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Durable response of cutaneous squamous cell carcinoma following high-dose peri-lesional injections of *Viscum album* extracts – A case report

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ABSTRACT

Background: Cutaneous squamous cell carcinoma (CSCC) is a common locally invasive skin cancer which rarely metastasises. First-line treatment is surgical excision, which is curative in most cases. *Viscum album* extract (VAE) is a widely used herbal cancer treatment with cytotoxic, apoptogenic and immunological effects, but has not been investigated in CSCC.
Case presentation: A 78-year-old patient with histologically diagnosed CSCC refused surgical excision and was treated with peri-lesional high-dose VAE. After 10 months of treatment the CSCC had disappeared clinically. The patient has been recurrence-free for 4 years.
Conclusion: The presented case shows clinical response of a CSCC to high-dose peri-lesional VAE injections. Further research on VAE in CSCC is warranted.

Introduction

CSCC is the second most common skin cancer after basal cell carcinoma, with a rising incidence. It is locally invasive, but perineural invasion and metastases in lymph nodes or other organs are rare (Madan et al. 2010). Most of the lesions are asymptomatic, though pain, itching or recurrent bleeding may occur. CSCC usually develops on sun exposed parts of the body (English et al. 1998). Environmental risk factors for CSCC are accumulated UV exposure, human papillomavirus, immunosuppression, photosensitising drugs, occupational factors, arsenic exposure and tobacco smoking. Personal risk factors are male gender and sun-sensitive skin (Madan et al. 2010). Prognostic factors are state of disease, horizontal and vertical size, localisation, histological features, and immunosuppression in the host.

Recommended treatment for the majority of CSCC cases is surgical excision. Cryotherapy, electrosurgery and radiotherapy are sometimes used in more superficial and histologically well-differentiated lesions. In high-risk lesions, Moh's surgery shows the best results regarding local recurrence and appearance of metastases (Motley et al. 2009). Topical treatments with various agents show diverse results in case series and small studies; side effects are local skin reactions like erythema, swelling, desquamation and tenderness (Madan et al. 2010). Dysregulation of signalling pathways in CSCC skin is under research and may lead to new targeted therapies in the future (Rodust et al. 2009). Overall cure rate after therapy is higher than 90% for the first 5 years. Primary lesions recur in about 8% of cases, metastases appear in 5.5% (Rowe et al. 1992), and case fatality due to CSCC is about 1–2% (Marks 1995). Patients with a primary lesion are at high risk (50%) of developing further skin cancer lesions in the following 5 years (Karagas et al. 1992). Spontaneous remission in CSCC is rare (Chodorowski et al. 2007; O'Regan and Hirshberg 1993).

VAEs are aqueous extracts made from European mistletoe, a hemi-parasitic plant that grows on different host trees (ash, birch, apple, oak and others). Use of VAE in cancer treatment was pioneered in anthroposophic medicine in the 1920s and today it is widely used among cancer patients in central Europe (Molassiotis et al. 2005). It is usually applied subcutaneously in low, slowly increasing dosage, but higher dosage and intra- or peritumoural or intravenous applications as well as instillations in visceral cavities are used occasionally. Isolated compounds as well as whole extracts of VAE are cytotoxic, induce apoptosis, activate lymphocytes, granulocytes, macrophages and NK-cells, induce different cytokines, and show DNA stabilising properties (Büssing 2000; Kienle and Kiene 2003a). Clinical studies show improvement of quality of life (Kienle and Kiene 2010) and potential effect on survival (Kienle and Kiene 2007). Tumour remissions were occasionally reported after high doses and local application (Kienle and Kiene 2003b, 2007; Kirsch 2007; Orange et al. 2010; Seifert et al. 2007). Side effects are dose-dependent local skin reactions and flu-like symptoms. Allergic reactions have been reported. Altogether, VAE is considered to be safe (Kienle and Kiene 2003a; Olaku and White 2010; Stein 2000;

