Acta Derm Venereol 2015; 95: 618–619

SHORT COMMUNICATION

Epidermal Cyst Formation and Hyperkeratosis in a Patient Treated with Vismodegib for Locally Advanced Basal Cell Carcinoma

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Accepted Nov 24, 2014; Epub ahead of print Nov 26, 2014

Vismodegib, a Hedgehog (Hh) pathway inhibitor, was approved by the US Food and Drug Administration (FDA) in 2012 for the treatment of locally advanced (la) and metastatic (m) basal cell carcinoma (BCC). Interim results of the largest clinical study of vismodegib have shown complete (17.5%) or partial (39.8%) response, and stable (39.0%) or progressive (2.8%) disease in 251 cases of laBCC and mBCC (1). Formation of squamous cell carcinoma (SCC) within the tumour area, as well as occurrence of SCC at other body sites, has been reported in patients treated with vismodegib (2–6). To our knowledge this is the first report of formation of epidermal cysts and hyperkeratosis within the tumour area during treatment with vismodegib.

CASE REPORT

A 52-year-old man was referred to our hospital with a recurrent BCC that was treated with cryotherapy 15 years previously, followed by multiple incomplete excisions. An area of scar tissue and minimal hyperkeratosis was visible on the nose, extending to his right cheek and upper lip (Fig. 1A). Several biopsies were taken, and showed infiltrative BCC invading the deep dermis; there was subtle hyperkeratosis, but no evidence of SCC or BCC with squamous differentiation (Fig. 2A). To avoid mutilating surgery, the patient was enrolled in a clinical trial with oral vismodegib 150 mg daily (7). This trial was approved by the ethics and scientific committee of the Maastricht University Medical Centre. After 7 weeks of treatment, hyperkeratosis increased and comedo-like lesions developed on the nose (Fig. 1B). Sequential skin biopsies showed epidermal cysts, but no residual BCC was found. Because of the impressive hyperkeratosis, we feared for progression into SCC despite the absence of malignancy in repeated biopsies, taking the possibility of a sampling error into account. Therefore, we performed Mohs' micrographic surgery 5 months after initiation of vismodegib therapy, which was continued until the day before surgery. Five stages of Mohs' surgery with 19 frozen sections, including nose amputation, were necessary to achieve clear margins. Histological examination showed residual infiltrative BCC, accompanied by epidermal cyst formation and some hyperkeratosis, but no evidence of SCC (Fig. 2B). Immunohistochemical analysis confirmed residual BCC cells by positive staining for Ber-Ep4, whereas epidermal cysts stained negative.

DISCUSSION

Pseudocyst-like structures as a result of tumour regression during the use of vismodegib have been reported previously; however, they were characterized by a different histology with so-called pseudocystic areas consisting of extensive fibrosis and some residual BCC cells but without keratin formation (8). Formation of SCC within the initial BCC has been reported in several patients treated with vismodegib as well as development of SCC and keratoacanthoma on other body sites (2–6). It is therefore important to be aware of the possibility of occurrence of SCC during vismodegib treatment and to perform sequential biopsies from suspicious areas.

