

CLINICAL REPORT

Imiquimod and Lymphatic Field Clearance: A New Hypothesis Based on a Remote Immune Action on Skin Cancer

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Basal cell carcinoma and actinic keratosis are frequent neoplasms. Topical treatments include the recently approved imiquimod cream. We describe here the case of a 68-year-old man with multiple actinic keratosis on the forehead, upper trunk and on the left cheek. In addition, an exulcerated basal cell carcinoma was observed. The patient was advised only to treat lesions on the forehead with imiquimod cream. This resulted in complete clearance of actinic keratosis within 6 weeks. At follow-up, a planned surgical excision of the basal cell carcinoma and actinic keratosis on the cheek was carried out. Histopathologically, both excision specimens no longer showed features of basal cell carcinoma or actinic keratosis, despite the fact that the imiquimod treatment was not applied to the cheek. Imiquimod cream is a topical immune response modifier, which has shown antiviral and anti-tumorous properties by inducing the production of cytokines as well as by stimulating dendritic cells and lymphocytes. Our observation supports the concept of lymphatic transport of immune cells and factors with subsequent immunological curing of tumours, not only in the treated area, but also those in the area between the imiquimod application site and the regional lymph nodes (the “lymphatic field clearance”). *Key words: actinic keratoses; basal cell carcinoma; imiquimod; lymphatic field clearance.*

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Basal cell carcinoma (BCC), a malignant neoplasm derived from non-keratinizing cells, is one of the most common skin cancers in humans (1). BCC usually develops on sun-exposed areas of the head and neck and is induced by exposure to ultraviolet light, particularly UVB radiation (wavelength 290–320 nm) (2, 3). BCC can be locally destructive and may result in tissue damage. Metastases are extremely rare (4).

Actinic keratosis (AK) is an intraepidermal neoplasm derived from atypical keratinocytes. AK has been regarded as a premalignant lesion; some propose that

AK should be considered as an incipient squamous cell carcinoma. AK is also caused by exposure to UVB, particularly in fair-skinned people. AK typically appears on sun-exposed areas, e.g. the face, arms, hand and upper back (5, 6).

The mainstays of AK and BCC therapy are physical destruction by cryosurgery, curettage, electrodissection, photodynamic treatment, fractionated radiotherapy, standard excision, laser, and Mohs micrographic surgery (for BCC). Topical treatments include 5-fluorouracil cream, diclofenac gel and chemical peels (for AK only) and the recently approved imiquimod cream for both AK and superficial BCC (7–10).

We describe here a patient with multiple AK on the forehead, a bowenoid AK and a BCC on the left lateral cheek. After treatment of the AK on the forehead with imiquimod, there was complete regression, not only of the AK on the forehead, but also of the untreated BCC and bowenoid AK on the cheek.

CASE REPORT

A 68-year-old man presented with multiple reddish-brown scaly lesions on the forehead, upper trunk and preauricular region on the left cheek. In addition, he had a partially exulcerated reddish patch (with a diameter of 40 mm) with small papules partially visible at the outer margin, clinically representing an exulcerated BCC and, to some extent, reddish scaling parts, mimicking an AK could be seen.

The patient was advised to treat only the lesions on the forehead with imiquimod 5% cream (Aldara[®], 3M Pharmaceuticals, Loughborough, Leicestershire, UK), three times a week on non-consecutive days for an initial period of 4 weeks. It was planned to surgically completely excise the lesion on the cheek thereafter because of the patient's holiday plans.

After 2 weeks of treatment the patient developed severe inflammatory reactions at the imiquimod application sites, with erosions, ulcerations and massive crusting. At that time, the clinical appearance of the lesion on the left cheek had also changed completely. Two separated lesions could now be identified, with signs of inflammation, a reddish hyperkeratotic and scaling patch (diameter 12 mm) and an exulcerated glassy patch with a diameter of 15 mm more dorsal

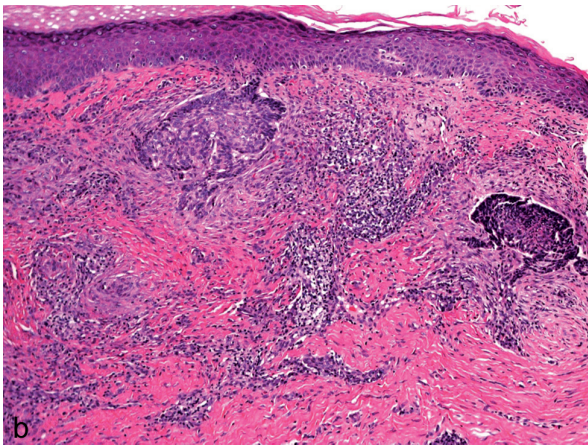


Fig. 1. The first biopsy from the left preauricular dorsal region, showing small round-oval aggregates of basaloid cells with “palisading of cells” and “clefts” in the superficial dermis. In the mid-dermis cords of basaloid cells intersecting a fibrotic stroma together with a lymphohistiocytic infiltrate and actinic elastosis were observed. Diagnosis: Basal cell carcinoma with a lymphohistiocytic infiltrate (haematoxylin and eosin (HE) $\times 100$).