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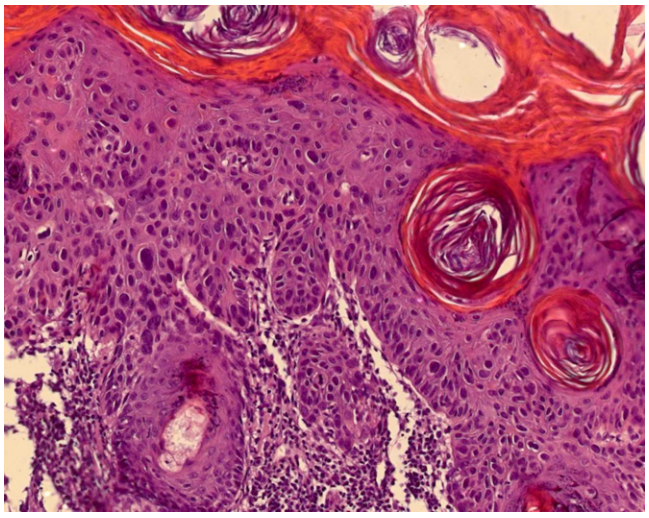

Fig. 1. Biopsy of the patient's tumour (medium power view, 200×): cellular atypia in all layers of the epidermis, epidermal tissue lying free in the connective tissue (subepidermal) with pleomorphism of nuclei, mitotic figures and giant nucleus formation.

Stein and Berg 2000) even in high dose application (Kienle et al. 2011).

Case presentation

An active 78-year-old patient with a past medical history of heart disease (myocardial infarction, coronary bypass surgery) went to his general practitioner (GP) with an 11 mm × 7 mm scabbed lesion (hyperkeratotic plaque with desquamation). He had discovered the lesion at the inner edge of his right eye a year before but felt no discomfort. In the dermatologic outpatient department of the nearby university hospital (Fachklinik Hornheide, Münster), a highly differentiated squamous cell carcinoma with a maximal vertical tumour thickness of 0.8 mm was diagnosed through punch biopsy (AJCC Classification I without any high risk features (Farasat et al. 2011)) (Fig. 1).

Surgical excision was proposed to the patient. The patient refused surgery because of the highly sensitive localisation of the tumour and his medical history of heart disease. His general practitioner suggested a peri-lesional VAE injection therapy. The experimental nature of this therapy and its uncertain outcome were thoroughly discussed with the patient, as well as other treatment options such as surgery and radiation therapy.

Preparations of AbnobaVISCUM® were used. They are classified by the marketing authorisation in Germany according to the Ph. Eur. monograph 01/2008:0765 EXTRACTS as "other extract". "Other extracts" are determined by the production process with meticulously defined specifications resulting in pharmaceutically comparable extracts. For "other extracts" the therapeutic active principle is the whole extract. Thus, it is not allowed to declare a certain content of a single constituent; for quality assurance constituents are measured regularly in a controlled and validated analysis process (ICH guideline Q2(R1)).

The treatment was started with VAE from the host tree ash (AbnobaVISCUM® Fraxini, vials of 0.02–2 mg; 2 mg contain about 2 μg mistletoe lectin/ml, the ML-concentrations in lower doses are respective) as peri-lesional fine needle injections for 24 weeks (Table 1). In this time tumour size increased slowly. Because there were no signs of remission at this point, the VAE preparation was changed to VAE from the host tree birch (AbnobaVISCUM® Betulae) in higher dosage (vials of 2–20 mg, for details see Table 2; 20 mg contain about 20 μg mistletoe lectin/ml, and 59 μg viscotoxins/ml; the concentrations in lower doses are respective), And after 4 weeks, a white scabbing developed over the lesion. Another 7 weeks later, the scab had fallen off and the lesion had decreased to <6 mm (largest diameter). Twenty weeks after the change to high-dose VAE betulae, the original tumour site showed only a small erythematous area without any signs of tumour growth or scarring. (The course of the lesion is shown in photographs, taken in intervals of 2 months: Fig. 2a–d.) The dermatologic department (Fachklinik Hornheide, Münster) clinically confirmed the complete remission of the tumour. Biopsy for histological confirmation of remission was refused by the patient. VAE treatment was continued with subcutaneous injections into the upper arm (3/week in different dosages: 2 mg, 0.2 mg, high dilution D10), carried out by the patient's wife at home; intermissions were later included (8 weeks of treatment followed by 4 weeks of intermission; then 4 weeks of treatment with 8 weeks of intermission, etc.).

