

Severe Systemic Reaction to Topical Imiquimod

Anna-Kaisa Heikkinen^{1,2} and Päivikki Susitaival²

Departments of Dermatology, ¹Oulu University Hospital and University of Oulu, PL 22, FI-90029 Oulu, and ²North Carelia Central Hospital, Joensuu, Finland. E-mail: annakhe@paju.oulu.fi

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Imiquimod, an imidazoquinoline amine, is an immune response modifier that stimulates both innate and adaptive immune responses through the production of interferon- α (INF- α) and other cytokines (1). In addition imiquimod appears to induce tumour cell apoptosis (2). Topical imiquimod 5% cream (Aldara[®]) has been used to treat a variety of skin conditions, e.g. viral warts, basal cell carcinoma and actinic keratoses. Local skin reactions, such as erythema, flaking, erosions, and crusting, are common (3). In addition, systemic side-effects, such as headache, fatigue, nausea, influenza-like symptoms and myalgia, have been reported, but they have mostly been mild or moderate (1, 4). In a meta-analysis of imiquimod treatment for actinic keratoses in more than 1,200 patients (3) there were not more serious adverse events in the patients treated with imiquimod than those treated with the vehicle control. In a multicentre study comprising more than 800 patients (4), imiquimod 5% cream was used for multiple actinic keratoses. In this study, four patients discontinued treatment due to systemic drug-related adverse reactions, none of which were severe. The most commonly reported systemic symptoms related to imiquimod were: headache (6.0%), myalgia (2.4%) and fatigue (2.3%) (4). Overall, topical imiquimod is considered to be well tolerated. In the literature we found only one case report (5) of severe, systemic side-effects due to topical imiquimod. The case was a fit 78-year-old man who was prescribed topical imiquimod 5% cream daily for 6 weeks for a basal cell carcinoma of the temple. After 2–3 weeks of imiquimod application he began to feel unwell, lost his appetite, lost 7 kg of weight and developed postural hypotension. We report here a similar case in which topical imiquimod treatment of actinic keratoses was associated with an extensive local reaction and severe long-standing systemic effects.

CASE REPORT

A healthy, slender, fit and physically active 69-year-old woman with no regular medication had used imiquimod for the first time in August 2009 for actinic keratosis of her nose. During treatment she experienced an intense local reaction and mild dizziness. The outcome of the first treatment was good. In early January 2010 she was started on imiquimod three times per week for 4 weeks for two actinic keratosis lesions on the forehead. After 2 weeks of treatment the treated lesions started oozing and scabbing. She continued with treatment and began

to experience dizziness and nausea. At the same time, the pain and oozing of the lesions increased considerably. She lost her appetite, resulting in a weight loss of 5 kg in one week. The dizziness became so severe that she could not walk without falling over, and 4 weeks after starting the treatment she was admitted via emergency department into the hospital for intravenous hydration for 4 days. She had discontinued imiquimod treatment 4 days previously. On admittance she was dehydrated, could not stand up and there was clear muscle weakness. On both sides of the forehead there were thick crusted lesions surrounded by erythema and swelling around the eyes (Fig. 1). The bacterial culture of the skin lesions grew penicillin-resistant *Staphylococcus aureus* (+++). A blood work-up showed ketoacidosis (arterial blood pH 7.30), probably caused by anorexia and vomiting, and mild leukopaenia (B-leuk 2.7 E9/l). Other blood parameters were, and remained, normal (e.g. B-Hb 149 g/l, P-CRP <5 mg/l). A computed tomography (CT) scan of the head was normal. In the extensive work-up, no reason other than the treatment with imiquimod could be detected for her symptoms. Two weeks after discontinuing the treatment the skin lesions were healing, but the patient was still very dizzy and her blood pressure was low (90/50 mmHg). Her appetite improved and her weight normalized within 3–4 weeks. The dizziness continued to decrease slowly, and she still had postural hypotension 9 months after the treatment. The healing of the skin lesions was excellent 2 months after starting the treatment.



Fig. 1. Thick crusted lesions on the forehead after 4 weeks of imiquimod 5% cream treatment for actinic keratoses.

DISCUSSION

In pharmacokinetic studies of topical imiquimod use, serum concentrations have been found to be very low, reflecting minimal dermal absorption (1, 6). It has been hypothesized that systemic side-effects may be caused, not by the drug itself, but by the locally produced cytokines spreading into the systemic circulation. Thus, the severity of the symptoms could be related to the surface area of the skin reaction (6, 7). The results of treatment tend to be better after intense local reaction (4, 8). In the case report of Hanger et al. (5), which closely resembled our case, the authors hypothesized that the absorption of imiquimod through very inflamed and vascular skin of the face and scalp may have been greater than expected from earlier studies. They also studied the low vitamin B12 level in their patient after the cessation of imiquimod. The authors speculated that imiquimod can affect B12 vitamin concentrations, but that the reduced vitamin B12 level was not the cause of the symptoms. It has been hypothesized that immune stimulation can oxidize antioxidants and B vitamins, which might lead to enhanced demand for folate and vitamin B12, together with homocysteinaemia (9). In our case, vitamin B12 or folate levels were not recorded. Interestingly, both patients were fit and physically active. This case is a reminder of potentially serious side-effects of topical imiquimod use.

The authors declare no conflict of interest.

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