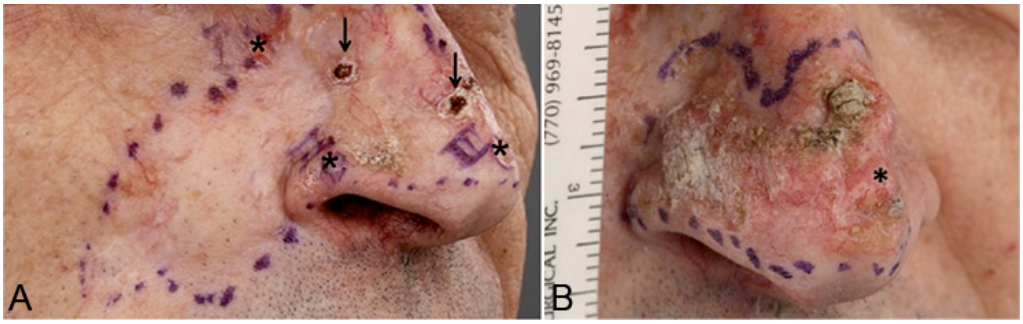

Fig. 1. (A) Clinical picture before treatment with vismodegib. Biopsy sites (*) were positive for infiltrative basal cell carcinoma (BCC). Crusts from earlier biospy sites (↓), also positive for BCC. (B) Clinical picture with extensive hyperkeratosis and comedo-like lesions after 7 weeks' treatment with vismodegib. Biopsy site (*).

 doi: 10.2340/00015555-2020
 ISSN 0001-5555

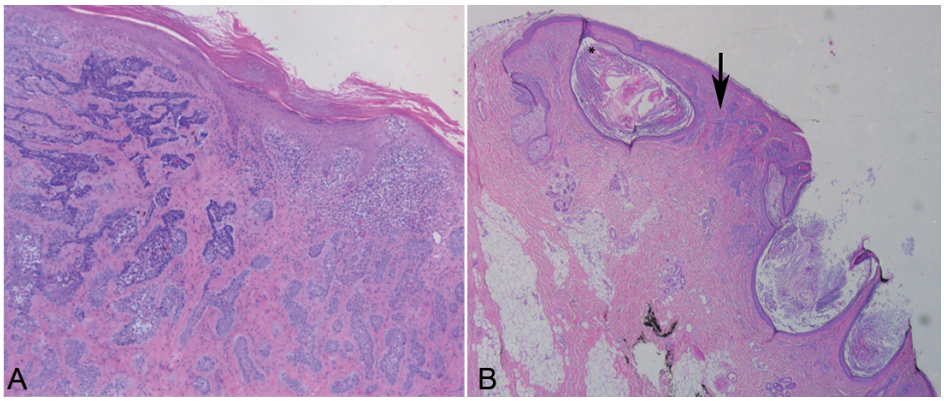

Fig. 2. Histological examination. (A) Skin biopsy before treatment with vismodegib, showing infiltrative basal cell carcinoma (BCC). (B) Skin excision specimen with epidermal cyst (*) formation and infiltrative BCC (↓). Haematoxylin-eosin stain (20×).

Tumour heterogeneity may underlie the emergence of SCC within the tumour area. Squamous differentiation is common in BCC and a subset of malignant squamous cells could become predominant when the BCC is treated with vismodegib. However, this does not explain the occurrence of squamous neoplasms on other sites of the body or, as in our case, the development of benign squamous neoplasia. Furthermore, the epithelial cell marker Ber-EP4 negative immunohistochemical staining of the epidermal cysts in our patient speaks against the survival of cells from the original tumour, as BCC and basosquamous carcinoma stain Ber-EP4 positive. A possible explanation for the emergence of the benign squamous neoplasms could be an effect of vismodegib on keratinocyte differentiation. In essentially all BCC, loss of function mutations in the tumour suppressor gene *Patched1* (*Ptch1*) prevent binding of Sonic Hh to the transmembrane protein Ptch1, resulting in activation of the Hh signaling pathway and eventually tumour formation. The Hh pathway seems to be important in keratinocyte differentiation and proliferation, as Indian hedgehog (Ihh), another member of the Hh ligand family, plays an important role here, and loss of Ihh promotes the progression of benign papillomas to SCC (9). Vismodegib treatment could mimic loss of Ihh, as both reduce Hh pathway activation. Therefore, an effect of vismodegib on keratinocyte differentiation seems plausible. Functional analysis might clarify the exact effect of vismodegib on keratinocyte differentiation and proliferation.

ACKNOWLEDGEMENTS

Conflicts of interest. Dr K. Mosterd is a member of the advisory board of Roche.

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