clinical diagnosis of AK, treatment with ingenol mebutate 0·015% gel for 3 consecutive days was indicated. Four weeks later, the patient's family requested an urgent visit because of the rapid emergence of a painful tumour over the previous lesion. The family explained that the patient had exhibited a moderate inflammatory reaction that was still present at the time of the consultation. The tumoural growth started in the first 2 weeks after applying the treatment. On examination, a 15-mm crateriform nodule with a keratotic core was seen (Fig. 1). Because of the rapid growth of the tumour and its macroscopic appearance, we suspected a keratoacanthoma and therefore surgical excision was performed.

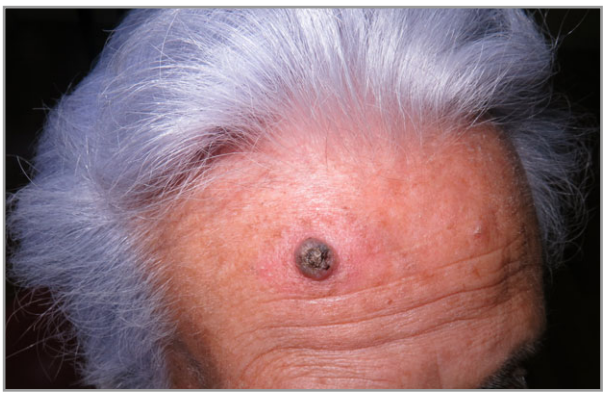

Fig 1. Case 1: 28 days after the application of ingenol mebutate gel; crateriform nodule on the forehead surrounded by ongoing erythema and scaling around the lesion in the area of treatment.

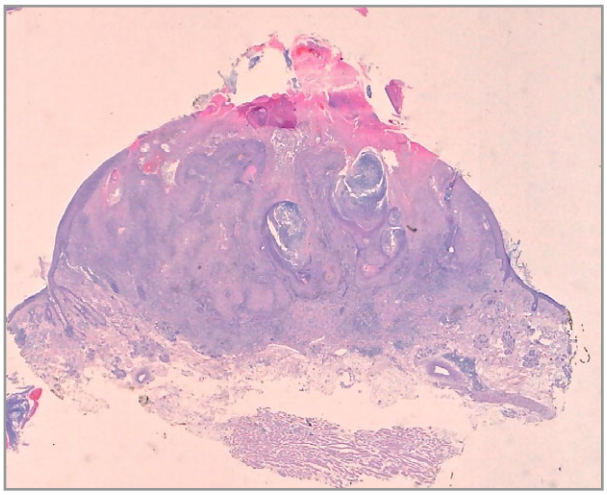

Fig 2. Case 1: overall appearance of the lesion, exhibiting dome-shaped configuration with keratin cap, and protruding margins in the dermal portion. Haematoxylin and eosin staining (original magnification ×2).

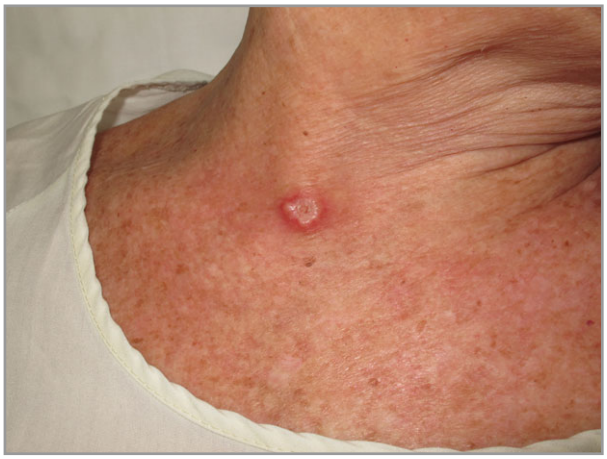

Fig 3. Case 2: 37 days after treatment with ingenol mebutate; ulcerated tumour at the base of the neck.

Histological examination revealed an epidermal lesion with an overall endophytic growth pattern. Extensive surface ulceration was noted. The lateral margins did not show sharp demarcation. The epithelial cells exhibited brisk mitotic activity, dyskeratotic figures and moderate nuclear atypia. The depth of this lesion showed infiltrative margins with chronic inflammatory infiltrate (Fig. 2). These features enabled a final diagnosis of keratinizing and moderately differentiated SCC.