position. Two biopsies of the lesions were performed at this stage. Histopathologically, the diagnosis of BCC mixed type with solid and micronodular component and with lymphohistiocytic infiltration was made (Fig. 1). Histopathology of a second 4 mm biopsy from the more ventrally located scaling patch showed a bowenoid AK (Fig. 2). Nevertheless, the patient continued with the treatment of the forehead lesions only, as advised, for 4 weeks.

Within 10 days of the end of imiquimod treatment, the wounds had healed completely and all AK on the forehead had disappeared. Again, the clinical presentation of lesions on the cheek had changed. The BCC area now resembled an atrophic scar, the bowenoid AK area was a light reddish patch. We performed the intended surgical excision of the BCC and the bowenoid AK areas on the

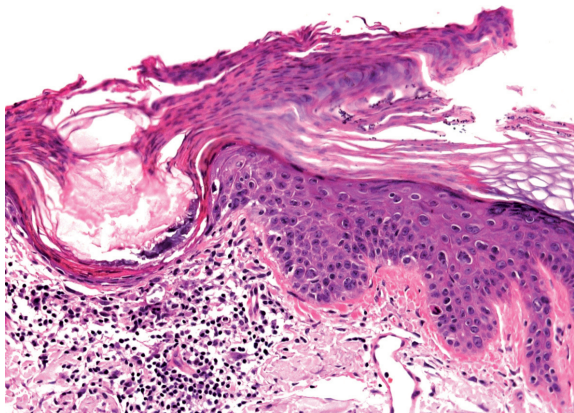


Fig. 2. The second biopsy from the left preauricular ventral region, showing a thickened epidermis with irregular downward buds, focal parakeratosis, loss of granular layer and atypical keratinocytes involving both lower and upper layers of the epidermis. A superficial lymphohistiocytic infiltrate was also present. Diagnosis: Bowenoid actinic keratosis with a lymphohistiocytic infiltrate (HE $\times 400$).

cheek. The AK excision wound was primarily closed; in the case of BCC a closure with rotational flap was performed. Histopathologically, both excision specimens showed a flat epidermis without atypical cells; in the dermis an increase in collagen bundles and fibroblasts, together with a mild perivascular lymphohistiocytic infiltrate, were observed (Fig. 3). Focal amorphous masses of elastotic material were also present in one specimen (Fig. 4). Further serial sections of both specimens did not show features of BCC or AK and confirmed the diagnosis of scar tissue.

The BCC and bowenoid AK on the cheek cleared completely without imiquimod treatment, simultaneously with the treated lesions on the forehead, but the AK on the upper trunk remained unchanged.

DISCUSSION

Imiquimod was initially introduced for the treatment of external genital warts, but has subsequently been found to be useful in treating many other conditions, such as molluscum contagiosum, verrucae planae, lentigo maligna and extramammary Paget's disease (11). Imiquimod 5% cream three times/week has been recommended for the treatment of AK, superficial squamous cell carcinoma and superficial BCC (5). With respect to the treatment of AK, the existing approved 5% imiquimod formulation is indicated only for the treatment of non-hyperkeratotic, non-hypertrophic AK on a very limited area of the skin for a full 16 weeks of treatment (11). Imiquimod has an agonistic activity towards toll-like receptors (TLR) 7 and 8. The anti-tumoral activity is based on activation of innate immune system, especially cutaneous dendritic cells (DCs) (5). Many pro-inflammatory chemokines and cytokines are produced by DCs (6). DCs shift the acquired immune system towards a TH-1 dominated immune response (12). On the other hand, imiquimod represents a potent stimulus for B cells, possibly in a more complex interaction with other immune cells, including plasmacytoid dendritic cells (PDCs) (13). PDCs from the blood are involved, expressing TLR-7 and reacting directly by producing large amounts of interferon (IFN)- α and other cytokines (14). It is unclear whether IFN- α mediates its anti-tumoural effects through stimulation of the immune system, by directly affecting tumour cells, or both (15). A population of PDCs that accumulates in the dermis and spleens of mice topically treated with imiquimod has been described previously, and the increased expression of IFN- α in spleen cells of the mouse has been demonstrated, showing that topical imiquimod may also have systemic effects (16).