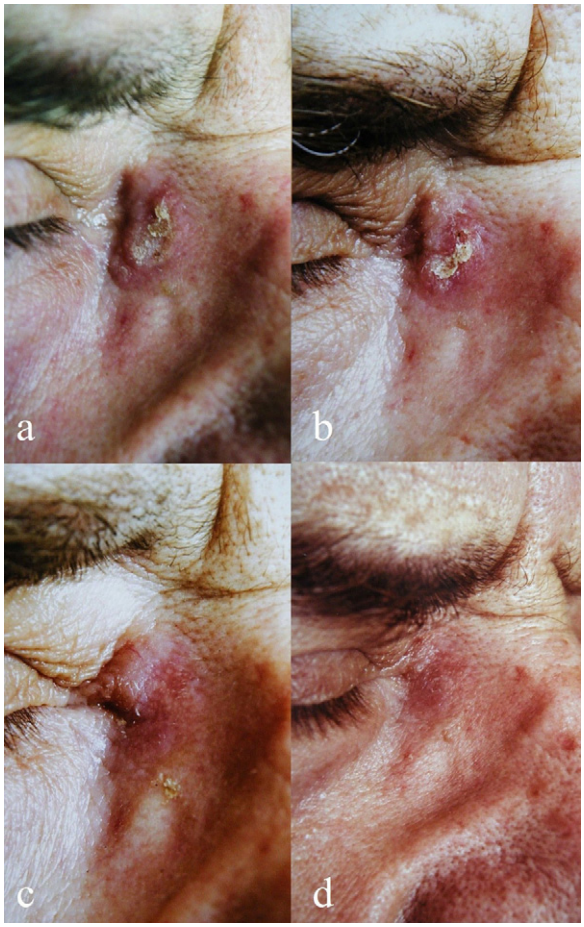

Fig. 2. Photographs of the patient's tumour. a: 3 weeks before VAE betulae; b: week 7 of VAE betulae; c: week 16 of VAE betulae; d: week 24 of VAE betulae.

Side effects of treatment were swelling of the skin at the injection site beginning about half an hour after application and lasting about 48 h, as well as occasional itching of the face and scalp for a few days. When VAE was used at higher dosages, periorbital swelling led to visual restriction of the right eye. Dimetindene (Fenistil®-drops, 1–1.5 mg 3×/d) was prescribed once to control itching.

At present, the 84-year-old patient is in a good state of health and rides his bicycle 25–40 km per day. At a recent visit to a dermatologist, no signs of recurrence were seen clinically. The patient was highly satisfied with this type of treatment and mentioned that he would prefer this option in case of recurrence or other tumour appearance.

Table 1
VAE fraxini therapy.

Week of treatment	VAE fraxini: perilesional injections per week[a]			Observations at the tumour site[b] (initial tumour size: 11 mm × 7 mm)
	0.02 mg	0.2 mg[a]	2 mg	
1	2			
2		1[c]		
3–4	2			No obvious change
5	2[d]			Softening of the skin
6–8		2		Scabbing
9–11		1		
12			1	
13		1		
14–21			1	
22			1	1st photograph (Fig. 2 a)
23	0			
24			1	

[a] Vials for injection contained 1 ml; of these, only 0.1–0.5 ml were used for each injection depending on the infiltration dose tolerated by the patient.
[b] Altogether, during the whole time covered by this table, tumour size slowly increased.
[c] No second injection because of swelling and reddening as a reaction to the prior injection.
[d] First injection 0.02 mg, second injection 0.02/0.2 mg (1:1).

Antecedent and concomitant therapies

Besides coronary bypass surgery (see above), the patient had undergone hip replacement surgery on his right hip after a femoral neck fracture. His coronary heart disease was treated with acetylsalicylic acid, metoprolol and Oleum strophanti. The myocardial function was not significantly reduced.

No tumour-specific therapy was applied apart from VAE.

Discussion

The presented case shows a complete clinical remission of a low risk CSCC under high-dose VAE treatment without recurrence in the following 4 years (until publication). Histological diagnosis of CSCC (Fig. 1) was confirmed by two independent dermatologists. As spontaneous remission of CSCC is rare and no other specific therapy was used, we presume the remission to have occurred as a result of the high-dose VAE injections. Post-treatment biopsy of the tumour site could not be performed to confirm the clinically diagnosed remission of the tumour. Still, in view of the long-term follow-up of the patient without any signs of recurrence, a complete tumour remission is most likely.

