Pemphigus-like lesions induced by imiquimod

ARTICLE in CLINICAL AND EXPERIMENTAL DERMATOLOGY · JUNE 2009

Impact Factor: 1.09 · DOI: 10.1111/j.1365-2230.2008.03181.x · Source: PubMed

CITATIONS
14

READS
36

4 AUTHORS:

Ana Bauzá
Hospital Universitari Son Espases
31 PUBLICATIONS 382 CITATIONS

SEE PROFILE

Luis Javier del Pozo
Hospital Universitari Son Espases
40 PUBLICATIONS 53 CITATIONS

SEE PROFILE

Carlos Saus
Hospital Universitari Son Espases
52 PUBLICATIONS 663 CITATIONS

SEE PROFILE

Ana Martín-Santiago
Hospital Universitari Son Espases
53 PUBLICATIONS 170 CITATIONS

SEE PROFILE

Available from: Ana Martín-Santiago
Retrieved on: 09 April 2016
Pemphigus-like lesions induced by imiquimod

A. Bauza, L. J. Del Pozo, C. Saus* and A. Martin

Departments of Dermatology and *Anatomopathology, Son Dureta University Hospital, Palma de Mallorca, Mallorca, Spain

doi:10.1111/j.1365-2230.2008.03181.x

Summary

Imiquimod is an immunomodifier recently approved for the treatment of superficial basal cell carcinomas (sBCC). Although local adverse events (AEs) are the most commonly reported, systemic AEs have also been described. We present the case of a 60-year-old woman who, after the application of two sachets of imiquimod cream per day for 5 days/week to two large sBCCs, developed pemphigus-like lesions both at and distant from the application site. Histological examination of a skin biopsy found intraepidermal acantholytic blistering but results of direct immunofluorescence examination were negative. The lesions resolved after cessation of imiquimod. Two previous cases of imiquimod-induced pemphigus have been reported, but this is the first case with lesions distant from the site of application. We suggest that systemic absorption of the drug or greatly increased synthesis of cytokines could explain this reaction and recommend the use of low doses of imiquimod in the treatment of large or multiple sBCCs.

Imiquimod (Aldara®; 3M Pharmaceuticals, St Paul, MN, USA) is an immune-response modifier that acts as a ligand of the Toll-like 7 and 8 receptors, favouring the expression of various cytokines such as interferon (IFN)-α, tumour necrosis factor (TNF)-α and various interleukins that stimulate both the innate and cellular immune response. The most common adverse events are erythema, exudation and erosions at the application site, but secondary systemic effects have also been seen.

Report

A 60-year-old woman presented with two large lesions located on the upper back and left shoulder, (30 mm and 50 mm in diameter, respectively; Fig. 1a). Histological examination of biopsy specimens confirmed them as superficial basal cell carcinomas (sBCCs). The patient had no relevant medical history.

Treatment with imiquimod was recommended at a dose of one sachet (250 mg) per day for both lesions (125 mg each) five times a week for 6 weeks. The patient presented 2 weeks later with intense erythema, pain and erosions on both carcinomas, and vesicles, crusts and erosions on the neckline and both lips (Fig. 1b). There was no involvement of the intraoral or other mucosa, but she reported occasional fever. The patient had applied imiquimod 500 mg (250 mg to each carcinoma) per day, and had applied any remaining cream to the neckline. She denied applying it to the lips. There was no family history for autoimmune diseases and she denied use of other drugs.

Imiquimod was suspended and treatment with oral prednisone (20 mg initial dose, then tapered by 5 mg every 3 days, over 2 weeks), oral amoxiclavulanic acid, and topical hydrocortisone and fusidic acid was started. There was complete lesion resolution after 2 weeks.

A skin biopsy taken from a vesicle and perilesional skin on the neckline showed an intraepidermal acantholytic blister with eosinophils compatible with pemphigus vulgaris (PV) (Fig. 2). Results of direct immunofluorescence and tests for serum antiepidermal antibodies were negative. Surgical treatment was difficult due to the size and location of the lesions. Thus, imiquimod 250 mg/day was restarted three
times a week, treating only the carcinoma on the upper back. After 2 weeks, the patient developed slight erythema and erosions in the upper zone of the treated carcinoma. No lesions were seen in other locations. Two months later, the second carcinoma was treated for a further 2 months, with the same result. One month after the end of treatment, only residual hypopigmentation in the treated zones remained. At follow-up after 1 year, there was no relapse of the carcinomas.

Drug-induced pemphigus is a well-established variant of pemphigus. The most common variant associated with drug exposure is pemphigus foliaceus (PF), but PV has also been described. Several drugs have been found to induce acantholysis via antibody formation (nonthiol drugs) or via biochemical mechanisms (thiol-containing or sulphur-containing drugs). Less common is the appearance of pemphigus after topical application of a drug (contact pemphigus).2 Imiquimod does not contain thiol or sulphur groups; however, local generation of antibodies to desmoglein 1 has been suggested.

Our patient is the third reported case of topical imiquimod-induced pemphigus. Previous reports have been limited to one case each of PV3 and PF,4 both limited to the application site. Our case is unusual for the presence of lesions both at and distant from the application site. This could be explained by systemic absorption of the drug or by greatly increased synthesis of cytokines. This hypothesis is supported by the absence of relapse on reducing the dosage to one sachet per day. The negative results from direct immunofluorescence and circulating antiepidermic antibody testing are also interesting. In the two previous reports,3,4 the authors suggested that local production of antidesmoglein antibodies could be the cause of pemphigus lesions in their patients. However, direct immunofluorescence was only carried out in one of these studies, and the results were positive. Our case suggests that there are mechanisms of producing acantholysis other than by antibodies, possibly the activation of enzymes causing keratinocyte disaggregation or the inhibition of enzymes causing keratinocyte aggregation. In addition, topical imiquimod is known to induce the production of some cytokines, such as IFN-α, TNF-α, interleukins 1, 6, 8, 10 and 12, and interleukin-1 (IL-1) receptor antagonist.5 Most of these can induce pemphigus or have been found at high levels in such patients. IFN-α has been shown to induce PV and PF, and high levels of this cytokine have been found in these diseases. TNF-α and IL-1 have been implicated in PV acantholysis via urokinase plasminogen activator, and raised levels have been shown in these patients, correlating with a high disease activity.6 In addition, anti-TNF-α drugs have been successfully used
in the treatment of some patients with pemphigus. Finally, other interleukins such as interleukins 6, 8, 10 and 12 are increased in patients with pemphigus.

In conclusion, we believe that in our patient the use of high doses of imiquimod contributed to more widespread disease, possibly due to systemic absorption or greatly increased synthesis of cytokines. For this reason, we recommend that in the presence of multiple large lesions, sequential treatment should be carried out to avoid high doses that may increase the risk of absorption and severe AEs.

References