Moreover, it has been shown that receptors and ligands of the Notch pathway were decreased in BCC tumour regions (17) and that Notch seems to function

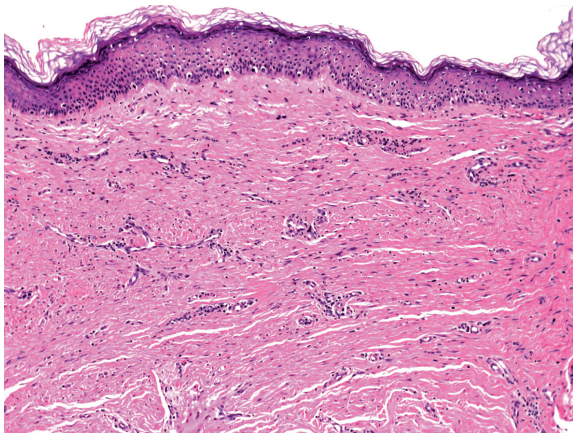


Fig. 3. Total excision of the basal cell carcinoma (BCC) area in the left preauricular dorsal region. The epidermis is flat and does not show atypical cells; in the dermis an increasing of collagen bundles and fibroblasts together with a mild perivascular lymphohistiocytic infiltrate were observed. Diagnosis: Scar tissue (HE $\times 100$).

as a tumour suppressor in skin (18). Imiquimod may act as a stimulator of the Notch pathway in BCC tumour cells by up-regulating protein expression of the Notch ligand, Jagged1, and so may exert tumour suppressor function (19).

In addition, imiquimod induces functional maturation of epidermal Langerhans cells *in vivo* and stimulates their migration from the skin to regional lymph nodes. Langerhans' cells promote a specific T-cell response in the lymph nodes (5). It is hypothesized that the increased appearance of Langerhans' cells from an area where tumour cells reside might lead to the increased presentation of tumour antigen in the draining lymph nodes and increased generation of tumour specific T cells; however, this has not been tested experimentally (20).

Regarding our patient, the induced local inflammatory response was clinically observed with the appearance of inflammation and erosion on the treated areas. His-

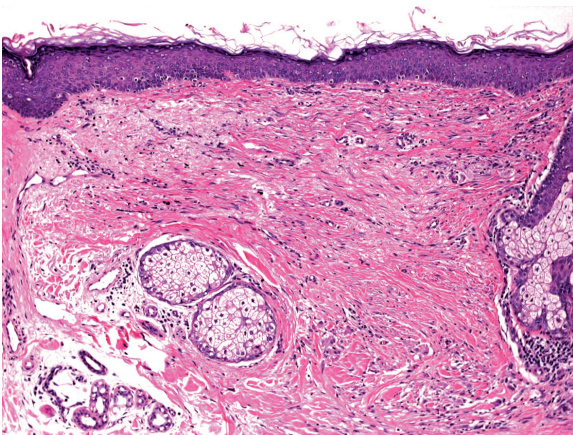


Fig. 4. Total excision of the actinic keratosis (AK) area in the left preauricular ventral region. The features are the same as those in Fig. 3, but focal amorphous masses of elastotic material are also present. Diagnosis: Scar tissue with focal solar elastosis (HE $\times 100$).

tologically observed inflammatory infiltration in punch biopsy specimen (Figs 1 and 2) may be due to imiquimod action. We speculate that the therapy of AK on the forehead with imiquimod had a remote curing effect on the BCC and bowenoid AK on the left cheek. We explain it according to the hypothesis of immigration of Langerhans' cells in the regional lymph nodes and the elimination of BCC and bowenoid AK through the already activated T cells and the stimulated immune system of the patient, as the lymphatic vessels of the cheek are located between the forehead vessels and the regional preauricular and cervical lymph nodes. Our observation supported a hypothesis of "lymphatic field clearance" of imiquimod. The term was chosen by analogy with the term "field cancerization" and because of the apparent imiquimod treatment effect in the regional lymph drainage area. We were not able to find an analogous description in the existing literature although imiquimod has been used for many years now. One may speculate that, in our patient, the observation was a result of a coincidence of several independent circumstances: only the frontal area was immediately treated with imiquimod, the patient responded well with severe inflammatory reactions in the treated areas, the intended surgical excision of the preauricular lesion was postponed and the lesions on the left cheek were exactly located in the regional lymph drainage area.

Regarding the bowenoid AK, a spontaneous regression cannot be excluded, although it seems unlikely.

Clearance due to a systemic effect of imiquimod is highly unlikely in our patient, because he had no generalized flu-like reaction, and the multiple AK on the upper trunk remained unchanged.

Our observations support the concept of lymphatic transport of immune cells and factors with subsequent immunological curing of tumours, not only in the treated area, but also in the area between the imiquimod application site and regional lymph nodes. Studies should be designed to evaluate whether imiquimod is able to act in larger areas by being applied only in small, but specifically relevant, areas of the skin, particularly with regard to lymphatic drainage.

The authors declare no conflicts of interest.

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