Dose dependency may be presumed because of lack of response under lower dosages, and stronger local skin reactions (reddening and swelling) and tumour remission under high dosage. The difference in effect may also have been due to using mistletoe grown on different host trees (Fraxinus versus Betula), but this seems less likely as the active compounds in the preparations used are similar (personal communication, Dr. Karin Schleisiek, Abnoba GmbH).

Tumour remissions with accompanying immunologic reactions under high dose VAE, often intra- or peritumourally injected, have been reported in other tumour entities as well, such as squamous cell carcinoma of the oral cavity (Scheffler et al. 1996), primary cutaneous B-cell lymphoma (Orange et al. 2012), Merkel cell carcinoma or breast cancer (Orange et al. 2010), and others (Kienle and Kiene 2003a, 2007). They have also been repeatedly observed in animal

Table 2
VAE betulae therapy, following VAE fraxini therapy (see Table 1).

Week of treatment	VAE betulae: perilesional injections per week		Observations at the tumour site
	2 mg[a]	20 mg[a]	
1–2	1		
3		1	
4		1	White scabbing
5		2[b]	White scabbing 5 mm × 8 mm; prescription of dimetindine
6		1	
7		1	2nd photograph (Fig. 2b)
8–10		1	
11		1	Scab had fallen off; tumour site < 6 mm
12		1	
13	0		
14–15		1	
16		1	3rd photograph (Fig. 2c)
17		1	
18		2	
19		1	
20		1	No palpable tumour, erythematous area at previous site
21	0		
22		1	
23		1	
24	0		4th photograph (Fig. 2d)

[a] Of the indicated vials of 1 ml only 0.1–0.45 ml were used for each injection depending on the infiltration dose tolerated by the patient.
[b] Two injections were applied in week 5 because the course of disease had shown positive effects in the week before and therefore a regimen change to twice weekly injections was considered.

experiments (Büssing 2000; Kienle and Kiene 2003a). Antitumoural effects of locally applied VAE may be explained by their strong cytotoxic and apoptosis-inducing potency and by immune stimulating effects (e.g. activation of antigen-presenting cells, effector cells, induction of cytokines, and others) as seen in *in vitro* and *in vivo* experiments (Büssing 2000; Kienle and Kiene 2003a). Still, further research of the *in vivo* mode of action of VAE in tumours is needed, especially histological and immunohistological analyses during and after local application of high dose VAE.

Local skin reactions like swelling of the surrounding skin as well as the erythema and itching are well known side effects of VAE (Kienle et al. 2011), and are also observed after application of other immune modulating therapies such as monoclonal antibodies or imiquimod (Alessi et al. 2009; Goodman et al. 1990; Madan et al. 2010). The occurrence of such side effects during treatment with epidermal growth factor receptor inhibitor seems to predict a better clinical outcome (Wacker and Nagrani 2007).

This paper describes one single case and no other cases were found on VAE in CSCC. As the primary therapy of CSCC – surgical excision – is curative in most cases, with few risks, patients should not be advised to employ alternatives. Although CSCC has a relative good prognosis, it can still progress, infiltrate or metastasise if not treated properly and the risks of delaying or withholding surgical excision have to be carefully balanced and critically discussed (Mistry et al. 2010). There can be situations as in the presented case with reasonable need for non-invasive treatment. Great interest has been generated in the search of non-invasive therapy options (Madan et al. 2010), and research on VAE in CSCC is therefore warranted.

Consent

Written informed consent was obtained from the patient for publication of the report and accompanying images. He read the final version of the paper and confirmed its content.

Conflict of interest

The authors declare to have no conflict of interest.

Author's contribution

PGW and GSK contributed to the case report design. GS was the physician in charge who provided the patient's information and arranged the photo documentation. PGW and HF collected and provided the data. PGW was the principle author of the paper, had full access to all data, and is guarantor. HF provided specific knowledge in AM. GSK supervised the report and the publication process.

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