Case 2

A 78-year-old Spanish woman presented with multiple AKs located on the neck base. She had a past history of a stage I superficial spreading melanoma 10 years before, diabetes

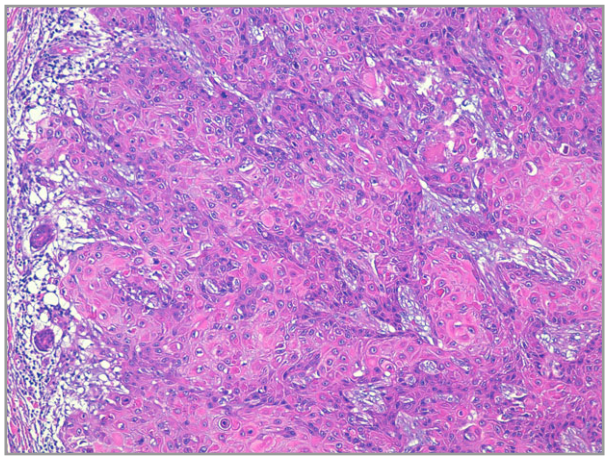

Fig 4. Case 2: higher magnification image shows squamous atypical cells, exhibiting pleomorphism, with diskeratotic figures. Notice the round-edged but infiltrative margins and the peripheral lymphocytic infiltrate. Haematoxylin and eosin staining (original magnification ×10).

mellitus and compensated virus C hepatitis. She had been treated for AKs on her face, chest and back areas with a single course of diclofenac 3% gel, 14 months previously, and repeated sessions of cryotherapy, the last 3 months before she presented. Because of the intense cutaneous atrophy that presented the patient in the area of treatment, 0·015% gel formulation of ingenol mebutate was recommended for 3 consecutive days.

Five weeks later, the patient presented to our hospital with an ulcerated tumour of about 14 mm in diameter in the same anatomical location (Fig. 3). The patient had shown a severe inflammatory site reaction. The tumoural growth started in the first 2 weeks after administering the treatment. A punch biopsy showed histological changes compatible with an infiltrating SCC. Surgical excision was performed and histological examination revealed a well-differentiated SCC, with a depth of 3·8 mm (Fig. 4).

Discussion

Ingenol mebutate is a macrocyclic diterpene ester extracted and purified from the plant *Euphorbia peplus*. The sap of this plant, also known as 'petty spurge' in the U.K. or 'radium weed' in Australia, has long been used as an alternative therapy for skin diseases, including cancerous lesions.[6] It has been used as a purgative and as a treatment for warts, corns, waxy growths, asthma, catarrh, skin cancers, and cancers of the stomach, liver and uterus.[7]

This molecule has a dual mechanism of action: the induction of rapid cellular death in the treated area, beginning a few hours after application, followed by an inflammatory response within days of application, able to eliminate residual cells.[8] The precise mechanism by which ingenol mebutate induces necrotic cell death in AKs is unknown.

Ingenol mebutate has the advantage of ease of compliance. All previous published studies have reported only local side-effects and it is considered to have a very favourable safety profile.

The most common side-effects include erythema, flaking/scaling and crusting. Swelling, blistering, pustulation and erosions/ulceration may occur. However, symptoms are transient and resolve spontaneously, generally within 2–4 weeks after discontinuation.[8] No serious treatment-related adverse events were reported in any of the studies.[9] No safety concerns were identified during longer-term follow-up.[10] We did not find any case of SCC in the literature induced or accelerated by treatment with ingenol mebutate.

Diagnosis of AK is frequently made on clinical appearance alone, but a skin biopsy may be indicated in selected cases when there is clinical doubt or suspicion of invasive malignancy.[1] In our cases, two different dermatologists with extensive experience in skin cancer had not suspected the presence of an invasive lesion, so histological study was not considered necessary and no skin biopsy was performed. We cannot rule out that before treatment, our patients had a minimally invasive SCC, but clinically the lesions were typically AKs. Anyway, in the two patients the tumours grew surprisingly fast a few days after the end of the treatment.

We hypothesize that the inflammatory process induced by ingenol mebutate in some AKs can accelerate their transformation to SCCs. Immune responses and adjacent normal keratinocytes modulate the behaviour of AKs.[11]

Around 50% of AKs show TP53 mutations and over-expression of cyclin D1 while independent activation of *HRAS* occurs in 16%.[12] It has been proposed that AK requires further genetic aberrations before the expression of clinical malignancy. Progression of AK into invasive SCC may involve deletion of the 9p21 region of the p16 (*CDKN2A*) tumour suppression gene. Perhaps there is a genetic susceptibility in our patients that motivated their paradoxical response to treatment. Further studies are needed to identify the underlying pathogenic mechanism.

The development of new field-directed topical agents represents a promising future in the treatment of AKs, but studies with larger series of patients are necessary. We believe that dermatologists should be alert to the possible emergence of new cases of SCC after treatment with ingenol mebutate.

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